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special issue

Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

editorial

Voices of endocrinology: contemporary insights in endocrine and metabolic disorders

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This special issue of the *Archives of Endocrinology and Metabolism* (AE&M) brings together invited narrative reviews written by experts from around the world. "*Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders*" highlights current advances, ongoing controversies, and emerging directions across endocrine science and clinical practice. Each article reflects both the state of the art and the personal perspectives of distinguished leaders who have contributed over the years to shaping our understanding of the topics addressed in this issue.

Manuel Aguiar-Oliveira and cols. describe the emerging field of dermatoendocrinology and discuss the clinical diagnosis of various cutaneous manifestations associated with endocrine disorders (1). Likewise, Svenja Leibnitz, Cihan Atila and Mirjam Christ-Crain from the University of Basel, Switzerland, explore novel concepts related to oxytocin, emphasizing its potential for future therapeutic applications (2).

Coagulation disorders and the increased risk of thromboembolic events in patients with Cushing's syndrome have been widely debated in recent years. In their article, Amit Akirov and Maria Fleseriu revisit current recommendations on anticoagulation therapy in this group of patients, addressing key gaps that hinder the implementation and standardization of protocols across different clinical settings (3).

The group led by Richard Quinton synthesizes the key elements of three recently published guidelines on female hypogonadism, providing a timely and practical update for clinicians managing this condition (4). Meanwhile, pediatric endocrinologists will benefit from the comprehensive review by Rodolfo Rey and his co-authors from Argentina, which offers an updated clinical approach to delayed puberty in males (5). At the opposite end of the age spectrum, Andrea Giustina and his group from Italy examine the role of vitamin D in preventing bone, muscle and adipose deterioration in the elderly, while Sergio Setsuo Maeda and his colleagues from the Federal University of Sao Paulo present an overview of the roles of micronutrients in bone health (6,7).

Multidisciplinary perspectives spanning bench-to-bedside approaches in the management of obesity, diabetes and metabolic disorders, are also featured in this special issue. Isabela Busto Silva and Manel Puig-Domingo review emerging mechanisms and current understanding of the thyroid-gut axis, highlighting its potential clinical implications (8). The pervasive nature of weight stigma in society and among healthcare professionals is covered in the review by Stuart Flint, Paula V. Sozza and Adrian Brown, who present and discuss a whole intervention framework aimed at reducing the impact of stigma on individuals living with obesity (9). Ana Flavia Moura and Roberto Pecoits-Filho provide a nephrology-oriented view on the cardio-kidney-metabolic framework, emphasizing the bidirectional relationship between kidney disease and cardiometabolic events and underscoring the need for enhanced multidisciplinary coordination (10). In a similar vein, the international team led by Anand

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Vaidya from Boston, USA, present novel evidence from pathology, biochemistry, proteomic and genetic studies, implicating subclinical primary aldosteronism in the pathogenesis of cardiorenal disease (11). Finally, the wide range of manifestations of diabetic autonomic neuropathy – one of the most serious and often under-recognized complications of diabetes – is addressed by Lucianne Tannus and Roberta Cobas in their review, which integrates basic, epidemiological, and clinical data to provide a comprehensive understanding of this condition (12).

Together, the articles of this special edition of AE&M provide clinicians, researchers, trainees and healthcare providers with a rich and diverse set of perspectives to guide the understanding and management of complex endocrine and metabolic disorders in an era of rapid scientific and clinical advancement.

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Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

invited review

Addressing weight stigma and communicating with patients

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ABSTRACT

Substantial evidence highlights the pervasive nature of weight stigma, reported by people of all ages and backgrounds. Weight stigma is experienced across the life course and in many settings across society. These harmful experiences may include verbal and physical behaviours, with long-lasting effects on mental and physical health. They may also impact the patient-practitioner when weight stigma is experienced in a healthcare setting, as well as reducing health seeking behaviour and avoidance of healthcare. It is therefore essential that weight stigma in healthcare is addressed given the important implications of these experiences in this setting, Interventions need to be longer term and given the widespread nature of weight stigma, change is needed throughout society from policy to practice. Thus, a whole system approach to weight stigma is needed to address the entrenched and often robust nature of weight stigma attitudes.

Keywords: Weight stigma; weight bias; healthcare; health policy; health communication

INTRODUCTION

Evidence highlighting the prevalence, impact and implications of weight stigma has increased substantially. Despite the continued misconception that weight stigma can be beneficial, there is an abundance of evidence that demonstrates these experiences have a detrimental impact on people living with obesity both on mental and physical health outcomes as well as behavioural responses. For instance, research has shown that weight stigma experiences are associated with higher depression and anxiety, reduced self-esteem, increased cardiometabolic risk factors, weight gain, increased risk of self-harming and eating disordered behaviours (1,2). Studies have also indicated that people living with obesity respond maladaptively including avoidance of settings where stigma occurs such as schools and education centres, social and community events and healthcare (3). Using a narrative review approach, our aim was to examine the empirical evidence examining the impact of weight stigma in healthcare and its impact on patients living with obesity. In doing so, we offer a range of strategies that can be implemented to reduce weight stigma.

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WEIGHT STIGMA IN HEALTHCARE AND HEALTH POLICY

Weight stigma is prevalent among healthcare professionals and within healthcare settings (4-6). Additionally, multinational studies indicate a high prevalence of weight stigma reported by doctors (5), with this stigma associated with biased beliefs about

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obesity (4). An important factor to highlight is that obesity is widely diagnosed based on Body Mass Index (BMI). This reliance can lead to inappropriate guidance and stigma in treatment, despite BMI having been originally designed for population-level analysis rather than individual assessment and not specifically to assess health. Furthermore, BMI is a limited measurement that does not adequately represent different racial and ethnic groups. Nevertheless, BMI remains widely used in clinical practice among healthcare professionals, even serving as an eligibility criterion for procedures (7) and referral for weight management interventions. The limitations of BMI as an individual assessment and diagnostic criterion for obesity are well recognized today. Recently, a new definition and diagnostic criterion were published to distinguish between preclinical obesity—characterized by excess adiposity without illness—and clinical obesity, defined by excessive adiposity along with dysfunctions in organs and cells, as well as reduced quality of life (8).

The evidence clearly demonstrates the complexity of obesity and weight gain. However, a widely held belief persists that weight is entirely under individual control and that modifying it simply requires effort in making dietary changes, maintaining a caloric deficit, and exercising more. This erroneous belief reinforces weight stigma and negative stereotypes about obesity, portraying individuals as lazy, uncommitted, undisciplined, and lacking the willpower to engage in changes that would lead to weight loss (1).

Weight stigma in healthcare settings is present across various fields, including medicine, surgery, nursing, psychology, nutrition, and dietetics, among other specialties, even those focused specifically on obesity treatment (1,9-11). Many patients report an excessive focus on weight and the promotion of weight loss strategies during consultations, with professionals disregarding their actual health concerns (10). Proper education on obesity is limited from the early stages of professional training, resulting in unprepared healthcare teams and facilities with inadequate infrastructure for larger bodies (10). Additionally, individuals living with obesity experience inequality in healthcare services, as professionals spend less time with them, provide less health education, are less likely to perform medical examinations and show less respect in their care compared to their treatment of individuals with lower body weight (1,2).

It is evident that individuals living with obesity experience negative emotions due to the pronounced weight stigma in healthcare settings. Patients feel devalued as a result of negative interactions with professionals, who often use derogatory language, exhibit dismissive nonverbal behaviour, fail to listen, and adopt a condescending attitude at various levels of healthcare (primary, secondary, and tertiary care) (6). And these settings frequently justify restricting access to services for individuals with obesity based on the mistaken belief that they are responsible for their weight and must demonstrate self-control by losing weight before accessing other treatments. Such justifications overlook the complexity of obesity, which involves biological, genetic, environmental, psychological, and social factors.

Public health also presents significant barriers concerning obesity, as governments fail to implement adequate actions to address the issue of weight stigma. Instead, many policies are stigmatizing, framing obesity as a matter of individual responsibility by emphasizing dietary changes and exercise while ignoring its multifactorial nature. While also putting obesity alongside other modifiable health risk factors such as smoking and alcohol consumption (1,12). Just as public health initiatives have historically placed blame on individuals for other chronic diseases, the same is now occurring with obesity, promoting the notion that people should be held accountable for their health (1,2). Furthermore, weight stigma is most pronounced among healthcare professionals who deprioritize government investment in obesity-related actions and research, reinforcing the fact that stigma can influence decisions regarding obesity and the allocation of funding for studies in this crucial field (4).

Research has also reported that there is problematic portrayal and framing of obesity treatment where for instance, bariatric surgery is portrayed as an "easy way out" or that it is a "easy choice" and often public opinions including those of people living with obesity (13,14). This framing infers that weight management

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through behavioural modification, namely reduced energy intake and increased expenditure, is both harder and more worthy – and as such moralises obesity, compared to bariatric surgery. This inference ignores the complexity of obesity that means for many people living with obesity, behavioural modification would not lead to significant weight change. Moreover, the framing of bariatric surgery as easy is far from reality, given the very difficult pre- and post-surgery requirements including behavioural changes that for many will require life-long changes. Unfortunately, this framing continues to exist, with people living with obesity internalising this perception, which in some cases, may lead to shame and self-deprecation amongst those who choose this treatment option. With the new wave of medications for obesity receiving significant attention, there is emerging evidence that this harmful framing is being applied to these treatments. The potential benefits of these medications beyond weight loss including reduced risk of major cardiac events, is concerning. Akin to bariatric surgery, these medications also require significant long-term behavioural changes with evidence informing that when these medications are ceased, this often leads to weight regain (15,16).

IMPACT OF WEIGHT STIGMA

It is well known that weight stigma is associated with psychosocial harm and is linked to an increased risk of depression, anxiety, and even suicide (6). Furthermore, weight stigma perpetuated by healthcare professionals may contribute to rising obesity rates due to the various levels of harm it can cause, leading to long-term mental and physical health deterioration, including worsening biochemical parameters associated with cardiometabolic risks and mortality (9). Prolonged exposure to the stress triggered by experiencing weight stigma can result in hormonal and physiological changes related to the onset of heart disease, stroke, and mental health diagnoses (17).

Experiencing weight stigma in healthcare settings can cause patients to experience stress induced by discrimination, leading to acute reactions that can negatively impact their health and the quality of their healthcare experience (17). These experiences are also associated with reduced engagement in healthcare and lower utilization of medical services, leading to avoidance and delays in seeking medical interventions (9). A significant factor to consider regarding stigma experiences in healthcare settings is the impact on internalized weight stigma, which refers to the acceptance of negative stereotypes and their application to oneself, resulting in self-devaluation due to weight. Internalized weight stigma is linked to feeling uncomfortable during physical examinations, perceiving medical judgment about one's body, and increased avoidance of medical visits and health screenings (5).

Such avoidance and delays in seeking medical consultations occur due to fears of weight-loss discussions, over focus on weight as the cause of medical issues, concerns about weight gain, and anxiety over being weighed during appointments (10). These factors contribute to an increased risk of health deterioration, particularly in the prevention of chronic diseases that require long-term specialized treatment. For instance, women living with obesity exhibit high rates of avoiding medical appointments due to fears of body judgment, leading to a lack of preventive screenings for pelvic and breast examinations (9), as well as people present inadequate cancer screenings (2,17).

Many treatments are denied to individuals with obesity due to BMI cut-off points being used as acceptance criteria for procedures and treatments such as surgeries, transplants, fertility treatments, and gender-affirming care (18), driving inequity of healthcare. Moreover, weight stigma acts as a barrier in healthcare settings, impairing the prescription and availability of treatment alternatives for individuals with obesity, such as medications for obesity and metabolic surgery (7). Regarding bariatric and metabolic surgery, recommended for individuals who have been unable to lose weight through other treatments and experience significant health impairments due to obesity, there is often a delay in recommending surgery or, in some cases, it is not recommended at all. This is due to the belief that individuals must first demonstrate their commitment and engagement by losing weight on their own. This notion has been shown to not impact on weight loss

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following surgery resulting in American Society for Metabolic and Bariatric Surgery (ASMBS) not recommending presurgical weight loss due to insufficient scientific evidence of its benefits (18,19). A similar issue arises with the prescription of medications for obesity. Such perspectives are often reinforced by government actions aimed at reducing expenditures on procedures and medications, which ultimately result in the exclusion of individuals in genuine clinical need of appropriate treatment (2). Additionally, access to healthcare can be hindered due to weight-based discrimination in the workplace, which can result in denied job opportunities, reducing monthly income needed for health insurance and medical services. Regarding healthcare settings, patients can often struggle to find facilities that are structurally adequate and free from stigma, and are weight inclusive, where for instance, there are appropriately sized facilities and equipment including blood pressure cuffs, gowns and armless chairs.

LANGUAGE MATTERS

Consistently reported in relation to stigmatising experiences in healthcare, is the language used by healthcare professionals and communication about weight. Research has reported that patients experience poor communication from healthcare professionals both when seeking care related and unrelated to obesity (4,5).

Several studies have examined preferences for weight-related terminology (20-23). highlighting that there are variations in opinions. Consistently, weight neutral terms are identified as the most preferred. Brown and Flint (20) also identified that there was a stronger dislike and a feeling of disgust for terminology that was accompanied by exacerbating verbs such as "super", "extremely" and "morbidly", and unlike other studies exploring weight-related preferences, their study also examined emotional response highlighting that sadness was associated with all terms. The least preferred terms were "super obese", "chubby", and "extra-large", and for parents the least preferred for healthcare professionals to use about children with obesity were "fat", "extra-large" and "extremely obese". Studies examining terminology and language used by healthcare professionals highlight that neutral terms such as "weight" are the most preferred, that language used in consultations can impact the patient practitioner relationship and empathetic and compassionate communication can have a beneficial impact on patient engagement and future health seeking behaviour. The differences in terminology preferences suggest that where possible, healthcare professionals elicit the patients' preferred weight-related terminology.

Healthcare professional communication about obesity has been reported to be unhelpful, and in some instances stigmatising and derogatory. This includes communication within patient-practitioner consultations where rhetoric is intentionally stigmatising reflecting stereotypes relating to lacking willpower and gluttony (24), whilst others occur unintentionally as a result of a lack of communication training.

ADDRESSING WEIGHT STIGMA IN HEALTHCARE

In response to the accumulating evidence of the pervasiveness and impact of weight stigma, there have been calls for interventions, with many intended to reduce weight stigma amongst healthcare professionals. Various types of interventions have been trialled including education, evoking empathy, conditioning, weight inclusive approaches and group dynamic based tasks to foster collaboration. Many of these interventions have reported limited success, and where reductions have been reported, these effects have often dissipated back to baseline overtime. The Health at Every Size (HAES) model represents a weight-inclusive approach that shifts focus away from weight and weight loss as primary health metrics, instead advocating for a comprehensive, multidimensional understanding of wellbeing. Research evidence indicates this paradigm demonstrates effectiveness in improving cardiometabolic outcomes, enhancing quality of life indicators, and increasing treatment compliance rates (25,26). Education about the aetiology and complexity of obesity that informs of the evidenced wide-ranging factors that may lead to obesity, including the factors either partially or solely outside of a person's control (e.g.,

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genetic, environmental) as well as education about weight stigma, appear to have the greatest effect, albeit limited (27). For instance, Velazquez and cols. (28) reported that a 4-hour education-based intervention was effective at reducing weight bias amongst healthcare professionals with the effect sustained at 4- and 12-months post-intervention.

Educational and training for healthcare professionals have emerged, with a focus on improving understanding of the aitiology and complexity of obesity, weight management interventions including behavioural, pharmacotherapy and surgery based on a person's and weight and health status, and importantly, training specifically to address weight stigma, communication and behaviour change techniques (29-31). Guidelines for healthcare professionals have also been created by professional organisation and societies for members (32,33), and by researchers (1,34). Research highlights the potential impact of stigmatising language in consultations that for instance, lead to negative emotional response that does not support behavioural changes (20). Stigmatising language can impact the patient-practitioner relationship and may lead to healthcare avoidance, opportunities to enhance communication techniques and where appropriate to elicit preferred language from patients in consultations is advised.

SUMMARY AND STRATEGIES TO REDUCE WEIGHT STIGMA IN HEALTHCARE

Addressing weight stigma is not going to be quick or easy given how ingrained it is in society. However, changes are needed, and we must embrace these changes given the substantial evidence about the detrimental effects of weight stigma experiences, with even small changes like the ones listed below having the potential to substantially improve the experience of people living with obesity within healthcare. These strategies address the limitations of previous efforts where for instance, education about obesity that has shown promise in reducing weight stigma attitudes and reduced attribution of blame also involves practical solutions to implement change. First, it is imperative that people living obesity are included and play a key role in the design and development of obesity related policy, services and research, which is currently rarely happening. Progress has been made, particularly in research, where research authorities and councils have stipulated patients and public involvement. Second, given the pervasiveness of weight stigma that means most people are exposed to weight stigma on almost a daily basis, we must be prepared to address our own biases and potentially behaviours; weight stigma may be implicit and intentional. Third, within healthcare, there is a need for improved empathy and compassion towards people living with obesity who have and, in some instances, continue to face inequity in access to care and discrimination in healthcare settings (1). Improvements in empathy are needed both in the consultation room through patient-practitioner interactions and in decisions about care. Fourth, appreciate the impact of weight stigma experiences and that addressing weight bias internalisation may be an important first step as part of any form of care package. Fifth, create weight inclusive healthcare environments that appropriate for people of all body sizes. This may include equipment and facilities such as armless chairs and appropriately sized gowns. Sixth, the adoption of a weight-inclusive narrative (as opposed to a weight-normative approach) in healthcare, research, and individual care should be prioritized. Seventh, increased training, education, and updated guidelines for healthcare professionals are essential to ensure alignment with current evidence on obesity. This includes highlighting its multifactorial origins, particularly the influence of environmental determinants, and moving beyond individual-centric blame narratives. Finally, strengthening psychosocial support systems and economic accessibility is crucial, as these factors significantly impact an individual's ability to obtain comprehensive healthcare, engage with supportive environments, and achieve overall well-being. Consequently, governments must implement coordinated public policies to guarantee equitable healthcare access and the necessary conditions for a healthy life.

SUMMARY

In this narrative review, we provide an overview of the key issues relating to weight stigma and its impact on

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people living with obesity. Weight stigma in healthcare is rife with evidence demonstrating that this is a key setting where people living with obesity experience it. Stigmatising communication from healthcare professionals has and continues to be reported, where blame and individual responsibility frequently cited despite the evidenced complexity of obesity that goes beyond individual agency. As such, weight stigma interventions are needed that address the myths and misconceptions of obesity, that are long-term and aligned across the system given that weight stigma is evidenced across society, and that reinforce compassion and empathy.

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special issue
Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

invited review

Subclinical primary aldosteronism

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ABSTRACT

Primary aldosteronism (PA) is a major contributor to hypertension and cardiovascular disease. Subclinical PA, a preclinical or early manifestation of PA, has been identified in individuals with normal blood pressure and in those with mild hypertension without signs or symptoms of overt PA, using evidence from histopathology, hormonal biochemistry, proteomic, and genetic studies. Longitudinal studies have shown that subclinical PA increases the risk for developing incident hypertension, adverse cardiovascular remodeling, major adverse cardiovascular events, and chronic kidney disease. Given the clinical relevance of subclinical PA on the pathogenesis of cardiorenal disease, future studies should focus on methods to enhance early detection and assessment of the impact of early aldosterone-directed interventions for preventing adverse clinical outcomes.

Keywords: Aldosterone; primary aldosteronism; subclinical primary aldosteronism; renin; adrenal

INTRODUCTION

Hypertension affects over 1.3 billion people worldwide and is the leading modifiable risk factor for both cardiovascular morbidity and mortality (1-4). Renin-independent, and relatively non-suppressible, aldosterone production, the underlying pathophysiology that characterizes primary aldosteronism (PA), can be found in over 25% of individuals with hypertension, translating to > 300 million individuals with underlying PA pathophysiology (5). This pathophysiologic aldosterone production results in inappropriate mineralocorticoid receptor (MR) activation, which contributes to cardiovascular disease through mechanisms such as oxidative stress, inflammation, and fibrosis (6). Compared to essential hypertension, PA carries a disproportionately higher risk of cardiovascular complications, independent of blood pressure (7). Identification of PA pathophysiology is crucial, as aldosterone-directed therapy can reduce the risk for cardiovascular disease (8,9). For this reason, modern clinical practice guidelines now recommend screening for PA for all individuals with hypertension (3,10).

The recent paradigm shift viewing PA as a spectrum rather than a dichotomous disease has enabled more research into its earliest manifestations, referred to as subclinical PA (5,11-16). Subclinical PA refers to the identification of biochemical renin-independent aldosterone production in individuals with normal blood pressure and those with mild hypertension without signs or symptoms of overt PA. Herein, we comprehensively review the evidence on the underlying pathogenesis and pathophysiology of subclinical PA and its relevance to adverse cardiovascular outcomes.

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THE PATHOGENESIS AND BIOCHEMICAL SIGNATURE OF SUBCLINICAL PA

Subclinical PA has been characterized using multiple modalities, including histopathology, steroid and hormonal biochemistry, proteomics, and aberrant receptor expression.

Histopathology

The development of immunohistochemistry for aldosterone synthase has been an important breakthrough in understanding the cellular origins of PA (17,18). Identification of what were initially termed aldosterone producing cell clusters (APCCs) through CYP11B2 staining helped redefine the pathology of PA from the dichotomous designation of unilateral adenoma vs bilateral hyperplasia towards a more nuanced understanding of PA (19,20). These APCCs, now referred to as aldosterone producing micronodules (APMs) were shown to frequently harbor pathogenic somatic driver variants for PA, elevated CYP11B2 expression, and hypothesized to be precursor lesions to aldosterone producing adenomas (APAs) (21-24). APMs harboring pathogenic somatic mutations can be detected in morphologically normal adrenal glands from individuals with normal blood pressure (24-26), and accumulate with age (26-28). These findings suggest that dysregulated expression of CYP11B2 is common, precedes the onset of overt PA, may characterize the subclinical phases of the disease, and could explain a large proportion of age-related hypertension.

Hormonal biochemistry

Many studies have demonstrated a biochemical spectrum of renin-independent aldosterone production in normotensive people (5,11,12,14-16,29). As aldosterone and renin levels exhibit significant variability (30), this continuum has been demonstrated using postural and dietary maneuvers to evaluate the regulation of the renin-angiotensin-aldosterone system (RAAS) system, including: sodium restriction and upright posture to stimulate plasma renin and angiotensin II (AngII) (14), seated sodium loading test (SST) to suppress aldosterone production (16), oral sodium loading test to suppress aldosterone production (11,12), and supine posture following oral sodium loading to suppress aldosterone production (15).

Using these carefully conducted phenotyping maneuvers, a continuum of renin-independent aldosterone production has been described in individuals with normal blood pressure that exhibits parallel responsiveness to both AngII and adrenocorticotropic hormone (ACTH) (5,12,15,16), akin to phenomena that have been observed in patients with overt PA (31-33). The altered sensitivity, or increased responsiveness, to these ligands may be driven by upregulation or sensitization of MC2-R (ACTH receptors) and AT1-R (type 1 angiotensin II receptors) in aldosterone-producing regions, with expression levels differing by genotype (34-37).

Another biochemical feature associated with subclinical PA is natriuretic peptide (NP) insufficiency (15). This finding was first observed in a population-based epidemiological study demonstrating an inverse relationship between aldosterone and NP levels in normotensive people (38). Aldosterone and NPs are reciprocal hormonal systems that regulate each other via intravascular volume but also via direct regulatory effects (39-42). In subclinical PA, aldosterone production results in NP insufficiency, which may then contribute to impaired natriuresis, vasodilation, and the inability to suppress aldosterone production, leading to the synergistic development of hypertension, fibrosis, and inflammation.

A recent study showed that in normotensive people, the magnitude of subclinical PA correlated with 18-hybrid steroid production (12). 18-hybrid steroids are well-established biomarkers of PA pathophysiology, reflecting dysregulated CYP11B2 activity and its co-expression with CYP17A1 (43,44). The demonstration that normotensive people exhibit a spectrum of renin-independent aldosterone production that correlates with 18-hydroxycortisol and 18-oxocortisol production supports the notion that there is a pathologic continuum of PA detectable among normotensive people.

Proteomics

The plasma proteome of PA has been previously described when compared to people with hypertension

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revealing dysregulated pathways related to inflammation, including neutrophil degranulation, phagocytosis, regulation of reactive oxygen species, and oxidative stress-induced apoptosis (45). These pathways were reinforced by another large-scale proteomic study which characterized the proteomic evolution of subclinical PA to overt PA (46). The proteomic signature of PA originated in normotensive people and was characterized by pathways implicated in cardiovascular disease pathogenesis including inflammation, vascular remodeling and redox imbalance (46). Within this study, Norrin or *NDP*, a Wnt/β-catenin ligand, showed robust, aldosterone dose-dependent trends across various physiological maneuvers, suggesting its potential role as a novel regulator in the pathogenesis of PA (46).

Aberrant receptor expression and other mechanisms

Aldosterone production has been shown to be regulated by eutopic and ectopic receptors in adrenal cortical tissue: AT1-R and MC2-R as described above, but also receptors for vasopressin, serotonin, GIP, leptin, mast cells, LH/HCG and neuropeptide substance P (47-52). The role of these ectopic receptors in the pathogenesis of subclinical PA remains to be studied directly.

Many other hypotheses have also been proposed for the origins of PA, including a two-hit model, where an initial germline pathogenic variant drives tumoral proliferation and a somatic pathogenic variant in PA susceptibility genes promotes aldosterone production (53,54).

Finally, the germline SNPs identified in genome-wide association studies of PA patients highlight a genetic susceptibility that predates clinical diagnosis (55-57). These genes include *CASZ1*, *RXFP2*, *LSP1*, *NDP*, *WNT2B*, *CYP11B1/2*, *TBX3*, *HOTTIP* and *ADGRB3* (55-57). Notably, the involvement of *NDP* in PA pathogenesis was subsequently validated in a study including normotensive and hypertensive people where SNPs in *NDP* were associated with dose-dependent increases in aldosterone production (46).

SUBCLINICAL PA AND RISK FOR INCIDENT HYPERTENSION

Subclinical PA has been associated with an increased risk for incident hypertension in longitudinal studies (13,58-61). A large prospective study from Canada found that a higher aldosterone-to-renin ratio (ARR) was associated with a greater risk of incident hypertension (adjusted OR, 1.29 [95% CI, 1.03-1.62]) (58). Similarly, a study by Markou and cols. found that normotensive individuals with elevated post-fludrocortisone-dexamethasone suppression test aldosterone levels and ARR had a significantly higher risk of developing hypertension over five years (59). Supporting this, Brown and cols. identified that higher aldosterone concentrations in the context of a low renin phenotype were associated with an increased risk for incident hypertension (13). A longitudinal analysis from adolescence (age 17) to adulthood (age 27) demonstrated a positive correlation between ARR at 17 and blood pressure at 27, suggesting that elevated adolescent ARR may predict future hypertension (62).

SUBCLINICAL PA AND RISK FOR INCIDENT MAJOR ADVERSE CARDIOVASCULAR OUTCOMES

Many studies have shown that the magnitude of the subclinical PA biochemical phenotype predicts the risk for incident cardiovascular disease (14,58,63-66).

Atherosclerosis, cardiac structure and function

A large study using data from the Multi-Ethnic Study of Atherosclerosis (MESA), which included adults free of cardiovascular disease at baseline and not taking blood pressure medications, found that higher aldosterone levels were associated with a higher coronary artery calcium, particularly when renin was low (65). It should be noted that the overall mean blood pressure in the cohort was 118.6 ± 18.5/69.4 ± 9.5 with approximately 85% of the participants considered to be normotensive (65). A retrospective analysis from a subgroup of normotensive participants from the longitudinal Atherosclerosis Risk in Communities (ARIC) study revealed that a low renin phenotype was associated with greater left ventricular (LV) mass index, LV end-diastolic and end-systolic volumes, and left atrial volume index (64).

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The deleterious impact of elevated aldosterone and ARR on cardiac structure was also demonstrated in individuals with familial hyperaldosteronism type I (FH-I) compared with matched controls, both groups having normal blood pressure (66). FH-I patients showed greater left ventricular wall thickness and impaired diastolic function, highlighting that aldosterone excess promotes adverse cardiac remodeling even in the absence of hypertension (66). Finally, a longitudinal cohort study from the CARTaGENE cohort demonstrated that the magnitude of subclinical PA was associated with greater arterial stiffness, evidenced by elevated central blood pressure and pulse wave velocity, as well as adverse cardiac remodeling, such as increased left atrial volume index, LV mass index, remodeling index and LV hypertrophy as measured by cardiac MRI (58). A sensitivity analysis excluding participants taking antihypertensive medication yielded similar results to the primary analyses (58).

Clinical outcomes

The CARTaGENE cohort of mostly normotensive people also yielded data linking subclinical PA magnitude to major adverse cardiovascular events (MACE), described as a composite of myocardial infarction, stroke (ischemic or hemorrhagic), hospitalization for heart failure, and cardiovascular death (63). Both the low renin phenotype (adjusted hazard ratio, 2.22 [95% CI, 1.02-4.76]) and higher ARR (adjusted hazard ratio, 2.43 [95% CI, 1.15-5.12]) were associated with a higher risk for MACE (63).

In the MESA cohort described above, aldosterone was associated with the increased risk of all-cause mortality when plasma renin activity was low over a median follow-up of 12.5 years (65).

SUBCLINICAL PA AND CHRONIC KIDNEY DISEASE (CKD)

A large study of more than 1900 healthy community-dwelling individuals found that both aldosterone and ARR were inversely associated with glomerular filtration rate, independent of multiple confounders including blood pressure, diabetes status and weight. Importantly, higher aldosterone was significantly associated with an increased risk of chronic kidney disease (67). In a study by Terata and cols., conducted in Japanese individuals without CKD and not on antihypertensive medication with an observation period of over 9 years, individuals who developed CKD had significantly lower baseline plasma renin activity and higher baseline ARR level (68).

CONCLUSION

Subclinical PA is a biochemical phenotype characterized by renin-independent, and relatively non-suppressible, aldosterone production that originates in normotensive people and precedes the development of hypertension. Subclinical PA is associated with higher risks for incident hypertension, cardiovascular disease, and CKD (**Figure 1**). The importance of recognizing this phenotype lies in the global burden of hypertension and the opportunity to identify mechanisms that allow targeted therapy with widely available mineralocorticoid receptor antagonists, and that may also be a potential target for emerging treatments such as aldosterone synthase inhibitors (69). However, more practical approaches are needed to identify pathophysiological aldosterone production without relying on complex physiological testing (70). Future efforts should focus on earlier and more pragmatic identification of subclinical PA pathophysiology, and the impact of early implementation of aldosterone-directed interventions on clinical outcomes.

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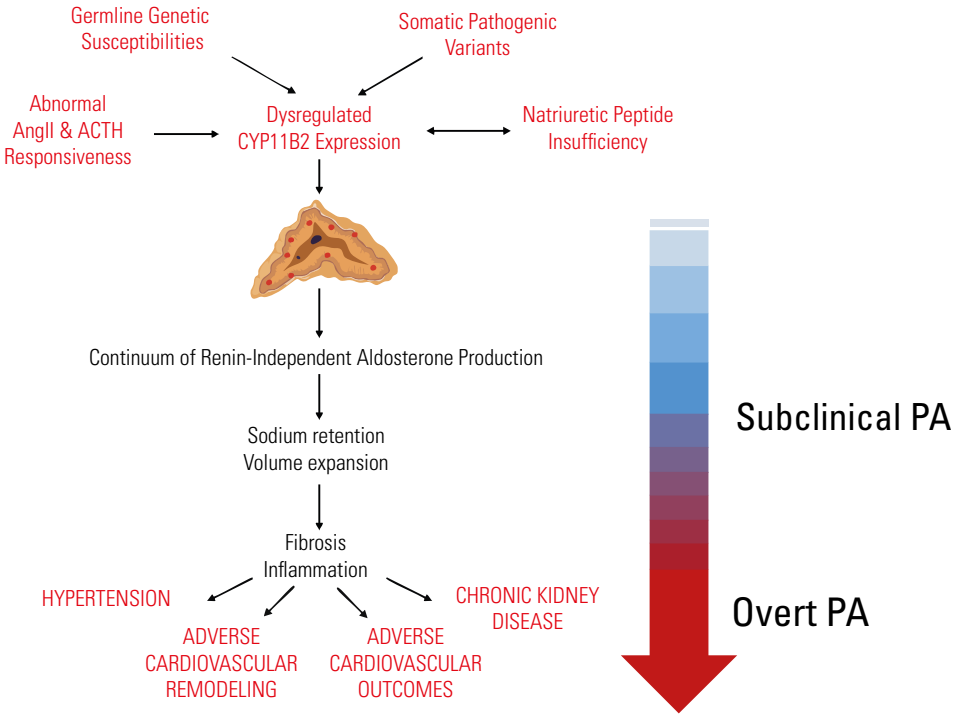


Figure 1. The pathophysiology of subclinical primary aldosteronism.

Subclinical PA is characterized by a continuum of non-suppressible, renin-independent aldosterone production, in normotensive or mildly hypertensive people without overt PA. The interplay of germline genetic susceptibilities, somatic pathogenic variants, natriuretic peptide insufficiency, and abnormal responsiveness to AngII and ACTH lead to dysregulated CYP11B2 expression and aldosterone production. Pathophysiologic aldosterone production causes sodium retention, volume expansion, fibrosis and inflammation, ultimately leading to hypertension, adverse cardiovascular remodeling and clinical outcomes.

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special issue
Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

invited review

Cardio-kidney-metabolic (CKM) framework: A nephrologist's perspective

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ABSTRACT

The recently proposed cardio-kidney-metabolic (CKM) framework underscores the interconnected nature of cardiovascular, renal, and metabolic diseases and represents an important step toward preventive, integrated care. However, its application in kidney care remains limited and dependent on additional supportive evidence. Chronic kidney disease (CKD) is often underrecognized in cardiovascular risk models and receives delayed attention within the CKM pathway. Nephrologists face unique challenges – including workforce shortages, late referrals, and fragmented care systems – particularly in low- and middle-income countries. Early detection is further hindered by the lack of CKD-specific risk assessment tools and limited access to essential diagnostics and therapies. Real-world data from global and national studies highlight substantial implementation gaps, suboptimal outcomes, and the heavy economic burden of delayed CKD management. Importantly, as emphasized by the American Heart Association, implementation of the CKM approach is still under construction and must remain data-driven, ensuring that strategies are grounded in robust evidence. This review offers a nephrology-oriented perspective on the CKM framework, emphasizing the bidirectional relationship between CKD and other CKM components, the prognostic implications of delayed diagnosis, and the need for improved multidisciplinary coordination.

Keywords: Cardio-kidney-metabolic syndrome; chronic kidney disease; obesity; diabetes; cardiovascular disease

INTRODUCTION

The cardio-kidney-metabolic (CKM) framework, recently proposed by the American Heart Association, emphasizes the interplay between cardiovascular, renal, and metabolic diseases in determining survival and quality of life (1). The impact of obesity, diabetes, kidney disease, and cardiovascular disease on mortality is well documented, with cardiovascular disease remaining the leading global cause of death (2-6). Individuals with a BMI > 25 kg/m² have a 30% higher mortality risk for every 5 kg/m² increment (3). Patients with diabetes or CKD also face higher mortality (4,5), and those with eGFR < 30 mL/min/1.73 m² live on average 20 years less than individuals with preserved kidney function (≥60 mL/min/1.73 m²) (4).

The relationship between CKM syndrome and CKD is bidirectional: CKD predisposes to hypertension, insulin resistance, and dyslipidemia, yet remains underrepresented in cardiovascular risk models despite its profound impact on outcomes (7,8). This underrecognition dilutes its clinical significance and delays targeted interventions, even though CKD independently increases cardiovascular risk and frequently coexists with diabetes, hypertension, and obesity.

While the CKM framework promotes integrated, multidisciplinary care, it does not fully capture the practical challenges of nephrology – particularly in low- and middle-income countries (LMICs), where workforce shortages, limited resources, and fragmented systems hinder early detection and intervention (9). In many LMICs, nephrologists are concentrated in tertiary centers or dialysis clinics,

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leaving large populations without specialist access (10). As a result, serum creatinine and albumin-to-creatinine ratio (UACR) testing – essential for CKD detection – are often underused due to infrastructure and training gaps (11).

These limitations have measurable consequences. REVEAL-CKD showed that patients with unrecorded stage 3 CKD experienced delayed initiation of disease-modifying therapies and inadequate risk stratification (12). The Brazilian CHECK-CKD study similarly highlighted systemic deficiencies in the interpretation of kidney function at the primary care level (13). With dialysis needs in Brazil projected to increase by 170.8% by 2032 (14), earlier nephrology engagement is critical.

This review provides a nephrology-oriented perspective on the CKM framework, emphasizing the importance of timely referral, access to kidney-protective therapies, and embedding nephrology within multidisciplinary teams to bridge current implementation gaps.

THE INTERSECTION OF CARDIO-KIDNEY-METABOLIC HEALTH: A NEPHROLOGY-ORIENTED PERSPECTIVE

The intersection between cardiovascular, renal, and metabolic systems is of growing relevance in nephrology. This is not only due to overlapping risk factors but also to the tightly intertwined pathophysiological mechanisms that drive CKD progression and its complications. Understanding these interactions is crucial for the modern nephrologist, as clinical and therapeutic decisions frequently require an integrated approach to managing these domains.

Core components of the CKM axis

The CKM framework includes a wide range of conditions distributed across three major domains. The cardiovascular domain encompasses hypertension, atherosclerotic vascular disease, ischemic heart disease, atrial fibrillation, heart failure (HF), and non-hemorrhagic cerebrovascular disease. The renal domain includes primary kidney diseases – such as glomerulopathies, nephrolithiasis, and polycystic kidney disease – as well as secondary CKD and end-stage kidney disease (ESKD). Metabolic disturbances within the CKM spectrum include central obesity, insulin resistance, dyslipidemia, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease, and polycystic ovary syndrome (15).

While the CKM framework appropriately highlights the intersection of cardiometabolic drivers such as obesity, diabetes, and hypertension with kidney disease, it risks underrepresenting a broad spectrum of primary renal disorders that do not fit neatly within this paradigm. Glomerulonephrites, hereditary cystic diseases, and obstructive urological disorders account for a substantial proportion of chronic kidney disease worldwide and are associated with unique trajectories and outcomes that cannot be fully explained by cardiometabolic clustering. Failure to integrate these conditions more explicitly within the CKM framework may inadvertently marginalize patients whose kidney disease arises from non-cardiometabolic pathways, thus limiting the generalizability of the model across the full spectrum of nephrology practice.

Hypertension in chronic kidney disease

Hypertension is the second most common cause of ESKD worldwide, and CKD is three times more prevalent among individuals with hypertension compared to the general population (16). Most hypertension-related renal injuries are attributed to the loss of autoregulatory mechanisms within the renal microvasculature, resulting in arteriolar wall hypertrophy, activation of endothelin-1 signaling pathways, and hyperactivation of both the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). These processes lead to efferent arteriolar vasoconstriction, sodium and water retention, and the initiation of pro-fibrotic and pro-inflammatory cascades (17). When sustained, these disturbances cause hemodynamic and histopathological alterations that impair glomerular function. Over the medium to long term, progressive deterioration of kidney function further amplifies these pathophysiological mechanisms, particularly RAAS hyperactivation, intensifying pro-inflammatory and pro-fibrotic responses and contributing to vascular dysfunction (17).

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INSULIN RESISTANCE AND CKD

Peripheral insulin resistance is frequently observed in CKD and inversely correlates with eGFR, even among non-diabetic individuals (18). This multifactorial condition is driven by chronic inflammation, RAAS activation, uremic toxins, metabolic acidosis, gut microbiota dysregulation, and oxidative stress – hallmarks of CKD – which collectively downregulate the GLUT4 glucose transporter responsible for insulin-dependent cellular glucose uptake (19,20). Diabetes is reported in approximately 28% of CKD patients and remains the leading global cause of ESKD (19,20).

OBESITY AND THE KIDNEY

Obesity is a central feature of CKM syndrome and is increasingly prevalent both in the general population and among CKD patients (21,22). Visceral adiposity induces a lipotoxic and pro-inflammatory state that promotes oxidative stress, endothelial dysfunction, and atherosclerosis (21,22). Moreover, visceral fat may exert mechanical pressure on the glomeruli, enhancing sodium reabsorption in the loop of Henle, activating tubuloglomerular feedback, and stimulating the RAAS axis—all contributing to hemodynamic alterations and kidney injury (22-24). Adipocytes also act as aldosterone secretagogues, further elevating the risk of hypertension and subsequent CKD progression (25).

Although obesity is a recognized risk factor for CKD onset and progression, it paradoxically appears to confer a survival benefit in dialysis patients – a phenomenon known as the "obesity paradox" (26). The mechanisms underlying this observation remain unclear and are under active investigation.

DYSLIPIDEMIA IN CKD AND ESKD

Dyslipidemia, particularly hypertriglyceridemia, is frequently associated with CKD and ESKD (27). The pro-inflammatory state in CKD exacerbates insulin resistance and impairs lipoprotein lipase (LPL) activity through the overproduction of inhibitory molecules and the development of secondary hyperparathyroidism (27). These alterations reduce the hydrolysis of chylomicrons and very-low-density lipoproteins (VLDL). Dialysis therapies – both hemodialysis and peritoneal dialysis – can further exacerbate dyslipidemia by intensifying systemic inflammation and promoting protein loss (27,28). Additionally, patients with nephrotic syndrome often present with pronounced dyslipidemia, especially elevated low-density lipoprotein (LDL) cholesterol (29).

CKM SYNDROME AS A RISK FACTOR FOR KIDNEY DISEASE

Beyond the factors described above, CKM syndrome itself has been independently associated with increased risk of developing CKD (30). Studies have shown that individuals with CKM syndrome have approximately a 1.5-fold higher risk of CKD compared to the general population (31). This risk rises progressively with the accumulation of CKM components—namely dyslipidemia, hyperglycemia, insulin resistance, obesity, and hypertension (31,32). Although the exact pathophysiological mechanisms remain unclear, they are thought to involve oxidative stress, endothelial dysfunction, glomerular injury, and pro-fibrotic signaling.

PROGNOSTIC IMPLICATIONS OF CKM SYNDROME

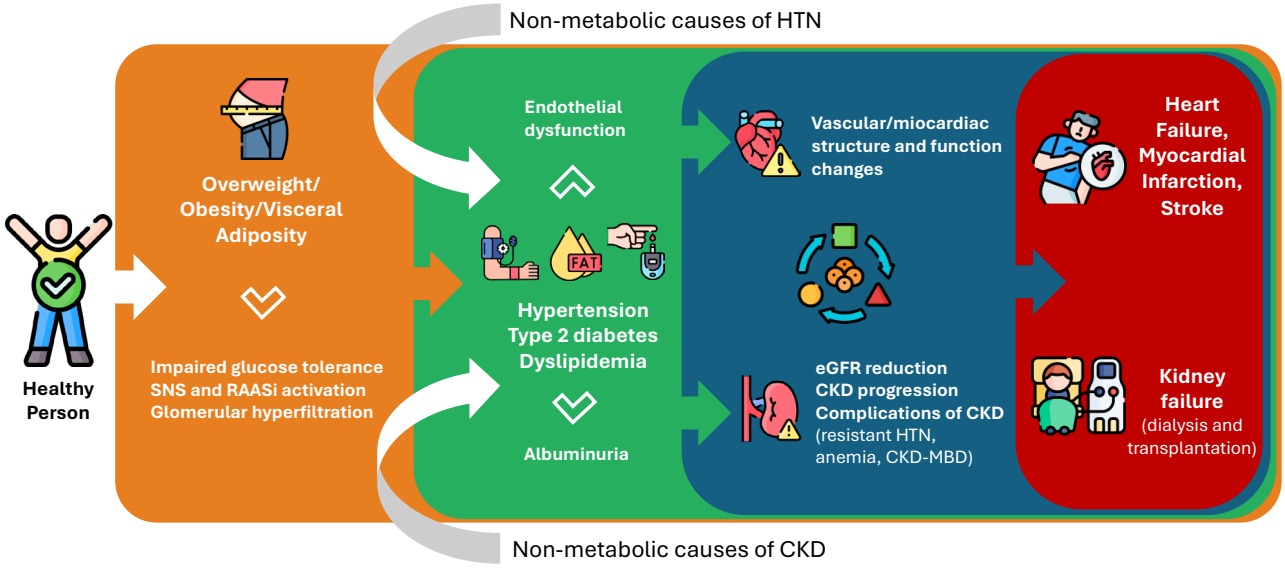
There is consistent evidence that CKM syndrome is linked to increased mortality and adverse cardiovascular outcomes (5,15). However, it remains unclear whether CKM syndrome continues to act as an independent risk factor after adjusting for the individual comorbidities that define it. Emerging studies suggest that CKM syndrome may indeed serve as an independent predictor, even after controlling for cardiovascular, renal, and metabolic variables (5,15,33). Additional studies are needed to confirm and refine these findings. **Table 1** summarizes the primary mechanisms linking CKM syndrome and CKD.

Figure 1 illustrates the bidirectional interactions between cardiovascular, renal, and metabolic domains, highlighting the pathophysiological mechanisms that drive CKM syndrome and its clinical consequences.

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Table 1. CKM mechanisms and Nephrology relevance

Domain	Pathophysiological Mechanism	Relevance to Nephrology
Cardiovascular	Systemic arterial hypertension	Second leading global cause of ESKD; key therapeutic target in CKD
Cardiovascular	Endothelial dysfunction and atherosclerosis	Increases cardiovascular risk in CKD patients
Cardiovascular	Sympathetic nervous system and RAAS activation	Contributes to renal fibrosis and proteinuria
Renal	Loss of renal microvascular autoregulation	Central mechanism in hypertensive CKD progression
Renal	Efferent arteriolar vasoconstriction and glomerular inflammation	Leads to hemodynamic changes that reduce GFR
Renal	Sodium and water retention	Promotes volume overload and resistant hypertension
Metabolic	Insulin resistance and hyperglycemia	Leading global cause of CKD; worsens tubular injury
Metabolic	Chronic inflammation and oxidative stress	Present across CKD stages; aggravates renal injury
Metabolic	Dyslipidemia (hypertriglyceridemia, increased LDL)	Associated with CKD progression and increased cardiovascular risk
Metabolic	Visceral adiposity and RAAS activation	Promotes glomerular injury and contributes to hypertension



SNS: sympatic nervous system; RAASi: renin-angiotensin-aldosterone system inhibitors; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HTN: hypertension; MBD: mineral bone disease

Figure 1. Mechanistic interplay between CKM syndrome and CKD progression.

CURRENT GAPS IN CKM FROM A NEPHROLOGY PERSPECTIVE

Despite the clear association between CKM syndrome and kidney disease, nephrology assessment and early identification of renal risk are not consistently addressed in clinical practice. Many current guidelines tend to emphasize individual risk stratification and the isolated management of cardiovascular, renal, and metabolic diseases, while offering limited guidance on integrated care strategies. This fragmented approach overlooks the importance of multidisciplinary coordination aimed at aligning diverse healthcare professionals toward a shared goal in the management of CKM patients (34).

An important limitation of the current AHA conceptualization lies in its outcome prioritization. The Presidential Advisory places considerable emphasis on cardiovascular morbidity and mortality, yet renal failure itself constitutes a major and devastating outcome, particularly for patients who progress to kidney replacement therapy. End-stage kidney disease carries not only profound prognostic and economic consequences but also a heavy social burden, often exceeding that of cardiovascular complications in certain regions and populations (14). By minimizing kidney failure as a primary endpoint, the framework risks perpetuating a cardiovascular-centric bias and diluting the urgency

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of interventions aimed at preventing progression of kidney disease.

Real-world evidence from the REVEAL-CKD study highlighted that a lack of reporting and delayed diagnosis are frequent and consequential: approximately 61% of patients with stage 3 CKD were undiagnosed (12), and a delay of just one year was associated with a 63% higher risk of kidney failure, a 40% higher risk of CKD progression, and an 8% increase in cardiovascular events. These findings illustrate how delayed detection and referral may significantly worsen outcomes (12).

Moreover, many clinical trials exclude patients with CKD, particularly those with ESKD, those undergoing dialysis, or kidney transplant recipients. As a result, there is a significant lack of prospective studies specifically addressing these population (21). Consequently, clinicians are often required to extrapolate recommendations and outcomes derived from studies conducted in other patient groups to individuals with kidney disease, which may not fully reflect their unique clinical context.

Another significant challenge lies in the diagnosis of kidney injury associated with CKM syndrome, as no well-defined diagnostic or histopathological criteria currently exist. Certain biomarkers, such as growth differentiation factor-11 (GDF-11), GDF-15, and urinary A-megalin, have shown correlation with CKM syndrome, yet they remain unvalidated for routine clinical use (35-37). Concurrently, in some countries, there is a lack of adequate training among primary care physicians (PCPs) in the interpretation of essential laboratory tests for CKD screening – such as UACR and serum creatinine measurement – thereby limiting early diagnosis and risk stratification (34). Furthermore, access to essential medications for the conservative management of CKD, T2DM and cardiovascular conditions remains restricted in many regions, undermining optimal disease control.

Although risk stratification is a highly emphasized aspect in CKM syndrome guidelines, there remains a lack of risk assessment tools that are appropriately tailored to patients with CKD or CKM syndrome. Most validation studies for such tools either exclude individuals with CKD or fail to incorporate markers of kidney function and structural kidney damage – such as UACR – as part of the risk criteria. The AHA Presidential Advisory on CKM syndrome acknowledges that most currently available cardiovascular risk calculators are suboptimal for use in patients with CKD and therefore refrains from endorsing any specific tool for this population (6). Instead, the advisory recommends stratifying CKM syndrome based on its core risk determinants, with particular emphasis on atherosclerotic cardiovascular disease (ASCVD) risk, the presence of T2DM, and CKD (6).

This gap carries important clinical implications. Using risk scores not validated in CKD populations may result in under-recognition of cardiovascular risk, especially in patients with significant albuminuria or reduced eGFR. Consequently, this can lead to under-treatment, delayed initiation of disease-modifying therapies, or inappropriate reassurance.

For instance, data from the CKDopps study revealed that fewer than 40% of non-dialysis CKD patients with hemoglobin levels below 10 g/dL received anemia treatment over a 12-month period. Similarly, iron supplementation was infrequently prescribed even among patients with iron deficiency. These findings underscore the risk of clinical inertia or misclassification when standardized nephrology-informed tools are not used (38).

Following the publication of the AHA Presidential Advisory on CKM syndrome, AHA introduced a novel cardiovascular risk stratification tool – the PREVENT score (39). This risk calculator incorporates renal, metabolic, and cardiovascular parameters, making it more suitable for individuals with CKD and CKM syndrome. Additionally, it expands the eligible population by including adults as young as 30 years of age, thereby supporting earlier intervention and lifelong risk assessment (39).

However, despite its strengths, the PREVENT score still does not incorporate risk of kidney failure (KF), nor does it integrate CKD-specific factors such as anemia, mineral and bone disorder (CKD-MBD), or electrolyte disturbances. This limits its utility for nephrologists aiming to manage cardio-kidney risk comprehensively.

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Finally, modeling from the IMPACT-CKD simulation study provided compelling evidence on the consequences of delayed CKD identification and the potential benefits of early intervention in eight countries (14). In Brazil, the simulation projected a 6.9% increase in the number of patients with stage 3-5 CKD over the next 10 years, resulting in approximately 370,000 individuals requiring dialysis by 2032 (14). Furthermore, it forecasted a 100.6% rise in CKD-related cardiovascular events and a 67.8% increase in mortality during the same period (14). Annual dialysis-related costs were estimated at around US$2.7 billion, representing 25.7% of Brazil's total healthcare budget across the decade (2023-2032) (14). These findings underscore the urgent need for early, coordinated CKD care models – including nephrology involvement – to mitigate clinical, enviromental, social, and economic burdens in the Brazilian context (14).

LEVERAGING THE CKM FRAMEWORK TO ADVANCE KIDNEY CARE

Risk stratification and implementation gaps

The AHA recommends that patients with CKM syndrome be stratified according to one of the five risk stages proposed in its Presidential Advisory (6). While this staging framework offers a clear path for tailoring interventions across different phases of cardiometabolic disease, its real-world application is challenged by significant gaps in implementation. Studies such as CKDopps and the CHECK and SEARCH initiatives have highlighted considerable variability in adherence to screening and referral guidelines, especially for CKD, which is a central component of CKM syndrome (13,38,40).

Although albuminuria testing is critical for risk stratification, it remains vastly underutilized in clinical practice. For instance, data from the CKDopps study reveal that albuminuria is routinely measured in fewer than 30% of patients with diabetes or hypertension in some health systems, including in Brazil, despite clear recommendations for its use in early CKD detection and cardiovascular risk prediction (11). Similarly, the CHECK study demonstrated that systemic barriers – including limited access to diagnostic tools, fragmented care pathways, and undertrained primary care teams – impede consistent implementation of evidence-based CKD screening practices (13).

Findings from the SEARCH study – a nationwide CKD screening campaign in Brazil – revealed that approximately 20% of high-risk individuals with diabetes and/or hypertension had previously undiagnosed CKD, with over 11% presenting albuminuria > 30 mg/g (40). Alarmingly, fewer than 9% of patients with moderate or severe albuminuria (A2/A3) had a repeat ACR measured within two years following diagnosis, despite receiving formal documentation of their CKD stage (40). These findings highlight the persistent underuse of albuminuria testing in real-world practice, even after disease recognition, and underscore a missed opportunity for risk stratification and early intervention in patients with cardiometabolic risk profiles (40).

These deficiencies have meaningful consequences. Modeling from the IMPACT-CKD study projected that by 2032, CKD prevalence would range between 11.7% and 16.5% in eight countries, increasing in seven of them (14). In Brazil, the number of patients requiring dialysis is expected to rise by 170.8% between 2022 and 2032 (14). These findings reinforce that failing to act during earlier CKM stages – especially stages 1 and 2 – carries high clinical and economic penalties.

Moreover, outcomes remain poor even for patients who do receive nephrology care in non-high-income countries. A recent multinational study evaluating over 6,000 patients under nephrology follow-up found that mortality and progression to kidney failure were significantly higher in low-resource settings, driven by late referral, limited access to essential therapies, and underutilization of evidence-based risk stratification tools such as albuminuria testing. These findings further emphasize the need for earlier engagement of nephrology services within the CKM framework, particularly in health systems facing structural limitations (41).

To address these issues, it is essential to integrate guideline recommendations into feasible, scalable care models. Routine inclusion of both serum creatinine and UACR from Stage 0 onward can improve early detection. Moreover, referral patterns to nephrologists must shift from a reactive

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to a proactive approach. The AHA and KDIGO both support earlier referral, particularly for patients at Stage G3aA3 or G3bA2, where intervention has the potential to significantly alter the disease course (6,7). Yet, as CKDopps data show, most referrals still occur at advanced stages, often when irreversible organ damage has already occurred (11).

Therefore, leveraging the CKM framework effectively requires not only clinical awareness but also health system reform. This includes training primary care providers to identify CKD risk early, embedding nephrology input in multidisciplinary teams, and ensuring equitable access to essential diagnostics and therapies. By addressing these implementation barriers head-on, it becomes possible to transform CKM staging from a conceptual model into a population-level strategy for improving kidney and cardiovascular outcomes.

BARRIERS TO IMPLEMENTATION IN NEPHROLOGY PRACTICE

Despite the high prevalence and clinical complexity of CKM syndrome, the implementation of integrated care remains suboptimal. While most major clinical guidelines provide robust frameworks for risk stratification and syndromic classification, they often fall short in translating these concepts into actionable care models. As a result, multidisciplinary coordination across cardiology, nephrology, and endocrinology is frequently fragmented, undermining the delivery of patient-centered, holistic care (7,12). Figure 2 summarize main barriers to CKM holistic care implementation.

Health system barriers

Many healthcare systems, especially in low- and middle-income countries, remain structurally oriented toward acute care and are ill-equipped to manage chronic, multisystem diseases like CKM syndrome. Diagnostic limitations are common: access to essential tests such as serum creatinine, UACR, and natriuretic peptides is often restricted or delayed, impairing timely identification of kidney, cardiac, and metabolic abnormalities. In Brazil, for example, fewer than 30% of high-risk patients undergo albuminuria testing despite guideline recommendations (11). Specialist referral is also frequently delayed due to diagnostic uncertainty, limited subspecialty availability, and centralized nephrology services located primarily in tertiary or dialysis-based settings.

Compounding these issues, some public health policies recommend delayed specialist referral (*e.g.*, to nephrologists only when eGFR falls below 30 mL/min/1.73 m²), largely to prevent overwhelming

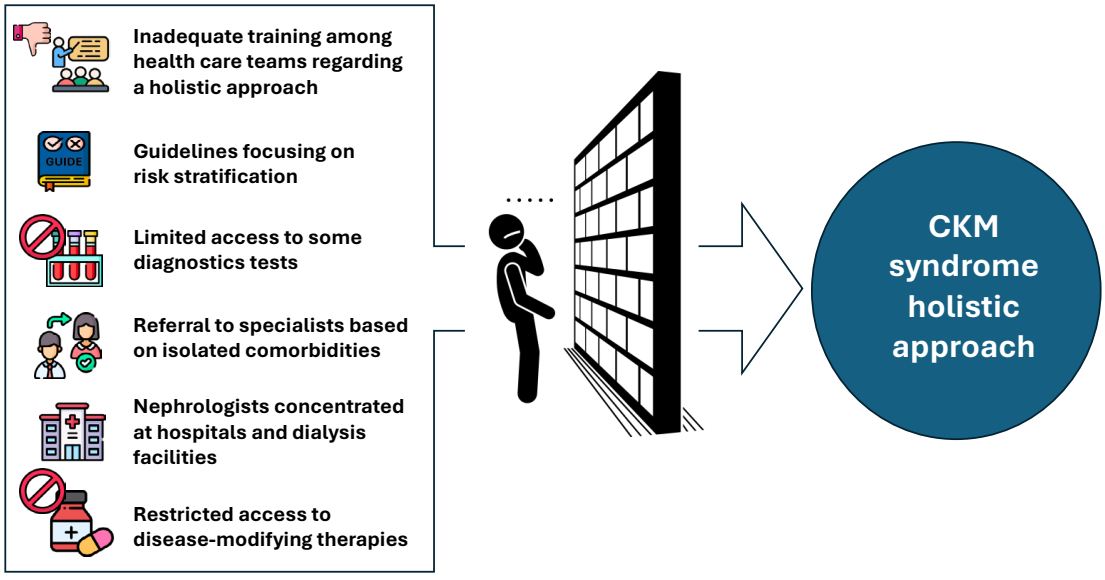


Figure 2. Key barriers to the implementation of holistic care in CKM syndrome.

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limited specialist capacity. However, this approach inadvertently leads to late-stage diagnoses and missed opportunities for early therapeutic intervention.

In response to the rising burden of CKD in low-resource settings, the World Health Organization (WHO recognized CKD as a growing public health priority through the first declaration dedicated to kidney disease. The WHO highlighted the need to strengthen early detection programs, expand access to essential diagnostic and therapeutic tools, and improve care coordination – especially for populations at risk due to environmental, occupational, and cardiometabolic factors (42). This declaration reinforces the urgency of developing national strategies that address CKD not only as a renal issue but as a systemic and societal challenge.

Educational and training barriers

Another key barrier lies in the undertraining of primary care professionals in CKD recognition and management. The CHECK study demonstrated that even when guidelines are well established, inadequate professional training and poor integration of nephrology expertise into primary care settings result in missed opportunities for early diagnosis and intervention (13). This educational gap contributes to late referrals, suboptimal risk stratification, and delayed initiation of kidney-protective therapies.

Even in specialized centers such as dialysis clinics, there is often a lack of familiarity with the broader CKM framework. In many cases, patients undergoing dialysis receive nephrology care that is narrowly focused on kidney replacement therapy, with limited attention to concurrent cardiovascular or metabolic conditions. This siloed care model perpetuates underrecognition of heart failure and atherosclerotic disease, which are common but often overlooked in the dialysis population (41). Given that dialysis teams frequently serve as the primary – if not sole – source of specialist care for these patients, equipping them to address all aspects of CKM syndrome is imperative.

Therapeutic access barriers

Access to key medications for CKD, T2DM, HF, and obesity – such as SGLT2 inhibitors, GLP-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists – remains limited in many healthcare systems. Cost, regulatory constraints, and supply chain limitations have all contributed to low uptake, particularly outside of urban tertiary centers. Although progress has been made in expanding coverage for select drug classes, such improvements remain uneven and insufficient to meet population-level needs. Without consistent access to these disease-modifying therapies, even timely diagnosis is unlikely to yield optimal outcomes.

FUTURE DIRECTIONS AND CALL TO ACTION

The multisystem nature of CKM syndrome presents complex challenges that demand truly integrated, multidisciplinary care (43). Telemedicine has emerged as a promising tool to strengthen communication among specialists, enabling more frequent and even real-time discussions that support coordinated management (44,45). Alternating teleconsultations with in-person visits can also facilitate closer follow-up, particularly for patients in rural areas or in countries with vast geographic distances and limited access to specialized services (45).

Future refinements of the CKM framework should therefore adopt a more balanced approach that equally acknowledges renal-specific outcomes alongside cardiovascular events. This would require explicit inclusion of kidney failure prevention as a co-primary goal, as recommended in recent KDIGO guidelines on CKD management (7). Moreover, a more comprehensive taxonomy of kidney diseases – including immune-mediated, genetic, and structural disorders – would strengthen the relevance of the framework for nephrology, ensuring that it reflects the true heterogeneity of kidney disease across global populations.

The American Heart Association has launched several initiatives to advance CKM care. The *Get With The Guidelines* (GWTG) program systematically collects clinical data, monitors adherence to evidence-based practices, and benchmarks institutional performance, fostering a learning health system (6). More recently, the CKM Centers of Excellence initiative was introduced to establish dedicated institutions that integrate cardiovascular, renal, and metabolic care under

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one framework. These centers are designed to model best practices, promote research, and serve as hubs for multidisciplinary training. Importantly, the AHA has emphasized that implementation of the CKM framework is still under construction and must remain data-driven, ensuring that best practices are guided by real-world evidence. At present, both GWTG and the Centers of Excellence remain U.S.-based initiatives, highlighting the need for global expansion.

International efforts are also gaining momentum. The International Society of Nephrology (ISN) will convene an expert forum on CKM syndrome in October 2025, bringing together leaders from nephrology, cardiology, endocrinology, and health policy. This forum will generate a consensus document outlining key messages from the group, expected to be published later this year. Such initiatives represent important steps toward building a coordinated global approach, but must also remain anchored in robust, data-driven strategies to ensure effectiveness and sustainability.

Bridging the gap between evidence and practice requires guidelines that provide real-world implementation strategies, expanded reimbursement criteria, and broader access to diagnostics and therapies. Workforce investment is equally important: developing career pathways and improving conditions for primary and secondary care providers can help attract specialists to non-tertiary settings, thereby expanding access for patients living with CKM syndrome. Continuing medical education and holistic patient assessment must also become routine across specialties. Finally, the systematic inclusion of CKD and ESKD patients in clinical trials is essential to generate evidence that reflects the populations most affected by CKM syndrome.

CONCLUSION

The CKM framework represents a critical step toward integrated, patient-centered care across cardiovascular, renal, and metabolic domains. Yet implementation remains limited by late recognition of CKD, fragmented health systems, and insufficient access to diagnostics and therapies. To realize its potential, the CKM model must embed nephrology expertise earlier in the care pathway, promote proactive screening and referral, and ensure equitable access to evidence-based treatments.

Initiatives such as the American Heart Association's *Get With The Guidelines* program and the CKM Centers of Excellence provide important models for advancing multidisciplinary care. Crucially, the AHA has stressed that implementation of the CKM approach is still in development and must remain data-driven – a principle that should guide all future actions. The upcoming International Society of Nephrology (ISN) expert forum on CKM syndrome in October 2025 represents another milestone, bringing together global experts to define priorities and publish a consensus document later this year.

Expanding these initiatives globally, while keeping data at the center of implementation, will be essential to address the rising burden of CKM-related disease. Ultimately, a coordinated international strategy – combining high-quality data, practical implementation tools, and cross-specialty collaboration – will be decisive in transforming the CKM framework from concept to practice and in improving outcomes for patients worldwide.

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special issue
Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

invited review

Clinical approach to the male with delayed puberty

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ABSTRACT

Disorders of pubertal onset and progression are a common cause for referral to paediatric endocrinologists, with delayed puberty in males being particularly frequent. Pubertal development depends on the hypothalamic-pituitary-testicular (HPT) axis, which is established during fetal life and undergoes distinct phases: fetal androgen production, postnatal "minipuberty", and reactivation during adolescence. Key regulators include GnRH neurons, Sertoli and Leydig cells, and biomarkers such as AMH, inhibin B, testosterone and INSL3. Puberty is marked clinically by testicular enlargement beyond 4 mL, usually at a median age of 11.5 years. Delayed puberty is defined as absence of testicular enlargement by age 14. The most common cause is self-limited delayed puberty (SLDP), often familial and benign. Functional hypogonadotropic hypogonadism due to chronic illness, and permanent central hypogonadism (congenital or acquired), account for additional cases. Congenital hypogonadotropic hypogonadism (CHH), including Kallmann syndrome, is frequently genetic, with variants in genes such as *FGFR1*, *ANOS1* and *GNRHR*. Clinical assessment includes family history, growth patterns, and red flags such as micropenis, cryptorchidism or anosmia.

Keywords: AMH; delayed puberty; FSH; inhibin B; testis

INTRODUCTION

Disorders affecting the onset or the progression of puberty are common reasons for referral to the paediatric endocrinologist. They are usually associated with a significant impact in the psychosocial sphere for both the patients and their families, and their management can be burdened with uncertainty. In this review, we will address the diagnosis and management of delayed puberty in males, based on the current knowledge of the physiology underlying the development of the hypothalamic-pituitary-testicular axis from fetal life through adulthood (**Figure 1**).

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Developmental physiology of the hypothalamic-pituitary-testicular axis

From fetal life to prepuberty

Fetal differentiation of the testes is initially independent of pituitary gonadotropins (1). In the 7th week of gestation, germ and Sertoli cells aggregate and form the seminiferous tubules; Sertoli cells secrete anti-Müllerian hormone (AMH), which induces the regression of the Müllerian ducts, *i.e.*, the anlagen of the uterus, Fallopian tubes and upper vagina, during weeks 8-10. In the 8th week, Leydig cells differentiate in the interstitial tissue and start secreting androgens, involved in the virilization of internal and external genitalia during weeks 8-13, and insulin-like factor 3 (INSL3), which together with androgens induce testicular descent to the scrotum in the 2nd and 3rd trimesters of gestation. Androgen and INSL3 production are regulated by placental human chorionic gonadotropin (hCG) during the 1st trimester of fetal life. The establishment of the hypothalamic-pituitary-gonadal axis occurs later, approximately during the 17th fetal week (2). Then, LH regulates Leydig cell hormone production, and FSH induces immature Sertoli cell proliferation and upregulates AMH and inhibin B secretion (3).

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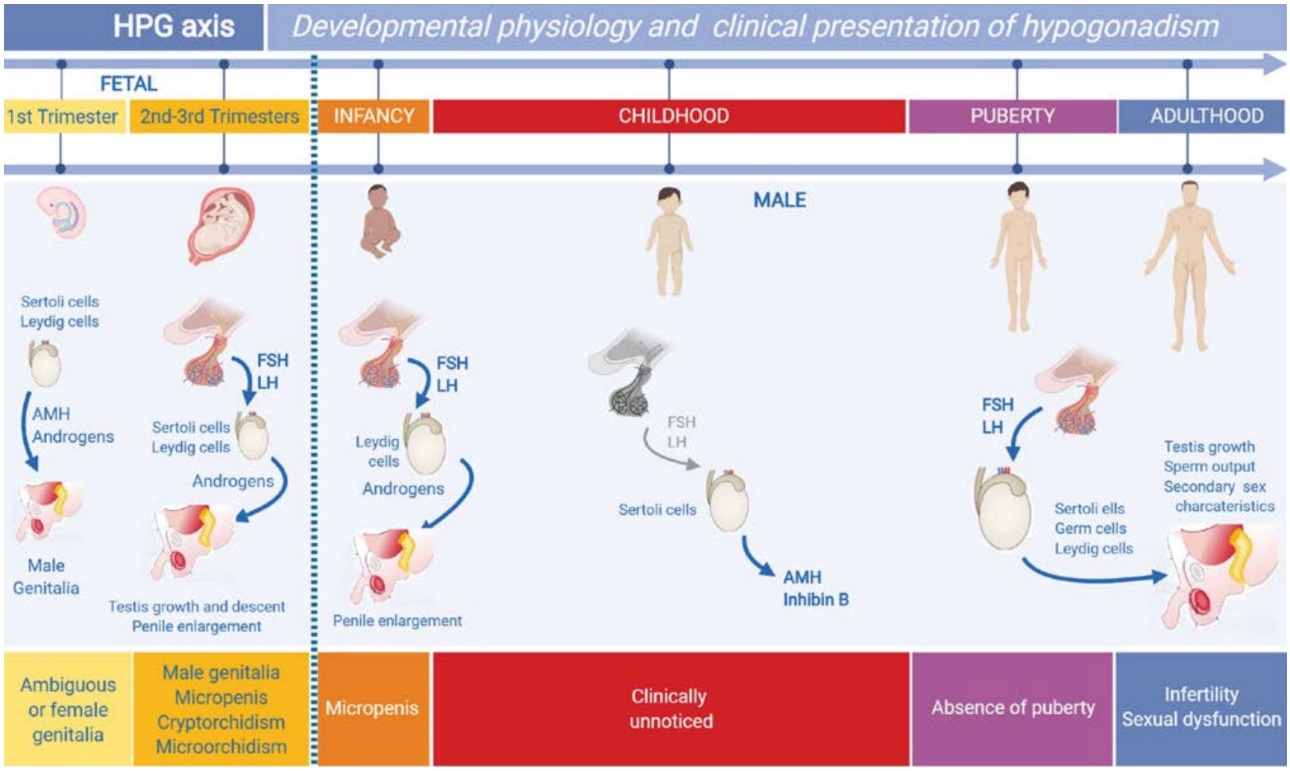


Figure 1. Ontogeny of the hypothalamic-pituitary-gonadal (HPG) axis in males, and its impact on clinical presentation of hypogonadism. In the first trimester of fetal life, the testis differentiates and secretes androgens and anti-Müllerian hormone (AMH), involved in genital sex differentiation, independently of pituitary gonadotropins. Hypogonadal states in this period lead to ambiguous or female genitalia. In the second and third trimesters, fetal FSH induces Sertoli cell proliferation and, consequently, testis enlargement, while LH regulates androgen secretion resulting in testicular descent and penile enlargement. Primary and central hypogonadisms result in micropenis, micro-orchidism and/or cryptorchidism. In infancy, gonadotropin and steroid secretion remain active for 3-6 months; hypogonadism prevents penile enlargement. During childhood. gonadotropins and androgens are normally low or undetectable; hypogonadism may go unnoticed unless AMH or inhibin B levels are assessed. During puberty, the axis is reactivated and results in pubertal maturation; hypogonadism leads to absent or incomplete sex development. Reprinted with permission from ref. (66).

Specifically, AMH secretion is a typical feature of immature (prepubertal) Sertoli cell activity.

Unlike most neuron types of the central nervous system, the gonadotropin-releasing hormone (GnRH) neuron arises from the olfactory placode and migrates to its final position in the hypothalamus following the olfactory nerve. GnRH neuron specification, proliferation and migration are regulated by Anosmin 1 (encoded by *ANOS1*), Chromodomain Helicase DNA-Binding Protein 7 (*CHD7*), Dual-Specificity Phosphatase 6 (*DUSP6*), FEZ Family Zinc Finger protein 1 (*FEZF1*), Fibroblast Growth Factors 8 (*FGF8*) and 17 (*FGF17*) and their receptor FGFR1, Heparan Sulfate 6-O-Sulfotransferase 1 (*HS6ST1*), Interleukin 17 Receptor D (*IL17RD*), Neuron-Derived Neurotrophic Factor (*NDNF*), NMDA Receptor Synaptonuclear Signaling and Neuronal Migration Factor (*NSMF*, also known as *NELF*), Prokineticin 2 (*PROK2*) and its receptor PROKR2, SRY-Box 10 (*SOX10*) and WD Repeat-Containing Protein 11 (*WDR11*) (4). Once established in the hypothalamic nuclei, the GnRH neuron is regulated by Kisspeptin (*KISS1*) and its receptor KISS1R, Leptin (*LEP*) and its receptor LEPR and Tachykinin 3 (*TAC3*) and its receptor TACR3. Another set of factors are implicated in the morphogenesis of the hypothalamus and pituitary, including HESX Homeobox 1 (*HESX1*), Lim Homeobox gene 4 (*LHX4*), Nuclear Receptor subfamily 0, group B, member 1 (*NR0B1*, also known as DAX1), PROP paired-like homeobox 1 (*PROP1*), and the SOX family factors SOX2 and SOX3 (5).

Gonadotropin, testosterone and INSL3 levels remain high during the 2nd trimester and decrease progressively in the 3rd trimester of gestation (6), probably in response to placental oestrogens. At birth, all pituitary and testicular hormones are low

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(7-9). During the first postnatal week, gonadotropins levels increase (8) and remain high for 3 to 6 months in boys. LH induces an increase in testicular secretion of testosterone and INSL3 (9-11). This period of life has been called "minipuberty" given its similarity with puberty in terms of gonadotropin and androgen serum levels. Beyond the 6th month, LH, testosterone and INSL3 levels decrease to very low or undetectable levels and remain so throughout childhood (**Figure 1**). Serum FSH, inhibin B and AMH also increase during the first week after birth. FSH and inhibin B decrease after "minipuberty", but remain clearly detectable. For its part, the AMH remains high during childhood, reflecting the immature status of Sertoli cells (12).

From a clinical standpoint, the size of the penis and testicular descent reflect the secretion and action of androgens in the 2nd and 3rd trimesters of gestation. On the other hand, testicular volume is a good indicator of FSH action, since the size of the testis mainly represents the number of Sertoli cells before puberty and Sertoli cell proliferation is FSH-dependent (3). Serum levels of LH, testosterone and INSL3 are good markers of the gonadotroph-Leydig cell axis from the 2nd week of life and through "minipuberty", *i.e.*, a maximum of 6 months. Conversely, FSH, inhibin B and AMH are biomarkers of the gonadotroph-Sertoli cell axis all through childhood (**Figure 2**). Despite the high intratesticular concentration of androgens during fetal life and "minipuberty", Sertoli cells do not mature because they start to express the androgen receptor only by the end of the 1st year of postnatal life (13,14). The germ cell population is limited to premeiotic spermatogonia.

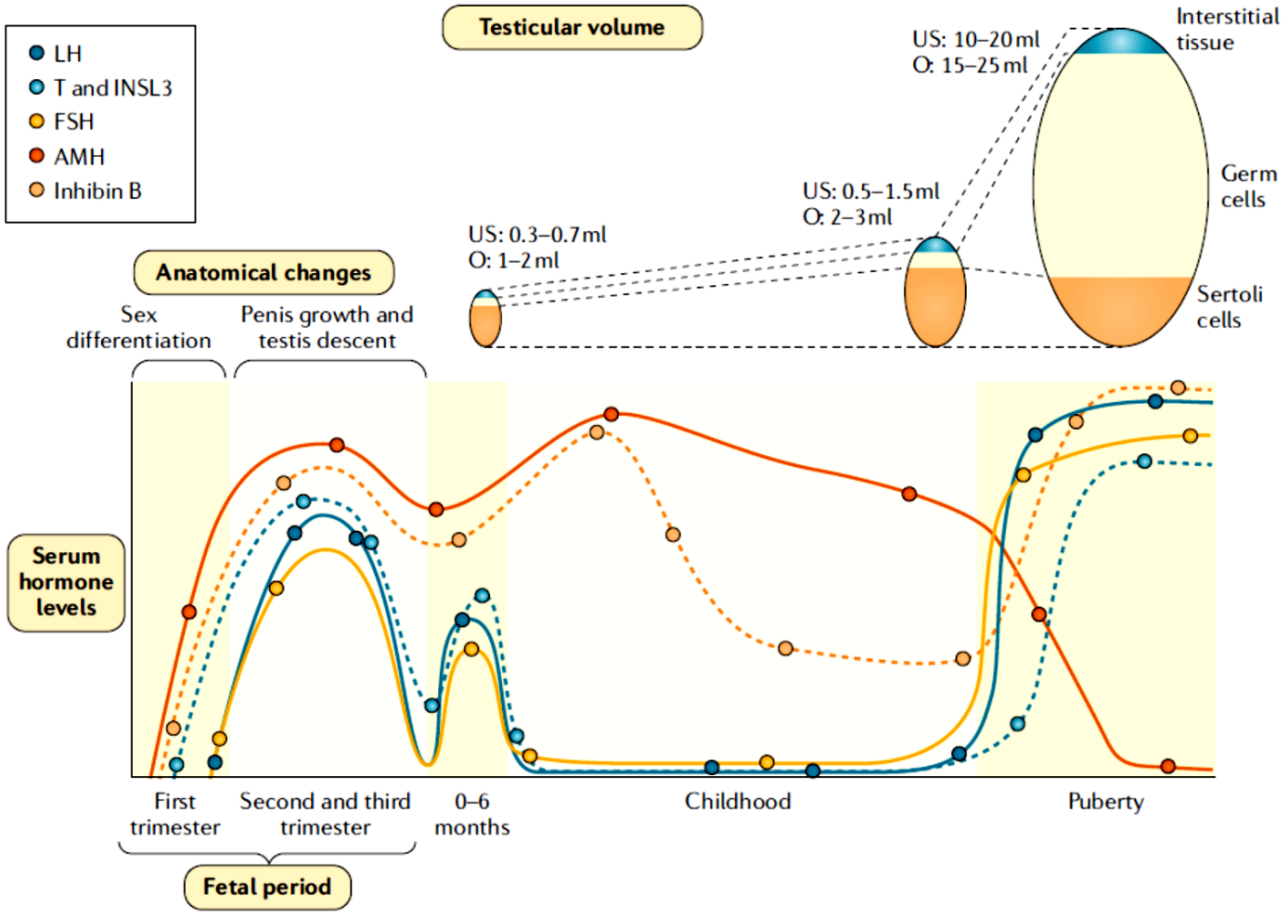


Figure 2. Serum hormone levels and changes in testicular size and genital features in males from fetal life through adulthood. Sertoli cells are the main component of the testes in fetal life and childhood, whereas germ cells are the major component during puberty and adulthood. INSL3: insulin- like factor 3; O: testicular volume measured by comparison to Prader's orchidometer; US: testicular volume measured by ultrasonography. Reprinted with permission from ref. (67).

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Puberty

Puberty is the period characterised by the development of secondary sexual characteristics, the acquisition of fertility and accelerated growth and bone maturation leading to adult height. The underlying physiological process relies on a progressive increase in gonadotropin pulse amplitude and frequency (15). FSH induces the proliferation of immature Sertoli cells and drives the initial increase of testicular volume from ~2 to ~4 mL (**Figure 3A**). LH reactivates androgen production, leading initially to very high intratesticular concentrations that induce Sertoli cell maturation (16). Sertoli cell do not proliferate any longer, AMH production declines (17,18) and inhibin B secretion rises (19,20). Serum testosterone increases only later during pubertal maturation. Androgens are aromatised to oestrogens, which can result in physiological transient gynecomastia in more than half of normal boys during mid- to late puberty. Steroid hormones are responsible for the occurrence of peak height velocity and peak bone mass. INSL3 secretion also increases during puberty but becomes gonadotropin-independent in adult Leydig cells (11). Germ cells enter meiosis and undergo complete spermatogenesis, leading to sperm production (**Figure 1**) and to the characteristic progressive increase in testicular volume to ~15-25 mL (**Figure 2**) (16). FSH and germ cells upregulate inhibin B secretion, which in turn exerts negative feedback on pituitary FSH (21). In adolescents and adults, inhibin B levels are very informative, since they reflect the whole pubertal maturation process: FSH and testosterone action on Sertoli cells and the complete spermatogenic process.

In the male, the clinical milestone of the onset of puberty is testicular volume reaching 4 mL (**Figure 3B**), occurring at a median age of 11.5 years (22). It is associated with enlargement of the scrotum and a change in the texture as well as reddening of the scrotal skin in the initial stage of pubertal maturation, considered as Tanner genital stage 2 (23); during this stage testis volume increases up to ~6 mL (24). Subsequently, in Tanner genital stage 3, there is further growth of the testes (8-10 mL) and scrotum together with penile enlargement. In Tanner stage 4, the penis further enlarges with development of glans, together with growth of the testes (12-15 mL) and enlargement and darkening of the scrotal skin; maximal growth acceleration occurs. Finally, in genital stage 5, genitalia are adult in size and shape, with testes 15-25 mL.

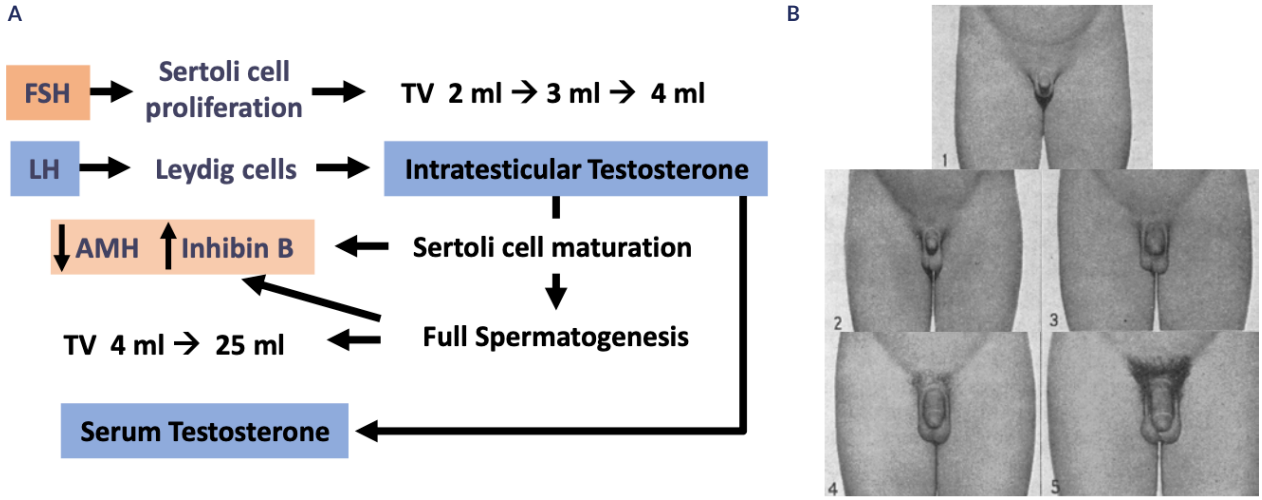


Figure 3. A. Testicular maturation during puberty. With the reactivation of the hypothalamic-gonadotroph axis, FSH increases immature Sertoli cell proliferation leading to testis enlargement from prepubertal (2 mL) to pubertal (4 mL) size. Concomitantly, LH induces Leydig cell differentiation and testosterone production. Initially, testosterone concentration increases within the testes and provoke Sertoli cell maturation. Mature Sertoli cells decrease anti-Müllerian hormone (AMH) secretion and become capable of supporting full spermatogenesis. The massive proliferation of germ cells results in a dramatic increase in testicular volume, up to 15-25 mL. FSH and germ cells induce an increase in Inhibin B. The elevation of serum testosterone to adult levels is a relatively late event, occurring between Tanner stages 3 and 5. **B.** Standards for genital rating during male puberty (stage 1: prepubertal; stage 5: adult), according to Marshall and Tanner. Reproduced with permission from ref. (23).

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Delayed puberty

In boys, delayed puberty is defined by the absence of clinical signs of reactivation of the hypothalamic-pituitary-testicular axis at an age at least 2 standard deviations later than that observed in the population mean. In practice, this means the failure to change from Tanner genital stage G1 to stage G2, characterised by enlargement of the testicular volume to reach 4 mL or testicular length to reach 25 mm, by the age of 14 years (23,25,26). Pubic hair development is not considered in the definition since it may reflect the activation of adrenal sex steroid secretion, *i.e.*, adrenarche (27).

The definition of pubertal delay is related to the timing of the onset of puberty. The fact that initial signs of puberty appear does not guarantee the completion of pubertal maturation. The pubertal tempo may be affected, resulting in an abnormally low progression and the adult stage is not reached within roughly 5 years after the initial signs of puberty (23); in some cases, pubertal maturation may come to a complete arrest. While pubertal delay may be transient, prolonged and arrested puberty usually reflect a morbid condition, as discussed below.

Aetiologies

The most frequent cause of the absence of pubertal signs by the age of 14 years in boys is self-limited delayed puberty (SLDP), also called constitutional delay of puberty. In these individuals, which represent 60%-80% of boys seeking medical attention for absence of pubertal signs (26,28-30), the onset of puberty usually occurs by the age of 18 years (**Table 1**). Another transient condition is functional central (or hypogonadotropic) hypogonadism, responsible for 10%-20% of the cases in males. It is associated with a wide variety of chronic or acute diseases, such as malnutrition, coeliac disease, cystic fibrosis, chronic kidney or liver disease, juvenile idiopathic arthritis and many others with chronic inflammation, Cushing syndrome, diabetes mellitus, *etc.* When the underlying disease is adequately managed, the function of the hypothalamic-pituitary-gonadal axis is re-established, and puberty progresses. Conversely, permanent central (or hypogonadotropic) hypogonadism (HH), which represents 8%-10% of the boys with delayed puberty, can be acquired or congenital. Acquired forms may be due to tumours of the central nervous system and their radiotherapy, hypophysitis, or trauma affecting the hypothalamus and/or pituitary, and are almost always associated with multiple pituitary hormone deficiencies. Congenital forms may also be associated with other pituitary hormone deficiencies, or they can present as isolated HH. Finally, primary (or hypergonadotropic) hypogonadism can be the underlying cause for the absence of puberty. This is rare in males (4%-5%) and is most often associated with anorchia (congenital or acquired), since primary testicular disorders, such as Klinefelter syndrome, longstanding cryptorchidism,

Table 1. Aetiologies of pubertal delay in males

Aetiology	Relative frequency	Examples
Constitutional delay of growth and puberty (CDGP)	60%-70%	
Primary hypogonadism	2%-7%	Bilateral anorchia/Testicular regression syndrome Mild testicular dysgenesis Klinefelter syndrome (47,XXY and variants) Bilateral orchitis/chemotherapy
Congenital hypogonadotropic hypogonadism (genetic)	2%	Isolated CHH (with or without anosmia) Multiple pituitary hormone deficiency
Acquired central hypogonadism	4%-6%	Surgery of the sellar/suprasellar region Pituitary tumours Cranial trauma High dose cranial radiotherapy
Functional central hypogonadism	16%-20%	Systemic diseases (coeliac or inflammatory bowel disease, diabetes, malnourishment, hypothyroidism, etc), emotional stress

AMH: anti-Müllerian hormone; FSH: follicle-stimulating hormone; LH: luteinising hormone.

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orchitis or chemotherapy, usually affect germ and Sertoli cells more significantly than Leydig cells, which retain sufficient steroidogenic capacity to induce penile and scrotal growth.

Congenital HH (CHH) most frequently has a genetic origin as a consequence of gene variants that impair early differentiation of the GnRH neurons at the olfactory placode or their migration to the hypothalamus, the regulation of GnRH secretion, or gonadotropin secretion in response to GnRH. Early embryonic defects involving GnRH differentiation or migration together with defects in the olfactory tract result in CHH with hyposmia or anosmia, known as Kallmann syndrome. Defects of GnRH synthesis, secretion or action result in normosmic HH (4,31-34). A recent systematic review of the phenotype-genotype correlation in males with CHH leading to absent or arrested puberty after the age of 18 years, with a metanalysis after reclassification of sequence variants following the recommendations of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) for the interpretation of the pathogenic potential of gene variants, identified 503 different disease-causing variants in 29 genes (**Table 2**) (35). These variants were associated with the absence of puberty (*i.e.*, complete forms of CHH) in 85.5% of the cases and with arrested puberty (*i.e.*, partial forms) in 14.5% of them. In males with complete CHH, variants in *FGFR1* and *ANOS1* accounted for 53.5% of all the disease-causing variants, whereas in patients with partial forms of CHH, variants in *FGFR1*, *NR0B1* and *GNRHR* were found in 70.3% of the cases.

Other conditions that can be associated with atypical forms of arrested puberty are X-chromosome polysomies, such as Klinefelter syndrome 47,XXY and its variants as well as in XX males (46,XX testicular DSD). These patients usually start and progress through puberty normally from an androgenic standpoint; however, mild hypoandrogenism may be observed in the latest stages of puberty. Furthermore, since there is meiotic failure with germ cell apoptosis and subsequent seminiferous tubule fibrosis, testicular volume arrests at 6-8 mL and then even regresses (36,37).

Self-limited delayed puberty shows high heritability. Although genome-wide association studies (GWAS) have identified several small-effect genes associated with pubertal timing (38-40), few causal genes have been identified in SLDP (26). A recent study on polygenic scores based on GWAS for timing of puberty in males and age at menarche in females has shown that common genetic variants associated with pubertal timing contribute to the genetics of SLDP, and that they are largely though not completely distinct from those associated with CHH (41). Another study in which burden tests analysed the frequency of rare variants in candidate genes for SLDP identified 14 high-impact and 7 moderate-impact variants in 19 candidate genes, with a potential role in pubertal delay (42).

Clinical assessment

As usual, a complete medical history and physical examination are the first steps in guiding the diagnosis in the cases of primary or acquired HH (33,43). Similarly, a deep phenotyping looking for extra-genital clinical manifestations could be helpful for the diagnosis of CHH. A recent systematic review (35) found associated manifestations in ~40% of patients with CHH carrying disease-causing gene variants. Particularly, adrenal insufficiency guided to variants in *NR0B1*, bimanual synkinesia or renal aplasia/dysplasia to defects in ANOS1, cleft lip and/or palate malformations and defects in dentition or hand/feet malformations were observed in association with variants in *FGFR1*, hearing defects guided to variants in *SOX10* and, when associated with facial dysmorphism and cardiovascular malformations, to variants in *CHD7* (Charge syndrome).

Conversely, the distinction between SLDP and isolated CHH may prove challenging. A family history of delayed puberty in parents, a gradual downward crossing of height centiles as compared to peers entering puberty, a delayed bone age and a delayed adrenarche are more characteristic of SLDP (30). Patients with SLDP present at slightly younger age, and are shorter and lighter than patients with HH (44). On the other hand, signs of deficient exposure to androgens in late fetal life and early infancy, such as micropenis and cryptorchidism, or of deficient exposure to FSH, leading to microorchidism, are

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Table 2. Characteristics of puberty, olfactory system and pituitary deficiencies in patients with disease-causing variants of congenital hypogonadotropic hypogonadism (CHH), according to the causal gene, in a systematic review and metaanalysis (*)

Gene	Index cases with disease-causing variants	Puberty			Olfactory disturbance			Abnormal olfactory bulb and tract			Other pituitary deficiencies		
		Absent	Arrested	NA	Yes	No	NA	Yes	No	NA	Yes	No	NA
	n	n (%)			n (%)			n (%)			n (%)		
FGFR1	153	133 (86.9)	20 (13.1)	0	103 (69.6)	45 (30.4)	5	58 (62.4)	35 (37.6)	60	2 (1.4)	141 (98.6)	10
ANOS1	101	95 (94.1)	6 (5.9)	0	94 (94.9)	5 (5.1)	2	41 (85.4)	7 (14.6)	53	0 (0.0)	82 (100.0)	19
NR0B1	64	44 (69.8)	19 (30.2)	1	1 (2.7)	36 (97.3)	27	1 (6.7)	14 (93.3)	49	1 (2.6)	37 (97.4)	26
GNRHR	47	34 (72.3)	13 (27.7)	0	0 (0.0)	47 (100)	0	0 (0.0)	20 (100.0)	27	0 (0.0)	47 (100.0	0
CHD7	24	20 (83.3)	4 (16.7)	0	17 (73.9)	7 (26.1)	0	3 (27.3)	8 (72.7)	13	0 (0.0)	22 (100.0)	2
TACR3	17	15 (88.2)	2 (11.8)	0	0 (0.0)	17 (100)	0	0 (0.0)	9 (100.0)	8	2 (11.8)	15 (88.2)	0
KISS1R	15	15(100.0)	0 (0.0)	0	0 (0.0)	14 (100.0)	1	0 (0.0)	12 (100.0)	3	1 (7.1)	14 (92.9)	0
SOX10	12	9 (75.0)	3 (25.0)	0	12 (100.0)	0 (0.0)	0	7 (87.5)	1 (12.5)	4	0 (0.0)	10 (100.0)	2
GNRH1	11	11 (100.0)	0 (0.0)	0	0 (0.0)	11 (100.0)	0	0 (0.0)	4 (100.0)	7	0 (0.0)	9 (100.0)	2
PROK2	8	6 (75)	2 (25.0)	0	5 (62.5)	3 (37.5)	0	4 (66.7)	2 (33.3)	2	0 (0.0)	7 (100.0)	1
PNPLA6	8	6 (75.0)	2 (25.0)	0	0 (0.0)	3 (100.0)	5	0 (0.0)	4 (100.0)	4	0 (0.0)	4 (100.0)	4
SOX2	7	6 (85.7)	1 (14.3)	0	0 (0.0)	3 (100.0)	4	0 (0.0)	3 (100.0)	4	2 (28.6)	5 (71.4)	0
PROKR2	5	4 (80.0)	1 (20.0)	0	3 (60)	2 (40)	0	1 (33.3)	2 (66.7)	2	0 (0.0)	5 (100.0)	0
WDR11	4	4 (100.0)	0 (0.0)	0	1 (33.3)	2 (66.7)	1	0 (0.0)	1 (100.0)	3	1 (50.0)	1 (50.0)	2
FGF8	4	4 (100.0)	0 (0.0)	0	2 (50.9)	2 (50,9)	0	0 (0.0)	3 (75)	1	1 (25.0)	3 (75.0)	0
POLR3B	3	3 (100.0)	0 (0.0)	0	0 (0.0)	1 (100.0)	2	0 (0.0)	2 (66.7)	1	1 (33.3)	2 (66.7)	0
TAC3	2	2 (100.0)	0 (0.0)	0	0 (0.0)	2 (100.0)	0	0 (0.0)	1 (100.0)	1	0 (0.0)	2 (100.0)	0
FGF17	2	2 (100.0)	0 (0.0)	0	2 (100.0)	0 (0.0)	0	1 (100.0)	0 (0.0)	1	0 (0.0)	2 (100.0)	0
CPE	2	2 (100.0)	0 (0.0)	0	0 (0.0)	2 (100.0)	0	0 (0.0)	1 (100.0)	1	2 (100.0)	0 (0.0)	0
PLR3A	2	2 (100.0)	0 (0.0)	0	0 (0.0)	1 (100.0)	1	0 (0.0)	1 (100.0)	1	0 (0.0)	1 (100.0)	0
FEZF1	2	2 (100.0)	0 (0.0)	0	2 (100.0)	0 (0.0)	0	2 (100.0)	0 (0.0)	0	0 (0.0)	2 (100.0)	0
HESX1	2	1 (50.0)	1 (50.0)	0	2 (100.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	2	0 (0.0)	2 (100.0)	0
RNF216	2	2 (100.0)	0 (0.0)	0	0 (0.0)	2 (100.0)	0	0 (0.0)	2 (100.0)	0	0 (0.0)	2 (100.0)	0
KISS1	1	1 (100.0)	0 (0.0)	0	0 (0.0)	1 (100.0)	0	0 (0.0)	1 (100.0)	0	0 (0.0)	1 (100.0)	0
LEPR	1	1 (100.0)	0 (0.0)	0	0 (0.0)	1 (100.0)	0	0 (0.0)	1 (100.0)	0	0 (0.0)	1 (100.0)	0
LHB	1	0 (0.0)	1 (100.0)	0	0 (0.0)	1 (100.0)	0	0 (0.0)	0 (0.0)	1	0 (0.0)	1 (100.0)	0
NDNF	1	1 (100.0)	0 (0.0)	0	1 (100.0)	0 (0.0)	0	1 (100.0)	0 (0.0)	0	0 (0.0)	1 (100.0)	0
NHLH2	1	1 (100.0)	0 (0.0)	0	0 (0.0)	1 (100.0)	0	0 (0.0)	0 (0.0)	1	0 (0.0)	0 (0.0)	1
PROP1	1	1 (100.0)	0 (0.0)	0	0 (0.0)	1 (100.0)	0	0 (0.0)	1 (100.0)	0	1 (100.0)	0 (0.0)	0
SEMA3A	1	1 (100.0)	0 (0.0)	0	1 (100.0)	0 (0.0)	0	1 (100.0)	0 (0.0)	0	0 (0.0)	1 (100.0)	0

Percentages are calculated based on available data. NA: data not available.
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considered "red flags" for the diagnosis of CHH (28,33,44). However, their absence should not rule out the diagnosis; indeed, they were present in less than 30% of males with *bona fide* gene variants of CHH (35). Cryptorchidism was more frequently associated with variants in *FGFR1*, *ANOS1*, *KISS1R*, *SOX10* and *GNRH1*, while micropenis was observed more frequently in patients with variants in *TACR3*, *KISS1R* or *GNRH1* (35).

Diagnosis

Elevated gonadotropin levels and and undetectable testosterone in the hormonal assessment rapidly points to primary hypogonadism. Functional hypogonadism may be ruled out using broad screening tests (*e.g.*, blood cell count, liver and kidney panels, blood chemistry, urinalysis, *etc.*); however, abnormal results are rarely found in the absence of clinical features

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or a history of a chronic illness (43). Imaging, especially magnetic resonance imaging (MRI), has a role in detecting central nervous system tumours, or defects in the olfactory tract guiding to the diagnosis of Kallmann syndrome.

The use of laboratory tests for the differential diagnosis between SLDP and CHH, essentially based on the measurement of LH and/or testosterone under basal and stimulated conditions, has not been completely satisfactory for many years (30,33). Conversely, recent studies focusing on FSH and Sertoli cell biomarkers, such as AMH and inhibin B, have provided significant improvements in diagnostic accuracy (45-48). The use of the product FSH (IU/l)×inhibin B (ng/mL) < 92 or FSH (IU/l)×AMH (pmol/l) < 537 show high sensitivity (>93%), specificity (≥92%) and positive predictive value (>92%) for CHH in male patients aged ≥ 13 and < 18 years presenting with a testicular volume < 4 mL and no other sign of pubertal onset (**Figure 4**) (48). The efficacy of genetic testing has dramatically improved with the advent of high throughput techniques, such as next generation sequencing (NGS), allowing for massive parallel gene testing (33,34,49). The positive diagnostic yield of the underlying gene variant may exceed 50% in boys having undergone deep phenotyping (4,34,48,50,51).

Management

Boys with SLDP often present at the age of 12-13 years, with concerns about their relative short stature and lack of secondary sex characteristics as compared to peers. Reassurance of the patient and his parents and watchful waiting may be sufficient. However, when the condition causes psychosocial stress leading to negative social interactions and depression, pharmacological treatment may be necessary. In patients with a confirmed diagnosis of HH, medical intervention should not be delayed, provided that bone age is 11 years or more. Similarly, in adolescents with SLDP hormone treatment should be indicated by the age of 14 years in order to maximise height potential and peak bone mass and minimise psychosocial impact (52).

Testosterone is the most frequently used medication in boys with SLDP or HH (28,33,52,53), and the only one for males with anorchia or severe primary hypogonadism (52,53). Typical schemes start with testosterone enanthate or cypionate 50 mg IM every 4 weeks for 6 months, then increasing gradually by 50 mg every 6-12 months over 2 to 3 years until reaching the adult dose of 200-250 mg every 4 weeks. In patients showing testicular volume enlargement, especially during the initial stages of treatment with low doses, spontaneous onset of puberty is likely, and testosterone treatment can be discontinued. Nonetheless, monitoring is needed to ascertain that pubertal maturation is completed within 2-3 years. Other oral or transdermal testosterone formulations have been scarcely used to induce pubertal changes (53). Androgen treatment results in the development of secondary sex characteristics and increased growth and bone mineral density, leading to an improved psychological well-being (53,54). There are, however, certain drawbacks in the pharmacokinetics, since serum testosterone peaks to supraphysiological levels in the first week and falls to low levels in the fourth week (55). Side effects need to be monitored, especially by assessing total blood count, haematocrit, haemoglobin levels and liver function in order to identify polycythaemia or hypertransaminasaemia (53). Bone age advancement may also need to be monitored along with height velocity.

In individuals with SLDP, a 6-month treatment with oral letrozole 2.5 mg/day induced gonadotrophin secretion and testicular growth, together with accelerated height growth (56,57).

In patients with HH, replacement treatment should be centred on the administration of GnRH or FSH plus LH, if a physiology-based approach is applied. If gonadotrophins are used, the logical scheme should start with FSH in order to induce immature Sertoli cell proliferation and initial testis size enlargement, followed by the addition of LH or hCG (58,59). The latter results in testicular androgen secretion leading to Sertoli cell maturation and full spermatogenesis, together with the already described testosterone effects on secondary sex characteristics, growth and well-being. The increases in testicular volume and serum inhibin B are useful to assess the efficacy of treatment on spermatogenesis (60). Several

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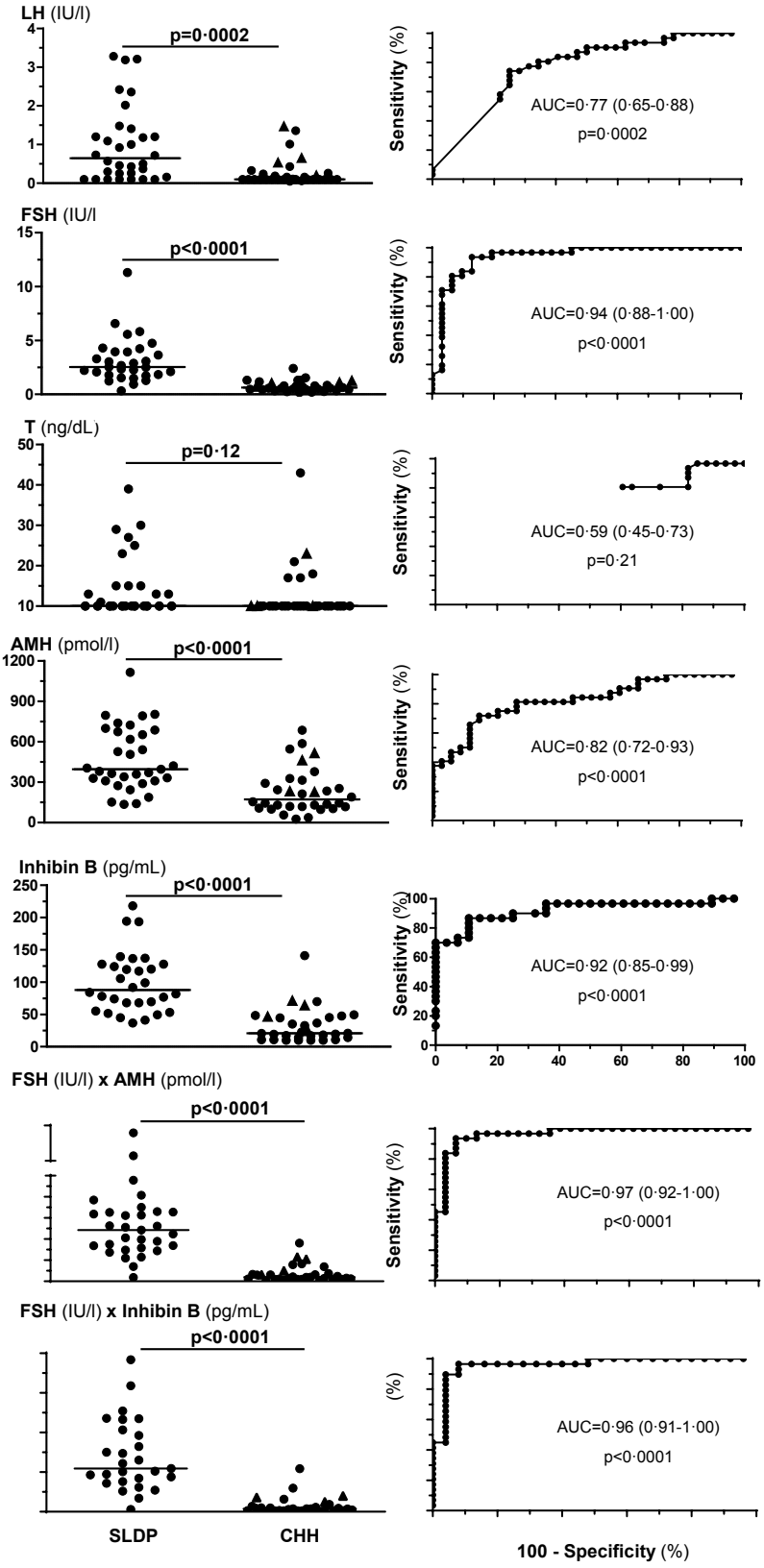


Figure 4. LH, testosterone (T), FSH, inhibin B and anti-Müllerian hormone (AMH) in the differential diagnosis between self-limited delayed puberty (SLDP) or congenital hypogonadotropic hypogonadism (CHH). Serum hormone levels at referral (main complaint: pubertal delay) in participants who were followed until a final diagnosis of SLDP or CHH was made: circles indicate complete form of CHH and triangles indicate partial form of CHH. ROC: receiver operating characteristic curves. AUC: area under the curve (95% confidence interval between parentheses). Reprinted with permission from ref. 48.

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treatment regimens exist. GnRH, which is not widely available, is administered with a mini-infusion pump delivering 25 ng/kg every 2 hours; dose titration may be needed to attain target serum testosterone (61). GnRH treatment seems to be more efficacious than gonadotrophins to induce spermatogenesis and increase testicular volume, with less oestrogen-related secondary effects such as gynaecomastia (62). Gonadotrophin treatment regimens usually start with subcutaneous recombinant FSH 75-150 IU 2-3 times/week for 2-3 months, with dose adjustments up to 225 IU in order to ensure serum FSH levels of 4-6 IU/l for 2-6 months. Thereafter, FSH is combined with LH (75 IU/day) or hCG (500-2000 IU once or twice a week) with dose titration aiming for serum testosterone of 350 ng/dL for another 6 months, and LH or hCG alone for 6-12 months until testicular volume reaches 10-12 mL (58,62-65).

FINAL REMARKS

Pubertal delay is a relatively frequent complaint in males. Primary hypogonadism is rarely the underlying cause; conversely, central hypogonadism may be difficult to diagnose timely based on clinical features and traditional biomarkers such as serum LH and testosterone levels. Some red flags, *e.g.*, a history of cryptorchidism, micropenis or microorchidism or smelling impairment, may guide the diagnosis. Serum levels of FSH and of Sertoli cell peptides, *i.e.*, AMH and inhibin B, have become excellent biomarkers to distinguish between SLDP and HH. When medical treatment is needed, testosterone administration is the standard of care, but replacement with GnRH or gonadotrophins have gained preference more recently. Whether the latter should be preferred over testosterone therapy in teenagers with HH remains unsolved. The use of GnRH or gonadotrophins appears as more "physiological", with FSH preceding LH or hCG. However, the evidence-based answer should come from sufficiently powered controlled clinical trials in teenagers aged 12-14 years followed for long-term until adulthood.

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special issue
Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

invited review

Oxytocin: a neglected hormone in pituitary disease – From function to the diagnosis of a deficiency, resulting clinical relevance, and potential treatment options in endocrinology

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ABSTRACT

Oxytocin (OXT) is a neuropeptide hormone that plays a central role in numerous physiological and socio-emotional processes. Similar to arginine vasopressin (AVP), it is synthesized in the supraoptic and paraventricular hypothalamic nuclei and released both centrally and peripherally. Peripherally, OXT regulates uterine contractions during childbirth and milk ejection during lactation, metabolism, bone health, and cardiovascular functions. Centrally, it modulates social behavior, influencing trust, empathy, stress regulation, and emotional processing. Despite its close connection to AVP, the clinical significance of OXT-Deficiency has only recently gained attention, particularly in patients with hypothalamic or pituitary damage with concomitant AVP-Deficiency. OXT-Deficiency may contribute to various neuropsychological symptoms seen in these patients, including social dysfunction, anxiety disorders, and reduced quality of life. However, a major challenge lies in accurately measuring OXT and thereby diagnosing a potential OXT-Deficiency. Basal plasma levels are unreliable, and most studied provocation tests only stimulate to a limited degree; hence, stronger provocation tests (e.g., using MDMA) and new surrogate parameters such as neurophysin I (NP-I) are gaining traction. Preliminary evidence from case reports and one small study suggests that intranasal OXT administration in patients with hypothalamic disorders may have beneficial effects on social behavior and emotion recognition. However, there is a clear need for larger, well-designed clinical trials, and several trials are currently underway to investigate the therapeutic potential of OXT in patients with AVP-Deficiency. OXT is also being explored as a possible treatment option in psychiatric conditions such as autism spectrum disorder, borderline personality disorder, and social anxiety disorder, with controversial results so far.

Keywords: Oxytocin deficiency; posterior pituitary; hypopituitarism; AVP deficiency; neurophysin I

OXYTOCIN – ANATOMY AND PHYSIOLOGY

Synthesis, storage, and release

Oxytocin (OXT) plays a crucial role in both neurobiological and physiological functions, ranging from reproductive processes to the regulation of complex socio-emotional behaviors. OXT is closely related to arginine vasopressin (AVP), which primarily regulates fluid balance. Both hormones are synthesized by magnocellular and parvocellular neurons located in the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus (1,2). These neurons project to the pituitary gland for peripheral hormone release and also enable central release via dendritic diffusion and axonal projections (3). OXT and AVP are both nonapeptides, differing by only two amino acids at positions 3 and 8, and are encoded in close proximity on chromosome 20 in their precursor forms (4). OXT is initially synthesized as an inactive prepropeptide together with its carrier protein, neurophysin I (NP-I), which is essential for transport and storage.

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The prohormone is then processed into the active peptide through cleavage and amidation (1,5). Both hormones signal through G protein-coupled receptors (V1AR, V1BR, V2R, OXTR), which show significant sequence homology and therefore allow cross-reactivity. The OXT receptor (OXTR) is widely distributed in the brain, including the hypothalamus, amygdala, anterior cingulate cortex, olfactory nucleus, and limbic areas (6,7). Notably, OXTR expression and density differ by sex (8) and vary across species, such as between monogamous and promiscuous voles (9). Peripherally, OXTRs are expressed in the uterus, ovaries, testes, mammary glands, kidneys, thymus, pancreas, adrenal glands, and adipose tissue (4). OXT concentrations in the brain are up to 1,000 times higher than in the blood, and its half-life in the central nervous system (CNS) is more than three times longer than in the periphery (19 *vs.* 6 minutes) (10-12).

Peripheral function

OXT is widely known for its role in human parturition and lactation, but it also exerts a broad range of physiological effects, including impacts on metabolism, bone health, the cardiovascular system, and psychosocial behavior (**Figure 1**). During pregnancy, uterine sensitivity to OXT increases significantly. Around the onset of labor, OXTR density rises up to 200-fold, facilitating uterine contractions (13,14). OXT also stimulates breast myoepithelial cells to initiate the milk let-down reflex during lactation. Infant suckling triggers further its release, promoting continued milk ejection (13,14). The peptide hormone also contributes to the regulation of metabolism. In rodents, central OXT administration reduces food intake and body weight, while increasing energy expenditure and brown fat thermogenesis (10). In normal-weight humans, intranasal OXT acutely improves glucose tolerance and beta-cell function, reduces both hunger- and reward-driven eating in obese men, and lowers snack intake in both normal-weight and obese individuals (15,16). Additionally, OXTRs are expressed in both osteoblasts and osteoclasts (17), and OXT has anabolic effects on bone, promotes ossification, and inhibits bone resorption (17-19). Clinically, low OXT levels have been associated with reduced bone mineral density (BMD) in patients with AVP-Deficiency (20). Moreover, OXT has been implicated in the modulation of atherosclerotic processes through its anti-inflammatory and antioxidative properties (21,22). In addition, its ability to reduce food intake, body weight gain, insulin resistance, and to regulate the hypothalamic-pituitary-adrenal (HPA) axis contributes to its potential cardioprotective effects (23).

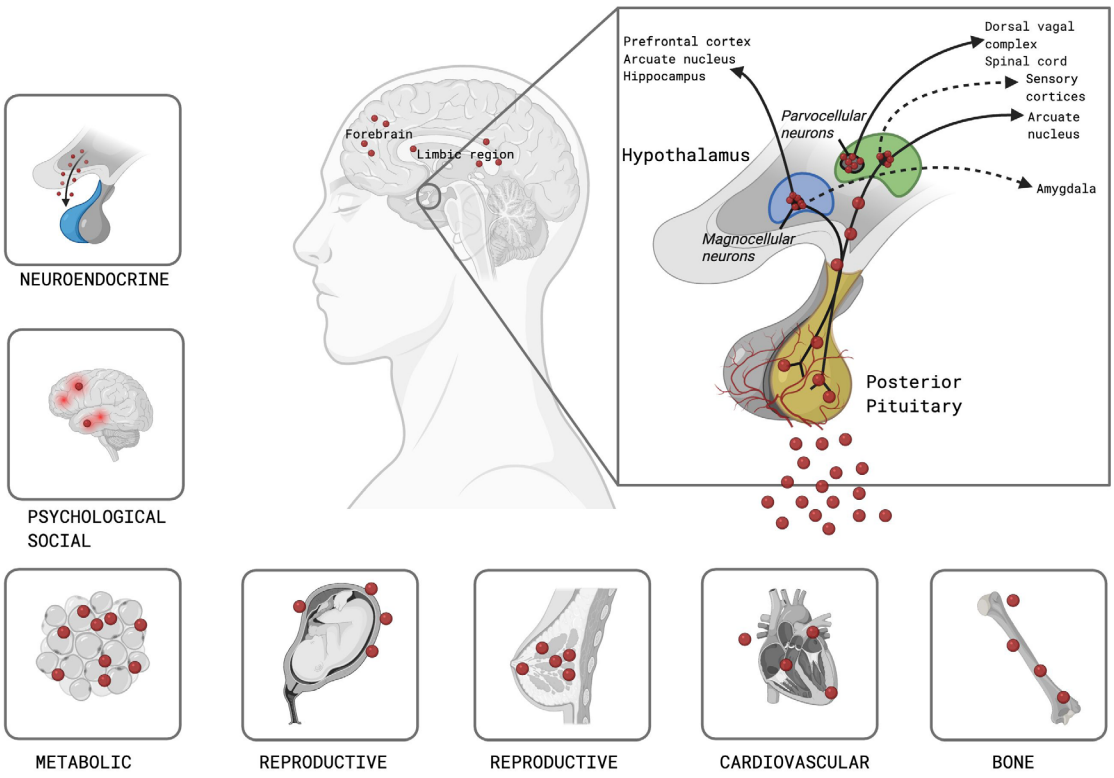
Social and behavioral function

OXT is increasingly recognized for its key role in regulating complex social-emotional and behavioral functioning (**Figure 2**) (24-28). In animal studies, central OXT administration increases partner preference in female prairie voles and promotes maternal behavior in female rats (29,30). Centrally given OXT also induces anxiolytic-like effects in rodents (31), partly mediated by the HPA axis (32,33), and intranasal OXT reduces aggressive behavior while promoting affiliation in male rats and mice (34,35). In humans, intranasal OXT enhances pro-social behaviors, including trust, intimacy, attachment, empathy, and emotion recognition (27,28,36,37). It also facilitates the formation of social memories and may enhance self-perception (38). Additionally, the anxiolytic effects of OXT are well established: It buffers responses to social stress, lowers cortisol levels during conflicts (39), decreases amygdala activity, and increases insular cortex activation in response to emotional stimuli (28,40), suggesting that OXT strengthens the stress-buffering role of social support (41). Notably, study participants receiving both social support and OXT exhibited the lowest cortisol levels during social stress (24). Similarly, endogenous OXT release during breastfeeding was associated with reduced pituitary-adrenal responses to psychosocial stress in postpartum women (42).

Exogenous administration of oxytocin

Because OXT is rapidly metabolized by chymotrypsin in the gut, oral administration is not possible. Intranasal delivery is therefore a practical and well-tolerated alternative, approved to support milk let-down in breastfeeding women, while intravenous OXT is commonly used to induce uterine contractions during labor. In research, intranasal OXT is typically administered in doses ranging from 6 to 48 IU, with 24 IU being the

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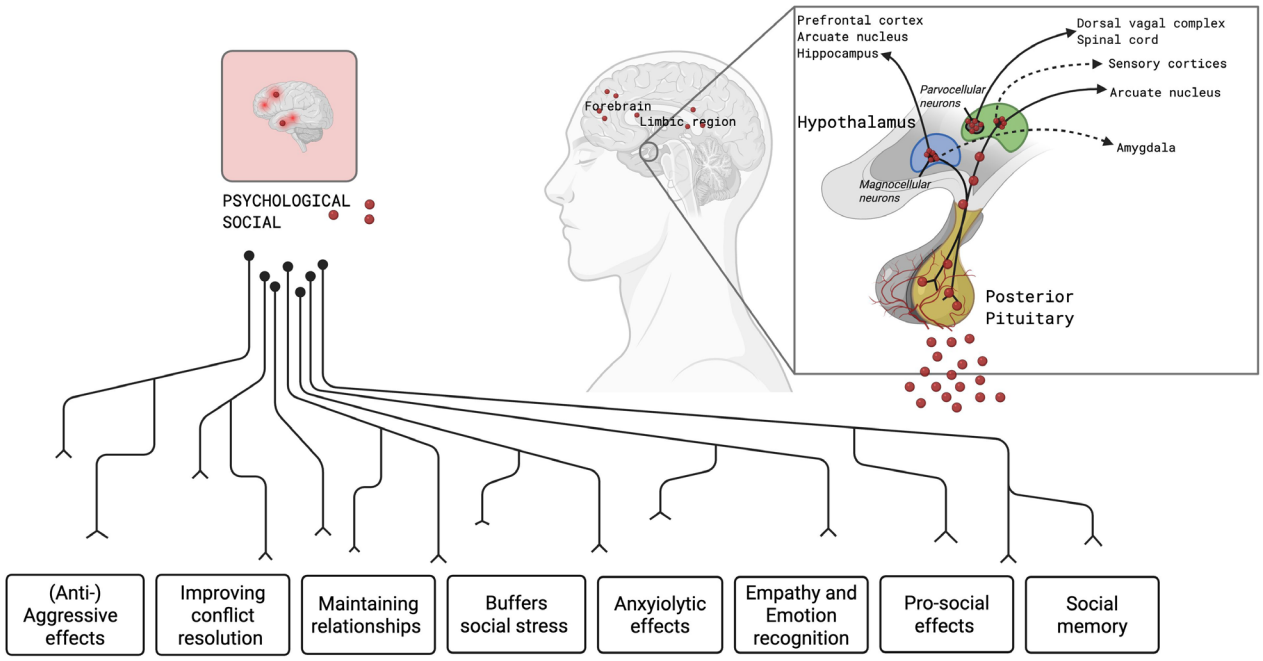
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Figure 1. The hypothalamic-posterior-pituitary axis. Schematic representation of the neuroanatomical and functional organization of the hypothalamic-posterior-pituitary axis and its systemic effects. The hypothalamus receives input from multiple brain regions, including the limbic system, prefrontal cortex, hippocampus, sensory cortices, and amygdala, which converge on parvocellular and magnocellular neurons. These neurons control the release of the neuropeptides oxytocin and vasopressin into the circulation via the posterior pituitary. The lower panels illustrate the wide-ranging systemic effects of this axis, including neuroendocrine stress regulation, socio-emotional and behavioural modulation, metabolic balance, reproductive functions (such as uterine contraction and lactation), cardiovascular control, and bone health.

most commonly used dose in human behavioral studies (40,43). Importantly, these studies do not address OXT treatment for a clinically diagnosed deficiency, as no such condition has yet been established with defined diagnostic criteria. Rather, they focus on the experimental administration of OXT in healthy participants.

Growing evidence indicates that intranasal application can produce functionally relevant central effects. The intranasal route largely bypasses the blood-brain barrier and allows efficient central delivery, with peak effects, particularly in amygdala reactivity, observed approximately 45 minutes after administration (44). For instance, studies show that 24 IU reduces amygdala responses to fear and improves recognition of ambiguous faces (44). Consistent with these findings, several trials report that standard intranasal doses enhance emotion recognition, promote empathy, and increase trust in context-dependent ways (37,44-46). Together, these observations point to the potential of peripheral administration to influence central mechanisms. Peak plasma levels usually occur 10 to 90 minutes after intranasal application (typically 24-30 IU) (47,48), while maximum cerebrospinal fluid concentrations are reached up to 75 minutes post-administration (49,50). Intravenous OXT is commonly administered to induce or augment labor and has a short plasma half-life of 3-6 minutes (51), reaching steady-state levels within 40 minutes and rapidly returning to baseline after cessation of infusion. Due to the typically low infusion doses used during labor (often totaling 5-10 IU), OXT does not significantly cross the placenta or the blood-brain barrier (52).

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Figure 2. Psychosocial and emotional functions of central oxytocin signalling. Oxytocin is synthesized by parvocellular and magnocellular neurons in the hypothalamus and released via the posterior pituitary. These neurons receive inputs from key limbic and cortical regions linking oxytocin signalling to emotional and social processing. The left portion of the figure illustrates the diverse psychological and social effects of central oxytocinergic signalling, including: (anti-)aggressive effects, conflict resolution enhancement, relationship maintenance, buffering of social stress, anxiolytic (anxiety-reducing) effects, empathy and emotion recognition, promotion of pro-social behaviours, social memory consolidation.

SYMPTOMS RELATED TO OXYTOCIN DEFICIENCY

Changes in psychosocial, emotional, and eating behaviour

Hypopituitarism (HPD) is a condition with an estimated prevalence of 21 to 42 cases per million, characterized by partial or complete deficiency of one or more pituitary hormones, resulting from damage or dysfunction of the pituitary gland or hypothalamus (53-55). Deficiencies of anterior pituitary hormones are well recognized, with established clinical implications and standardized guidelines for hormone replacement (53). Similarly, deficiency of the posterior pituitary hormone AVP (formerly known as central diabetes insipidus) is well-characterized and treated with desmopressin (56). However, despite OXT being produced alongside AVP and released both centrally and peripherally via the posterior pituitary, its potential deficiency and clinical relevance have only recently begun to be explored. Disruptions of the vasopressinergic neurons causing AVP-Deficiency could potentially result in an impairment of oxytocinergic neurons and thereby causing an additional OXT-Deficiency due close proximity of both systems (57). Hence, it is plausible to assume that a concomitant accompanying OXT-Deficiency is partly responsible for the increased psychopathology and decreased quality of life (QoL) seen in AVP-deficient patients (57).

HPD is associated with comorbidities such as sexual dysfunction, neuropsychological symptoms, altered eating behaviours, obesity, metabolic disorders, and osteoporosis (58-63). Specifically, HPD is linked to greater psychopathology, including increased severity of anxiety, depression, and alexithymia (difficulty identifying and expressing emotions). Patients with HPD also experience social dysfunction, impulsive behaviours, and hyperphagia, contributing to obesity and reduced QoL.

Recent research suggests a potential OXT-deficient state in HPD, particularly in patients with hypothalamic-posterior-pituitary damage. Given the anatomical location of hypothalamic OXT-producing

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neurons, patients with hypothalamic-pituitary dysfunction who develop AVP-Deficiency (64), often due to suprasellar lesions such as craniopharyngiomas (CP) and germinomas or following hypothalamic-pituitary surgery, are presumably at the highest risk for co-existing OXT-Deficiency (65-70). Other causes include infiltrative or malignant diseases, neurosurgery, radiotherapy, head trauma, and congenital abnormalities. Early findings indicate that damage to OXT neurons may contribute to symptoms of HPD, including emotional dysregulation, social dysfunction, and metabolic disturbances (65-70). Therefore, given OXT's role in modulating mood, social behaviour, impulse control, and eating habits, a deficiency in OXT signalling may contribute to these symptoms observed in HPD. However, particularly in CP patients, these symptoms may also result directly from hypothalamic injury, whether caused by the tumor or secondary to surgical intervention.

More than half of individuals treated for sellar tumours develop hyperphagic obesity, which is associated with reduced functional capacity, metabolic syndrome, cardiovascular disease, and increased mortality (15,71). Hypothalamic damage, particularly in the PVN, disrupts energy homeostasis, leading to excessive hunger and reduced energy expenditure (72-75). The extent of hypothalamic damage and presence of AVP-Deficiency are predictors of hypothalamic obesity (74,76,77). Many studies have focused on CP, a condition associated with a high risk of causing damage to vasopressinergic and oxytocinergic neurons (78). A long-term study of 10 years identified changes in personality and social deficits (75,78-80). While desmopressin therapy improves clinical outcomes, there is evidence indicating that patients still may not attain population norms in terms of QoL and socio-emotional abilities (81-83). Data from the so-far largest survey study in patients with AVP-Deficiency showed a high prevalence of self-reported psychological problems: 25% reported heightened anxiety, 25% sleep disturbances, 23% depressed mood, 18% stress management disturbance, and 12% personality change (84). In total, 64% reported lower QoL affecting recreation and fun, social activities, and both physical and mental well-being (84). This was observed in patients with and without additional anterior pituitary hormone dysfunctions, which challenges the notion that reduced anterior pituitary hormone dysfunctions are the primary cause of psychological changes. Importantly, adult patients with growth hormone (GH) deficiency are frequently neither evaluated for nor treated with GH replacement therapy, which may contribute to reduced QoL and should be considered alongside potential effects of presumed OXT-Deficiency.

However, while patients with AVP-Deficiency are presumed to be at the highest risk for OXT-Deficiency, not all individuals with AVP-Deficiency necessarily experience OXT-Deficiency. Some may retain or regenerate OXT-producing neurons, particularly in milder cases. Importantly, recent studies also highlight higher ACTH and cortisol response to stress in patients with AVP-Deficiency compared to controls, indicating impaired HPA axis regulation (85,86). Among other mechanisms, co-existing OXT-Deficiency in these patients may contribute to elevated cortisol levels, as OXT is known to modulate stress responses and attenuate HPA axis activation.

Changes & complications in obstetric functions

OXT has well-known obstetric functions (87,88). The current data are limited to case series involving patients with hypopituitarism, and there has been insufficient investigation on difficulties with breastfeeding or complications during labour in patients with AVP-Deficiency (89-93). Within these cases, some patients reported successful spontaneous labour without the need for OXT administration (89,90). This aligns with the observation that, at hospital discharge, only half of the patients were breastfeeding, implying that OXT from the pituitary may not be mandatory or could be partially preserved for the initiation of spontaneous labour or milk let-down (93-95).

UNMASKING AN OXYTOCIN DEFICIENCY

Few initial studies measured OXT in patients with HPD and mainly focused on basal measurements (65,69,96,97). One of the first studies assessed fasting and postprandial saliva OXT in long-term CP survivors

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and healthy controls, with no noteworthy difference between the groups. Contrary to these results, another study in patients with hypopituitarism compared to healthy controls demonstrated lower basal OXT levels regardless of the presence of AVP-Deficiency (97). The lower OXT level was also associated with impaired ability to identify facial expressions accurately (97). In a study that focused on male patients with AVP-Deficiency, symptoms and signs of depression, anxiety, and alexithymia were greater compared to both patients with hypopituitarism but without AVP-Deficiency and healthy controls (98). Basal OXT levels were similar in all groups; however, patients with AVP-Deficiency had a slightly lower level when plasma OXT was pooled over an hour (98). On the contrary, Eisenberg and cols. noted increased basal OXT levels in patients compared to healthy controls, once again raising doubts about the reliability of basal OXT levels as an indicator of a potential deficiency (96,99).

These controversial findings might partly be explained by difficulties in accurately measuring OXT, given its technical complexities, and ideal sampling methods are currently the subject of research (see below) (100,101). Importantly, as indicated by a meta-analysis, central levels of OXT correlate with peripheral levels only following stimulation, not at baseline (102). Therefore, a provocation test is crucial in assessing a possible OXT-Deficiency. Unlike other endocrine axes, there is no established "normal" reference range for OXT in any biological fluid, and its pulsatile secretion means that a single measurement may not accurately reflect OXT status (103). Moreover, central and peripheral OXT release do not always align, further complicating interpretation. To overcome these challenges, a provocative test, similar to those used for adrenal insufficiency and growth hormone deficiency, is needed to unmask OXT-Deficiency. Various provocation tests have already been examined for OXT (**Table 1**). Overall, the weak and clinically irrelevant OXT stimulation is considered insufficient for diagnosing OXT-Deficiency. Supraphysiological stimulation is required for a valid provocation test, and psychoactive stimulation is necessary to assess the central action.

To this purpose, MDMA (3,4-methylenedioxymethamphetamine, 'ecstasy') was recently used as a stimulus for OXT (110). A single 100 mg dose resulted in an eightfold increase in plasma OXT in healthy adults but had no effect in patients with AVP-Deficiency. This striking differentiation makes MDMA a strong candidate for OXT-Deficiency testing. However, its potential side effects (*e.g.*, cardiovascular) and regulatory restrictions limit its widespread use. Lower doses may be explored as a safer alternative. MDMA increases peripheral OXT levels and central OXT-mediated behavioural effects associated with its empathic and prosocial profile. These effects include increased closeness and openness to others, enhanced trust, elevated happiness, and an overall sense of well-being (111-114). Basal plasma OXT levels showed no difference in patients with AVP-Deficiency and matched healthy controls. In response to MDMA, in controls, plasma OXT increased 8-fold, without a response in patients. In patients, psychoactive effects induced by MDMA (*e.g.*, "good effect", "liking effect" "feeling high") were either blunted or absent compared to controls. Both patients and healthy controls showed a comparable increase in state anxiety at the start of the experiment. While anxiety levels decreased in the controls at the peak OXT concentration, the patients experienced no anxiolytic effect. The strong rise and subsequent action of OXT in central key areas linked to fear processing, like the amygdala, may be responsible for the anxiolytic effects seen during MDMA stimulation. Supporting this observation, the *Facial Emotion Recognition Task* showed decreased recognition of negative emotions (such as "fearful") in healthy controls but not in patients. Notably, half of the patients exhibited clinically relevant anxiety and symptoms of emotional blindness, even though this study only included patients without actively treated psychological co-morbidities. Taken together, these results demonstrate that, in contrast to the predicted effects in controls, nearly all the psychoactive effects of MDMA were either blunted or absent in patients. This pattern is indicative of the OXT's absence and the ensuing dysfunction in key brain areas essential for socioemotional processing.

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Table 1. Selected oxytocin provocation tests in humans

Provocation Test*	Measurement	Participants	Effect on Oxytocin	Findings on psychological endpoints	Limitations
MDMA (110,168)	Plasma OXT	Healthy controls Patients with AVP-D	500%-800% increase in healthy controls. No increase in patients.	Under stimulation the typical prosocial, anxiolytic and positive effects of MDMA in healthy controls. No relevant or reduced psychoactive effects in patients under MDMA.	Cardiovascular side effects. Restriction to use in clinical practice.
Ethinyloestradiol or Oestradiol or physiological menstrual cycle (169-171)	Plasma OXT	Healthy controls Female patients undergoing reproductive stimulation	100%-400% increase in healthy controls.	N/A	High doses of Oestrogen-derivates have the risk of thromboembolism.
Insulin Tolerance Test (104,170,172)	Plasma OXT	Healthy controls Patients with AVP-D	100% increase in healthy controls. No increase in patients.	N/A	Test specific side effects and patient discomfort (*e.g.,* hypoglycaemia-induced symptoms). Contraindications in common populations.
Physical Exercise or sexual self stimulation (69,70,173)	Salivary OXT	Healthy controls Patients craniopharyngioma	50%-200% increase in healthy controls. No OXT increase in patients.	Patients showed lower empathy and emotional recognition, higher depression and anxiety scores, and higher self-reported autistic traits compared to healthy controls.	Might show high variability and lack reproducibility.
Psychosocial Stress (TSST) (173,174)	Plasma/Salivary OXT	Healthy controls	50%-150% increase in healthy controls.	Higher stress-induced oxytocin secretion is associated with greater cortisol reactivity during the stressor, followed by parasympathetic recovery in the post-stress phase.	Might show high variability and lack reproducibility.
Hypertonic Saline (108)	Plasma OXT	Healthy controls		N/A	Test specific side effects (*e.g.,* hypernatremia, strong thirst, general malaise). No sufficient increase to be administered as a diagnostic stimulation test.
Kisspeptin (109)	Plasma OXT	Healthy controls	20% increase from baseline.	N/A	Not established stimulation test. Increase only observed in men. No sufficient increase to be administered as a diagnostic stimulation test.
Glucagon (105)	Plasma OXT	Healthy controls Patients with AVP-D	20% increase from baseline in both groups	N/A	Test specific side effects and patient discomfort. No sufficient increase to be administered as a diagnostic stimulation test.
Melatonin (107)	Plasma OXT	Healthy controls Patients with hypopituitarism	20% increase from baseline in healthy controls. No increase in patients.	Greater depression symptoms, alexithymia, impaired sexual function and worse QoL in patients compared to healthy controls.	No sufficient increase to be administered as a diagnostic stimulation test.
Corticotropin-Releasing Hormone (106)	Plasma OXT	Healthy controls Patients with hypopituitarism	No major effect	Greater psychopathology, sexual dysfunction and worse QoL in patients compared to healthy controls.	No sufficient increase to be administered as a diagnostic stimulation test. Currently not available as a stimulation test.
Arginine (108)	Plasma OXT	Healthy controls	No major effect	N/A	Test specific side effects and patient discomfort (*e.g.,* nausea). No sufficient increase to be administered as a diagnostic stimulation test.
Macimorelin (108)	Plasma OXT	Healthy controls	No major effect	N/A	No sufficient increase to be administered as a diagnostic stimulation test.

* Listed studies are only provided as explanatory examples. Abbreviations: MDMA = 3,4-Methylenedioxymethamphetamine; TSST = Trier Social Stress Test; OXT = Oxytocin; N/A = Not applicable; AVP-D = Arginine Vasopressin Deficiency (formerly central diabetes insipidus).

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However, not all patients, particularly those with cardiovascular conditions, are suitable candidates for MDMA stimulation, and its implementation into clinical routine poses challenges (115). The proposed use of MDMA as a diagnostic tool raises important considerations of tolerance, interindividual variability, and ethics (116). Evidence from clinical trials in post-traumatic stress disorder (PTSD) shows no development of tolerance or loss of efficacy with the limited short-course dosing regimens typically used (117,118). Nonetheless, individual variability should be considered. Regarding safety, adverse events are usually mild and transient, with serious complications rarely reported, yet comprehensive long-term safety data are lacking. Ethically, it is important to emphasize that, as of September 2025, MDMA-assisted therapy is not FDA-approved for PTSD (119). Although it received *Breakthrough Therapy* designation in 2017, the FDA approval is pending, and MDMA use remains restricted to controlled clinical research settings (120). Thus, application of MDMA in diagnostics outside trials is currently not permissible. Therefore, future research should focus on developing alternative, simplified approaches. One possibility may be to mimic the action of MDMA using substances that have already obtained approval (121,122).

An additional key barrier to identifying OXT-Deficiency is the lack of standardized and validated OXT measurements. due to methodological and biological complexities (99,123-126). A key challenge is the unclear relationship between central and peripheral release as only few human studies have assessed OXT at baseline or in response to stimuli (127-130). According to a meta-analysis, no correlation between cerebrospinal fluid (CSF) and plasma levels was found at baseline, though a positive correlation appeared after stress in non-human species (102). Thus, peripheral levels do not reliably reflect central activity at baseline but in response to stimuli. Biological sex and age influence OXT (131,132); in women, the menstrual cycle, menopause, and hormonal therapy add variability (133). Lifestyle factors such as exercise, smoking, food, alcohol, nicotine, or caffeine show little association when proper extraction is used (131). The variability in replication arises from inconsistent extraction, different biological matrices, and diverse assays, with little correlation between measurement techniques (123,134-136). Standardization and cross-laboratory harmonization are therefore critical. Preanalytical factors also matter: fasting status, stress, tube type (*e.g.*, EDTA with inhibitors), centrifugation, storage, and freezing delays should be documented. Another complication is the pulsatile nature of OXT, which means that repeated or dynamic sampling is preferable (102,103,137,138). Common analytic methods include radioimmunoassay (RIA), enzyme-linked immunoassay (EIA/ELISA), and liquid chromatography-mass spectrometry (LC-MS). All require validation for specificity, precision, recovery, parallelism, and stability (139-141). A major debate concerns extraction, which removes interference and enriches peptide concentrations. Without extraction, immunoassays yield inflated results (136,142-144). A meta-analysis illustrates the impact: blood (unextracted ≈ 275.61 pg/mL *vs.* extracted ≈ 4.75 pg/mL), saliva (4.92 *vs.* 3.15 pg/mL), urine (47.42 *vs.* 13.20 pg/mL), and CSF (17.31 *vs.* 17.29 pg/mL) (131). These findings confirm that extraction is essential for plasma and urine, less so for saliva, and negligible for CSF (136).

Measurement of NP-I could help address some of the problems in OXT measurement. NP-I, the carrier protein co-released with OXT, has potential as a biomarker for assessing endogenous OXT secretion (145). Since it is secreted in equimolar concentrations to OXT and has a longer half-life, it may provide a more stable and reliable measure of OXT release over time. Unlike OXT, which is rapidly degraded by aminopeptidases and fluctuates in response to various stimuli, NP-I may offer a less transient readout of OXT dynamics. Previous studies, including pregnant women or estrogen administration, indicated strong correlations between NP-I and OXT (100,146-149). However, validation under acute OXT stimulation conditions is lacking. A recent secondary study using MDMA demonstrated an 8-fold increase in OXT and a 20-fold increase in NP-I in healthy participants, while patients exhibited only minimal changes in both biomarkers (149). NP-I levels strongly correlated with OXT (R = 0.92) and with subjective psychosocial

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effects, such as increased trust and reduced fear. Additionally, NP-I demonstrated superior analytical performance, requiring no complex extraction steps and reducing measurement time from 16-24 hours for OXT to under two hours (101). These findings establish NP-I as a robust and practical biomarker for assessing OXT function, comparable to how copeptin serves as a surrogate for AVP (150). By overcoming the limitations of direct OXT measurement, NP-I opens new avenues for research into conditions such as autism spectrum disorder, anxiety, and depression, offering deeper insights into their pathophysiology and potential therapeutic targets. NP-I could serve as a valuable surrogate marker for studying OXT-Deficiency and the response to OXT-based therapies in conditions such as hypopituitarism and neuropsychiatric disorders.

OXYTOCIN REPLACEMENT THERAPY IN PATIENTS WITH AVP-DEFICIENCY

To date, no preclinical studies have investigated the effects of OXT on socio-emotional behavior in AVP-deficient animal models. Moreover, clinical evidence remains scarce (**Figure 3**). A systematic review of the OXT system in patients with CP, a condition at high risk of developing AVP-Deficiency (78), identified only two case reports describing long-term low-dose intranasal OXT administration and one pilot study assessing the acute effects of a single OXT dose on emotion recognition (66,67,151,152).

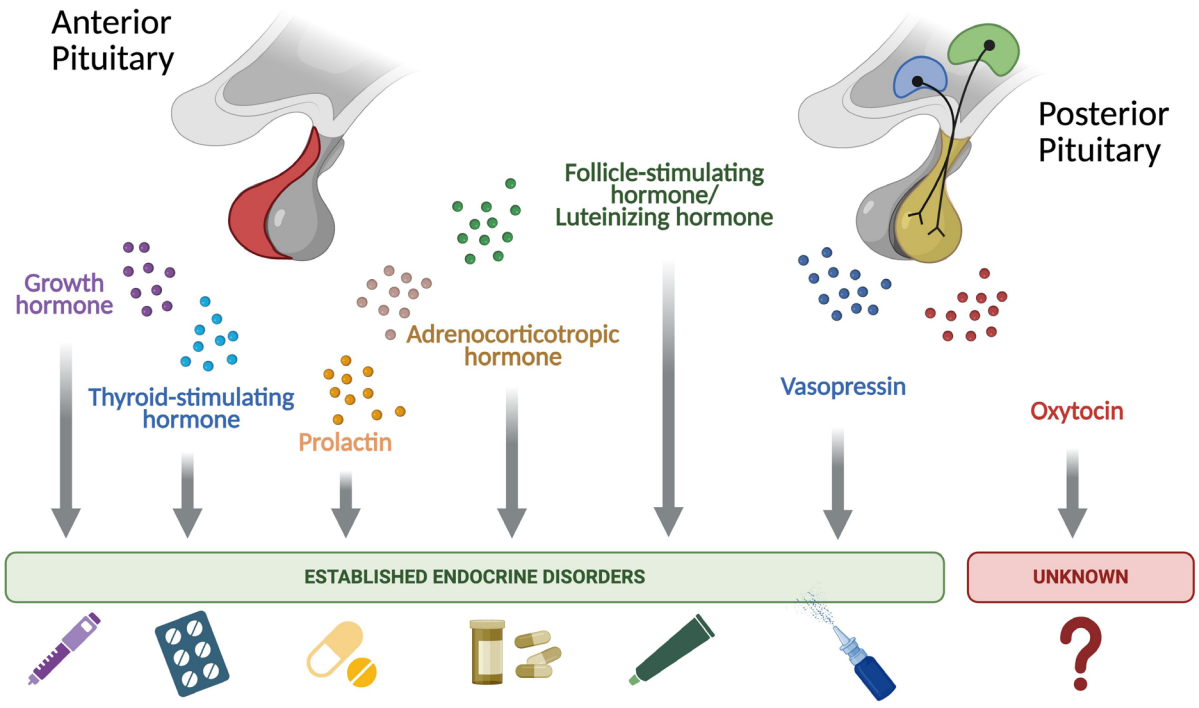
One case report described a 6-year-old girl with panhypopituitarism and hypothalamic damage following CP resection, who developed socio-emotional dysfunction (67). Treatment with 4 IU/day intranasal OXT was associated with improved social engagement and family bonding. Another case involved a 13-year-old boy with hypothalamic obesity post-CP resection, treated with 6 IU/day OXT for 10 weeks, followed by combined therapy with naltrexone (100 mg/day) for an additional 38 weeks (152). This regimen led to reductions in BMI and hyperphagia, suggesting that OXT may modulate reward-driven eating through HPA axis regulation and glucose metabolism. In a pilot cross-sectional study of 10 patients with childhood-onset CP (nine of the patients having AVP-Deficiency), a single 24 IU intranasal OXT dose increased salivary and urinary OXT levels and improved recognition of negative emotions (66). However, the small sample size and absence of placebo control limit the strength of conclusions regarding the therapeutic potential role of OXT in patients with AVP-Deficiency. Considering the high prevalence of psychosocial comorbidities and neurobehavioral dysfunction in this patient population, potentially linked to underlying OXT-Deficiency (69,96,98), there is a clear need for larger randomized controlled trials.

In this line, three randomized, double-blind, placebo-controlled trials are currently being conducted at the University Hospital of Basel in Switzerland to investigate intranasal OXT as a novel treatment for psychological symptoms and socio-emotional dysfunction in AVP-Deficiency. The largest of these is a multicenter, parallel-arm study enrolling 112 AVP-deficient patients, who are randomly assigned to receive either intranasal OXT (24 IU twice daily) or placebo over a 28-day period. Primary outcomes include changes in anxiety and emotion recognition, assessed through validated questionnaires and computerized empathy and emotion recognition tasks. In addition, two smaller cross-over studies, each involving 21 AVP-deficient patients and matched healthy controls, are investigating the effects of intranasal OXT (24 IU once daily) versus placebo. One study focuses on the recognition of facial emotions and body expressions, as well as physiological and psychological responses to acute social stress, while the other study examines the impact of OXT on sexual well-being and intimacy. Finally, a further diagnostic study aims to evaluate whether low-dose MDMA (25 or 50 mg) can safely stimulate OXT release in AVP-deficient patients, potentially offering a novel diagnostic tool for assessing OXT-Deficiency. The outcomes of these trials may have the potential for a paradigm shift in clinical management of AVP-Deficiency.

OXYTOCIN TREATMENT IN OTHER DISORDERS

Over recent decades, evidence has suggested that OXT function might be impaired in mental disorders

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Figure 3. Established *vs.* unexplored endocrine disorders of the pituitary hormones. Overview of key hormones secreted by the anterior and posterior pituitary glands and their clinical relevance. Anterior pituitary hormones, including growth hormone, thyroid-stimulating hormone, prolactin, adrenocorticotropic hormone, and the gonadotropins, are well-characterized and their deficiency or excess is linked to clearly defined endocrine disorders, each with established diagnostic and therapeutic pathways. The posterior pituitary secretes vasopressin, whose deficiency results in a well-defined clinical syndrome with clear treatment options. In contrast, although oxytocin is similarly secreted by the posterior pituitary, its deficiency is not linked to a recognized disease state in humans, and no formal diagnostic criteria or replacement therapies currently exist.

associated with social deficits (153,154). Intranasal OXT has recently gained attention as a potential treatment for these conditions, but findings, especially in autism spectrum disorder (ASD), remain mixed and sometimes controversial (155-158). In borderline personality disorder, intranasal OXT has been shown to enhance empathy and social approach, particularly by improving responses to negative social cues (159). In generalized social anxiety disorder, OXT reduces amygdala hyperactivity in response to threatening social stimuli, as demonstrated in functional MRI studies (160). In ASD, where social communication deficits are a core feature, clinical trials have shown inconsistent results. One randomized controlled trial (RCT) in male youth with ASD showed improved performance on the *Reading the Mind in the Eyes Task* with OXT compared to placebo (161). However, a large 24-week placebo-controlled trial found no significant effects of OXT on social or cognitive outcomes (162). A meta-analysis of 28 studies reported some positive effects on social functioning, but no consistent improvements in non-social symptoms (158). Overall, heterogeneity in study designs, dosages, participant characteristics, and symptom profiles complicates comparisons across trials (162). While OXT may promote prosocial behavior, its effectiveness across all core ASD symptoms remains uncertain (156). Importantly, unlike AVP-Deficiency, no primary OXT-Deficiency per se has been identified in these disorders. Current evidence is largely observational, linking variations in social behavior to alterations in peripheral OXT levels (163), genetic differences in OXT signaling pathways (164), or OXT receptor expression (165).

Evidence from diet-induced obese animal models has shown that OXT administration reduces food intake, increases energy expenditure, and leads to body weight reduction (10). Therefore, OXT has recently been proposed as a promising treatment option for obesity. Although a pilot trial in adults with obesity demonstrated a clinically relevant BMI reduction (166), a recent placebo-controlled study found that intranasal OXT,

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administered four times daily for eight weeks in adults with obesity, did not reduce body weight or improve body composition (167).

CONCLUSION AND OUTLOOK

OXT is far more than a "birth hormone" – its central role in emotional, social, and metabolic regulation makes it a compelling target for clinical research and therapy. While the pathophysiological foundations and therapeutic potential of OXT-Deficiency in patients with AVP-Deficiency are becoming increasingly clear, standardized diagnostic procedures and robust clinical evidence are still lacking. The use of NP-I as a surrogate marker, along with promising results from MDMA-based provocation testing, may pave the way for more accurate diagnostics. Ongoing clinical trials on OXT replacement therapy in patients with AVP-Deficiency have the potential to transform current treatment approaches. Meanwhile, research on OXT in psychiatric disorders shows promise but remains heterogeneous. Overall, there is a strong need for further well-controlled studies to clarify the diagnostic and therapeutic role of OXT in both endocrinological and neuropsychiatric contexts.

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special issue
Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

invited review

Autonomic neuropathy in diabetes

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ABSTRACT

Diabetic autonomic neuropathy (DAN) is a serious and often under-recognized complication of diabetes that can affect any division of the autonomic nervous system (ANS), presenting with a wide range of signs and symptoms. The pathophysiology of DAN involves a complex interplay of hyperglycemia-driven metabolic and vascular pathways, oxidative stress, inflammation, and autonomic imbalance, ultimately leading to progressive nerve dysfunction. Cardiovascular autonomic neuropathy (CAN) has emerged as a particularly severe condition, associated with heightened risk of arrhythmia, silent myocardial ischemia, heart failure, and mortality. DAN, however, extends beyond the cardiovascular system, encompassing gastrointestinal (GI), genitourinary (GU), and sudomotor dysfunctions, that strongly impair quality of life. Despite its impact, DAN remains largely overlooked in clinical practice due to its subclinical onset, non-specific symptoms, and limited routine screening. This review integrates basic, epidemiological, and clinical data to provide a practical understanding of DAN with the aim of helping clinicians to suspect, investigate and manage DAN, with particular attention to its cardiovascular (CV), GI, and GU manifestations.

Keywords: Diabetic neuropathy; diabetic autonomic neuropathy; cardiovascular autonomic neuropathy; diabetes mellitus; heart rate variability

INTRODUCTION

Diabetic autonomic neuropathy (DAN) is a common and serious condition (1,2). DAN is defined as 'a disorder of the autonomic nervous system (ANS) occurring in the context of diabetes or metabolic disturbances associated with prediabetes, after the exclusion of other causes' according to the Toronto Consensus (3). Despite its impact on quality of life and morbimortality, DAN remains underrecognized and poorly understood (4).

The ANS comprises two main branches, the sympathetic (SNS) and parasympathetic (PNS) nervous systems. Although functionally antagonistic, they act in coordination to maintain homeostasis. SNS activation triggers "fight-or-flight" responses, such as increased heart rate (HR), blood pressure (BP), energy mobilization, and alertness. In contrast, PNS activation counterbalances these effects, slowing HR, reducing cardiac contractility, and promoting digestion (5). This dynamic balance enables adaptation to physiological demands and its disruption may lead to maladaptive responses in multiple organ systems, sometimes detectable only by specific tests (3).

This review integrates basic, epidemiological, and clinical data to provide a practical understanding of DAN with the aim of helping clinicians to suspect, investigate and manage DAN, with particular attention to its cardiovascular (CV) gastrointestinal (GI), and genitourinary (GU) manifestations.

EPIDEMIOLOGY AND RISK FACTORS

The prevalence of cardiovascular autonomic neuropathy (CAN) is highly variable according to the studied population and the diagnostic criteria applied (6,7). It can manifest early in the onset of diabetes and its prevalence increases with longer duration, older age and worse glycemic control (6,7). Overall, CAN affect ~20% of individuals with diabetes and up to 65% of older individuals with long-standing disease (8,9). In prediabetes, data are limited, but the KORA study

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indicate a stepwise increase with worsening glycemic status: 4.5% in normoglycemia, 5.9% in impaired glucose tolerance (IGT), 8.1% in impaired fasting glucose (IFG), and 11.4% in combined IFG and IGT (10).

In The Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION), including 299 participants with type 2 diabetes (T2D), CAN prevalence increased from 9% at 6 years to 15% at 13 years, corresponding to an annual incidence of 1.8% (11), lower than previously reported of 4.6%-6% per year (9,12), probably reflecting early diagnosis and intensive treatment (8,11). In the SEARCH study (13), prevalence was 12% in youth with type 1 diabetes (T1D), and 17% in those with T2D, higher than in ADDITION study (11), partly due to methodological differences in CAN assessment.

In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study in individuals with T1D, CAN prevalence increased from 5% at baseline to 44% after 23 years of follow-up (14).

In a Brazilian multicenter study, including 1,712 individuals with T1D, CAN prevalence was 23.4% (15). Traditional risk factors included older age, poor glycemic control, diabetic kidney disease (DKD), diabetic retinopathy (DR), hypertension, elevated cholesterol levels and smoking (15), as well as emerging risk factors, such as lower socioeconomic status and poorer health-related quality of life (15). Glycemic variability and psychological conditions such as depression have been associated with the presence of CAN (16).

GI autonomic neuropathy affects 30%-50% of individuals with diabetes (17-19). Gastroparesis is the most common clinical manifestation (6), though confirmed prevalence remains relatively low. However, gastroparesis-related hospitalizations have increased, partly due to greater use of motility-impairing agents, including opioids, GLP1 receptor agonists (GLP1-RA), and recreational marijuana (1,6). A meta-analysis reported a global prevalence of 9.3% (4.6% in women and 3.4% in men), higher in individuals with T2D (12.5%) than T1D (8.3%) (20).

GU dysfunction encompasses bladder and sexual dysfunction, as well as recurrent urinary tract infections (UTI) (18,21,22). A meta-analysis including 67,040 individuals with diabetes, reported a pooled prevalence of sexual dysfunction of 61.4% (95% CI: 51.8%-71.0%), with substantial heterogeneity (I^2 = 71.6%) (22). In the National Health and Nutrition Examination Survey (NHANES), lower urinary tract symptoms (LUTS) (nocturia, hesitancy, or incomplete emptying) were more frequent in individuals with diabetes compared with the overall population (52.7 *vs.* 36.5%) (23). In women with diabetes, LUTS prevalence ranges from 24% to 49% (24). In the DCCT/EDIC, moderate-to-severe LUTS developed in ~20% of men with T1D after 10 years of follow-up (mean diabetes duration 22.1 years) (25). Among women, any and at least weekly urinary incontinence (UI) was reported in 38% and 17%, respectively, with advancing age, higher body weight, and prior UTI as risk factors (26).

PATHOGENESIS OF DAN

Diabetic neuropathy (DN), including DAN, results from multifactorial mechanisms in which oxidative stress and inflammation play central roles, leading to neuronal damage, endothelium dysfunction and neural ischemia (19,27,28).

Data from the DCCT (29) and United Kingdom Prospective Diabetes Study (UKPDS) (30) indicate that hyperglycemia is the main driver, with additional contributions from dyslipidemia, hypertension, genetic predisposition, obesity (particularly in T2D), low insulin and C-peptide levels, and autoimmunity (notably in T1D) (7,27,28).

Over the next lines we will summarize the intracellular molecular mechanisms involved in neural and endothelial damage.

Chronic hyperglycemia increases intracellular glucose, accelerating glycolysis and electron flux in the mitochondrial electron transport chain (27,28). This enhances mitochondrial production of reactive oxygen species (ROS), particularly superoxide, leading to oxidative stress, mitochondrial dysfunction, reduced ATP generation, and neuronal apoptosis (19,27,28). ROS-induced mitochondrial DNA damage activates poly (ADP-ribose) polymerase (PARP), which inhibits glycolysis via glyceraldehyde-3-phosphate dehydrogenase (GAPDH) inactivation (7,27), causing accumulation of upstream glycolytic intermediates.

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These compounds are redirected into four key major pathways – the polyol, the advanced glycation end-product (AGE), the hexosamine and the protein kinase C (PKC) pathways – resulting in oxidative injury, reduced nitric oxide (NO) bioavailability and endothelial dysfunction, sorbitol-induced osmotic stress, neuroinflammation, and ultimately nerve damage with demyelination and impaired nerve conduction (19,27,28).

Insulin signaling supports nerve metabolism and function via PI3K mediated ATP production (31) while impaired signaling affects T1D and T2D differently: in T2D, insulin resistance limits metabolic and bioenergetic function, and compromise axonal growth and myelination in peripheral nerves (19,32), whereas in T1D, preserved insulin sensitivity allows better neuropathic outcomes with insulin therapy (33). Hyperglycemia further inhibits the PI3K/Akt signaling pathway in Schwann cells, leading to apoptosis, demyelination, and impaired nerve conduction (34).

Defects in the interactions between afferent and efferent autonomic local neural pathways are involved in the pathogenesis of GI and GU autonomic neuropathy. As a result, GI motor, sensory and secretory functions may be impaired (35) as well as bladder sensation, capacity and urinary retention (21).

Endothelial dysfunction besides autonomic nerve damage may lead to reduced cavernosal smooth muscle relaxation, altered sensory function, and impaired motor control of erectile muscles in men and decreased arousal and inadequate lubrification in women (21,24).

In the early stages of T2D, CAN is marked by sympathovagal imbalance (8,36,37). Insulin resistance and compensatory hyperinsulinemia drive sustained SNS overactivation (6,8), through endothelium-dependent vasodilation, baroreflex activation, hypothalamic pathways, and chemoreceptor sensitization (6-8,37). DN progresses in a length-dependent manner, making the vagus nerve – the longest autonomic nerve responsible for ~75% of PNS activity – particularly vulnerable. Its early involvement reduces PNS tone, and reinforces SNS predominance (8,37).

Beyond the contribution of inflammation to DAN, autonomic dysfunction itself may exacerbate inflammatory processes (38). In CAN, vagal impairment reduces cholinergic anti-inflammatory signaling, while SNS overactivity enhances macrophage activation and cytokine release, perpetuating inflammation (38-41). These alterations in the inflammatory reflex suggest a role of the ANS in modulation immune and inflammatory responses (39-41,42).

In summary, the pathophysiology of DAN is complex and multifactorial, involving metabolic, vascular, inflammatory, neurotrophic, and emerging molecular mechanisms. Despite significant advances in understanding its underlying pathways, further studies are needed to fully elucidate the intricate processes involved and to identify effective and targeted therapeutic strategies.

CLINICAL SPECTRUM, DIAGNOSIS AND MANAGEMENT OF DAN

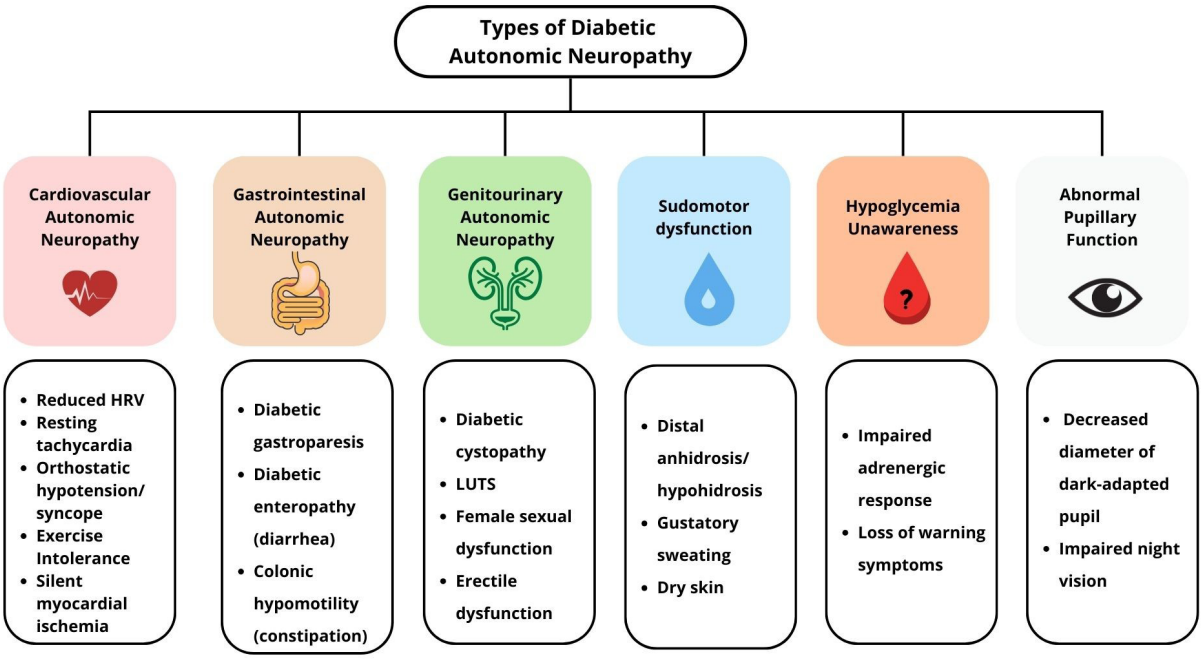
DAN encompasses a broad spectrum of manifestations involving CV, GI, and GU systems, among others (**Figure 1**). Symptomatic forms are relatively uncommon (43), except for erectile dysfunction (ED), which is multifactorial, and GI symptoms, which are frequent in the general population and not strongly associated with objective GI motor dysfunction or cardiovascular autonomic reflex tests (CARTs) abnormalities (43).

Cardiovascular Autonomic Neuropathy

CAN and Other Microvascular Complications

CAN often precedes albuminuria (44,45) and independently predicts both the development and progression of DKD in individuals with diabetes (42,46,47). Proposed mechanisms include sympathovagal imbalance, nocturnal SNS hyperactivity increasing BP and glomerular pressure (9,48), enhanced tubular reabsorption via renal SNS innervation, angiotensin-mediated microvascular injury, and erythropoietin-deficiency anemia (47,49). In advanced stages, daytime orthostatic hypotension (OH), may further impair renal hemodynamics (9,50). In the Atherosclerosis Risk in Communities (ARIC) study (n = 13,241 adults; 11.5% with diabetes), higher resting HR and lower heart rate variability (HRV) increased risk of end-stage renal disease and chronic kidney disease related hospitalizations over 16 years (47).

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HRV: heart rate variability; LUTS: lower urinary tract symptoms.

Figure 1. Clinical spectrum of diabetic autonomic neuropathy.

Diabetic autonomic neuropathy may affect multiple systems, including cardiovascular, gastrointestinal, genitourinary, and sudomotor pathways, as well as pupillary function and hypoglycemia awareness. Each subtype presents with characteristic symptoms that reflect widespread autonomic dysfunction in diabetes.

CAN is also linked to peripheral diabetic neuropathy (PDN) and DR development and progression (15,51-53). A systematic review demonstrated that the PDN presence and severity was correlated with worse autonomic outcomes, suggesting shared pathophysiological mechanisms (54). Prospective data from a study involving 725 adolescents with T1D, and follow-up of 3.8 years, demonstrated that CAN predicted the incidence of DR and early kidney dysfunction, even after adjusting for glycated hemoglobin (A1c) and diabetes duration (53). Likewise, in a 3-year cohort study of 4,850 adults with T2D, lower high-frequency (HF) power, a marker of autonomic dysfunction, was an independent predictor of DR progression, alongside mean A1c and baseline proliferative DR (55).

These findings underscore the importance of integrated, systematic screening of microvascular complications in diabetes.

CAN and its impact on cardiovascular morbidity and mortality

Evidence from the Framingham Offspring Study indicates that autonomic imbalance may precede diabetes onset (50). In 1,882 participants, higher resting HR and lower HRV, sex, age, and smoking, predicted hypertension, hyperglycemia, diabetes diagnosis, cardiovascular disease (CVD) and mortality over 12 years (50). These findings suggest a bidirectional relationship between autonomic dysfunction and glucose abnormalities that warrants further investigation.

CAN also contributes to myocardial dysfunction, left ventricular (LV) hypertrophy and heart failure (56). Diastolic dysfunction, the early manifestation of diabetic cardiomyopathy, manifests as impaired ventricular relaxation and filling (9,56,57). In the DCCT/EDIC, CAN was associated with increased LV mass and mass-to-volume ratio, markers of concentric remodeling (56).

CAN may also impair coronary flow autoregulation, lowering the threshold for myocardial ischemia, and increasing the risk of silent myocardial ischemia (SMI) and infarction. Multiple studies confirm the strong association between CAN and CV risk and mortality in both T1D and T2D (8,9,57-59). In the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects (DIAD) study, including 1,123 asymptomatic individuals with T2D, abnormal Valsalva response (OR

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5.6), longer diabetes duration (OR 5.2) and male sex (OR 2.5) independently predicted SMI over 5 years, whereas traditional risk factors failed to predict its occurrence (60).

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, involving 8,135 participants with T2D, CAN was associated with a 1.55 to 2.14-fold higher risk of mortality, independent of baseline CVD, diabetes duration, and other risk factors (61). Likewise, in the EURODIAB Study of 2,787 individuals with T1D, CAN [HR 2.40 (1.32-4.36)] was one of the strongest predictor of all-cause mortality, alongside macroalbuminuria [2.39 (1.19-4.78)] and PDN [1.88 (1.06-3.35)] (62). A meta-analysis of 15 studies confirmed increased mortality risk, particularly when CAN was defined by ≥ 2 abnormal tests [relative risk 3.45 (95% CI: 2.66-4.47) compared with only one abnormality [1.20 (95% CI: 1.02-1.41)] (63).

SNS cardiac denervation is an important prognostic marker in heart failure and ischemic cardiomyopathy. In The AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF), reduced cardiac SNS innervation, assessed by I-123 mIBG scintigraphy (abnormal heart-to-mediastinum ratio < 1.6), predicted heart failure progression, arrhythmic events and cardiac death in 961 individuals with New York Heart Association (NYHA) class II/III heart failure and LV ejection fraction ≤ 35% (64). Similarly, in the Prediction of ARrhythmic Events with Positron Emission Tomography (PAREPET) study, SNS denervation, measured by 11C-HED PET, strongly predicted sudden cardiac arrest in patients with ischemic cardiomyopathy (65). These findings highlight that, beyond cardiovagal impairment, SNS denervation predicts cause-specific mortality from sudden cardiac death (57).

CAN has also been linked to increased risk of stroke (9,57,58), arterial stiffness (66), perioperative morbidity and mortality, due to hemodynamic instability (9,58,67), and sudden cardiac death, often associated with arrhythmias and QT interval prolongation (68,69).

The relationship between CAN and impaired awareness of hypoglycemia (IAH) remains complex. IAH, characterizes by reduced perception of hypoglycemia and blunted adrenergic responses, increases the risk of severe hypoglycemia (70). Although CAN has been associated with severe hypoglycemia in studies such as ACCORD (70-72), evidence indicates that even a single hypoglycemic episode may trigger IAH, and improvements are possible regardless of autonomic status, as shown in HypoCOMPaSS (71,73-75). Thus, while CAN may exacerbate IAH, it is not considered its primary determinant (2).

In summary, CAN is a major contributor to excess CV risk and mortality in diabetes, independent of traditional risk factors.

Clinical presentation of CAN

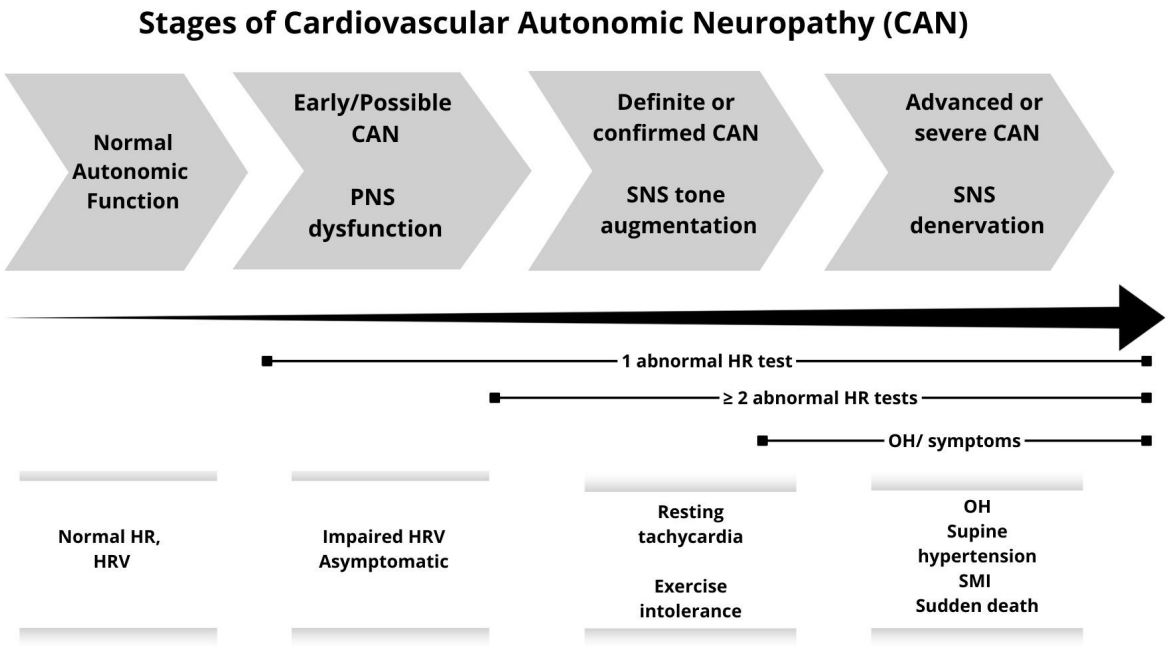
CAN is frequently underdiagnosed because early stages are often asymptomatic (1,8,40,59) (**Figure 2**). At this stage, it can only be detectable by reduced HRV, making early diagnosis challenging (1,6,8,9,19,38). Initial clinical manifestations include resting tachycardia (up to 130 beats/min). With worsening autonomic dysfunction, chronotropic and inotropic impairment can result in a fixed HR, often manifesting as exercise intolerance (8,9,40).

Advanced autonomic dysfunction may cause dizziness, unsteadiness, syncope and circadian BP dysregulation (non- or reverse-dipping), raising nocturnal CV risk (48,76). Importantly, while resting tachycardia may indicate CAN, its absence does not exclude the diagnosis.

OH, defined as a fall in systolic blood pressure (SBP) ≥ 20 mmHg (or ≥ 30 mmHg in individuals with hypertension) and/or diastolic blood pressure (DBP) ≥ 10 mmHg (or ≥ 15 mmHg in individuals with hypertension) within 3 minutes of standing (8,77), results from efferent SNS vasomotor denervation, leading to impaired splanchnic and peripheral vasoconstriction. Additionally, a blunted HR response and reduced cardiac output further contribute to the development of orthostatic symptoms (77,78).

In the EURODIAB IDDM Complications Study, including 3,007 individuals with T1D, OH prevalence was 5.9%, 18%, and 32%, depending on definition (a fall in SBP >30, >20, and >10 mmHg, respectively), with 18% reporting orthostatic symptoms (79). These

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ANS: autonomic nervous system; CAN: cardiovascular autonomic neuropathy; CARTs: cardiovascular autonomic reflex tests; HR: heart rate; HRV: heart rate variability; OH: orthostatic hypotension; PNS: parasympathetic nervous system; SMI: silent myocardial ischemia; SNS: sympathetic nervous system.

Figure 2. Stages of cardiovascular autonomic neuropathy.

Diabetes affect ANS in an ascending length-dependent manner, with the vagus nerve usually being the first to be affected. CAN evolves from a subclinical stage, characterized by HRV abnormalities, to a clinical stage where PNS dysfunction leads to abnormal CARTs and symptoms of SNS predominance. Symptomatic CAN generally appears in the later stages, when cardiac involvement becomes more evident and progression is further marked by SNS denervation, orthostatic intolerance, and increased cardiovascular risk.

symptoms are often worse in the morning, after meals, with heat, prolonged standing, or exercise (80) and increases the risk of fall.

Medical guidelines recommend screening all patients with diabetes for autonomic symptoms as the first step in DAN evaluation (7,9). However, as symptoms typically appear late and are nonspecific, their utility for early diagnosis is limited. Standardized questionnaires, such as the Composite Autonomic Symptom Score 31 (COMPASS 31) (81) and the Survey of Autonomic Symptoms (SAS) (82,83) address multiple autonomic domains, and provide practical, low-cost tools. COMPASS 31 shows fair diagnostic accuracy for CAN (AUC 0.75, sensitivity of 75% and 70% and specificity of 65% and 67% for global and confirmed CAN, respectively) (84). Strong diagnostic performance was also observed with SAS, which demonstrated an AUC of 0.828 (82).

However, evidence suggests that the diagnostic performance of COMPASS 31 may vary according to diabetes type. In a study evaluating 79 individuals with T1D and 140 individuals with T2D (85), the COMPASS score was significantly associated with confirmed CAN in T1D but not in T2D. Correlations between COMPASS 31 and CARTs were also observed only in T1D. Moreover, COMPASS 31 demonstrated higher sensitivity in T1D (81.2%) compared to T2D (67.7%) and fair diagnostic accuracy for confirmed CAN in T1D but not in T2D (AUC 0.61) (85). These differences should be considered when applying COMPASS 31 in clinical practice.

In addition to symptom-based questionnaires, clinical risk scores are being developed to support CAN detection in clinical practice. In a retrospective cross-sectional study, including 115 individuals with T1D and 161 with T2D, standard CARTs were performed and a CAN risk score was developed based on the strength of associations between clinical variables and confirmed CAN (defined by the presence of ≥ 2 abnormal CARTs) (86). The score incorporated variables such as resting HR, A1c, DR, DKD and CVD in both types of diabetes, with additional parameters

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including HDL cholesterol, SBP, and smoking in T1D, and insulin treatment and physical activity in T2D. The CAN risk score demonstrated high diagnostic accuracy, with an AUC of 0.890 in T1D and 0.830 in T2D. Using a cut-off of 4, sensitivity was 88% in T1D and 78.6% in T2D, specificity 74.4% and 73.5%, and negative predictive value 95.7% and 97.3%, respectively (86). Although promising, these scores still require external validation before being adopted as universal screening tools.

CAN diagnosis

Assessment of CAN in clinical settings combines the evaluation of autonomic signals and symptoms with standardized tests of CV autonomic regulation (8). Because several comorbidities and medications may mimic autonomic dysfunction, careful exclusion of these conditions is essential before confirming CAN (7). Resting tachycardia (HR > 100 bpm) can result from anemia, hyperthyroidism, dehydration, smoking, CVD, or the use of sympathomimetic, ephedrine or pseudoephedrine, dietary supplements, alcohol, caffeine or recreational drugs (7). OH, in turn, may instead reflect intravascular volume depletion, adrenal insufficiency, CVD or the use of diuretics, antihypertensives, sedatives, anticholinergics, neuroleptics and other drugs (7).

In clinical practice, tachycardia, OH, QT prolongation and abnormal 24 h ambulatory BP monitoring (ABPM) patterns are non-invasive, widely available tools that may provide early clues to CAN before specialized testing (8,9,87). The Toronto Consensus recommends routine screening for orthostatic symptoms and annual OH testing in all patients with diabetes, particularly those > 50 years or with hypertension (9).

ABPM is useful to detect nondipping (nocturnal BP fall < 10%) or reverse dipping patterns (no decline or a rise) (8) which may guide antihypertensive treatment (9). However, the day-night SBP difference shows high specificity (95%) but low-sensitivity (25%) as a marker of CAN (88).

Similarly, a prolonged QT interval has high specificity (86%) but low-sensitivity (28%) for CAN diagnosis (89). Rather than a screening tool, it aids arrhythmic risk stratification and predicts mortality, thus being more relevant for prognostic evaluation (8,43,59,69).

According to the Toronto Consensus (9), CARTs are the gold standard for CAN assessment, being sensitive, specific, reproducible, safe, and standardized (9,59). CARTs assess autonomic CV function through physiological maneuvers that induce HR and BP oscillations (9,43,90). Ewing's battery includes HR responses to deep breathing, Valsalva maneuver, and lying-to-standing, which assess PNS function, while BP responses to standing (OH) or sustained handgrip, reflects SNS activity (9,91,92). The latter is no longer recommended due to technical difficulty, low sensitivity, limited reproducibility, and risk of hemodynamic stress (8,9,93).

There is no evidence that one autonomic test is superior, nor consensus on the exact number of tests required for CAN diagnosis (58). However, most guidelines recommend more than one autonomic test to reduce the likelihood of false positive results (9,43,94). CAN staging is based on the number of abnormal CARTs: one suggests early or possible CAN, two confirm the diagnosis, and HO indicates advanced disease, associated with increased morbidity and mortality (9,77,90).

Given their physiological basis, CARTs must be standardized, with attention to confounding factors and proper instructions for performance and interpretation (9,43). Caffeine, alcohol, nicotine and drugs affecting ANS function should be avoided prior to testing, as well as strenuous exercise within 24 h (9,43). CARTs should be performed at fasting or at least 2 h after a light meal, with adequate glycemic control, and postponed in the presence of acute conditions such as fever, infection, dehydration, or significant emotional stress, given their potential to transiently alter CV autonomic regulation (9,43).

Interpretation should be based on normal age-related reference values due to the physiological decline of HRV with aging (43). In the lying-to-standing test, approximately 25% of the SBP drop depends on baseline supine SBP, with greater decreases observed at > 160 mmHg and blunted responses at < 120 mmHg, potentially causing false-positive or negative results, respectively (43). Additionally, the

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presence of cardiac arrhythmias or the presence of a pacemaker invalidate the performance of CARTs (43), and the Valsalva maneuver should be avoided in individuals with proliferative DR due to the small risk of intraocular hemorrhage or lens dislocation (92).

However, CARTs are not widely available, and short-term (5-minute) HRV analysis has been investigated as a simpler alternative (92,95). HRV is obtained from resting electrocardiogram (ECG) recordings, ideally under paced breathing, and analyzed by specific software that measures beat-to-beat (RR) intervals, providing time- and frequency-domain indices of sympathovagal integrity and balance. Time domain measures include RR mean, the difference between the longest and shortest RR intervals, the standard deviation of all normal-to-normal RR intervals (SDNN; a measure of both SNS and PNS activity) and root mean square of successive differences between RR intervals (RMSSD; a primarily measure of PNS activity) (5,58). Longer recordings also allow calculation of the percentage of consecutive RR intervals differing > 50 ms (pNN50) (87).

In frequency domain (spectral) HRV analysis, electrocardiographic signals from sequential RR intervals are processed by algorithms to decompose the signal into its frequency components (9,43,58). Results are displayed as an amplitude-frequency diagram, showing oscillation magnitude (HR fluctuations per second) as a function of frequency (hertz). Three main components are distinguished in spectral analysis: very low frequency (VLF, 0.01-0.04 Hz), reflecting vasomotor tone fluctuations related to thermoregulation and sweating, predominantly under SNS control; low frequency (LF, 0.04-0.15 Hz), associated with the baroreflex, reflecting both SNS and PNS modulation; and high frequency (HF, 0.15-0.40 Hz), corresponding to PNS activity (87,95,96) (**Figure 3**). Short-term recordings cannot estimate long RR intervals fluctuations, such as the VLF component (97). Hence, apart from the VLF, LF and HF components provide information on both autonomic branches, and abnormal results may indicate impaired HRV, while the LF/HF ratio is commonly used as an index of sympathovagal balance (87,96,98).

HRV tests are sensitive, and require no active patient cooperation, but they may not necessarily identify CAN in same individuals as CARTs. Impaired HRV indices can precede CARTs abnormalities (87). However, HRV has low reproducibility and is prone to technical artifacts and physiological variation (87,99). Therefore, HRV is best regarded as complementary to CARTs, offering earlier and more prognostic information rather than a substitute tool in clinical practice (87).

Other methods for CAN assessment (9), include baroreflex sensitivity, muscle sympathetic nerve activity, plasma catecholamine measurement, and cardiac sympathetic imaging using nuclear medicine techniques. Their use is largely limited to research because of technical complexity, limited availability, and high cost (9,87).

The American Diabetes Association (ADA) recommends annual CAN evaluation in all individuals with T2D and in those with T1D of ≥ 5 years' duration (7).

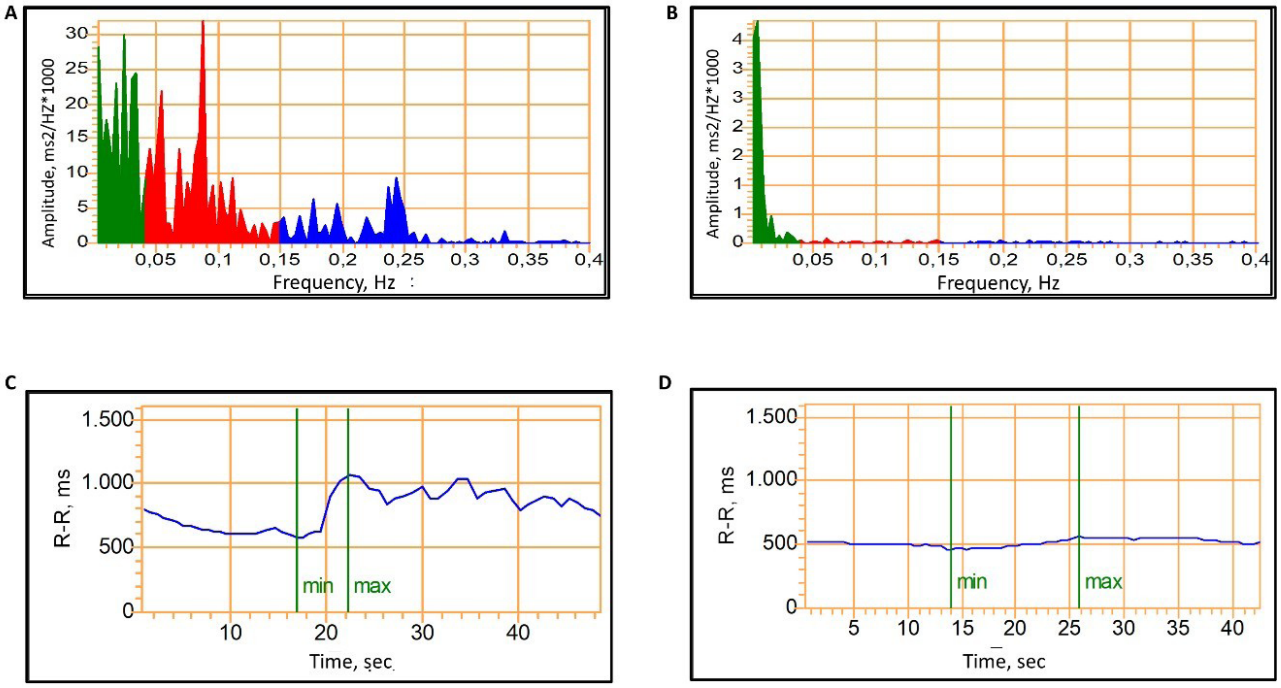
The Toronto Consensus (9), the ADA (7), the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) (100) and the Italian Society of Diabetology (43) recommend screening for CAN, particularly in individuals with diabetes and long-standing disease, poor glycemic control, or other complications. All endorse symptom evaluation, but guidance on CARTs differs: they are considered the gold standard by the Toronto Consensus; recommended by the AACE/ACE and Italian Society; and regarded as optional by the ADA, mainly in symptomatic patients (*e.g.*, tachycardia, poor glycemic control or clinically suspected CAN), though potentially useful in asymptomatic individuals. The ADA favors a symptom-based approach for cost and feasibility reasons.

Management of CAN

At present, no disease-modifying therapy is available for CAN. Prevention strategies include lifestyle modifications, as demonstrated in the Diabetes Prevention Program (DPP) study (101), where participants engaging in ~150 min/week of exercise plus a low-fat diet had improved HRV and reduced incidence of T2D compared with metformin or placebo (101).

Several studies support the benefits of exercise on CAN, showing that regular physical activity

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CAN: cardiovascular autonomic neuropathy; CARTs: cardiovascular autonomic reflex tests; HF: high frequency; HR: heart rate; HRV: heart rate variability; LF: low frequency; PNS: parasympathetic nervous system; RR: RR interval; SNS: sympathetic nervous system; VLF: very low frequency.

Figure 3. Example of spectral analysis study of HRV and CART in individuals with and without cardiovascular autonomic neuropathy.

Panels A and B depict HRV amplitude plotted as Amplitude (Y axis) against Frequency (X axis), derived from spectral analysis. This method reflects both the magnitude of HRV and its frequency-specific oscillations, enabling a distinction between the relative contributions of the SNS and PNS: blue corresponds to the HF band (0.15–0.40 Hz), which reflects PNS activity; red to the LF band (0.04–0.15 Hz), which is associated with baroreflex activity; and green to the VLF band (0.01–0.04 Hz), which reflects vasomotor tone fluctuations related to thermoregulation and sweating, predominantly under SNS control. Panel C and D depict the HRV response expressed in milliseconds over time during the performance of the Valsalva maneuver (an example of CART). In **Panel A**, a greater oscillation amplitude is observed in all three spectral bands (patient without CAN), whereas patients with CAN show a reduced amplitude in HRV, demonstrating impaired HRV (**Panel B**). **Panel C** illustrates the results of a Valsalva maneuver in a patient without CAN, demonstrating an expected reduction in RR interval during forced expiration followed by an expected increase in RR interval after release, reflecting an appropriate autonomic response. In contrast, this variability is absent in patients with CAN (**Panel D**).

(especially aerobic training) is associated with improved HRV (higher SDNN, RMSSD, pNN50, and HF; lower LF and LF/HF ratio), reflecting enhanced PNS activity and reduced SNS overactivity (102,103). However, data are limited and of low-quality in T2D without or with early CAN and scarce in established CAN or T1D (8).

Because individuals with diabetes and CAN are at increased risk of SMI, the ADA advises performing an exercise stress test before initiating an exercise program (104). Exercise prescriptions should also include safety precautions: avoid activities involving rapid postural changes in individuals with OH to reduce fainting risk; monitor intensity by HR reserve and perceived exertion in those with blunted HR response; and, in general, avoid hot environments and ensure adequate hydration (104).

Evidence suggests a stronger impact of glycemic control on CAN outcomes in T1D than in T2D. In T1D, the DCCT reported a 53% reduction in CAN incidence after 6.5 years of intensive insulin therapy, and the EDIC study confirmed a persistent protective effect for up to 14 years, despite subsequent convergence of A1c levels (33). In T2D, results are less consistent: the UKPDS demonstrated a 25% reduction in microvascular complications, but no clear reduction in CAN (30) and the VA Cooperative Study found no significant difference in CAN prevalence after two years of intensive therapy (105). By contrast, the Steno-2 trial (106) reported a 68% reduction in CAN incidence with a multifactorial strategy addressing glycemic, BP, lipid and albuminuria treatment, lifestyle modification, and smoking cessation, underscoring the importance of comprehensive risk factor

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management beyond glucose lowering. Accordingly, the ADA recommends early and intensive glycemic control to prevent CAN in T1D, a multifactorial approach targeting glycemia and other CV risk factors in T2D, and lifestyle interventions in individuals with prediabetes (7).

Currently, no antidiabetic drug has demonstrated consistent benefits for CAN. A small study demonstrated that metformin-related decrease in plasma free fatty acid and insulin resistance was associated with an improvement in sympathovagal balance (107). Although sodium-glucose cotransporter-2 inhibitors (SGLT2i) improve CV outcomes, their direct impact on autonomic dysfunction remains unclear. SGLT2i induces BP reductions without compensatory increase in HR in major trials, suggesting a SNS activity dampening (108). In the EMBODY trial (109), 96 patients with T2D after acute myocardial infarction treated with empagliflozin for 24 weeks demonstrated within-group HRV improvements (higher SDNN and lower LF/HF ratio) and better HR turbulence. In contrast, the EMPA-HEART CardioLink-6 Holter analysis in 66 patients with T2D with stable coronary artery disease demonstrated no significant HRV changes after 6 months of empagliflozin versus placebo, suggesting no measurable impact on autonomic tone (110).

Studies with GLP1-RAs suggest a potentially unfavorable autonomic profile (111). Experimental data demonstrate increased HR and SNS activity with reduced HRV (8,112). This increase in HR may be explained by an action of GLP1 on receptors present on cardiomyocytes and an increase in SNS activity both directly and mediated by the GLP1-driven increase in endogenous insulin (8). However, clinical studies reported inconsistent effects of GLP1-RA on HRV, likely reflecting species-specific receptor patterns, agent differences, while not excluding direct effects on the sinus node (8). These findings should be weighed against the robust CV benefits of GLP1-RAs demonstrated in large clinical trials (8,107).

Pathogenesis-based therapies for CAN have yielded mixed results. Alpha-lipoic acid improved HRV in both T1D and T2D, via antioxidant and anti-inflammatory effects (113,114). Aldose reductase inhibitors demonstrated inconsistent HRV benefits and potential adverse effects (8,115). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers produced similarly inconsistent findings (8,9). Cardioselective β-blockers may help restore sympathovagal balance and manage resting tachycardia (116). Overall, some agents appear promising, but require larger, long-term trials to establish efficacy.

Managing OH remains challenging. In individuals with OH, office BP assessment should emphasize postural changes from supine to standing rather than seated values, as these measurements guide therapeutic decisions and individualized target definition (117). First-line management is non-pharmacological and include: reducing or discontinuing aggravating medications, when possible (*e.g.*, tricyclic antidepressants, diuretics, vasodilators, α1-blockers) (118); dietary strategies such as increased fluid and salt intake to expand plasma volume (9,118) and rapid ingestion of 500 mL of water (119), if not contraindicate; small low-carbohydrate meals and alcohol restriction to minimize splanchnic postprandial blood pooling (1,6,7); lower limb strengthening exercises and counter-maneuvers (gradual positional changes, leg crossing and squatting.), while avoiding heat exposure and prolonged standing (9,118); elevation of head of the bed 10-30° at night to reduce nocturia and morning orthostatic intolerance (9,118); and compression garments to minimizing venous pooling in the legs and abdomen (7,9,118).

Pharmacological treatment for OH is reserved for refractory cases. Food and Drug Administration (FDA) approved options for symptomatic OH are midodrine, an α-1 adrenergic agonist that induces vasoconstriction and increased peripheral resistance; and droxidopa, a norepinephrine precursor that enhances SNS tone (1,2,19,59).

Fludrocortisone, a mineralocorticoid, expands plasma volume via sodium and water retention, but may induce supine hypertension, heart failure, edema and hypokalemia (1,19,59), requiring caution. Other less established agents include pyridostigmine, octreotide, desmopressin, and erythropoietin (8). All drugs should be initiated in the morning at low

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doses, titrated gradually, and avoided in the evening to minimize supine hypertension.

Treating supine hypertension is particularly difficult, as BP must be lowered without worsening OH. It is defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg after 5 minutes in the supine position (117). Pharmacological therapy is usually reserved for more severe cases (SBP ≥ 180 mmHg or DBP ≥ 110 mmHg) (118). Short-acting antihypertensives given at bedtime, such as clonidine, captopril and losartan are recommended (8,118). The goal of therapy is symptom relief, prevention of syncope and falls, and preservation of functional independence, rather than strict BP normalization, and higher BP thresholds can be tolerated (2,8,117,118).

Detection of CAN in asymptomatic patients provides key information for risk stratification of diabetes complications, CV morbidity and mortality, and perioperative risk for major surgery (8,9). It also guides therapeutic strategies, helping to define individualized glycemic targets. In symptomatic patients, identification of clinical CAN enables tailored management of its consequences – such as tachycardia, non-dipping, nocturnal hypertension, and OH – and assists clinical decisions, including avoiding medications that prolong QT interval or impair sinoatrial node function, refraining from using seated BP as therapeutic target, incorporating 24-hour BP monitoring, and developing a personalized, safe physical activity plan (8,9).

Gastrointestinal autonomic neuropathy

The gastroenteropathy associated with diabetes may present with nonspecific despite burdensome symptoms (17). Autonomic neuropathy has an important role on its pathogenesis and may involve any part of the GI tract (17).

In a population study including 8,657 individuals, 453 (4.9%) with self-reported diabetes, symptoms of abdominal pain or discomfort (13.5% *vs.* 10.8%), early satiety (5.2% *vs.* 4.3%), postprandial fullness (8.6% *vs.* 5.2%), bloating (12.3% *vs.* 11.4%), heart burn (13.5% *vs.* 10.8%), nausea (5.2% *vs.* 3.5%), dysphagia (5.4% *vs.* 1.7%), vomiting (1.7% *vs.* 1.1%), diarrhea or constipation (15.6% *vs.* 10.0%), anal blockage (7.7% *vs.* 5.0%), fecal incontinence (2.6% *vs.* 0.8%), urgency (7.4% *vs.* 5.5%), esophageal symptoms (15.4% *vs.* 11.5%), upper dysmotility symptoms (18.2% *vs.* 15.3%) and any bowel symptom (26% *vs.* 18.9%) were significantly more frequent in individuals with diabetes than in controls, respectively (120). In diabetes, gallstones may be asymptomatic or cause discomfort or pain (121).

There is no clinically available method for screening GI neuropathy in diabetes. Therefore, active symptom inquiry is essential with exclusion of other GI disorders and drug-related side effects (17). Validated questionnaires are useful for deciding when to investigate GI autonomic neuropathy (17).

Esophageal symptoms, such as dysphagia and odynophagia, may occur in patients with diabetes, although dysmotility may be asymptomatic. Mechanical and infectious causes (*e.g.*, esophageal candidiasis) must be excluded (17) and treatment follows the same principle as for patients without diabetes. If dysmotility is suspected, patients should be instructed to drink water after taking oral medications to prevent pill esophagitis (17).

Gastroparesis

Gastroparesis is characterized by delayed gastric emptying in the absence of organic causes such as gastric or duodenal obstruction (7,122). It complicates glycemic management, contributes to glycemic variability or unexplained postprandial hypoglycemia due to a mismatch between nutrient absorption and insulin pharmacokinetics (6). It also leads to unpredictable drug absorption (40).

In 2020, a United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on gastroparesis defined gastroparesis as a chronic condition, in which nausea and vomiting are cardinal symptoms, often accompanied by early satiety, epigastric pain, bloating, and postprandial fullness. Its symptoms may overlap with functional dyspepsia (123) and should be investigated (122,123).

In case of weight loss, eating disorders must be excluded (123). The impact of drugs, such as opioids, anticholinergics and incretins-based therapies on gastric emptying should also be considered, as they may precipitate or exacerbate symptoms (7,124).

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Upper GI Endoscopy is mandatory to rule out mechanical obstruction (122,123) and mucosal disorders (17). Retained gastric food is not diagnostic of gastroparesis (122,123).

According to the American College of Gastroenterology (ACG) (122) and the ADA (17), gastric emptying scintigraph with a solid meal over ≥ 3 hours is the gold standard test for diagnosing gastroparesis. The stable isotope breath test is a reliable test (17,122). Similarly, the 2020 European Consensus (123) endorsed both methods as valid diagnostic tools. Wireless motility capsule testing may be considered (122), although not validated by the European consensus (overall agreement of 33%) (123). Radiopaque markers testing is not recommended by ACG (122).

Optimization of glycemic control before testing for gastroparesis (ideally between 70-180 mg/dL) is recommended. Testing should be avoided during hyperglycemia or hypoglycemia, since acute hyperglycemia delays gastric emptying, whereas hypoglycemia accelerates it (125). Medications that affect gastric emptying should be discontinued 48 hours before testing (122), and patients should abstain from smoking or alcohol (17,18,121).

Management of gastroparesis is challenging. Conservative and educational strategies should be implemented, including withdrawal of drugs that delay gastric emptying, dietary changes (small, frequent, low-fat, low-fiber meals, liquid or small-particle diet) (17,122), avoidance of reflux-triggering foods and alcohol, and remaining upright for 1-2 hours after meals (18,35,126). Treatment may require antidiabetic therapy adjustment, such as reducing preprandial insulin dose or delaying its administration. Continuous subcutaneous insulin infusion therapy is an alternative in cases of marked glycemic variability (18,35,126).

Pharmacological therapy is reserved for refractory symptomatic cases (122). Metoclopramide is the only Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved prokinetic, but its use should be limited to ≤ 3 months due to late-onset dyskinesia risk (18,35). Domperidone represents an alternative with fewer central nervous system (CNS) effects; however caution is required given its arrhythmogenic potential, also reported with metoclopramide (17,35,122). Erythromycin and other macrolides are limited to short-term use due to tachyphylaxis (typically after 2-4 weeks) (17,35). Serotonin 5-HT4 receptor agonists (*e.g.*, prucalopride) may also enhance gastric emptying (122,123).

For refractory nausea and vomiting, gastric electrical stimulation may be considered in non-opioid users (122), although not endorsed by all guidelines (123). Enteral feeding can be indicated in severe weight loss or malnutrition (17,121,123). Benefits of surgical interventions remain uncertain (122,123,121). Central modulators are not recommended for gastroparesis management (122,123).

Chronic constipation

The 2023 American Gastroenterological Association (AGA)/ACG guideline (127) made some useful recommendations on chronic idiopathic constipation (CIC) in adults, although not specifically associated with DAN. The guideline focused on otherwise healthy individuals and does not apply to children, pregnant women or individuals with opioid-induced constipation or malignancy (127).

Definition of functional constipation may vary in literature. According to the Rome IV criteria for adults (128), diagnosis requires symptoms for > 6 months, with at least two or more of the following manifestations occurring in at least 25% of defecations during the past three months: straining; hard or fragmented stools (Bristol 1-2); sensation of incomplete evacuation; sensation of anorectal obstruction; manual maneuvers to facilitate defecation; less than three spontaneous bowel movements per week; loose stools should rarely occur without the use of laxative and criteria for irritable bowel syndrome are not met (128).

A detailed clinical history, including dietary habits, and complementary tests are required to exclude other causes of constipation, such as medications, mechanical obstruction, metabolic disorders, myopathies and neurologic diseases (17,129).

The panel suggested the use of fiber supplementation with low certainty of evidence (127). Adjusting a low fiber intake through diet or supplements can be used as first-line therapy.

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Only psyllium appears effective, while data on bran and inulin supplementation are limited. Adequate hydration should accompany fiber intake (127).

Polyethylene glycol (PEG) is strongly recommended as an osmotic laxative after or combined with fiber supplementation, with moderate certainty of evidence. Evidence supports PEG efficacy in CIC for up to six months, while long-term efficacy and safety data remain unavailable (127).

Magnesium oxide was suggested with very low certainty of evidence (127), however, should be avoided in patients with renal dysfunction due to the risk of hypermagnesemia. Lactulose may be considered in adults unresponsive to fiber and over-the-counter therapies, although the certainty of evidence was also very low (127).

Short term use (≤4 weeks) of stimulant laxatives such as bisacodyl or sodium picosulfate as rescue therapy had a strong recommendation with moderate certainty of evidence. Long-term use is probably appropriate, but lacks supporting data (127). Senna was suggested with low certainty of evidence, and long-term safety data are also missing (127).

Patients unresponsive to over-the-counter agents, other agents such as lubiprostone, plecanatide, linaclotide and prucalopride had specific recommendations by the panel (127). For refractory cases, management should follow specific guidelines (129).

Chronic diarrhea

Diabetic diarrhea is typically chronic, painless, and watery, often occurring at night (121). A detailed clinical history is essential, with careful evaluation of medications use such as metformin, GLP1- RAs, lipase inhibitors, sugar alcohols (*e.g.*, sorbitol) (17). The temporal relationship between drug initiation and the symptom onset must be well investigated.

As diabetic diarrhea is an exclusion diagnosis, the 2019 AGA clinical practice guideline's recommendations for functional diarrhea (130), are useful to exclude other causes of chronic diarrhea in immunocompetent patients (130). They include fecal calprotectin or lactoferrin as screening tools for inflammatory bowel disease, testing for *Giardia* and screening for celiac disease (130).

Delayed small intestine transit may lead to small intestinal bacterial overgrowth (SIBO), a cause of diarrhea. Colonic involvement is also frequent (131).

Management of lower GI symptoms also includes glycemic control and dietary adjustments. Antidiarrheal agents (*e.g.*, loperamide) may be effective but may worsen constipation and upper GI symptoms. SIBO is commonly treated with antibiotics (18,35,121).

Genitourinary autonomic neuropathy

Voiding is a coordinated process requiring sustained detrusor contraction, relaxation of the bladder neck, sphincter and urethra, and absence of outlet obstruction (132). These functions are regulated by the ANS through a neural network involving peripheral nerves, spinal cord, and CNS (133,134). The SNS facilitates bladder storage by inhibiting the detrusor activity and stimulating the trigone and proximal urethra contraction (134), while the PNS mediates voiding through detrusor contraction and sphincter relaxation (4).

In diabetes, GU autonomic neuropathy manifests mainly as sexual dysfunction and LUTS (7), after exclusion of organic causes such as hypogonadism, medication effects, prostatic disease, and pelvic disorders (7,126,135-137).

Sexual dysfunction

In men with diabetes, ED occurs earlier, is more severe, and often less responsive to treatment than in the general population (138). Male dysfunction may also involve orgasmic, ejaculatory, and libido abnormalities (21).

In T1D, good glycemic control reduces ED incidence, while evidence in T2D is less consistent (7). Lifestyle measures such as weight optimization, BP and lipid control, and smoking cessation can improve ED (7). First-line therapy includes phosphodiesterase type 5 inhibitors (tadalafil, sildenafil, vardenafil). Intracavernosal or intraurethral prostaglandins, vacuum devices, and penile prostheses are reserved for advanced cases (7,138,139).

In women, sexual dysfunction manifests as reduced libido, arousal and lubrication, as well as dyspareunia (7,138). Management includes glycemic control,

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treatment of urinary/genital infections, lubricants or moisturizers, pelvic floor physiotherapy, and psychological support (19,140).

LUTS

Diabetic cystopathy is initially characterized by reduced bladder sensation and increased capacity, often accompanied by overactive bladder (OAB) symptoms including urinary frequency, urgency and UI (140).

With progression, detrusor impairment leads to incomplete emptying and underactive bladder, culminating in combined storage and voiding dysfunction (140,141). This manifests as delayed initiation of micturition, reduced bladder sensation, increased post-void residual (PVR), urinary retention, overflow incontinence, and recurrent UTI (140).

Additional LUTS include nocturia, weak urinary stream and hesitancy (7,21). In men, concomitant benign prostatic hyperplasia (BPH) is common and may overlap symptoms with LUTS (140,142).

Diagnosis of LUTS is predominantly clinical (1,7). The European Association of Urology (EAU) (136,143) and the National Institute for Health and Care Excellence (NICE) (137,144) guidelines recommend initial evaluation with a comprehensive medical history, validated symptom questionnaires, and a ≥ 3 days bladder diary documenting volume and timing of voids. These recommendations apply to the general population, not specifically to individuals with diabetes.

Individuals with diabetes with recurrent UTI, pyelonephritis, UI or a palpable bladder should undergo evaluation of urinary dysfunction, including urinalysis and assessment of renal function (4).

When LUTS are associated with UTI, reassessment is required after antibiotic treatment (143). Urinary tract or prostate ultrasound with PVR measurement may be indicated (136,137,143,144). A complete urogynecological examination is advised to rule out structural abnormalities, along with a pelvic floor assessment to evaluate muscle contraction (135,138,144). Urodynamic testing and cystoscopy are reserved for selected cases as indicated by specialist (4,136,143,144,144).

Treatment of LUTS includes behavioral, pharmacological, and, in selected cases, surgical approaches (140).

Behavioral strategies involve fluid restriction at night to minimize nocturnal polyuria, moderation of caffeine and alcohol intake, voiding techniques (relaxed or double voiding, urethral milking), bladder training, distraction techniques for urgency control, constipation management (136,137), and, in women, weight loss and pelvic floor muscle training (143,144). Intermittent catheterization may be required in significant voiding dysfunction with severe upper urinary tract involvement to preserve renal function, and medication review is advised to discontinue drugs that worsen LUTS, particularly diuretics and drugs such as amitriptyline (136,140,145,146).

Pharmacological treatments are recommended for bothersome moderate-to-severe LUTS, with comorbidities, concomitant treatments and sex-specific factors guiding treatment choice (136,137,143,144).

In men, α1-adrenergic antagonists (doxazosin, tamsulosin, alfuzocin, terazocin, silodosin and naftopidil) provide rapid relief of storage and voiding symptoms (136,137), but may cause asthenia, dizziness, and OH, requiring caution in patients with CAN, CVD or concomitant vasoactive drugs (137,147,148).

5α-reductase inhibitors (dutasteride and finasteride) may be considered in prostatic enlargement, elevated PSA (Prostate-Specific Antigen), or other progression risk factors (*e.g.*, older age), as they reduce prostate volume (137,148) and the risk of acute urinary retention (148).

Combination therapy offers superior efficacy but higher adverse events, and should be reserved for moderate-to-severe LUTS with progression risk (137,148). For patients with refractory symptoms, the EAU and NICE guidelines provide specific recommendations (137,143,144,148).

According to the EAU guidelines, direct (bethanechol, carbachol) and indirect (neostigmine, distigmine) parasympathomimetics are not recommended for underactive bladder (148).

In cases of OAB and urgency UI/storage symptoms, antimuscarinic (*e.g.*, oxybutynin, tolterodine and

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solifenacin) or β3-adrenergic agonists (vibegron or mirabegron) are the main options when conservative measures fail (137,143,144,148). Antimuscarinics may cause dry mouth, constipation and cognitive effects, requiring caution in older or cognitively impaired patients (144,148).

Individuals with diabetes also have a higher risk of asymptomatic bacteriuria (149), but screening or treatment is not recommended by the Infectious Diseases Society of America guideline (150), given the absence of benefit and risk of antimicrobial resistance and *Clostridioides difficile* infection (151).

SGLT2i may increase the risk of urogenital infections (particularly fungal) (152-154), and enhance urine output, potentially worsening LUTS such as frequency, urgency and nocturia (155,156). Evidence on the safety and efficacy of SGLT2i in individuals with structural or functional urinary tract abnormalities remain limited (157). Thus, LUTS severity should be assessed before SGLT2i initiation, and treatment individualized, particularly in severe cases with indwelling catheters, ileal conduits, recurrent UTI, or high PVR, with close follow-up to minimize complications (157,158).

CONCLUSION

In conclusion, the ANS regulates multiple organs and systems through an extensive network of afferent and efferent nerve fibers. DAN is a heterogeneous condition with a broad spectrum of manifestations – including CV, GI, and GU involvement – progressing from early, asymptomatic small-fiber involvement to severe, advanced manifestations. DAN is a frequent but underrecognized complication, with substantial impact on morbidity and mortality. Early diagnosis is essential for CV risk stratification, optimization of therapeutic targets, and timely symptom management. Although no disease-modifying therapies are currently available, management strategies are primarily symptomatic, aiming to alleviate clinical manifestations. Current recommendations emphasize glycemic control, comprehensive CV risk management, and individualized treatment of clinical manifestations to improve quality of life and potentially influence long-term outcomes.

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special issue
Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

invited review

Clinical dermatoendocrinology: saving lives by looking at the skin

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ABSTRACT

The separation of the interior from the exterior environment through the skin was fundamental for the evolutionary progression from prevertebrates into vertebrates. The development of the skin also established an internal environment controlled by hormones. The skin is influenced by different hormones; it is also the largest endocrine organ, producing several hormones. Skin inspections often save lives from skin cancer but can also diagnose potentially deadly endocrine diseases. The objectives of this review were to describe the emergence and definition of dermatoendocrinology and to focus on the clinical diagnosis of cutaneous manifestations of endocrine disorders, some of which are potentially fatal. This narrative review was based on a comprehensive search using the term "dermatoendocrinology" since its creation in 2001 in the PubMed® database. Subsequently, a complementary search was performed with combinations of the keywords "skin", "insulin", "diabetes", "thyroid", "adrenal", "sex hormones", "parathyroid hormone", and "growth hormone." A total of 111 articles were included. The cutaneous manifestations of Itabaianinha syndrome (isolated growth hormone deficiency) and five anecdotal cases that enabled life-saving therapeutic measures are reported. The dermatoendocrine conditions described include acanthosis nigricans and androgenetic alopecia (insulin resistance), necrobiosis lipoidica diabeticorum and granuloma annulare (diabetes), pretibial myxedema (hyperthyroidism), xerosis cutis (hypothyroidism), purple striae and facial plethora (hypercortisolism), hyperpigmentation (primary adrenal insufficiency), dryness and urogenital atrophy (hypoestrogenism), hirsutism and virilization (hyperandrogenism), pruritus and calcium deposition (hyperparathyroidism), thinness, wrinkling, and reduced sweating (growth hormone deficiency), and thick oily skin with excessive sweating (acromegaly). Skin inspection allows the diagnosis of serious endocrinopathies.

Keywords: Skin; endocrinology; dermatology

INTRODUCTION

In this review, we aim to reaffirm the currently overlooked concept that skin examination allows the diagnosis of endocrine diseases, whose treatment might be life-saving. We begin by describing the evolutionary relationship between skin and hormones, followed by a brief overview of the cutaneous anatomy and physiology, as well as the origins of dermatology, endocrinology, dermatoendocrinology, and neuroendocrinology of the skin. We conclude by developing the concept that endocrinologists, dermatologists, and general practitioners should routinely examine the skin, as it offers valuable insights into endocrine diagnostics relevant to their patients' quality of life and lifespan.

The skin was the earliest organ to evolve, as evidenced by the existence of proto-skin in sponges (1). The separation between the internal and external environments provided by the skin was fundamental for the evolutionary progression from prevertebrates into vertebrates (2). In humans, the skin is composed of epidermis, dermis, and hypodermis. The epidermis

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is the outermost stratified layer, consisting of 95% squamous epithelial cells (keratinocytes) at various stages of differentiation (including the basal, spinous, granular, lucid, and corneal layers) in a cycle that lasts 2 to 4 weeks and concludes with cutaneous desquamation. Other cell types making up the epidermis include melanocytes, Langerhans cells (which serve immunological functions), and Merkel cells (which play a role in sensory perception). Melanocytes are derived from the neural crest and are distributed in the basal layer of the epidermis (one melanocyte is surrounded by approximately 36 keratinocytes), forming a complex network of interacting regulatory pathways that are essential for melanin's protective effect against DNA-damaging ultraviolet (UV) rays (3). The basement membrane of the epidermis is attached to the dermis, which is rich in connective tissue with blood vessels, hair follicles, nerves, and immune cells. Structural extracellular matrix proteins – including collagen, elastin, various glycoproteins, and proteoglycans – provide the skin with tensile strength, resilience, and turgor and serve as a storage site for growth factors. Dermal connective tissue connects all cells and tissues of the skin as a functional organ (4). Fibroblasts are the main component of connective tissue; they produce and organize structural extracellular matrix proteins, interact with endogenous stem cell niches in the skin, and are essential for skin homeostasis and senescence (4,5). The subcutaneous fat tissue, which consists predominantly of adipocytes, plays a crucial role in regulating body temperature and providing mechanical protection to the inner organs. The evolution of bipedal posture may have driven the development of scalp hair to minimize heat gain from solar radiation, particularly in large-brained hominids. Hair undergoes a process consisting of three phases: the growth phase (anagen), lasting 2 to 6 years and comprising 90% of scalp hairs; the apoptosis phase (catagen), lasting 3 weeks and comprising less than 1% of scalp hairs; and the resting phase (telogen), comprising 10% of scalp hairs and not involving proliferation or apoptosis. Some authors also identify an additional phase, known as the exogen (or shedding) phase, during which the mature hair shaft is shed as new hair begins to grow (6). Another essential acquisition for thermoregulation is the activity of sweat glands. The eccrine glands open directly onto the skin surface and are distributed throughout the body. Apocrine glands are associated with hair follicles and are found in the armpits, anogenital region, eyelids, external auditory canals, and breasts. Sebaceous glands protect and moisturize the skin, hair, and other parts of the body through the production of sebum. They consist of the acinus and its sebocytes, which connect to the surface of the epidermis through an excretory duct that runs continuously with the hair follicle wall.

The evolution of skin established an internal environment controlled by secretions (homeostasis), which evolved into the concept of hormones. Although the origins of dermatology and endocrinology predate the birth of Jesus Christ, the scientific period for both specialties dates back to the 19th century. Scientific dermatology began in 1878 with the publication of the first section of the masterpiece On Cutaneous Diseases by Robert Willan (7). Endocrinology, in turn, emerged in the second half of the same century, building on the experimental studies conducted by Claude Bernard (1813-1878), the clinical observations of Thomas Addison (1793-1860), and the experimental and clinical studies of Brown-Séquard (1817-1894) (8).

Dermatologists and endocrinologists have long been fascinated by the complex relationship between hormones and human skin in health and disease (8). However, it was not until 2001 that dermatoendocrinology was established in Berlin with the founding of a working group by Christos Zouboulis, Ralf Paus, and Markus Böhm, within the *Arbeitsgemeinschaft Dermatologische Forschung* (9,10). This fundamental milestone established the concept that the skin is not only influenced by several hormones but is also the largest endocrine organ in the body, producing a series of hormones that have systemic or local action and express a myriad of cognate receptors, which are exposed to autocrine, paracrine, and intracrine mechanisms (11). Since then, dermatoendocrinology has been consolidated as the field that explores how hormones influence the skin and how skin conditions may reveal underlying endocrine disorders. It encompasses the research and

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clinical practice of understanding and managing skin conditions with an endocrine component, recognizing that the skin can reflect underlying hormonal imbalances (12). A current example can be found in aging research, in which the skin is used in models of mini-organs that not only respond to systemic hormones via cognate receptors but also synthesize and metabolize many of these hormones (12). In this sense, neurohormones produced within hair follicles on the human scalp exhibit mechanisms similar to those produced by the specialized hypothalamic-pituitary-adrenal (13) and hypothalamic-pituitary-somatotropic axes (14). The study of these interactions is fundamental for understanding skin physiology and pathology, as well as for effectively treating dermatological conditions and delaying skin and overall aging through the development of new anti-aging therapies (4).

Currently, dermatoendocrinology and skin neuroendocrinology are venturing into new frontiers that neither conventional endocrine research nor investigative dermatology has explored extensively (9). These frontiers will be partially covered in the present article, which will describe the most relevant clinical interactions between the skin and the endocrine glands, with emphasis on the somatotropic system (2,15-20). This article is intended for general endocrinologists, dermatologists, and general practitioners and will not address the dermatological manifestations of rare hereditary endocrine syndromes, as it is not intended to be an exhaustive description of the cutaneous manifestations of endocrine diseases or to recommend endocrine and dermatological treatments for these conditions.

Skin inspection is often used to save lives from skin cancer (21,22), but it can also diagnose potentially deadly endocrine diseases, such as tanned skin suggesting the diagnosis of primary adrenal insufficiency.

SUBJECTS AND METHODS

This narrative review summarizes quantitative studies without referencing the statistical significance of the results (23) and was conducted by one of the authors. based on a comprehensive search using the term "dermatoendocrinology" since its inception in 2001 in the PubMed® database. A complementary search was subsequently performed using combinations of the keywords "skin", "insulin", "diabetes", "thyroid", "adrenal", "sex hormones", "parathyroid hormone", and "growth hormone." Additional articles were identified from the references cited in the retrieved articles. The inclusion criteria were peer-reviewed articles published in English and Spanish. Exclusion criteria included articles with unavailable abstracts and conference abstracts. A total of 111 articles were retrieved, of which 13 were published by the present study's authors. The final quality check of the literature selected for analysis was conducted by another authors.

This narrative review is complemented by our research experience with cutaneous findings in patients with Itabaianinha syndrome, characterized by isolated growth hormone (GH) deficiency (GHD) (2,15-20), along with nearly 25 years of clinical experience. Among the authors, the youngest clinician is an endocrinologist with 7 years of practice who holds both a master's and a doctoral degree in the field, and the oldest clinician has 47 years of clinical practice. The authors also include a dermatologist, with 27 years of practice, who completed medical residency and holds a master's degree in science. All authors except for one, work at the *Hospital Universitário de* Aracaju at the *Universidade Federeal de Sergipe*. From the patients receiving care in this institution, we selected anecdotal cases to demonstrate that a correct diagnosis enabled potentially life-saving therapeutic measures. The inclusion criteria were live patients with accurate clinical and biochemical diagnoses who were receiving appropriate therapeutic interventions (diet, medication, or surgery when indicated) and undergoing regular follow-up.

RESULTS

Table 1 presents some of the skin findings observed in major hormonal imbalances. **Figures 1 to 5** display cases in which an accurate diagnosis led to life-saving therapeutic measures. Below, we describe important dermatoendocrine conditions related to the endocrine glands and the somatotropic system.

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Table 1. Skin findings in major hormonal imbalances

Insulin resistance	Acanthosis nigricans, acrochordons, xanthelasma, eruptive xanthomas, androgenetic alopecia
Diabetes mellitus	Necrobiosis lipoidica diabeticorum, granuloma annulare, bullae, diabetic dermopathy, ulcers, infections
Hyperthyroidism	Thin skin, fine and downy hair, hyperhidrosis, facial flushing, palmar erythema, thyroid acropachy, jaundice, urticaria, onycholysis, alopecia areata
Hypothyroidism	Xerosis cutis, myxedema, pallor, carotenemia, vitiligo, alopecia areata, trichodystrophy, madarosis, frail nails, onycholysis
Hypercortisolism	Purple striae, facial plethora, acne, folliculitis, hirsutism, acanthosis nigricans, fungal infections, easy bruising
Hypocortisolism	Tanning, mucosal hyperpigmentation, vitiligo, loss of axillary and pubic hair
Hypoestrogenism	Dryness, itching, thinning, atrophy, wrinkling, sagging, urogenital atrophy, poor wound healing, hidradenitis suppurativa, reduced hair growth, increased facial hair growth
Hyperandrogenism	Androgenetic alopecia, sebaceous gland hypertrophy, thick skin, acne vulgaris, seborrhea, hirsutism, temporal baldness, acanthosis nigricans
Hyperparathyroidism	Pruritus, calcium deposition
Hypoparathyroidism	Hyperkeratotic and eczematous skin, brittle nails, sparse hair, mucocutaneous candidiasis
Growth hormone Deficiency	Thin and wrinkled skin, normal hydration and reduced sweating, decreased or normal sebum secretion, lower resistance and elasticity
Acromegaly	Thick skin, acanthosis nigricans, acrochordons, increased sebum and sweating, oily skin, acne

Endocrine pancreas

Acanthosis nigricans is the most common dermato-endocrine manifestation of insulin resistance. It is characterized by symmetrical, hyperpigmented, velvety plaques with poorly defined borders, primarily affecting intertriginous areas (neck, axilla, elbow, and groin) (24), but it can also involve finger joints, particularly in Latinos, in whom it serves as an early marker of insulin resistance even in the absence of overweight or obesity (25). Insulin resistance is a crossroads of common diseases, including obesity, type 2 diabetes, hypertension, metabolic syndrome, dyslipidemia, and cancer (liver, pancreatic, endometrial, colorectal, and postmenopausal breast cancer); it is also involved in several diseases such as polycystic ovary syndrome, androgenetic alopecia, nonalcoholic steatohepatitis (26,27), and congenital (**Figures 1A and 1B**) or acquired lipodystrophies (27,28), among other serious conditions (**Figure 2**).

Another finding frequently associated with insulin resistance is the presence of acrochordons (or skin tags), which are benign, pedunculated skin growths commonly found in the neck, axillary, and groin regions (25,29). The presence of multiple acrochordons (eight or more) has been observed to be more sensitive than acanthosis nigricans in identifying patients with hyperinsulinemia (30). Hyperinsulinemia stimulates IGF-I receptors on fibroblasts' cell surface (31),

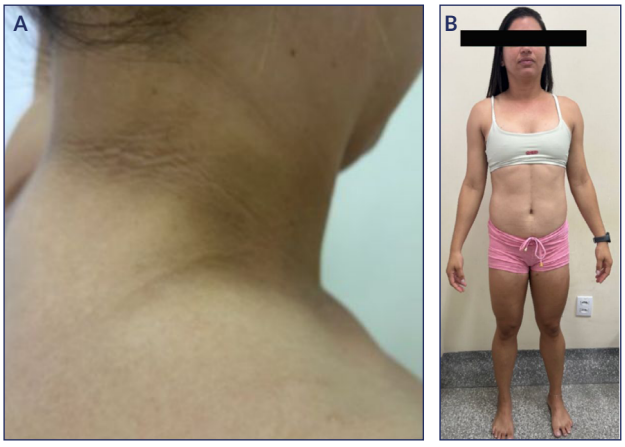


Figure 1. (**A and B**). Acanthosis nigricans in a woman with congenital partial lipodystrophy and severe hypertriglyceridemia, who exhibits acromegalic facies, truncal adiposity, muscle hypertrophy, polycystic ovary syndrome, liver steatosis, prediabetes, and hypertension. The diagnosis of congenital partial lipodystrophy led to intensified treatment, which improved the patient's comorbidities and quality of life, and certainly prolonged her lifespan.



Figure 2. Axillary and cervical acanthosis nigricans and bilateral gynecomastia in a male patient with obesity and hypogonadotropic hypogonadism. Treatment of hypogonadism and obesity improved the patient's acanthosis nigricans and probably reduced his cardiovascular risk.

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although other signaling pathways may participate in this process, including the epidermal growth factor cascade (32) and the leptin pathway (33). Multiple skin tags occur in about half of patients with acromegaly, suggesting GH dependence (34,35). However, we reported one isolated acrochordon in an individual with congenital isolated GHD who exhibited increased insulin sensitivity (17), emphasizing that it is the multiplicity, rather than the mere presence of skin tags, that suggests insulin resistance, as found in acromegaly. Other cutaneous conditions have also been reported in association with insulin resistance (and increased cardiovascular risk), such as ear lobe creases (by the involvement of structures beneath the skin), xanthelasma (associated with hypercholesterolemia), and eruptive xanthomas (associated with hyperchylomicronemia and severe hypertriglyceridemia) (25).

Another finding associated with insulin resistance and unfavorable cardiovascular outcomes is androgenetic alopecia, characterized by diffuse thinning of crown hair in women, with preservation of the frontal hairline in most, but not all cases (36). Androgenetic alopecia may be also associated with hyperandrogenic conditions other than insulin resistance in women, including polycystic ovaries, adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome, and metabolic dysfunction associated with steatotic liver disease, which require preventive strategies with lifestyle modifications and pharmacological measures to avoid progression to liver cirrhosis and type 2 diabetes along with its costly complications (37,38). The Food and Drug Administration (FDA)-approved therapeutic options for androgenetic alopecia include topical minoxidil at 2% for women and 5% for men, oral finasteride (for men), hair restoration surgery, and low-level light therapy (39). Non-FDA-approved therapeutic options for men include oral dutasteride, while for women, options include cyproterone acetate, spironolactone, and topical estradiol (39).

Androgenetic alopecia must be distinguished from alopecia areata, an autoimmune disease that causes patchy hair loss on the scalp, face, and other parts of the body. It must also be differentiated from telogen effluvium, a type of non-scarring, often acute (but sometimes chronic) alopecia characterized by diffuse and excessive loss of resting or telogen hair (10 to 15% of scalp hair) following metabolic stress, hormonal changes, or medication use. Stress-induced alopecia involves multiple causes and is managed by a multidisciplinary team, with emphasis currently placed on the role of hormones from the hypothalamic-pituitary-adrenal axis (corticotropin-releasing hormone [CRH], ACTH, and cortisol) (40,41).

Skin manifestations can occur in most (if not all) patients with diabetes mellitus and are linked to some degree to glycemic control. They include necrobiosis lipoidica diabeticorum (erythematous, non-scaly papules in the pretibial area that evolve into dermal and epidermal atrophy and ulcers), granuloma annulare (quite similar to necrobiosis lipoidica diabeticorum but without epidermal atrophy), diabetic dermopathy (characterized by pigmented pretibial papules that begin as pink, 0.5 to 1 cm patches in the pretibial and lateral calf areas and progress to brown hyperpigmentation and surface atrophy with fine scaling) (**Figure 3**), ulcers, diabetic bullae, and thick skin. Several cutaneous infections – by candida, dermatophytes, and bacteria such as *Staphylococcus aureus*, beta-hemolytic streptococci (impetigo, folliculitis, furunculosis, carbuncles, ecthyma, cellulitis, and erysipelas), and *Pseudomonas aeruginosa* (malignant external otitis) – can also occur (42).

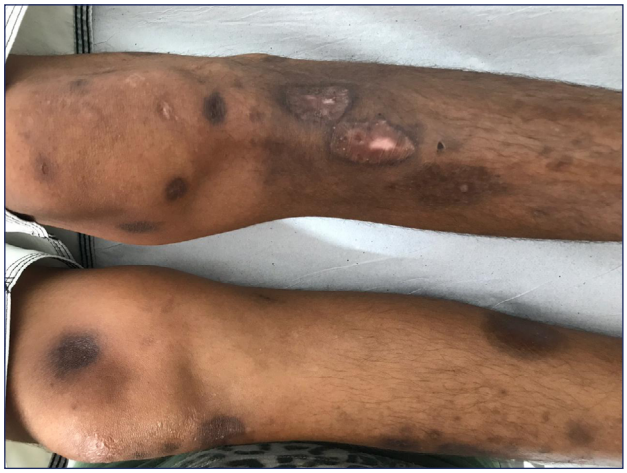


Figure 3. Diabetic dermopathy in a male patient with poorly controlled type 1 diabetes. Intensification of the insulin regimen led to an improvement of the lesions and, subsequently, better metabolic control, with benefits in terms of future complications.

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Thyroid

Numerous interconnections exist between the skin and the thyrotropic axis, with cutaneous manifestations being conspicuous manifestations of thyroid hormone dysregulation (6). Hair follicles express thyrotropin-releasing hormone (TRH) and its receptor, as well as TSH and its receptor; the epidermis is also an extrapituitary source of TSH and a target for its effects (43,44). However, thyroid hormone action on the skin is primarily mediated by thyroid hormone receptors present in sebaceous glands, fibroblasts, smooth muscle cells, and vascular endothelial cells, as well as various cell types that constitute the hair follicle. Notably, T3 stimulates the growth of epidermal keratinocytes and dermal fibroblasts and inhibits the synthesis of hyaluronate (6).

Pretibial myxedema (or thyroid dermopathy) – characterized by well-demarcated pink or purple atrophic or transparent papules – is a well-known manifestation of Graves' disease, with a 4:1 female-to-male ratio. Commonly coexisting with thyroid autoimmune ophthalmopathy, pretibial myxedema seems to arise from TSH receptor stimulation by substantially elevated antibodies in skin fibroblasts (45), most commonly confined to the pretibial area (44). Other cutaneous findings in hyperthyroidism include thin (yet not atrophic) skin, fine and downy hair (46,47), hyperhidrosis, facial flushing, and palmar erythema. More rare skin manifestations of hyperthyroidism include thyroid acropachy (digital swelling and nail clubbing associated with thyroid ophthalmopathy and dermopathy) (48), jaundice (likely due to an imbalance between hepatic oxygenation and blood flow reducing bile transport and cholestasis) (49), onycholysis or Plummer's nails (distal separation of the nail plate from the nail bed), alopecia areata (hair loss without scarring, found in both Graves' disease and Hashimoto's thyroiditis) (50), chronic (51) or acute urticaria (due to hyperthyroidism or use of antithyroid agents) (52), and urticarial vasculitis (53).

Xerosis cutis (excessively dry and scaly skin) is the most common skin finding in hypothyroidism, whereas myxedema (thyroid dermopathy) is the most classic. The former results at least partially from a reduction of T3 binding to its receptor, causing hyperkeratosis (54), which occasionally takes on the appearance of ichthyosis (large fish-like thick scales that are adherent to the skin). Patients with myxedema have non-pitting edema in periorbital and pretibial regions (with abundant diffuse mucin within the dermal fenestrations as large amounts of glycosaminoglycans in the dermis), together with facial changes and sometimes macroglossia (55). Other skin manifestations of hypothyroidism include pallor (due to cutaneous vasoconstriction) and carotenemia (due to deficient conversion of carotene into vitamin A). The yellowish appearance of carotenemia can be mistaken for jaundice; one way to distinguish between the two is the involvement of the sclera, which is spared in carotenemia but not in jaundice.

Patients with autoimmune hypothyroidism (Hashimoto's thyroiditis) may develop vitiligo, an autoimmune destruction of melanocytes and hypopigmentation (56). The most common hair manifestations of hypothyroidism are alopecia and trichodystrophy, which is characterized by dry, coarse, brittle, and slow-growing hair that sheds easily (6). Alopecia develops due to an increased amount of hair in the telogen phase. Patients may also exhibit madarosis, a specific type of alopecia characterized by the loss of the lateral third of the eyebrows and the loss of eyelashes. After starting levothyroxine treatment, patients with hypothyroidism may initially experience worsening of alopecia as more hair sheds while follicles transition from the telogen to the anagen phase (57). The most common nail manifestations in hypothyroidism are increased fragility, slow growth, thinning, onycholysis, and brittleness (58).

Adrenal

The skin is a barrier between the external and internal milieu and is, therefore, exposed to various external stressors, including UV radiation, injury, and foreign antigens, which can lead to an inflammatory response. Notably, the skin can synthesize glucocorticoids *de novo*. Recent research has revealed that these glucocorticoids – synthesized locally by keratinocytes mainly but also by melanocytes, dermal fibroblasts, and hair follicles – are likely to act in a paracrine or autocrine manner and have important physiological roles in local homeostasis,

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cellular development, and immune cell activation (59). Importantly, keratinocytes can also synthesize and activate cortisol (60). In fact, the skin expresses all elements regulating the activity of the hypothalamic-pituitary-adrenal axis, including CRH, urocortin, and proopiomelanocortin (POMC), along with their products ACTH, alpha-melanocyte-stimulating hormone (MSH), and beta-endorphin (59). The presence of the corresponding receptors on the same cells suggests that paracrine or autocrine mechanisms of action are involved (61). Recent evidence suggests that angiotensin II plays a role in cutaneous wound healing by promoting the differentiation of bone marrow-derived mesenchymal stem cells into keratinocytes (62). Blocking of the mineralocorticoid receptor alleviates glucocorticoid-induced skin atrophy in healthy human skin explants (63).

Since at least 1% of the population chronically uses glucocorticoids as anti-inflammatory or immunosuppressive agents, cutaneous manifestations of exogenous hypercortisolism are quite common; however, these manifestations can also reveal severe cases of endogenous hypercortisolism (64). These include purple striae (**Figure 4**), facial plethora, acne, folliculitis, hirsutism (**Figure 5**), acanthosis nigricans, fungal infections, and easy bruising. Fortunately, most cases resolve with the discontinuation of exogenous glucocorticoids or within 1 to 2 years after resolution of endogenous Cushing's syndrome (65).

In primary adrenal insufficiency, the reduced cortisol production by damaged adrenal glands leads to increased production of CRH, POMC (an ACTH precursor), and MSH. Elevated MSH levels consequently trigger melanin synthesis by epidermal melanocytes, causing the tanning of the skin typical of Addison's disease (47,66). This hyperpigmentation is most prominent in areas exposed to sun or trauma, such as scars and nevi, as well as the axillae, areolae, perineum, and palmar creases. Hyperpigmentation of mucosal surfaces may also occur and can be observed on the tongue and the inner surface of the lip, as well as in the buccal, gingival, and vaginal mucosa (67,68). Vitiligo, caused by autoimmune destruction of dermal melanocytes, occurs in 10 to 20% of individuals with autoimmune adrenalitis (69). Women with Addison's disease may experience loss of axillary and pubic hair, which is caused by the loss of adrenal androgen production (70). This manifestation is also observed in secondary hypocortisolism (in the context of hypopituitarism), in which skin pigmentation is clearly lacking (71).

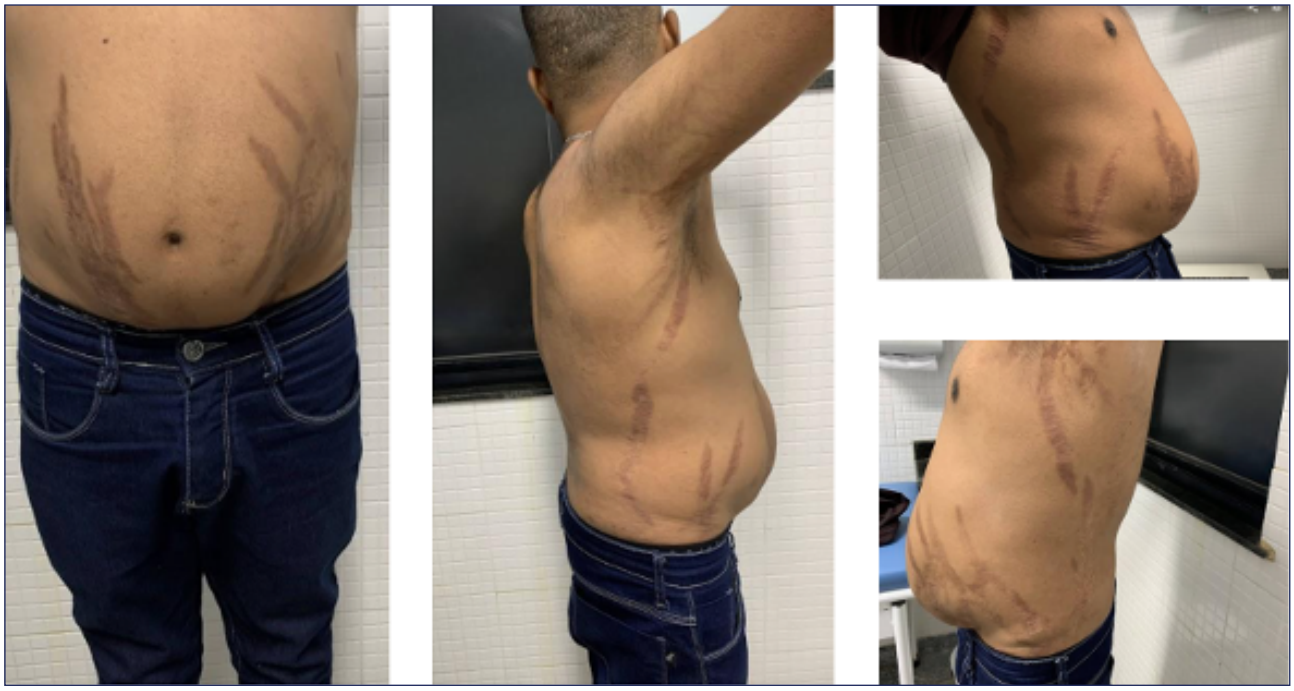


Figure 4. Broad, violaceous striae in a patient with adrenocorticotropic hormone-dependent Cushing's syndrome due to ectopic adrenocorticotropic hormone secretion (thymic neuroendocrine tumor). At 18 months after tumor resection, the disease remained in remission.

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Figure 5. Hirsutism and folliculitis in a female patient with central obesity, diabetes, and hypertension due to Cushing's disease. After pituitary surgery, the patient lost 17 kg, experiencing a drastic improvement in glycemic control and hypertension, along with a reduction in skin lesions.

Gonads

Estrogens contribute to increased skin thickness (through the production of collagen types I and III and transforming growth factor beta), moisture (by increased water retention in the stratum corneum and content of glycosaminoglycans, mucopolysaccharides and hyaluronic acid in the dermis), skin pigmentation (through estrogen receptors on melanocytes), and hair growth (by prolonging the anagen period through receptors on hair follicles that in turn express the enzymes 5-alpha reductase, aromatase, and 17-beta hydroxysteroid dehydrogenase, which are involved in estrogen synthesis) (44,72-74). Not surprisingly, pregnancy increases skin pigmentation and prolongs the anagen phase of hair growth. Additionally, estrogens and androgens stimulate sebum production (75).

Often overlooked, the cutaneous and mucosal manifestations of menopause are the most common dermatological findings associated with endocrine conditions and have a substantial negative impact on quality of life. They include dryness and itching, thinning and atrophy, wrinkling and sagging, poor wound healing, and reduced vascularity (75,76), along with an increased risk of other conditions such as hidradenitis suppurativa (due to relative androgen excess) and psoriasis (77). Hair symptoms of menopause include reduced hair growth and density on the scalp (including diffuse effluvium due to follicular rarefaction and female pattern androgenetic alopecia), disturbed hair quality and structure, and increased hair growth in facial areas (77,78). Estrogens also induce glycogen production by vaginal and cervical epithelial cells. The decline in estrogen at menopause results in urogenital atrophy and loss of vaginal epithelial cells (79), low levels of lactobacilli, fewer antimicrobial and anti-inflammatory agents, and increased susceptibility to mucosal lesions (80) and dyspareunia, further worsening quality of life. As in other dermatoendocrine conditions, treatment of the endocrine condition (hormone treatment) is expected to reverse the dermatological manifestations.

Progesterone can also influence hair follicle growth through central action (inhibitory effect on luteinizing hormone [LH] secretion, causing a decrease in thecal synthesis of androgens), as well as action on the hair follicle, decreasing the conversion of testosterone to dihydrotestosterone (through inhibition of 5-alpha reductase activity) (81). The primary role of progesterone is to counteract the effects of estrogen on the endometrium (82). It is unclear whether progesterone deficiency may contribute to the clinical manifestations of menopause-related relative hyperandrogenism or whether progesterone replacement may alleviate them.

The relative increase in androgens (testosterone and dihydrotestosterone) during menopause leads to miniaturization of hair follicles and decreased body and scalp hair, and may cause androgenetic alopecia (83), transforming small light vellus hairs in hormone-sensitive areas on the face into darker terminal hair follicles, as well as causing hypertrophy of the sebaceous glands (83,84).

Outside the universal context of menopause, hypoestrogenism (of ovarian or central origin) or hyperandrogenism (of gonadal, adrenal, or exogenous origin) may present characteristics similar to those of menopause, often with greater severity. Androgen-related disorders are most commonly due to increased sensitivity of the pilosebaceous unit to normal plasma androgen levels. Among the conditions associated with excess androgen, polycystic ovary syndrome is the most prevalent, affecting over one in ten women worldwide (83,85). Other causes of hyperandrogenism are congenital adrenal hyperplasia, ovarian and adrenal tumors, and drugs (anabolic steroids, progestogens, danazol) (70). Depending on the hyperandrogenism severity, the skin becomes

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thickened, rough and oily, with acne vulgaris and seborrhea, often accompanied by androgenetic alopecia, acanthosis nigricans, and hirsutism (increased androgen-dependent terminal hair growth on the lips, chin, chest, abdomen, linea alba, lower back, buttocks, inner thighs, and external genitalia). The most severe cases of hyperandrogenism are accompanied by virilization, which may include temporal baldness, voice deepening, muscle mass increase, feminine body contour loss, and clitoromegaly (70). In a retrospective analysis of 228 patients investigated for hyperandrogenism, 44.3% had hirsutism with elevated androgens and eumenorrhea, 27.6% had polycystic ovary syndrome (defined as hirsutism, elevated androgens, and oligomenorrhea), 22.4% had normal androgens with acne or alopecia and eumenorrhea, 3.1% had isolated low sex-hormone binging globulin (SHBG), 1.8% had nonclassical congenital adrenal hyperplasia, and 0.9% had ovarian tumors. In the study, the hirsutism score correlated positively with serum androstenedione, dehydroepiandrosterone sulfate, and salivary testosterone levels, and negatively with SHBG levels (86). Salivary testosterone had the highest correlation coefficient. These data illustrate the clinical and laboratory heterogeneity of hyperandrogenism (87).

Parathyroid

Cutaneous manifestations of hyperparathyroidism are scarce and include pruritus and calcium deposition. In hypoparathyroidism, the skin is dry, scaly, hyperkeratotic, eczematous, and swollen. The nails become dull and brittle, developing transverse grooves. The hair becomes coarse and sparse (70). Mucocutaneous candidiasis may be observed in autoimmune hypoparathyroidism (88). Chronic hypoparathyroidism can also cause brittle nails and dry, scaly skin, in addition to its well-known manifestations of lethargy, weakness, fatigue, cataract, personality changes, and eventual permanent brain damage – all of which could be prevented by observing the skin (89). Skin inspection may aid in the diagnosis of calciphylaxis, a serious condition associated mainly with hyperparathyroidism secondary to chronic renal failure, but rarely occurring in patients with normal renal function, with a 2-year mortality rate of 50 to 80% due to sepsis. It occurs due to calcium deposition in arterioles, leading to ischemic ulceration of the overlying skin (90). Parathyroidectomy may be justified in some cases (91).

Somatotropic system

As mentioned above, the separation between the internal and external environment through the skin was fundamental for the evolution of prevertebrates – whose growth occurs through extrapituitary circuits such as insulin, insulin similar growth, and local production of growth factors – into vertebrates – whose growth occurs through the somatotropic axis (*i.e.*, pituitary GH and circulating IGF-I) (2,15,16). As the skin covers the entire body, the somatotropic axis is expected to have a considerable influence on its structure and function. However, considering that the skin long preceded the appearance of vertebrae in animal evolution, the extrapituitary circuits, which preceded the somatotropic axis, may retain important actions on the skin in vertebrates and, consequently, in humans (2), as discussed below. All skin cell types express GH receptors, while keratinocytes and their stem cells also express the IGF-I receptor, enabling direct actions of GH or indirect actions involving the synthesis and modulation of IGF-I. This intricate process contributes to the homeostatic regulation of cell differentiation and proliferation within the skin tissue (11,92). In this sense, fibroblast-derived IGF-I is the main orchestrator of skin aging, integrating GH, estrogens, retinoids, and melatonin effects. The release of IGF-I is profoundly reduced in senescent fibroblasts (93). Insufficient IGF-I concentrations suppress cell growth, resulting in reduced ribosome numbers, suppressed protein translation, skin atrophy, and aging (4). Keratinocytes *per se* are unable to synthesize IGF-I; however, along with their stem cells, they express the IGF-I receptor, as stated previously. Therefore, keratinocytes, their stem cells, and other stem cells in the skin critically depend on the local IGF-I production by fibroblasts (4,11).

An analysis of cutaneous manifestations associated with conditions of GH excess or deficiency highlights the importance of the interrelationship between the somatotropic and integumentary

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systems. For example, individuals with acromegaly exhibit thickened skin, acanthosis nigricans, numerous pigmented acrochordons, and increased size and function of sweat and sebaceous glands, resulting in pronounced body odor, excessive sweating, oily skin, and acne (94-96).

The cutaneous consequences of GHD are difficult to clearly characterize, as they are often described in patients with acquired GHD who also have concomitant pituitary deficiencies that may not be adequately replaced (e.g., thyroid hormones, sex steroids, glucocorticoids) – all of which can greatly impact the skin. In this context, the skin of individuals with GHD is characterized by thinness, wrinkling, reduced sweating (97), and decreased sebum secretion (98-100). A cleaner model to assess the effect of GHD is represented by a cohort of individuals with severe isolated GHD caused by a homozygous mutation (c.57+1G→A) in the GH-releasing hormone (GHRH) receptor (GHRHR) gene (*GHRHR* OMIM n. 618157), described in the Brazilian city of Itabaianinha (*i.e.*, the Itabaianinha syndrome) (2,15-20,101,102). These individuals maintain consistently low levels of circulating pituitary GH and IGF-I throughout their lives (102), likely exhibiting compensatory extrapituitary circuits in important organs such as the skin. Due to the specific cause of GHD, these individuals have otherwise normal anterior pituitary function. They enjoy normal longevity (103) and quality of life (104) with high levels of physical activity (105) and abundant sun exposure through outdoor activities, which may influence skin health, photoaging, and the frequency of skin cancer (17).

These individuals with untreated isolated GHD exhibit wrinkled skin (2,15-19) and reduced sweating (20). The wrinkled skin reflects their lower skin resistance and elasticity (2), likely reflecting reduced content of collagen and elastin, which are crucial for the mechanical properties of the skin: collagen provides mechanical resistance to extension, while elastin allows deformation, providing a tailored mechanical response to accommodate body flexibility and movement and to prevent tears (106). The wrinkled skin in these individuals with isolated GHD seems to hold only cosmetic relevance, as they are very active in physical work and sports without easily tearing the skin (2,15-19). In contrast, sweating impairment has also been reported in patients with childhood-onset GHD (107), in men with adult-onset GHD (108), and in Laron's dwarfism, which is caused by GH insensitivity, thus featuring IGF-I deficiency (109). Another important skin finding in the Itabaianinha cohort is that the frequency of photodamage and skin cancer does not differ from that in local controls. The frequency of skin cancer appears to be related to a significant familial component rather than isolated GHD *per se* (2,17). Their melanin content is normal in the forearm but lower in the buttocks, with hydration and sebum levels similar to those of controls (2). The normal melanin content in sun-exposed areas supports adequate photosensitivity, allowing prolonged sun exposure with few sequelae in terms of photoaging and cancer. Not surprisingly, these individuals have normal serum levels of 25-hydroxyvitamin D (20) and actually seem to have a healthier aging bone phenotype compared with controls (110). They present normal skin hydration (2), despite severely reduced sweating (20), as previously reported in hypopituitarism with GHD (92,94), but with normal skin sebum content (2). Accordingly, patients with acromegaly have increased sebum secretion (94). While in acromegaly the amount of sebum production appears to be related to GH and IGF-I levels, as well as disease duration and severity (94), the decrease in sebum secretion in GHD is only partially reversible by GH treatment (100), suggesting that other hormonal deficiencies may contribute to this reduction (2). Interestingly, the sebum content among the Itabaianinha individuals with isolated GHD is very similar to that of Turkish normal individuals, in whom sebum content was measured using the same methodology (111). Therefore, hydration and sebum production may also be maintained by extrapituitary circuits, without being severely impaired by the reduction in pituitary GH and circulating IGF-I levels (2).

IMPLICATIONS FOR FUTURE RESEARCH

In this review, we have consolidated the concept that the skin, which is readily accessible through simple inspection, is a marker of endocrine diseases. The treatment of these endocrine diseases restores the skin and

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the general health of the affected individuals, potentially saving lives. This is particularly important in an era of digitized medical records, artificial intelligence, and online consultations. We encourage researchers to report other cases of cutaneous manifestations of endocrine diseases, with the same goal of saving lives and persuading journal editors of the importance of this effort.

In conclusion, through careful observation of the skin, we can diagnose and assess various endocrine diseases, improving patients' quality of life and extending their life expectancy.

Contributions: CSBO, BSS, RS, CRPO, and MHAO: conceptualization; methodology; investigation; supervision. CSBO, BSS, RS, CRPO, ACL, and MHAO: writing - original draft; writing - review & editing.

Ethics approval and consent to participate: the protocol for this research project and the statement of consent for the projects included in this short review were approved by the Institutional Review Board of the *Universidade Federal de Sergipe*. All participants were informed about the purpose of this study.

Consent to publish: written Informed Consent was obtained from the subjects for anonymous publication of their individual details. The consent form is held by the authors and is available for review if requested.

Consent for publication: all authors have reviewed the submitted manuscript, approved its content, and validated the accuracy of the data.

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special issue
Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

invited review

Hypercoagulability in Cushing's syndrome: past, present, future

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ABSTRACT

Cushing's syndrome is a chronic disorder characterized by prolonged glucocorticoid exposure, leading to significant multisystem complications. Multiple epidemiological studies have demonstrated a substantially elevated risk of venous thromboembolism in patients with Cushing's syndrome, including deep vein thrombosis and pulmonary embolism, particularly during active disease, the perioperative period, but more importantly also after biochemical remission. Hypercortisolism promotes a hypercoagulable state through multiple mechanisms, including persistent endothelial dysfunction, increased procoagulant factors such as von Willebrand factor and factor VIII, impaired fibrinolysis, and venous stasis. Additionally, common comorbidities in Cushing's syndrome, such as obesity, hypertension, and diabetes, further amplify thrombotic risk. Given these findings, recent consensus recommends thromboprophylaxis for most patients with Cushing's syndrome, with anticoagulation therapy initiated at diagnosis, continued perioperatively, and extended post-remission when appropriate in patients both after surgery and also in patients on medical therapy. Low molecular weight heparin is the preferred anticoagulant, while direct oral anticoagulants require further investigation in patients with Cushing's syndrome. Despite these recommendations, clinical practice varies significantly across centers and countries, highlighting the need for standardized thromboprophylaxis protocols. Future research should focus on refining risk stratification models, optimizing prophylaxis duration, and evaluating the long-term thrombotic risk in Cushing's syndrome remission. Additionally, studies exploring the safety and efficacy of direct oral anticoagulants and personalized medicine approaches through biomarker-driven strategies may further improve patient outcomes. Addressing these gaps will enhance thromboembolism prevention strategies in Cushing's syndrome and ultimately may reduce morbidity and mortality in this high-risk population.

Keywords: Cushing's syndrome; Thrombophilia; Thromboembolism

INTRODUCTION

Endogenous Cushing's syndrome (CS) is classified as adrenocorticotropic hormone (ACTH)-dependent or ACTH-independent. Adrenocorticotropic hormone-dependent cases (60% to 70%) are primarily due to Cushing's disease (CD) from a corticotroph pituitary adenoma (80% to 90%) or ectopic ACTH secretion (6% to 10%) linked to neuroendocrine tumors. Adrenocorticotropic hormone-independent CS (20% to 30%) is mainly caused by adrenal adenomas, carcinomas, or bilateral adrenal hyperplasia (1,2).

Cushing's syndrome is a chronic disorder caused by prolonged glucocorticoid exposure, with an estimated incidence of 2 to 8 cases per million people annually and a prevalence of 57 to 79 cases per million, though underdiagnosis is likely. It predominantly affects females, with a female-to-male ratio of approximately 4:1, and is most commonly diagnosed between ages 30 and 49, though cases have been reported from ages 5 to 75 (1,2).

Excess cortisol affects multiple systems, leading to hyperglycemia, muscle and bone loss, weight gain, hypertension, immune suppression, neurocognitive impairment, osteoporosis, and mood disorders such

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as depression (1). Mortality is higher than in general population and infections and cardiovascular disease are the leading causes of death, while thromboembolic events, including pulmonary embolism (PE) and deep vein thrombosis (DVT), also contribute significantly (1,3). Common CS-associated conditions, including hypertension, diabetes mellitus, osteoporosis with fractures, immune suppression, and cancer, are known risk factors for venous thromboembolism (VTE) (4,5). Additionally, surgery and hospitalizations, which are often necessary for CS treatment, further increase VTE risk (6). Surveys over the last decades showed that awareness is expanding on risk of VTE in patients with CS, however, albeit increasing, a low percentage of patients has been treated prophylactically, with large centers and countries dissimilarities (7). The Pituitary Society Consensus guideline suggested increased perioperative anticoagulants use in patients with CS; however, no consensus was reached regarding the duration of anticoagulation after remission (8).

This year, a Delphi position statement on thromboprophylaxis in endogenous CS recommends anticoagulant therapy at diagnosis, during the perioperative period, and for several months post-remission, provided there are no contraindications (9).

This review aims to summarize the epidemiology, pathophysiology, management strategies and future directions for VTE prevention in patients with CS.

EPIDEMIOLOGY

Multiple studies have demonstrated an increased risk of VTE in patients with CS, particularly during active disease, the postoperative period, and even after achieving remission. Interestingly, an increased risk of VTE events is also observed in patients with exogenous CS (10).

Active Cushing's syndrome

Patients with active CS are at a significantly increased risk for VTE compared to the general population. A Danish population-based study found that the risk of VTE in patients with CS was 2.6 times higher than in matched controls, with the highest risk occurring around the time of diagnosis (11). Similarly, a Swedish nationwide study reported a standardized incidence ratio (SIR) of 11.5 for thromboembolism during 3 years before diagnosis, suggesting that hypercoagulability is present even before treatment (12). A systematic review and meta-analysis by Wagner and cols. further supported these findings, reporting an odds ratio (OR) of 17.82 for VTE in patients with CS compared to the general population (13). Additionally, a nationwide cohort study conducted by our group found that the 5-year risk of VTE in patients with CS was nearly five times higher than in controls from the general population with a hazard ratio (HR) of 4.71 (14). The study identified age ≥ 60 years, hypertension, ischemic heart disease, kidney disease, and prior VTE as significant predictors of thromboembolic events (14). Collectively, these studies highlight that CS itself, independent of treatment, predisposes patients to a hypercoagulable state, likely due to increased levels of procoagulant factors such as von Willebrand factor (vWF) and factor VIII, as well as impaired fibrinolysis.

When compared to patients with nonfunctioning pituitary adenomas (NFPA), the risk of VTE remains higher in those with CS. A multicenter cohort study from the Netherlands found that patients with ACTH-dependent CS had a postoperative VTE incidence of 3.4% within 3 months of surgery, a significantly higher rate than in patients with NFPA, suggesting that the endogenous cortisol excess in CS contributes to a higher thrombotic risk compared to other pituitary disorders, even when controlling for risk related to surgical interventions (15).

The risk of VTE in CS has also been compared to that in patients with mild autonomous cortisol secretion (MACS), a condition characterized by subtle cortisol excess without overt CS symptoms in patients with adrenal adenomas. A retrospective analysis of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database found that postoperative VTE was significantly more common in patients with CS than in those undergoing adrenalectomy for MACS (2.6% *versus* 0.9%; $p = 0.007$). Patients with CS were younger, had higher body mass index, and were more likely to have diabetes mellitus ($p < 0.001$). They also experienced longer operative times and hospital stays ($p < 0.001$), which

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were associated with increased VTE risk (16). These findings indicate that mild cortisol excess carries a lower thrombotic risk than overt hypercortisolism, further reinforcing the role of cortisol excess in promoting coagulation abnormalities.

Perioperative period

The postoperative period represents a particularly high-risk window for VTE in patients with CS. A Danish study reported an extremely high risk of VTE in the 3 months following surgery, with a HR of 59.9 (11). Similarly, a Swedish nationwide study found a peak in thromboembolism incidence from diagnosis until 1 year post-remission, with an SIR of 18.3 (12). A large, US single-center retrospective study by Suarez and cols. confirmed an increased risk of thromboembolism 30 to 60 days postoperatively (17), while Manetti and cols. reported that this risk remained elevated beyond 1 year after pituitary surgery (18). Findings from the European Registry on Cushing's Syndrome (ERCUSYN) further emphasize the importance of postoperative risk, as 87% of the 95 VTE events recorded among 2,174 patients occurred after surgery, with nearly half occurring within 6 months (19). Key risk factors here included male sex, high urinary free cortisol levels at diagnosis, and multiple surgeries (19). A recent systematic literature review that included 25 relevant studies reported that the pooled incidence of postoperative VTE in patients undergoing transsphenoidal surgery for CD was 2% (58/2,997), while VTE-related mortality was 0.2% (6/2,077). No cases of postoperative VTE were reported in 191 patients undergoing adrenalectomy for benign ACTH-independent CS. Most reported VTE cases were DVT (48%), while cerebral venous sinus thrombosis was rare (6%). Perioperative thromboprophylaxis strategies varied significantly, but studies comparing different anticoagulation approaches suggested that extended prophylaxis was more effective than shorter-duration regimens (20). These studies highlight the need for extended thromboprophylaxis in the perioperative period, as patients with CS may remain at elevated risk for months following surgical intervention.

Disease remission

Even after achieving biochemical remission, patients with CS continue to face an increased risk of thromboembolism. A Swedish study found that while the SIR for VTE declined over time, it remained significantly elevated at 4.9 during long-term remission (12). Similarly, Manetti and cols. reported that coagulation abnormalities persist beyond 1 year postoperatively, suggesting that the prothrombotic state in CS may not fully resolve even after successful treatment (18). These findings underscore the need for ongoing monitoring and individualized risk assessment in patients with a history of CS, even after remission has been achieved.

Together, these studies highlight that patients with CS carry an elevated risk for VTE not only during active disease, but also risk is significantly increased in the postoperative period and even during long-term remission.

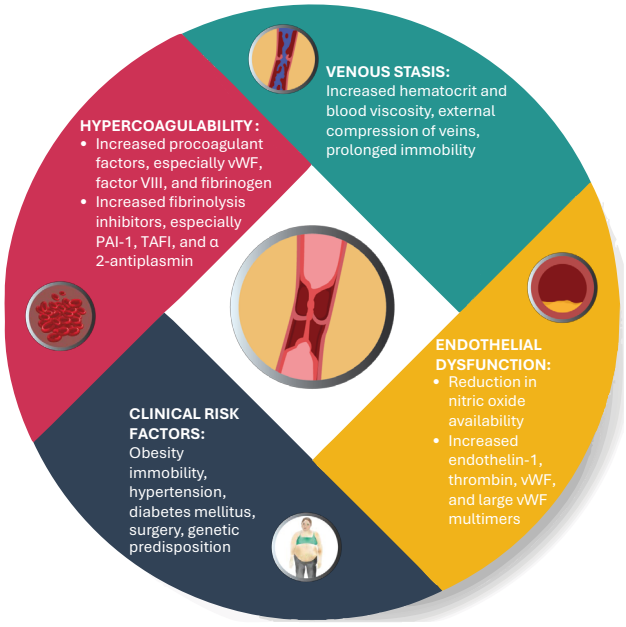
PATHOPHYSIOLOGY

Clinical studies have demonstrated significant abnormalities in coagulation and fibrinolysis in patients with hypercortisolism, contributing to an increased risk of thromboembolic events (21). Hypercortisolism promotes a hypercoagulable state through multiple mechanisms, including endothelial dysfunction, increased procoagulant factors coupled with impaired fibrinolysis, and venous stasis (22). These changes align with Virchow's triad, which describes the key contributors to thrombosis: vascular abnormalities, hypercoagulability, and stasis (21) (**Figure 1**).

Endothelial dysfunction

Factors such as obesity, diabetes mellitus, hypertension, dyslipidemia, and insulin resistance, all frequently observed in CS, contribute to impaired endothelial function by disrupting nitric oxide availability and increasing endothelin-1 levels (1,23-25). Elevated markers of endothelial dysfunction, such as intercellular adhesion molecule-1 and serum N-acetyl-β-glucosaminidase activity, have been reported in patients with hypercortisolism (24). Additionally, increased levels of vWF and unusually large vWF multimers indicate endothelial activation, further enhancing the thrombotic potential (26,27).

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PAI-1: plaminogen activator inhibitor-1; TAFI: thrombin-activatable fibrinolysis inhibitor; vWF: von Willebrand factor.

Figure 1. Pathophysiology of venous thromboembolism in patients with Cushing's syndrome. Hypercortisolism promotes a hypercoagulable state through multiple mechanisms, including endothelial dysfunction, increased procoagulant factors, impaired fibrinolysis, and venous stasis.

Hypercoagulability and imbalance in coagulation factors

Cushing's syndrome is characterized by increased plasma levels of procoagulant factors, including factors II, V, VIII, and IX, alongside shortened partial thromboplastin time (PTT), likely due to elevated factor VIII levels (15,18,28,29). The persistence of elevated vWF, factor VIII, and factor IX even after remission suggests a lasting prothrombotic state (29). While some studies have reported increased levels of anticoagulants such as protein C, protein S, and antithrombin, this appears to be a compensatory response to heightened coagulation activity (28,30). However, hypercortisolism also impairs fibrinolysis by increasing inhibitors such as plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI), further promoting clot formation (28,29,31,32). Studies have shown increased clot formation speed and clot strength in patients with active CS, particularly in those with obesity, reinforcing the role of cortisol excess in accelerating thrombogenesis (33). Inflammatory and prothrombotic endothelial damage has also been observed in patients with CS even after remission: the early remission phase following the correction of hypercortisolism is marked by persistent low-grade inflammation, lasting up to 1 year post-surgery, and patients with CS who also have obesity or hyperglycemia are at a higher risk of elevated inflammatory markers during the postoperative period, potentially increasing their susceptibility to thromboembolism during this time (34).

Venous stasis

Venous thrombi commonly form in areas of slow blood flow, such as the deep veins of the legs (35). Patients with CS may exhibit increased hematocrit and blood viscosity, which can lead to reduced venous flow and promote clot formation (35,36). Additionally, external compression of veins and prolonged immobility, common in severely affected CS patients, further increase the risk of stasis-related thrombotic events (21).

Comorbidities and clinical risk factors

Thromboembolic events in CS are often triggered by additional risk factors, including surgery, malignancy, as well as conditions such as arterial hypertension, diabetes mellitus, obesity, and smoking that contribute to a prothrombotic state. Studies have found that many patients with VTE unrelated to surgery had multiple acquired risk factors, such as metabolic disorders and infections (37). In addition, genetic predispositions, such as polymorphisms in the VWF gene promoter and inherited thrombophilic defects like factor V Leiden and prothrombin gene mutations, can exacerbate the hypercoagulable state in CS (38). Moreover, patients with ectopic CS and adrenal carcinoma face a heightened risk of VTE due to underlying malignancy (21). The combination of high vWF levels, genetic predisposition, and acquired risk factors likely amplifies the risk of thrombosis in CS.

THROMBOPROPHYLAXIS MANAGEMENT

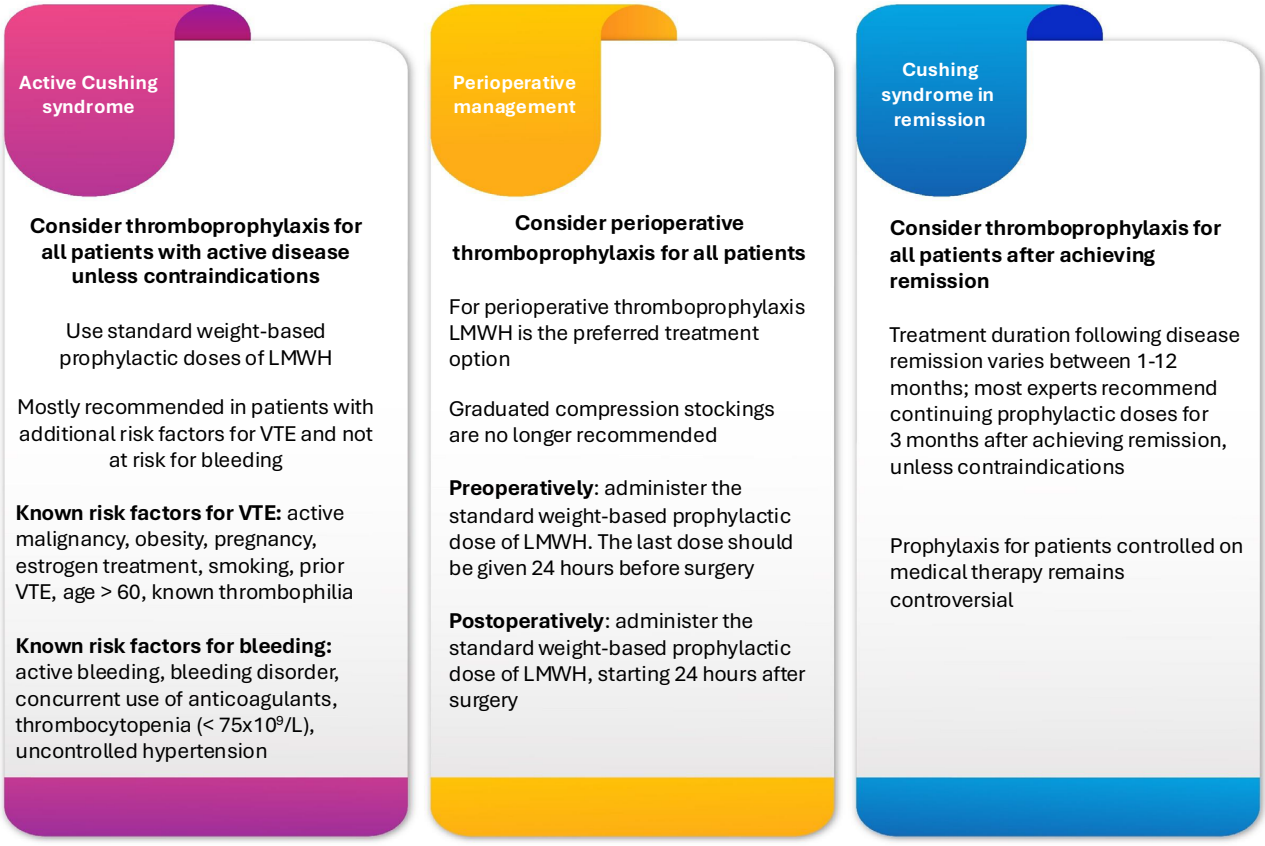
Current clinical practices for thromboprophylaxis management in patients with CS vary between countries and even centers (8,22,39); a study across EU Reference Network Rare Endocrine Conditions (Endo-ERN) reference centers reported notable

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differences in treatment protocols (40). The recent Delphi consensus on VTE management in CS which included endocrinologists, epidemiologists, neurosurgeons and hematologists highlights the critical need for thromboprophylaxis in most patients due to their elevated thrombotic risk. The recommendations outlined in the position statement aim to standardize care and enhance patient outcomes (9) (**Figure 2**).

Active Cushing's syndrome

According to aforementioned position statement, thromboprophylaxis should be considered for all patients with CS but should only be initiated after confirming the diagnosis, except in cases of severe hypercortisolemia. The decision to administer anticoagulation must be carefully weighed in high-risk populations, as certain conditions significantly increase the risk of bleeding, including active bleeding, acquired bleeding disorders (e.g., liver failure), concurrent use of anticoagulants, acute stroke, thrombocytopenia (platelet count <75 × 10^9/L), uncontrolled hypertension (blood pressure >200 mmHg systolic or > 120 mmHg diastolic), untreated inherited bleeding disorders (e.g., hemophilia, von Willebrand disease), or recent or planned surgical procedures. On the other hand, thromboprophylaxis should be strongly considered in patients with additional risk factors, such as active malignancy, sedentary lifestyle, smoking, estrogen therapy, pregnancy, age over 60, known thrombophilia, obesity, significant comorbidities (e.g., cardiovascular disease, pulmonary disorders, acute infections, inflammatory conditions), or a personal or family history of VTE. While the use of oral estrogen is not contra-indicated in patients with active CS, temporarily discontinuing oral estrogen therapy in female patients prior to surgery should be considered and alternate modes of estrogen deliveries or other contraceptive measures without oral estrogen initiated



VTE: venous thromboembolism; LMWH: low molecular weight heparin.

Figure 2. Thromboprophylaxis in patients with Cushing syndrome.

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as needed (41). Hospitalized patients with active CS should receive thromboprophylaxis, regardless of the reason for admission or the severity of hypercortisolism, as long as no contraindications exist.

Low molecular weight heparin (LMWH) in standard weight-based prophylactic doses is the preferred anticoagulant for thromboprophylaxis in patients with CS, similar to the American Society of Hematology guidelines on the management of VTE in patients with cancer (42). Direct oral anticoagulants (DOACs) are not currently approved for this indication and should be used with caution. In contrast with previous guidelines, graduated compression stockings are not recommended at this time, as a recent systematic review found no additional benefit in preventing VTE or reducing mortality and their use poses a risk of skin complications, which is particularly relevant in patients with CS with fragile skin (43).

Inferior petrosal sinus sampling

Although some reports have indicated a higher incidence of VTE events with inferior petrosal sinus sampling (IPSS), the decision to administer periprocedural anticoagulation for all patients remains controversial (44,45). In the latest Delphi position statement, consensus was reached that patients not already receiving anticoagulation should be started on it approximately 12 hours before IPSS. For those already on anticoagulation, prophylactic doses of LMWH can be maintained during the procedure, but higher doses should be withheld 24 hours before and resumed 48 hours after the procedure. Direct oral anticoagulants regimens vary, with discontinuation 24 to 72 hours before the procedure, bridging with LMWH, and resumption 48 hours post-procedure.

Perioperative management

If thromboprophylaxis was not started at the time of CS diagnosis, its perioperative use should be re-evaluated for all patients with CS undergoing surgery, especially in more severe cases, provided there are no clear contraindications [9]. Preoperatively, the standard weight-based prophylactic dose of LMWH should be administered, with the last dose given 24 hours before surgery. Postoperatively, thromboprophylaxis should resume 24 hours after surgery and LMWH remains the preferred anticoagulant in this setting.

Aspirin has been also previously suggested perioperatively to prevent VTE, but experience in patients with CS is scarce (46,47).

Disease remission

For patients who have achieved biochemical remission, thromboprophylaxis should generally continue for 3 months unless contraindications exist. However, expert opinions varies for a treatment duration ranging from 1 to 12 months post-remission. In cases in which the patient has no additional thrombotic risk factors, thromboprophylaxis may not be necessary after biochemical remission, but there is a lack of studies on this topic. In patients with CS who have achieved remission, oral estrogen use immediately post-remission should be carefully evaluated due to the potential ongoing increased risk of thromboembolism, though further research is needed to gain a clearer understanding of this concern. Alternative therapies or other deliveries (e.g., transdermal) to oral estrogen should be explored to help mitigate this risk.

It remains unclear whether medical management of CS influences coagulation risk beyond achieving biochemical remission. Short-term biochemical remission with a combination of pasireotide, cabergoline, and ketoconazole did not show significant improvement in hypercoagulable markers (29). However, emerging data suggest some direct effects on coagulation factors. While subcutaneous pasireotide treatment for 6 to 12 months did not significantly alter clotting factors (48), relacorilant, a glucocorticoid receptor selective blocker in development, has been shown after 3 to 4 months to induce significant mean changes in factor VIII (-18.9%; $p = 0.022$), aPTT (+1.5 s; $p = 0.046$), and platelet count (-68.8 × 10^9/L; $p < 0.0001$) (49). Interestingly, vWF remained largely unchanged. Differences in the effects of these drugs on coagulation factors may be attributed to their distinct mechanisms of action, with pasireotide carrying an additional risk of hyperglycemia.

If VTE is diagnosed in a patient with CS, therapeutic anticoagulation should be administered for 3 to 6

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months as per guidelines for VTE treatment, followed by prophylactic dosing for at least three months after hypercortisolism is resolved. However, treatment decisions should be individualized based on ongoing risk factors.

Risk of bleeding

While the primary haemostatic concern in CS is hypercoagulability and the associated risk of VTE, there is also a notable risk of bleeding. This risk is particularly evident in the context of gastrointestinal complications, such as peptic ulcers and gastrointestinal bleeding, which are associated with hypercortisolism (11,50), and may also arise following surgical interventions.

Few studies have examined the risk of bleeding in patients with CS who are anticoagulated, either short- or long-term. In patients with brain tumors who underwent various neurosurgical procedures, a meta-analysis on thromboprophylaxis found a slightly increased risk of minor hemorrhagic complications (risk ratio = 2.02), though no significant increase in major bleeding events (51).

FUTURE DIRECTIONS

Future research should focus on refining thromboprophylaxis strategies for patients with CS to optimize patient outcomes while minimizing risks. A major priority is the development of standardized protocols, as current practices vary significantly across centers. Prospective studies are needed to establish the optimal timing, duration, and choice of anticoagulant therapy, particularly given the lack of consensus on thromboprophylaxis duration, which currently ranges from 1 to 12 months post-surgery. Need for anticoagulation for patients in biochemical remission also needs to be further studied. Additionally, defining the period during which patients remain at an elevated thrombotic risk after biochemical remission is crucial to improving long-term management.

Risk stratification algorithms incorporating both general and CS-specific factors, such as the Padua Score or CS-VTE score, could enhance individualized thromboprophylaxis. Implementing these tools may allow clinicians to better assess thrombotic risk and tailor prophylaxis accordingly, reducing unnecessary anticoagulation in low-risk patients while ensuring adequate protection for those at higher risk. Further research is also needed to clarify the role of long-term anticoagulation, as hypercoagulability in CS may persist for months following surgical remission. Understanding the balance between thrombotic and bleeding risks will help guide decisions on extended anticoagulation therapy.

The potential use of DOACs in CS represents another important area for investigation. While DOACs offer advantages in other hypercoagulable states, their use in CS remains limited, and safety data are lacking. A particular concern is the reported higher bleeding risk associated with DOACs compared to LMWH (52). Dedicated clinical trials are necessary to evaluate their efficacy, safety, and suitability for CS patients.

Currently, there is insufficient evidence to provide clear recommendations regarding thromboprophylaxis in patients with mild CS or MACS. Further research is needed to determine the thrombotic risk in these populations and guide management strategies accordingly.

Finally, future research should explore personalized medicine approaches through genetic and biomarker-driven strategies to refine thromboprophylaxis. Identifying molecular markers that predict VTE risk could enable a more individualized approach, ensuring that high-risk patients receive appropriate prophylaxis while avoiding unnecessary anticoagulation in those at lower risk. By addressing these gaps, future studies have the potential to improve patient safety, standardize care, and enhance outcomes in this high-risk population.

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invited review

Vitamin D in the elderly: the phil-rouge in preventing bone, muscle and adipose deterioration?

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ABSTRACT

The pleiotropic role of vitamin D in human health has been implicated in modulating bone metabolism and other several extra-skeletal areas, including muscle and adipose tissues regulation, and in influencing general and systemic outcomes. In the elderly, vitamin D deficiency is considered as an emerging public health issue affecting 40%-70% of older adults worldwide with higher rates occurring in institutionalized individuals or patients with multiple chronic comorbidities. The pathophysiology of vitamin D deficiency in the elderly is multifactorial and includes age-related reduced skin synthesis, limited sun exposure, declined renal and liver function, and long-term use of interfering medications. Given its pleiotropic effects, vitamin D deficiency in the elderly has been consistently associated with progressive bone deterioration and muscle and adipose dysfunctions, concurring to the occurrence of the osteosarcopenic obese phenotype. This multifaced deleterious scenario is strongly correlated with an increasing risk of fragility fractures, falls, functional and metabolic decline, all of which contribute to higher morbidity and mortality. Early diagnosis and screening with individualized criteria, targeted and personalized strategies for supplementation, and structured follow-up monitoring are required to reduce the clinically significant impact of vitamin D deficiency in this highly vulnerable population.

Keywords: Vitamin D; elderly; osteoporosis; osteosarcopenic obesity; COVID-19

VITAMIN D DEFICIENCY IN THE ELDERLY: MECHANISMS AND EPIDEMIOLOGY

Pathophysiological mechanisms

Vitamin D is a fat-soluble prohormone that plays central roles in calcium-phosphorus and bone metabolisms, and in several extra-skeletal conditions influencing muscle and adipose health, and cellular growth (1). In humans, vitamin D is mostly synthesized endogenously by the skin after the exposure to ultraviolet B (UVB 290-315 nm) radiation, and, in a minor part, it can be also obtained exogenously through foods ingestion (1,2). The two main primary forms of vitamin D are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Cholecalciferol is the biologically most common form synthesized in the skin and present in animal-based foods such as fatty fish, egg yolk, and dairy products. Instead, ergocalciferol is mostly derived from plants and fungi (1). Cholecalciferol and ergocalciferol differs in structural conformation for the presence of an additional carbon double-bond and a methyl group in the side chain of vitamin D2, and in available sources for humans since vitamin D3 is primarily synthesised in the skin and, in contrast, vitamin D2 is exclusively obtained from exogenous sources (3). In humans, vitamin D2 and D3 were considered equally biologically active for several decades, but current knowledge indicates that the efficacy of vitamin D2 is less than one-third of vitamin D3 (3).

The cutaneous skin synthesis is the primary source of vitamin D3 for most individuals, and it is influenced by aging, season, latitude, skin pigmentation, and sun exposure habits. In subjects with limited UVB exposure, such as older adults, individuals living at high latitudes, or those with occupational or cultural sun

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restrictions, the vitamin D dietary intake and supplementation are critical sources of this hormone (4). Once produced by the skin or introduced from foods sources, circulating vitamin D is biologically inactive until it is processed by a two-step hydroxylation process occurring the first-one in the liver and the second-one in the kidneys to finally constitute the biologically active form responsible for most of the vitamin D systemic effects.

Aging significantly alters vitamin D metabolism impairing each process involved in its synthesis and activation by reducing cutaneous synthesis, impairing liver and renal functions, and also by altering vitamin D bioavailability in circulation (4). These changes occurring in the elderly population can be combined with additional behavioural and environmental factors, as dietary restriction and prolonged institutionalization, further impairing vitamin D metabolism and contributing to the very high prevalence of vitamin D deficiency commonly present in older subjects (5).

One of the most detrimental effect of aging on vitamin D metabolism is the progressive decline in skin synthesis of vitamin D3. This decline is mainly related to a gradual reduction in epidermal 7-dehydrocholesterol levels, the precursor molecule required for vitamin D3 synthesis. It is well demonstrated that at the age of 70-80 years, 7-dehydrocholesterol cutaneous decreases by 50%-75% as compared to younger population, significantly impairing the cutaneous ability to synthesize vitamin D3 (4). Indeed, recent studies estimate that vitamin D3 cutaneous synthesis declines by approximately 13% per decade, and older individuals effectively produce only about one-half of the vitamin D3 that younger adults (6). Moreover, besides the marked reduction in vitamin D3 cutaneous synthesis, additional several behavioural changes typically occurring in the elderly are known to negatively influence vitamin D metabolism. Spending less time outdoors, wearing more protective clothing, and avoiding sun exposure due to concerns about skin cancer and photoaging are known to reduce the skin sun exposure and the associated vitamin D synthesis (4). Institutionalized subjects and individuals with mobility impairments are recognized to be particularly vulnerable as they experience minimal UVB exposure (7). In addition, in respect to western population, geographical and seasonal factors further influence vitamin D synthesis since in regions above 37° latitude, as for most of Europe and North America countries, UVB radiation is known to be markedly insufficient during winter months to stimulate vitamin D cutaneous production (4).

Organ dysfunctions, especially involving liver and kidneys, and age-related comorbidities, can be associated to a further disruption in vitamin D metabolism. The first hydroxylation step necessary for the activation of vitamin D metabolites occurs in the liver where the enzyme vitamin D-25-hydroxylase (CYP2R1) converts both cholecalciferol and ergocalciferol into 25-hydroxyvitamin D [25(OH) vitamin D] (also named calcifediol), the main circulating form. There is also a unique additional activation pathway for vitamin D2 promoted by hepatic 24-hydroxylase (CYP24A1) leading to 24(OH) vitamin D2 synthesis that can undergo to further activation (3). Chronic liver disease, as in case of cirrhosis and non-alcoholic fatty liver disease (NAFLD), are known to profoundly impair the CYP2R1 activity reducing 25(OH) vitamin D synthesis (8,9). While these detrimental effects of chronic liver diseases are well-known, evidence suggests that elderly itself can affect hepatic vitamin D metabolism even in the absence of overt liver pathological conditions (5,6). With increasing age, the hepatic CYP2R1 activity progressively declines, and liver volume and hepatic blood flow decrease by 0.3%-1.5% per year after the age of 40 years (10). Moreover, older age is also associated with progressive increase in liver fat accumulation, even in individuals without NAFLD, which alters vitamin D storage, metabolism, and release of vitamin D-binding proteins (DBPs) in circulation needed to facilitate vitamin D distribution throughout the tissues since its lipophilic nature (1). The second step of vitamin D activation occurs through the activity of the renal enzyme 1α-hydroxylase (CYP27B1) which converts 25(OH) vitamin D into 1,25-dihydroxyvitamin D [1,25$(OH)_2$ vitamin D] (also named calcitriol). Even in the absence of a clinically diagnosed form of chronic kidney disease (CKD), renal function progressively declines in the elderly impairing the activation

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of vitamin D metabolites (11). The impairment of renal vitamin D metabolism results from a decline in CYP27B1 activity and a progressive loss of nephrons and reduced renal perfusion leading to a decline in glomerular filtration rate (GFR) by approximately 1 mL/min per year after the age of 40 years (4,11).

Different drug medications commonly used in older populations, such as corticosteroids, anticonvulsants and proton pump inhibitors (PPIs) can contribute to vitamin D deficiency in these subjects (4). Corticosteroids have profound detrimental effects on vitamin D metabolism, calcium homeostasis, and musculoskeletal health. Their long-term use promotes vitamin D degradation, impairs calcium absorption, and disrupts bone turnover significantly increasing the risk of osteoporosis, fragility fractures and sarcopenia, particularly in older adults (12-14). Corticosteroids negatively impact on vitamin D metabolism leading to upregulation of CYP24A1, the enzyme responsible for converting both 25(OH) vitamin D and $1,25(OH)_2$ vitamin D into inactive metabolites. In addition, corticosteroids suppress renal CYP27B1, the enzyme responsible for converting 25(OH) vitamin D into its biologically active form. Corticosteroids can also impair gastrointestinal absorption of vitamin D and calcium through gut microbiota alterations and intestinal barrier dysfunction (15). Anticonvulsants, including phenytoin, phenobarbital, and carbamazepine, significantly interfere with vitamin D metabolism by inducing hepatic cytochrome P450 enzymes, in particular CYP24A1 and CYP3A4, increasing the catabolism of both 25(OH) vitamin D and $1,25(OH)_2$ vitamin D (16). Patients taking antiepileptic drugs had up to a 30% lower serum 25(OH) vitamin D concentration compared to non-users predisposing to progressive bone loss (17,18), and long-term use of enzyme-inducing antiepileptic drugs is strongly associated with decreased bone mineral density (BMD) and increased risk of fragility fractures (19). PPIs are widely prescribed for gastroesophageal reflux disease (GERD) and peptic ulcer disease. Long-term use of PPIs has been demonstrated to impair the absorption of calcium and vitamin D by altering gastric pH (20). Indeed, these compounds inhibit hydrogen-potassium ATPase in gastric parietal cells leading to hypochlorhydria which reduces the food solubilization and the intestinal absorption of fat-soluble vitamins, including vitamin D (21), and long-term PPI therapy has been linked to an increased risk of osteoporotic fractures (22).

Epidemiology of vitamin D deficiency in the elderly

Vitamin D deficiency is a widespread public health issue worldwide with older population as one of the most affected by this detrimental condition linked to age-related cutaneous changes, reduced sun exposure, inadequate dietary intake, and progressive impairment of liver and kidney functions (23-25). In Italy, between 60% and 80% of older subjects are characterized by suboptimal serum 25(OH) vitamin D levels (<50 nmol/L/20 ng/mL), with circulating levels decreasing in winter especially in northern regions. Among institutionalized elderly individuals, vitamin D deficiency issue is even more severe, with up to 90% experiencing severe deficient vitamin D status (<30 nmol/L/12 ng/mL). In the United States, NHANES data (2001-2018) indicate that 17.2% of women and 16.8% of men older than 80 years present circulating 25(OH) vitamin D concentrations <50 nmol/L/20 ng/mL, while 2.4% of women and 2.1% of men present levels below <25 nmol/L/10 ng/mL (26). The prevalence of subjects presenting 25(OH) vitamin D levels below 25-50 nmol/L/10-20 ng/mL is notably higher during winter months, affecting 28.9% of the population as compared to 17.0% in summer. Although the vitamin D deficiency issue is widely recognized to mainly affect populations living in geographic regions with limited sun exposure, an impaired vitamin D status highly characterizes also those living in tropical regions, especially in the elderly. In a recent cross-sectional study including 212 community dwellers aged ≥80 years in Sao Paulo, Brazil (Lat 23.5 oS), vitamin D deficiency (defined with circulating 25(OH) vitamin D levels <20 ng/mL) and severe vitamin D deficiency (<10 ng/mL) were observed in the 56% and in the 13% of the cohort, respectively (27). *In vitro* model data also demonstrated an impaired cutaneous vitamin D3 synthesis during the winter months in the tropics (28), as confirmed by the pronounced seasonality observed in serum circulating 25(OH) vitamin D

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concentrations in the population living in these specific regions (29).

Based on the multiple risk factors for vitamin D deficiency in older adults, public health initiatives should consider screening for deficiency in high-risk groups, improving dietary intake through food fortification and promoting safe sun exposure and supplementation, as also recently stated in the updated guidelines of the Endocrine Society recommending supplementation in the elderly even without specific vitamin D status assessments (30). Evidence from Finland supports the effectiveness of food fortification in reducing vitamin D deficiency rates (31). After the generalized fortification of dairy products and fats in 2003, the prevalence of vitamin D deficiency in Finnish older population dropped from 12% to 0.6% between 2000 and 2011, with a mean serum 25(OH) vitamin D level increasing from 48 nmol/L to 65 nmol/L.

Vitamin D deficiency in the elderly: definition and diagnosis

The accurate diagnosis of vitamin D deficiency is essential to prevent its detrimental impact in the elderly. Circulating serum 25(OH) vitamin D is widely recognized as the most reliable and useful biochemical marker of vitamin D status, reflecting both endogenous synthesis, dietary intake and supplementation (5). However, definition of the optimal serum 25(OH) vitamin D levels remains of ongoing debate with recent guidelines and consensus recommendations refining the diagnostic thresholds based on individual risk factors and different clinical scenario.

Based on bone health, the 2011 report on dietary requirements for calcium and vitamin D from the Institute of Medicine (IOM) recommended the following diagnostic thresholds for vitamin D status (32): deficiency in case of 25(OH) vitamin D levels <12 ng/mL (<30 nmol/L); insufficiency in case of 25(OH) vitamin D levels 12-20 ng/mL (30-50 nmol/L); sufficiency in case of 25(OH) vitamin D levels ≥20 ng/mL (≥50 nmol/L). The 2011 Endocrine Society clinical practice guidelines, focused primarily on skeletal health and prevention of osteomalacia, established the following diagnostic thresholds for vitamin D status (33): severe deficiency in case of 25(OH) vitamin D levels <10 ng/mL (<25 nmol/L); deficiency in case of 25(OH) vitamin D levels 10-20 ng/mL (25-50 nmol/L), insufficiency in case of 25(OH) vitamin D levels 21-29 ng/mL (52.5-72.5 nmol/L), sufficiency in case of 25(OH) vitamin D levels ≥30 ng/mL (≥75 nmol/L). Of particular note, in 2024, the Endocrine Society propose an updated clinical practice guideline for vitamin D management in general population for the prevention of extra-skeletal diseases avoiding measurements of 25(OH) vitamin D levels in older subjects (30). The Endocrine Society no longer endorsed 25(OH) vitamin D level diagnostic thresholds to define vitamin D sufficiency, insufficiency, and deficiency status, even though this recommendation was specifically related to general population for the prevention of extra-skeletal diseases and not to those with skeletal disorders. Concerning to the general population aged 50 to 74 years, routine 25(OH) vitamin D testing and vitamin D supplementation beyond the recommended Dietary Reference Intake for this population (34) were not suggested. Moreover, also in the general population aged 75 years and older a routine testing for 25(OH) vitamin D levels was not suggested, and an empiric vitamin D supplementation was recommended due to its potential to reduce the risk of overall mortality (30). Indeed, a systematic review including 25 trials with a total of 49,879 participants assessing the effects of vitamin D supplementation on all-cause mortality was performed, and meta-analysis suggested that vitamin D use, in most trials given as a daily dose of cholecalciferol either alone or combined with calcium, reduces mortality compared to placebo, with an estimated absolute effect size of 6 fewer deaths per 1,000 people with no differences according to risk of bias, gender, calcium co-administration, vitamin D dosage (high vs standard), setting (community, hospitalized, institutionalized) and vitamin D status (30).

The 2024 Consensus Statement of the 6th International Conference "Controversies in Vitamin D" highlighted how vitamin D assessment and supplementation need to be based on specific

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patients' clinical risk factors and, differently by the 2024 Endocrine Society's recommendations, the Consensus Statement proposes a treat-to-targeted approach ensuring an adequate supplementation when most beneficial and effective, especially in the elderly (5). The 2024 Consensus recommended that in frail and high-risk older adults vitamin D supplementation is prioritized over measurement, as its deficiency is highly prevalent in this population. In addition, serum 25(OH) vitamin D levels ≥30 ng/mL (≥75 nmol/L) are recommended in these individuals to prevent skeletal fragility, and monitoring 25(OH) vitamin D levels during supplementation is recommended to ensure adequate vitamin D status and to modulate supplementation as appropriate.

With respect to vitamin D status biochemical assessment in older population, since circulating serum 25(OH) vitamin D levels also depend by DBPs, which serves as the primary transporter of vitamin D in circulation, fluctuations in DBP levels occurring in the elderly can impact on laboratory accuracy (5,8). Additional significant challenges in the vitamin D assessment are also due to variability in the laboratory measurement of serum circulating 25(OH) vitamin D which can be currently performed with different several commercial methodologies available in clinical practice including liquid chromatography-tandem mass spectrometry, immunoassays techniques and enzyme-linked immunosorbent assays, leading to potential inconsistencies between laboratories (5,8). Moreover, the presence of two serum 25(OH) vitamin D forms in circulation, 25(OH) vitamin D3 and 25(OH) vitamin D2, leads to additional difficulties in the biochemical assessment of the circulating total serum 25(OH) vitamin D concentration (35). Laboratory specimens available in clinical routine can differently detect and distinguish the two circulating forms potentially leading to underestimate or overestimate the vitamin D status in presence of substantial amounts of 25(OH) vitamin D2 (5,8). However, the specific concentrations of 25(OH) vitamin D2 in circulation are generally very low in most populations except in rare cases of highly use of vitamin D2 enriched food or specific supplements.

Vitamin D deficiency in the elderly: impact on muscle, bone and adipose tissues

Muscle

Vitamin D is essential for muscle contraction, neuromuscular coordination, and muscle protein synthesis through its regulation of calcium-mediated signalling pathways (36). Several biological pathways support the effects of vitamin D on muscle. Vitamin D receptor (VDR) is essential in activating the intracellular signalling pathways relative to calcium metabolism and myoblast proliferation and differentiation, fundamental for preserving adequate muscle mass and strength (36). Vitamin D was demonstrated to enhance mitochondrial biogenesis increasing the expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha and the upregulation of mitochondrial DNA copy number. In addition, it was proved to increase adenosine triphosphate production capacity and to improve oxidative function enhancing the activity of electron transport chain complexes (37,38). Conversely, vitamin D deficiency was proven to lead mitochondrial dysfunction, to decrease ATP and energy production, and to increase reactive oxygen species production and oxidative intracellular damage. Vitamin D deficiency was also linked to a dysregulation of myogenic regulatory factors, as the Notch signalling pathway, responsible for muscle progenitor cell differentiation and renewal (36-38). Interestingly, vitamin D was also implicated in the muscle reparative process promoted by the gut microbiota which regulates muscle regeneration via RORγ+ Treg cells. These cells play a critical role in the homeostasis of extra-gut tissues and accumulate in the damaged muscle where can shield differentiating muscle stem cells from IL-17A (39-41). Vitamin D was recognized as a central actor in these processes by enhancing gut microbiota diversity, promoting T-cell plasticity, and by inducing the development of RORγt/FoxP3+ Tregs (41-44).

Clinical evidence also supports the role of vitamin D in preserving muscle mass, especially in older populations. A large study including 4,139 older adults assessed the relationships between vitamin D status and physical activity evaluated with different

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diagnostic tools, and reported that serum 25(OH) vitamin D levels and physical activity were linearly related to timed up-and-go test (TUG) performance and handgrip strength (45). A large meta-analysis including over 5,600 adult individuals with a mean age of 61.1 years showed a significant positive effect of vitamin D supplementation on muscle strength measured by grip strength, leg extension and quadriceps muscle strength. Importantly, the supplementation with vitamin D was most effective in improving muscle strength especially in subjects presenting 25(OH) vitamin D levels lower than 30 nmol/L (12 ng/mL) and who were 65 years of age or older (46). Similar findings were observed in another study showing an interactive effect between serum 25(OH) vitamin D and physical activity on functional tests and muscle strength (47). In a recent meta-analysis of 4 randomized controlled trials (RCTs) not specifically focused on older individuals, overall, a short-term treatment with moderate to high daily doses of vitamin D did not affect muscle health or quality of life even though a potential beneficial effect was present on muscle strength in severely obese subjects and on quality of life in those with vitamin D deficiency (48).

Bone

Vitamin D deficiency is associated with profound negative consequences for bone health, primarily by disrupting calcium-phosphorus homeostasis. Vitamin D promote sufficient intestinal calcium and phosphate absorption required for bone mineralization, and inadequate vitamin D status is known to impair this process contributing to osteomalacia and osteoporosis occurrence. In addition, vitamin D deficiency is recognized as a common cause of secondary hyperparathyroidism which exacerbates calcium mobilization from skeletal tissue to maintain serum calcium homeostasis (49). Chronic secondary hyperparathyroidism, typically observed in vitamin D-deficient individuals, is associated with increased bone resorption, cortical bone porosity and trabecular deterioration, increasing fragility fracture risk (50). In case of severe and prolonged vitamin D deficiency, the impaired bone mineralization caused by the lack of vitamin D leads to osteomalacia, a detrimental pathological condition characterized by an excess of unmineralized osteoid, skeletal deformities, and diffuse bone pain (49).

Clinical trials strongly support vitamin D supplementation as an effective strategy for treatment of osteoporosis and fracture prevention, especially when associated with calcium supplementation. Meta-analyses show that vitamin D supplementation, when combined with calcium, can reduce hip fractures by 16%-39% and non-vertebral fractures by 5%-26%, with the greatest benefits observed in high-risk elderly populations (5). The VITAL Study, a recent large RCT involving 25,800 adults, found that vitamin D3 supplementation, at doses of 2,000 international unit (IU) daily, without calcium, did not significantly reduce fracture risk over 5.3 years (51). Importantly, the participants enrolled in this trial were characterized by relatively high baseline 25(OH) vitamin D levels (mean levels of 30.7 ng/mL), with very few having severe deficiency (< 12 ng/mL) which is the group of patients that might have benefited more from supplementation, potentially explaining the null results of the study. Additionally, different evidence suggest that vitamin D deficiency may also reduce the response to anti-osteoporotic therapies, such as bisphosphonates, potentially limiting their effectiveness in preventing bone loss and fragility fractures, as well as to predispose to secondary endocrine-driven osteopathies (52-55).

Adipose tissue

Vitamin D deficiency is well-known to be associated with obesity and related comorbidities, and adipose tissue is the main storage site for vitamin D and its metabolites. Indeed, vitamin D is a fat-soluble steroid hormone and its volumetric dilution into adipose tissue mass when increased is recognized as one of the most plausible explanations for the relationship between vitamin D deficiency and obesity (56,57). Experimental studies suggest that obesity is associated with decreased expression of specific genes that regulate the metabolism of vitamin D by altering synthesis of the enzymes CYP2R1 and CYP27B1 (58). On the contrary, an upregulation of CYP24A1 activity which promotes vitamin D

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catabolism has been suggested in experimental models (59).

Several other pathophysiological mechanisms have been proposed to explain the recognized association between vitamin D deficiency and obesity in humans (60-62). Patients with obesity tend to spend less time in outdoor activities with limited skin exposure to sunlight. Lower dietary intake of vitamin D, impaired hepatic 25-hydroxylation (63), impaired hydroxylation in adipose tissue, and alterations in VDRs (60-62) are additional factors. Obese patients are typically characterized by lower levels of 25(OH) vitamin D, which are inversely correlated with body mass index (BMI) and adiposity (64,65). The prevalence of vitamin D deficiency is reported to be 35% higher in individuals with obesity than in normal weight individuals (64). Moreover, obese patients often require larger amounts of vitamin D supplementation than their normal-weight counterparts. A recent meta-analysis showed that, after administration of equal doses of vitamin D, 25(OH) vitamin D levels were lower by about 15.2 ng/mL (38 nmol/L) compared with eutrophic individuals, with doses ranging from 4,000-6,000 to 40,000-60,000 IU weekly (66).

On the other hand, a causal role for low serum 25(OH) vitamin D in body mass accumulation has also been suggested (67). Indeed, it was demonstrated that adipose tissue itself is a direct target of vitamin D which can influences its distribution, metabolic and endocrine functions (68). The VDR is present in the pre-adipocytes and adipocytes in both visceral and subcutaneous adipose tissue (69) and serves as the mechanistic mediator of these properties. *In vitro* studies on mouse adipocytes showed that calcitriol, the active form of vitamin D, increases basal and stimulated lipolysis and decreases lipogenesis (70) resulting in a catabolic reduction in adipocyte number and size by decreasing lipid and triglycerides accumulation. Conversely, increased parathyroid hormone secretion secondary to low 25(OH) vitamin D levels is associated with a raise of intracellular calcium in adipocytes stimulating lipogenesis and weight gain. On the other hand, with respect to energy expenditure in murine models, the knockout for VDR and CYP27B1 leads to a lean phenotype and less adipose tissue than wild type mice promoting resistance to diet-induced obesity (71,72). It was also demonstrated that CYP27B1 knockout mice presented lower leptin levels and consumed significantly more food than their wild type counterparts (73,74), and targeted expression of human vitamin D receptor in adipocytes reduced lipolysis, fatty acid beta-oxidation and induced obesity in mice (75).

Based on these findings, it has been suggested that vitamin D supplementation may have a role in obesity and associated metabolic disorders. However, the results of the main RCTs exploring the effects of vitamin D supplementation on body fat mass and body weight are still inconclusive (76), even if significant effects in reducing the risk of diabetes in high-risk populations and in positively modulating glucose metabolism in general population were consistently reported by several large studies (77-81).

Vitamin D deficiency in the elderly: key-role in osteosarcopenic obesity

Based on the findings described above, emerging evidence highlights the role of vitamin D deficiency in osteosarcopenic obesity, a pathological condition defined by the concomitant presence of osteoporosis, sarcopenia, and obesity, which can typically affect the older population (**Figure 1**) (82,83). Ostesarcopenic obesity is now recognized as a specific clinical entity with several metabolic alterations which occur in the skeletal muscle of individuals with obesity that may negatively impact muscle mass and function, and bone health (82-86). This pathological condition is often underrecognized, despite being associated with poor metabolic and functional outcomes (87). Epidemiological studies highlight that osteosarcopenic obesity has a prevalence ranging from 5% to 37% in older adults, depending on sex, ethnicity, and diagnostic criteria, with higher rates observed especially in the elderly and in individuals with metabolic syndrome (85,86). The coexistence of alterations in bone, muscle, and adipose tissue is demonstrated to exacerbate physical decline, insulin resistance and glucose metabolism impairment, and chronic systemic inflammatory processes, and to increase the risk of falls, fractures, daily impairment

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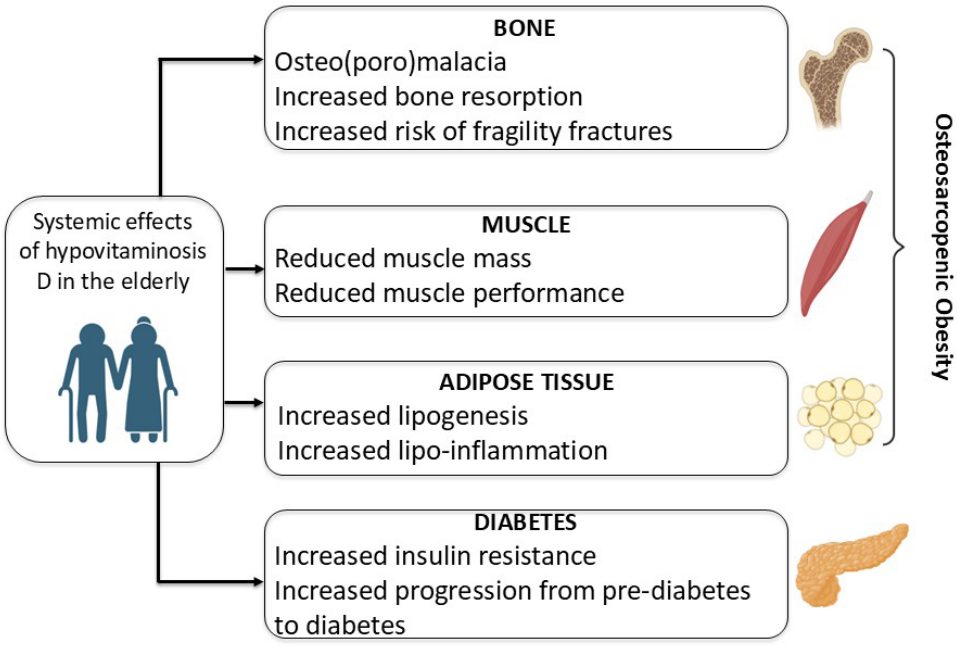


Figure 1. Systemic effects of hypovitaminosis D in the elderly.

and mortality on the elderly (82). Inflammation and oxidative stress exert catabolic effects on skeletal muscle and bone loss, and fat accumulation with fatty muscle infiltration (myosteatosis) results in lipotoxicity and alterations in muscle stem cells determining a shift towards adipocyte differentiation (88).

In addition to the muscle damage and loss of strength, vitamin D deficiency was also implicated in promoting neuromuscular dysfunction and cognitive impairment. Consistent evidence supports that vitamin D plays a crucial role in brain health with its deficiency being associated with cognitive decline and an increased risk of neurodegenerative diseases (89). Several studies indicate that subjects with lower serum 25(OH) vitamin D concentrations are characterized by worse cognitive performances and by a higher prevalence of dementia (90,91). Clinical and preclinical researches suggest that vitamin D exerts its beneficial effects on brain through multiple pathways including the modulation of neuroinflammation, reduction of oxidative stress and enhancement of amyloid-beta clearance (90-93). The negative impact of vitamin D deficiency on cognitive function of older individuals further exacerbates fragility fracture susceptibility and falls (4). In individuals with osteosarcopenic obesity, the excess in visceral and intramuscular fat contributes to the reduced muscle quality and the impaired bone remodelling. Concomitantly, the increased vitamin D sequestration in the adipose tissue significantly reduces its circulating bioavailability, worsening bone loss and muscle weakness (94).

Beyond its direct effects on skeletal and muscle function, vitamin D is also known to regulate the bone-muscle crosstalk, modulating key endocrine mediators such as osteocalcin, sclerostin, VEGF, IGF-1, and myostatin, all of which are essential for bone integrity and muscle trophism (36,82).

A multicenter, controlled, double-blind, parallel-group trial that included 380 sarcopenic older individuals, divided into an active group receiving vitamin D and protein nutritional supplementation or isocaloric control products only, showed that the intervention was effective in improving postprandial muscle protein synthesis, appendicular skeletal muscle mass, and lower-extremity function measured using the chair stand test (95).

Falls are a common and severe health issue among older adults, especially in those with osteosarcopenic obesity, leading to significant morbidity and mortality. Sarcopenia and osteoporosis have been directly

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linked to an increased susceptibility to falls, fractures, and mortality in multiple studies (96). Recent large RCTs found no significant reduction in fall risk with high-dose vitamin D supplementation in the elderly, however, the fall assessments in these trials were not rigorous (97). On the contrary, large interventional studies suggest a U-shaped relationship between vitamin D status and fall risk with optimal 25(OH) vitamin D levels for minimizing risk of falls ranging between 20-40 ng/mL, or as high as 60 ng/mL, with risk increasing at both lower and higher levels (98-101).

The high risk of fractures and falls associated with osteosarcopenic obesity in the elderly requires a comprehensive prevention strategy also including non-medical compounds as recently suggested in combining vitamin D supplementation and mechanical hip protectors (102). Indeed, besides the positive effect of vitamin D on skeletal and muscle health, hip protectors have been proposed as an adjunctive useful strategy to reduce fracture risk in frail older individuals. Although the compliance with these mechanical compounds remains a challenge, the technique advancement with next-generation airbag-based hip protectors is promising in improving adherence and fracture prevention outcomes (102). Thus, a multifaceted therapeutical intervention combining vitamin D supplementation, structured resistance training, and targeted nutrition may optimize muscle mass, bone density, and metabolic function in individuals with osteosarcopenic obesity (**Figure 1**).

Vitamin D deficiency in the elderly: why, when and how to supplement?

The 2024 Endocrine Society guidelines have recently recommended the use of vitamin D supplementation in all adults older than 75 years, regardless of baseline vitamin D status (30). This approach was supported by suggesting that routine supplementation may be more cost-effective than 25(OH) vitamin D measurement testing given the high prevalence of vitamin D deficiency and its association with overall increased mortality in this population. Fortified foods and specific vitamin D supplements are recommended, with daily dosing preferred over high-dose intermittent regimens to require stable vitamin D serum levels and reduce adverse effects (30). The 2024 Consensus Statement recommended a treat-to-target supplementation strategy highlighting individual risk assessment rather than the same therapeutical approach for every subject (5). While most of clinical trials have yielded inconsistent findings about the efficacy of vitamin D supplementation for different extra-skeletal outcomes, Consensus recommendations highlighted the importance in characterizing high-risk groups as older individuals with osteoporosis, sarcopenia, obesity, CKD, or malabsorption syndromes, for whom maintaining serum 25(OH)D levels above 30-40 ng/mL may potentially provide significant musculoskeletal and systemic benefits as reported in the post-hoc analyses of the major RCTs. The Consensus Statement supports selective vitamin D assessments also in this population to avoid unnecessary supplementation in those with sufficient levels and to stratify vitamin D deficiency severity identifying the more tailored therapeutical approach to adopt (5).

Vitamin D supplementation is available in different forms with distinct characteristics suitable for different specific clinical settings. Cholecalciferol (vitamin D3) is generally the preferred option for supplementation as it is characterized by greater bioavailability, a longer half-life, and a stronger effect in raising and maintaining adequate serum 25(OH) vitamin D levels as compared to ergocalciferol (vitamin D2) (5). However, in different specific clinical conditions an alternative approach may be required. For patients with severe vitamin D deficiency, malabsorptive syndromes, obesity, or liver impairment, calcifediol may represent a more effective therapeutical strategy (5,8). Differently to cholecalciferol, calcifediol bypasses hepatic hydroxylation leading to a faster correction of circulating 25(OH) vitamin D levels. In this regard, promising therapeutic strategies recently propose the use of biofortified foods directly with 25(OH) vitamin D3 also (103). In murine models, it was reported that biofortifying 25(OH) vitamin D3 in egg yolk effectively raises serum 25(OH) vitamin D concentrations than normal or high-fat diet. Other evidence from supplementation studies with hens showed that only dietary 25(OH) vitamin D3, and not vitamin D3

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supplementation, resulted in a pronounced increase of 25(OH) vitamin D3 concentration in the eggs (104). Recently, the European Food Safety Authority concluded that the novel food calcifediol monohydrate proposed for use in food supplements in humans can be considered as a bioavailable and safe source of vitamin D under the proposed conditions of use and amounts, i.e. up to 10 µg/day for children ≥ 11 years old and adults, including pregnant and lactating women, and up to 5 µg/day for children 3-10 years of age (105). Thus, the efficacy and utility of potential dietary sources of 25(OH) vitamin D is worthy to be further investigated.

For individuals with moderate to severe CKD, inactive forms of vitamin D supplementation cannot be sufficient as the renal hydroxylation process is impaired. In these cases, the use of active vitamin D metabolites, such as calcitriol, or analogs like alfacalcidol, is necessary (5,8). However, active analogs are also characterized by a very short half-life and narrow therapeutic ranges with higher risk to induce hypercalcemia and vascular calcification, particularly in fragile older individuals (5,8).

In older adults, the 2024 Endocrine Society guidelines recommended that a routine daily vitamin D supplementation of 800-2,000 IU is generally sufficient (30,32-34), although it is well-known that individuals with severe deficiency, obesity, chronic illnesses, or those on medications that affect vitamin D metabolism may require doses up to 4,000 IU per day (5,8). Even though the tolerable upper intake of vitamin D recommended by the National Academy of Medicine is set at 4,000 IU daily, when necessary, the use of higher doses may be considered given the demonstrated safety without specific severe concerns (5,8). The Calgary Vitamin D study showed that the safety profile of vitamin D supplementation, used in a cohort of healthy adults aged 55 to 70 years with serum 25(OH) vitamin D levels ranging from 12 to 50 ng/mL, was similar for doses of 400, 4,000, and 10,000 IU daily, and hypercalciuria, which occurred more frequently with higher doses, was mostly rare, mild, and transient (106).

Maintaining serum 25(OH) vitamin D levels above 20 ng/mL (50 nmol/L) is considered adequate for bone health and fracture prevention, while levels above 30 ng/mL may be needed in those with osteoporosis or calcium-phosphorus metabolism disorders (5). Although some studies explored the efficacy of high-dose intermittent supplementations (*e.g.*, monthly or annual boluses of 50,000-300,000 IU), these therapeutic strategies were associated to potential increased risk of falls (5,97-100,107,108).

Finally, for individuals at higher risk of vitamin D deficiency, 25(OH) vitamin D levels monitoring can be recommended with a biochemical assessment 2-3 months after starting supplementation allowing clinicians to evaluate the patient's response and adjust dosing, if necessary, due difficulty of certain high-risk groups in maintaining adequate vitamin D status is compromised by the underlying conditions (5).

Vitamin D deficiency and COVID-19: two modern pandemics highly affecting the elderly

The knowledge about extra-skeletal effects of vitamin D was improved by the recent observations consistently associating vitamin D deficiency with the occurrence of worse outcomes in the COVID-19 pandemic, especially in older populations (109-113) (**Figure 2**).

Vitamin D is well-demonstrated to influence innate and adaptive immunity, supporting antimicrobial and antiviral immune responses (1,5,114). Several retrospective case-control studies, meta-analyses, as well as prospective studies with low-risk of biases, consistently revealed inverse associations between hypovitaminosis D and the risk of severe COVID-19 (115-117). In older patients affected by COVID-19, vitamin D deficiency was associated with a more severe lung involvement, longer disease duration and mortality risk (118). In addition, older individuals with vitamin D deficiency and critically ill COVID-19 were characterized by a high risk of delirium as compared to those with normal vitamin D status (119). The association between vitamin D status and COVID-19 outcomes in patients older than 60 years was assessed in a recent systematic review including 11 studies and reporting that those with vitamin D deficiency had worse clinical outcomes such as mortality, oxygen therapy and invasive mechanical ventilation

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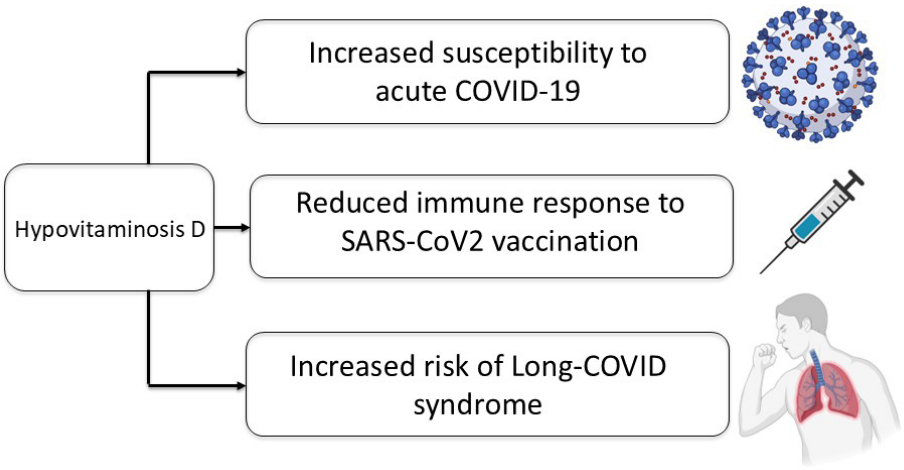


Figure 2. Impact of hypovitaminosis D in COVID-19 pandemic.

requirement (120). The authors also showed that patients supplemented with vitamin D were characterized by better outcomes as compared to the non-supplemented group (120). In the COvid19 and VITamin d TRIAL (COVIT-TRIAL) study, a single oral high-dose of cholecalciferol administered at diagnosis improves the 14-day overall survival in adults older than 65 years as compared to the standard-dose cholecalciferol (121). These results are in accordance with the previous findings reported in different large meta-analyses, not only focused on older individuals, assessing the impact of vitamin D supplementation in COVID-19 patients and showing benefits mostly in reducing mortality and intensive care unit (ICU) admission rates (122,123). Even if most of the studies included in these meta-analyses specifically investigated the impact of supplementation with cholecalciferol form, promising data were also shown in studies assessing the efficacy of treatments with calcifediol demonstrating its benefits in reducing the risk for severe COVID-19, ICU admission and mortality (124-132). Given the lesser sequestration in adipose tissue, the shorter half-life, and the potential faster elicitable increase in circulating serum 25(OH) vitamin D concentrations obtained with calcifediol when compared to cholecalciferol, these data may be relevant for future investigations in this specific clinical setting, especially when treating severely obese patients or those with malabsorptive conditions as typically occurs also during acute systemic illness.

Interestingly, the relationships between vitamin D deficiency and adipose tissue and glucose metabolism were also observed in this specific clinical context. In a single center cohort-study, lower 25(OH) vitamin D levels were associated with high blood glucose levels and higher BMI in COVID-19 patients predicting a more severe disease (133). In particular, patients presenting both hyperglycemia and hypovitaminosis D, and those presenting hyperglycemia or hypovitaminosis D, were markedly characterized by worse outcomes as compared to those with normal glucose and 25(OH) vitamin D levels. Since vitamin D deficiency also characterizes diabetic patients with retinopathy (134), it was hypothesized that lower 25(OH) vitamin D levels could worsen the predisposition of patients with diabetes to the microvascular systemic damage typical of COVID-19. Accordingly, patients presenting both overweight and hypovitaminosis D, and those presenting overweight or hypovitaminosis D, were markedly characterized by worse outcomes as compared to those with normal BMI and 25(OH) vitamin D levels (133). These data supported the importance of a potential synergistic negative impact of hypovitaminosis D and adipose and glucose alterations as unfavorable prognostic factors in patients with acute COVID-19.

Besides the impact on acute COVID-19, the extra-skeletal effects of this hormone in vitamin D were recently implicated also in influencing the post-acute disease recovery and Long COVID syndrome. Long COVID is a novel multisystemic syndrome involving

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multiple tissues and leading to neurocognitive, cardiorespiratory, constitutional, and musculoskeletal sequelae not explained by other medical diagnoses and potentially attributed only to the previous infection and continuing for more than 12 weeks after recovery (135). Several pathophysiological mechanisms have been proposed for Long COVID including viral persistence, hyperinflammatory state, immunological changes, and microbiota alterations (136), with an increasing risk observed in individuals with comorbidities such as obesity, glucometabolic and endocrine dysfunctions, and frailty (137-142). A potential role of vitamin D in the post-acute disease recovery of patients previously affected by COVID-19 was hypothesized on the basis of its multisystemic effects in influencing musculoskeletal health and function, in reducing nonspecific musculoskeletal pain, myalgia, and arthralgia (143,144), in influencing neurocognitive functions and disorders (145,146) and, also, in promoting respiratory recovery after pneumonia (147,148). In a single center cohort-study, lower 25(OH) vitamin D levels, evaluated at follow-up visits scheduled six months after hospital discharge, were observed in subjects with Long COVID than those without (149). Long COVID was diagnosed using the National Institute for Health and Care Excellence (NICE) guidelines with a multidisciplinary evaluation performed 6 months after hospital discharge (135). Regarding the affected health areas assessed, lower 25(OH) vitamin D levels were observed in particular in those with neurocognitive symptoms than those without. In addition, negative correlations between 25(OH) vitamin D and glucose levels at follow-up were also reported, reinforcing this association previously observed in patients with acute COVID-19 and in general population. This finding was proposed to represent an additional mechanism implicated in the Long COVID syndrome since in general population hypovitaminosis D was demonstrated to increase the risk of diabetes (5,30,81), and this latter was associated with a higher occurrence of Long COVID (149-151).

CONCLUSION

The last decades, growing evidence highlights a marked association between vitamin D deficiency and different adverse health effects, especially in high-risk groups as the older population. These individuals are particularly susceptible to vitamin D deficiency on a multifactorial basis, and to the occurrence of its detrimental consequences. In the elderly, a progressive age-related impairment of bone, muscle and adipose health can typically occur, and these processes can be further worsened by the lack of an adequate vitamin D status. Vitamin D deficiency has been linked to impaired muscle function, bone deterioration and metabolic negative consequences (**Figure 1**). Thus, vitamin D deficiency appears to contribute to frailty in the elderly through multifaced mechanisms. This promotes the occurrence of an osteosarcopenic obese phenotype in older individuals exacerbating their systemic complications and overall morbidity and mortality. Given the complex interplay between vitamin D and bone, muscle and adipose tissues, the emerging problem of vitamin D deficiency in the elderly requires a well-structured approach including a prompt diagnosis and screening based on individualized criteria, a personalized therapeutic strategy with treat-to-target supplementation approaches, and a structured follow-up monitoring to optimize both safety and efficacy, enhancing the overall benefits of vitamin D on muscle, bone and adipose tissues, and ultimately improving the quality of life of this vulnerable older population.

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invited review

Synthesizing the latest guideline-based recommendations for the management of female hypogonadism

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ABSTRACT

Over the past year, three new key guidelines have been published in the area of female hypogonadism, one from the Society for Endocrinology covering the full spectrum of causes of female hypogonadism in adult life, which will form the core of this review; another solely covering premature ovarian insufficiency from a consortium comprising the International Menopause Society (IMS), the European Society of Human Reproduction & Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) that updates the 2016 ESHRE guidance, and a third covering Turner syndrome across all stages of life from the International Turner Syndrome Consensus Group. In this review, we aim to synthesize the key elements from all of these documents, providing a timely update for clinicians managing affected women.

Keywords: Female hypogonadism; premature ovarian insufficiency; hypothalamic amenorrhea; Turner syndrome; hormone replacement therapy; estradiol

INTRODUCTION

Over the past year, three new key sets of guidelines have been published in the area of female hypogonadism (FH), comprising Society for Endocrinology (SfE) guidance covering the full spectrum of causes in affecting women of reproductive age, which will form the core of this review (1); guidance specifically for POI from an international consortium comprising the International Menopause Society (IMS), the European Society of Human Reproduction & Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) that updates the 2016 ESHRE guidance (2), and for Turner syndrome across all stages of life from the International Turner Syndrome Consensus Group (3). In this overview of FH, we aim to review the evidence, with an emphasis on highlighting novel or important new concepts arising from these latest guidelines.

FH is defined as the lack of ovarian reproductive hormone secretion during the normal post-menarcheal to premenopausal age range and is usually associated with prolonged amenorrhea and subfertility (1). It is classified into primary and secondary forms, and this distinction has important implications. Primary hypogonadism usually reflects an intrinsic depletion of hormone-secreting follicles in the ovaries, and principally results from gonadal dysgenesis, oophorectomy, or premature ovarian insufficiency (POI), but can also be due to rare disorders of estradiol synthesis or the secretion of biologically inactive gonadotropins.

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As with normal menopause, it is associated with abnormally high levels of follicle-stimulating hormone (FSH: >25 IU/L) and luteinizing hormone (LH) due to the loss of central negative feedback by ovarian steroid and peptide hormones. Secondary (*i.e.*, hypogonadotropic or central) hypogonadism results from ovarian under-stimulation due to inadequate gonadotrophin secretion, which translates into low (or inappropriately normal) FSH and LH levels with low estradiol and/or a thin endometrium.

FH presents with a multitude of symptoms, including prolonged amenorrhea, diminished physical, mental and emotional well-being, subfertility and impaired muscle, bone, urogenital and sexual health. Vasomotor symptoms commonly occur in adult-onset FH and are universal with acute surgical or medical oophorectomy in premenopause, but are rare in FH of congenital origin or of prepubertal onset; in the latter, there is instead a failure to fully develop external and internal secondary sexual characteristics or to experience normal menarche. Amenorrhea is classified as primary (absence of menarche by age 15) or secondary (lack of menses for 3 months if previously regular cycle, or for 6 months if cycle was previously irregular). Whether amenorrhea was primary or secondary maps approximately onto whether FH was of prepubertal or postpubertal onset.

APPROACH TO THE DIAGNOSIS AND CLASSIFICATION OF FH

It is vital to measure gonadotropin levels in order to distinguish primary from central hypogonadism, because the approach to the second-order investigations and fertility counselling is notably divergent (e.g., karyotype or copy number variation in primary FH, and serum prolactin and MRI pituitary in secondary FH). Other investigations are required for determining etiological causes within these two categories and may be ordered in case-by-case settings depending on the associated clinical manifestations present. Indeed, certain non-reproductive defects allow a fairly confident presumptive diagnosis of FH to be made even in normal prepubertal childhood, such as anosmia (suggesting Kallmann syndrome), or the constellation of clinical features that characterize Turner syndrome. In these individuals, pubertal induction with estradiol should be anticipatory from age 11 years, rather than reactive to the experience of pubertal delay (4).

Primary FH is always caused by organic pathology. However, secondary FH may be either organic (e.g., due to a genetic defect of hypothalamic-pituitary hormone secretion, parasellar mass lesion, radiotherapy, traumatic brain injury or surgery), or functional/reversible due to non-gonadal illness (e.g., systemic illness, low fat mass, excessive exercise or stress), opiate intake/treatment, or hyperprolactinaemic states. In functional secondary FH (commonly known as hypothalamic amenorrhea – HA), there are two key clinical judgments to make, one diagnostic and the other therapeutic. First, a judgement needs to be made as to how exhaustively to exclude organic disease by, for instance, checking anterior pituitary function, iron studies and/or MRI scanning. Second, for how long should one persist in attempting to achieve remission by targeting the underlying cause, e.g., through behavioural treatments, versus prescribing hormone replacement therapy (HRT)?

Although diagnosing primary FH or POI should be straightforward, patients commonly experience prolonged delays in accessing appropriate treatment; the diagnosis took longer than two years in 23% of Australian women, with at least two clinicians having been consulted on average (5) and, in a low-income (Medicaid) urban USA population, the median time from first presentation to diagnosis was 4 years (6). These delays may be related to clinicians finding it difficult to even consider the possibility of menopause in younger women, in situations when there are other potential causes for amenorrhea, or in the early years after disease onset when amenorrhea is not sustained and there may be intervals of cyclical bleeding. The latest international POI guidance has therefore commendably attempted to streamline the diagnostic process by no longer requiring a second raised FSH (>25 IU/L) concentration for diagnostic purposes (2).

The diagnosis of FH is even more difficult for secondary causes, where the diagnostic guiderail of a raised FSH concentration (>25 IU/L) is lacking and clinicians may not readily consider checking the estradiol concentration. Even if available they may be uncertain as to how

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to interpret the result. Specifically, laboratory printouts giving normative ranges for serum estradiol across the female menstrual cycle are unhelpful because healthy menstruating women rarely need measurements of estradiol levels. The range of quoted values (typically 100-2,000 pmol/L) is irrelevant to the context of prolonged amenorrhea where any temporal relationship to the menstrual phase is necessarily lacking.

Therefore, based on the range of estradiol concentrations observed in studies of women with prolonged lactational or hypothalamic amenorrhea (HA), SfE guidance recommends that a serum estradiol concentration < 200 pmol/L associated with prolonged amenorrhea is suggestive of FH (1).

The importance of early diagnosis and treatment of FH cannot be overstated. Aside from issues of patient symptoms and quality of life, prolonged hypoestrogenism is an important risk factor for cardiovascular disease, osteoporosis and fracture, and possibly even dementia (7,8). Although estrogen replacement therapy in preventing dementia remains controversial in the literature (9), there are established benefits to both cardiovascular and bone health in women with POI (onset prior to age 40 years) and early menopause (onset 40-45 years) (1,10). Considering that most hormone replacement therapy (HRT) studies have been conducted with post-menopausal women without specifying a menopausal age onset, further research is still needed in younger populations and, lacking large clinical trials, patient registries are likely to provide key data.

THE REGULATION AND PHYSIOLOGICAL ROLES OF OVARIAN HORMONES

Gonadotropin-releasing hormone (GnRH)-stimulated FSH and LH pulses of increasing amplitude from the pituitary gland herald the onset of ovarian steroidogenesis, corresponding to thelarche (Tanner B2). Estradiol secreted by the granulosa cells of developing follicles in response to FSH is central to the acquisition of key secondary sex characteristics and growth and maturation of the uterus over a period of 3-4 years. This highlights the importance of an appropriate tempo of incremental estradiol administration so as to mimic normal puberty, avoiding premature progesterone exposure, which can limit full development of the breast by limiting the branching morphogenesis necessary for complete development of the ductal tree (4,11), and may also limit uterine development (12). Although pulsatile subcutaneous GnRH treatment has been used both to induce puberty in girls and, more commonly, to achieve ovulation in adult females with central hypogonadism of hypothalamic origin, its complexity, the associated costs and availability in only very few countries, combine to explain why it is rarely used nowadays (13).

GnRH neurons are not a site of any significant estradiol negative feedback, and the secretion of GnRH at their terminals at the median eminence is directly regulated by Kisspeptin (Kp) secreted by neurons having their cell bodies in the arcuate (ARC) and anterior periventricular (APV) nuclei of the hypothalamus. Kp secretion is determined through the integration of both external environmental and internal homeostatic inputs, including leptin secreted by fat cells and estradiol, progesterone and anti-Müllerian hormone (AMH) secreted by the ovaries. Broadly, estradiol inhibits Kp secretion by KNDy neurons in the ARC, but stimulates Kp secretion by APV neurons, thereby forming the oscillator circuit that creates cyclical hormone secretion and gametogenesis in females compared to the steady-state system in males (14). Other peptides secreted by KNDy neurons that help to regulate GnRH secretion include neurokinin B (NKB – stimulatory) and dynorphin (inhibitory). Crucially, inactivating mutations of Kp, NKB and GnRH peptide hormones, or far more common of their G-protein-coupled receptors, are among the recognized genetic causes of congenital hypogonadotropic hypogonadism (CHH) (15). In contrast, the higher concentrations of AMH (secreted by granulosa cells in small antral and preantral ovarian follicles) promote a higher frequency of GnRH pulses that favors LH secretion, as occurs in PCOS.

In reproductive life, estradiol is essential for cyclical endometrial repair and cellular proliferation after each menstruation during the follicular phase, and for the expression of endometrial progesterone receptors, thereby underpinning the necessary changes that are required for embryo implantation and the establishment of pregnancy (16). It is also essential for

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the proliferation of epithelial mucosal cells of the vagina and vulva, maintaining the integrity and lubrication of the vulvo-vaginal epithelium, and for the ongoing health and functionality of the urogenital tract.

Estradiol promotes epiphyseal fusion and is also crucial to achieving peak bone mass and maintaining it thereafter. During puberty, the rise in sex hormone levels, particularly estradiol, stimulates osteoprotegerin activity and decreases RANKL expression in osteoblasts. Estradiol also inhibits the secretion of proinflammatory cytokines, which in turn reduces osteoclastic activity, leading to decreased bone resorption and increased repair of microfractures, thereby augmenting trabecular bone thickness in particular. In contrast, estrogen deficiency promotes osteoclastic activity and subsequent bone resorption via several pathways, including tumor necrosis factor-α, interleukin-1β, RANK-ligand and sclerostin (Wnt signaling) pathways (1), which may also be exacerbated by upstream disturbances in extragonadal reproductive hormones (17).

Estradiol plays an important role in modulating cardiovascular risk through its signaling via ER-alpha and ER-beta receptors. As oxidative stress plays a significant part in the pathogenesis of atherosclerosis, myocardial dysfunction, cardiac hypertrophy, heart failure, and myocardial ischemia, excess reactive oxygen species (ROS) resulting from hypoestrogenic states lead to the increased 10-year cardiovascular risk observed on POI and early menopause. Estradiol is thought to act in the upregulation of antioxidant gene expression, increasing Endothelial nitric oxide synthase (eNOS) activity and decreasing superoxide production, with subsequent reduced apoptosis and necrosis of cardiac and endothelial cells. Altogether, the ensuing actions result in a more favorable lipid profile with increased levels of HDL and decreased levels of LDL and total cholesterol (18,19). Estradiol also promotes cerebral blood flow and vasodilation and reduces oxidative stress and neuroinflammation, as well as enhancing functioning of the hippocampal and prefrontal cortices (20,21). Additional effects of estradiol on mitochondrial activity, regulation of insulin sensitivity and the renin-angiotensin-aldosterone system further contribute to its broadly favorable metabolic effects (22,23).

CAUSES OF FH

Primary hypogonadism, including premature ovarian insufficiency (POI)

POI is characterized by oligo-amenorrhea (>4 months duration) in conjunction with a raised FSH level (>25 IU/L), occurring in women <40 years old and having characteristic signs or symptoms, including sleep disturbance, vasomotor fluctuations, low libido and energy, altered urinary frequency, dyspareunia due to vulvovaginal atrophy and cognitive disturbances. Recent international POI guidelines indicate a prevalence of 3.5% and recommend that a single FSH assessment (>25 IU/L) in a symptomatic woman is sufficient for diagnosis; a second FSH measurement four weeks later only being required where there is diagnostic uncertainty (2).

Although the etiology of most cases of POI remains undefined based on present knowledge and techniques, further investigation of the cause should nevertheless be undertaken, including a personal and family medical history, karyotype (or copy number variation test), thyroid-stimulating hormone (TSH) level, thyroid peroxidase (TPO) antibody concentration, and fragile-X testing (*FMR1* gene). Genomic evaluation should be performed in younger women once other potential causes have been excluded, but from the perspective of other family members, there are benefits in making it across the age spectrum of POI, especially in respect of *FMR1* (2).

Women with primary amenorrhea and absent puberty are likely to have gonadal dysgenesis (see below), although type 1 galactosemia (*GALK1* gene), *FMR1* gene mutations and even Turner syndrome (TS) can equally present with secondary amenorrhea post-puberty. Autoimmune oophoritis is a major post-pubertal cause, albeit anti-ovarian antibody tests are non-specific, and so the diagnosis is usually inferred from the presence of other autoimmune conditions, thyroid, adrenal, celiac disease, or pernicious anemia.

Gonadal dysgenesis and Turner syndrome

Gonadal dysgenesis refers to a broad range of conditions characterised by impaired gonadal development due to alterations of genetic material or abnormalities in cell division that lead to dysplastic or streak gonads and a prepubertal female phenotype irrespective of

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sex chromosomes. The karyotype can thus be 46XX, 46XY (Swyer syndrome), or 45X0 (or variants thereof) in Turner syndrome (TS). Unless there were other characteristic features leading to the clinical suspicion and diagnosis of TS in prepuberty, gonadal dysgenesis otherwise presents invariably with primary amenorrhea and absent puberty.

TS is the most prevalent sex chromosome disorder in women, affecting 5 per 10,000 live births (24). There is complete or partial absence of one X chromosome, with ovarian insufficiency primarily associated with deletions or structural abnormalities of the long arm (Xq13-27), which contains genes critical for ovarian development and function, and short stature with haplo-insufficiency for the *SHOX* gene on the pseudo autosomal region 1 of the short arm (Xp22.3). In early fetal life, there is accelerated oocyte apoptosis and impaired formation of primordial follicles, leading to depletion of germ cells (25). Characteristic intrauterine features on prenatal sonography comprise increased nuchal translucency, cystic hygroma, intrauterine growth restriction and cardiac anomalies, but a minority of cases entirely lack any notable physical dysmorphisms, whether *in utero* or postnatal life. Longitudinal studies have identified abnormally raised FSH and LH concentrations during postnatal minipuberty and from late prepuberty onwards.

If the diagnosis of TS was made in prepuberty, then annual measurement of FSH, LH and AMH concentrations should be undertaken from age 8-9 until 11-12 years, to identify those girls who will need early pubertal-induction proactively. AMH levels < 4 pmol/L and raised FSH are highly correlated with absent puberty (3) and, in these girls, estrogen replacement should not be delayed until thelarche fails to appear at the upper limit of the normal age of onset; rather it should begin at 11 years of age with incremental doses of 17□-estradiol until the adult replacement dosage is reached over the next 3-4 years, and with longitudinal monitoring of Tanner staging and sonographic assessment of uterine dimensions and maturity (2-4). It is also recommended that the final adult dose should achieve serum estradiol concentrations in the 350-550 pmol/L (100-150 pg/mL) range as this seems to be associated with better uterine maturation (3). Nevertheless, POI guidance still does not recommend adjusting HRT doses according to the serum estradiol concentration (2).

The TS phenotype is highly variable, depending to some extent on whether all or part of the X-chromosome is missing and whether there is mosaicism (albeit the ratio of total somatic cells with normal or abnormal chromosomes cannot be reliably extrapolated from that observed in culture of peripheral blood leukocytes). The initial presentation and diagnosis may thus arise as a result of prenatal diagnostics, childhood growth retardation, failure of puberty with primary amenorrhea, or even with the onset of secondary amenorrhea due to POI (25). Up to one third of girls with TS may develop spontaneous thelarche, but spontaneous menarche only occurs in 5%-20% and < 10% go on to develop regular periods, albeit with an increased risk of miscarriage in pregnancy and an unquantified increased risk of developing POI in later life.

Natural conception is not possible for women with gonadal dysgenesis and streak ovaries, in whom egg-donation is the only means of carrying a pregnancy to term, but pregnancy may still occur in up to 10% of TS women, being the vast majority of cases among those with mosaic karyotypes and a history of spontaneous menarche. For TS women of reproductive age who are menstruating normally and have the necessary psychological maturity (but are either not in a relationship or not ready to start a family), oocyte cryopreservation is recommended. Contraceptive measures should also be considered in those who are sexually active if pregnancy is not desired. Although a potentially promising technique for younger TS girls (26), ovarian tissue preservation should only be offered in the context of a formal research protocol (3).

Autoimmune

Autoimmune oophoritis accounts for up to 30% of cases of POI, most commonly associated with thyroid and adrenal disturbances, but less frequently pernicious anemia, T1 diabetes mellitus, rheumatoid arthritis, Crohn's disease, myasthenia gravis and lupus (27). Up to 60% of cases diagnosed with APS-1 (autoimmune polyendocrinopathy-candidiasis-ectodermal

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dystrophy – APECED), characterized by mutations in the autoimmune regulator (*AIRE*) gene, will develop POI. There is a significant correlation between positive adrenal 21-hydroxylase antibodies and POI, and monitoring of adrenal as well as thyroid function should be considered in younger females with POI of unknown cause, albeit POI usually presents a decade before the onset of clinical adrenal involvement (27).

Women may experience brief disease remissions that allow them to ovulate and fall pregnant, particularly in the early years after onset when AMH levels are > 4 pmol/L, and with an approximately 5% lifetime chance of conceiving naturally (28). Although nearly three-quarters of women with 46XX POI retain ovarian follicles, chronically raised LH levels promote premature luteinization that diminishes the chances for spontaneous ovulation over time (1). Despite promising results in murine models (24), there are no disease-modifying therapies for autoimmune oophoritis, albeit the impact of oophoritis caused by cytotoxic drugs such as cyclophosphamide, can be mitigated by contemporaneous treatment with a GnRH-analogue to induce gonadotropin suppression and ovarian quiescence (29).

Iatrogenic

In addition to the obvious immediate implication of bilateral oophorectomy, removal of benign ovarian cysts (especially if large or the surgery is repeated) predisposes to POI. Moreover, there is also a growing population of young women who have survived cancer and its treatment. The risks from chemotherapy and pelvic radiotherapy vary by regimen, dose, and age at administration. The high toxicity is associated with alkylating agents such as busulfan and cyclophosphamide, and high-dose lomustine; larger doses and older age are linked to poorer outcomes in terms of ovarian function (30-32). If time permits, patients should always be referred for a consultation regarding strategies for fertility preservation prior to undergoing treatment (32). Many younger patients later recover gonadal function following an initial phase of chemotherapy-induced POI, and a higher AMH level is predictive of this (33), but their depleted ovarian reserve may later predispose them to POI or early menopause (34,35). Finally, even if pregnancy is achieved, previous pelvic radiotherapy limits the ability of the uterus to support pregnancy to term, resulting in a much higher likelihood of miscarriage, preterm labor, low birth weight and other complications (36).

Genetic mutations and environmental factors

A premutation in *FMR1* is the most common single gene abnormality associated with the development of POI, accounting for 3%-5% of cases; some 12.9%-24% of women carrying it will experience POI, with a younger age of onset occurring across successive generations ("anticipation") (37) and has been linked to an increased risk of mental retardation, tremor and ataxia syndrome in affected males (38). However, more extensive genetic screening is now becoming a standard of care in POI, with one study suggesting a prevalence of genetic defects in up to 23% of younger patients and those presenting with primary amenorrhea (39). Nevertheless, data from the UK Biobank suggest that, for the vast majority of women, POI is not commonly caused by autosomal dominant variants of genes previously reported or currently evaluated in clinical diagnostic panels; most cases instead likely being oligogenic or polygenic in nature (40). However, further studies in different populations are still needed to solidify recommendations and to better understand the roles of gene regulatory pathways and transcription factors in ovarian development and follicle maturation.

Environmental factors, such as cigarette smoking, hysterectomy, recurrent viral infections, exposure to phthalates, bisphenol A and pesticides, as well as Endocrine Disrupting Chemicals (EDCs), have also been linked to an earlier onset of menopause, most likely via an epigenetic effect or, potentially, an impact of on the ovarian vascular supply depending on the individual risk factor (41).

Central hypogonadism

Central hypogonadism in women results in impaired ovarian function due to lack of gonadotropin stimulation. It may be congenital or acquired and, if acquired, either organic or functional. Congenital forms are among the very rare causes of FH, including CHH

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(female prevalence of 1-in-40 to 125,000), CHARGE syndrome (see below; 1-in-15,000), combined pituitary hormone deficiency (CPHD; 1-in-5 to 10,000) and septo-optic dysplasia (SOD; 1-in-10,000), with perhaps 60% of the latter two exhibiting gonadotropin deficiency.

In contrast, hypothalamic amenorrhea (HA), a form of functional central FH, is among the most frequent causes of amenorrhea during reproductive life, and is by far the most common cause of FH. Other frequent causes of functional central FH include hyperprolactinemia, whether induced by prolactinoma, with serotoninergic and anti-dopaminergic drugs, opiates, or depot injections of medroxyprogesterone acetate (MPA). It is likely that, in many cases, functional CH may result from a combination of predisposing factors that individually might not be sufficiently severe to disturb menstrual cyclicity.

Nevertheless, similar principles of diagnosis and treatment apply to all forms of CH (42) and, indeed, there are shared genetic predispositions in relation to CHH, CPHD, SOD, CHARGE and HA (43-46).

Congenital hypogonadotropic hypogonadism (CHH)

This is characterized by a congenital defect of GnRH secretion or (less commonly) GnRH action. Around two-thirds of CHH patients present with absent puberty, which is associated with complete GnRH/LH apulsatility, and the remaining one-third exhibit arrested partial puberty at presentation, which is associated with low-frequency, low-amplitude, or nocturnal-only pulse patterns. However, primary amenorrhea is ubiquitous in any case. In a European web-based survey, the median age at diagnosis and clinically meaningful treatment in females was 20.7 ± 7.4 years by patient recall, probably due to diagnostic confusion by their clinicians with self-limiting delayed puberty (SLDP) or HA, both of which share a common biochemical signature with CHH. This delay in diagnosis and effective treatment was associated with enduring psychological and psychosexual morbidity (47).

CHH can occur as an isolated neuroendocrine defect in 30%-40% of cases or in association with other developmental anomalies, most commonly anosmia that defines Kallmann syndrome (around 50% of cases), but also hearing loss (10%), midline defects (cleft lip/palate – 5%), synkinesia, renal agenesis, dental and skeletal anomalies (collectively around 5%). The link between anosmia (lack of sense of smell) and GnRH deficiency is explained by the extracranial origin of GnRH neurons within the embryonic olfactory placode and their migration alongside fascicles of the olfactory, terminal and vomeronasal nerves during fetal life (42,48,49).

Pathogenic mutations in over 60 genes have been linked with CHH, acting either alone or in combination (oligogenic disease), with perhaps 50% of cases now having a robust genetic explanation. Mutations that disrupt GnRH neuron development and migration usually manifest as Kallmann syndrome (KS), whereas those that disrupt GnRH homeostasis, secretion or action present exclusively as pure neuroendocrine CHH. Synkinesia and renal agenesis are particularly associated with *ANOS1* mutations, hearing loss with *CHD7* and *SOX10* mutations, and midline, digital and dental defects with mutations of *FGFR1* or its cognate ligand *FGF8*. Given that X-linked KS (*ANOS1*) comprises only around 10% of KS cases (5% of total CHH), the genetic architecture of CHH provides no clues as why it is around 3-4-times less common in females (15).

Hypopituitarism and combined pituitary hormone deficiency (CPHD)

Acquired hypopituitarism in adulthood is most commonly caused by benign parasellar tumors, comprising in descending order of frequency, pituitary adenomas (most commonly prolactinomas or non-functioning), craniopharyngiomas, Rathke's cleft cysts, meningiomas, gliomas and germinomas. Prolactinomas cause functional CH through both hormonal and mass effects. Other causes include CNS infections, traumatic brain injury (especially military blast trauma), radiation, surgery and, rarely nowadays in the developed world, Sheehan's syndrome (pituitary infarction caused by severe post-partum hemorrhage) (50).

Combined pituitary hormone deficiency (CPHD) is defined by the deficiency of at least two pituitary hormones and is often diagnosed and treated postnatally or in early childhood. However, gonadotrophin deficiency may not become apparent until puberty fails

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to initiate or, as hormone deficiencies may manifest metachronously, with the onset of secondary amenorrhea in later life. Several genes have been identified, comprising either pituitary transcription factors or CHH-related genes, but the vast majority of cases remain without an identified genetic cause (51-53). There are characteristic MRI appearances of pituitary fossa hypoplasia and/or posterior pituitary ectopia that are also seen in isolated GH deficiency. SOD is a related developmental brain malformation that can present with pituitary hormone deficiencies, severe visual impairment, neurocognitive disability and neurodivergent traits, as well as agenesis of the corpus callosum or optic nerve hypoplasia (54).

CHARGE syndrome

The constellation of coloboma (ocular malformation of the lens, iris, or retina), congenital heart defects, choanal atresia (abnormal formation of the nasal cavity), retardation of growth and development, genital hypoplasia, and ear anomalies (both external and internal) associated with deafness define CHARGE syndrome, a condition of multiple congenital anomalies that also frequently includes severe learning difficulty, facial asymmetry and immunologic problems (55). Most patients exhibit CHH, with or without anosmia, and it may not be easy to distinguish between milder forms of CHARGE syndrome from the more severe KS phenotypes. Approximately two-thirds of cases are explained by large *de novo* deletions in the Chromodomain-helicase-DNA-binding protein 7 (*CHD7*) and, although the same gene is also involved in both normosmic CHH and KS, inherited point mutations are more typical in these conditions (56).

Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a rare genetic disorder (1/10,000-25,000), associated with severe hypothalamic dysfunction caused by lack of expression of the paternal copy of maternally imprinted genes in the chromosome region 15q11-13. Subtypes are classified into deletions (70%), maternal uniparental disomy (25%-30%), imprinting center defects (3%-5%) and rare unbalanced translocations. It typically causes profound physical, mental and social disability. Puberty is usually delayed or incomplete due to CHH, but may occasionally be precocious, and females are usually infertile. As well as HRT, patients typically benefit from growth hormone treatment during childhood and adolescence and, crucially, long-term management of hyperphagia and obesity (57).

Functional central FH including hypothalamic amenorrhea

Definition

Functional central FH is fully reversible when the external constraint to gonadotropin (or GnRH) secretion is removed. One form of this, hypothalamic amenorrhea (HA), is among the most common pathological causes of secondary amenorrhea, and results from suppression of GnRH secretion by an active systemic disease process, stress, or a state of relative energy deficit, whether from excessive exercise or disordered/restricted food intake (58). It is likely to have been programmed by evolution to prevent pregnancy during times of scarcity or long-distance migration. Although most women and girls presenting with HA do not have an active eating disorder such as anorexia nervosa, many will have disordered eating or a history of eating disorder, along with high-achieving or perfectionist personality traits and sleep deprivation.

Pathophysiological basis and differential diagnosis of HA

Secretion of leptin by adipose cells is heavily influenced by energy balance and fat mass, and leptin deficiency inhibits Kp secretion. Reduced Kp secretion initially slows GnRH pulse frequency, which favors FSH secretion as per early puberty, but with extremely low leptin levels signaling critical undernutrition, the reproductive axis then shuts down entirely. Nevertheless, whereas infusions of pulsatile GnRH and twice daily subcutaneous injections of leptin fully restored reproductive axis function in women with HA (59), the effect of Kp infusions was less marked and not sustained (60).

South Asians appear more protected from HA due to higher fat mass than Caucasians with a similar BMI, whereas athletes may exhibit HA with normal (or even raised) BMI due to high muscle mass. However,

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there must also be individual factors that determine why females with apparently similar body habitus and activity levels are discordant for HA. Indeed, HA females are more likely to harbor monoallelic gene variants associated with CHH than control populations, which may increase their susceptibility to environmental stressors (1). In clinical practice, functional HA is commonly linked to stress – whether metabolic, physical, or psychological – as well as weight loss resulting from reduced caloric intake or intensive physical activity (61).

It may be difficult to distinguish HA from CHH in women with primary amenorrhea, or from an organic pituitary process in secondary amenorrhea, but aside from the clinical history, there are some helpful indicators, including BMI (usually <23 kg/m^2 in HA), congenital defects (present in 60-70% of CHH), fasted 9 AM anterior pituitary function (normal in CHH aside from LH and FSH; potentially abnormal in organic pituitary disease), potentially low free T3 and IGF1, but high-normal cortisol and GH in HA; iron studies (high ferritin and iron binding saturation in iron overload), MRI of the pituitary gland (normal in CHH and HA, but usually abnormal in CPHD and organic acquired hypopituitarism) and olfactory bulbs (absent or hypoplastic in KS), body composition by DXA or bioimpedance (low fat mass and/or high lean body mass in HA), and potentially also genomic evaluation as a final consideration.

Management

Removing or addressing the underlying cause of HA (where achievable) allows normal function of the HPG axis to resume with restoration of normal ovarian hormone secretion, menstruation, fertility and bone mass. Teaching has thus traditionally emphasized the primacy of behavioral (dietary, exercise or psychological) interventions (62-64). However, many women with HA find these adjustments to be unacceptable or unachievable, and others may already have experienced a significant impact on bone, sexual or urogenital health in the years prior to their initial consultation. Therefore, under these circumstances, the SfE recommends considering HRT at the initial consultation, which could either form a bridging therapy pending the outcome of behavioral interventions, or if there is no resolution, continued until the normal age of menopause. In any case, the recommendation for HRT should not be deferred for longer than 6-12 months beyond the initial discussion if there is no resolution (1).

Similar principles apply to women with other forms of functional central FH, e.g. induced by opiates or hyperprolactinaemia. Although the initial aim would be to seek to achieve resolution of hyperprolactinaemia through dopamine-agonist treatment of prolactinoma or substitution of anti-dopaminergic or serotonergic drugs with alternative neuroleptics, or weaning of opiate medication, this strategy cannot be open-ended. Again, HRT should be recommended at the outset if there is little realistic possibility of achieving this aim (e.g., patient or psychiatrist unwilling to risk destabilizing mental health by substituting a prolactin-neutral drug; pain or addiction specialist unable to wean opiates), or if resumption of menstruation has not occurred within 6-12 months of the initial consultation.

Conventional ethinylestradiol-based combined oral contraceptive (COC) are best avoided due to the inferior bone protection they confer compared with transdermal estradiol, which is likely mediated by greater inhibition of liver IGF1 secretion, and greater thrombosis risk. Nevertheless, for sexually active women in whom pregnancy would not be desirable, it is vital to discuss contraception at the initial consultation, due to the potential for reproductive function to recover rapidly and unpredictably in all forms of functional CH. If other contraceptive options are not acceptable, then a 17-estradiol-based COC (or if not available, systemic estradiol combined with progesterone only pill) could be prescribed as an alternative to HRT (1).

Hormone treatment

Estrogen

Estrogen replacement therapy in women with FH is essential to maintain secondary sexual characteristics, optimize sexual functioning, and prevent vasomotor or neurocognitive symptoms, bone loss and fragility fractures, urogenital atrophy, and (although not proven) premature cardiovascular disease.

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There are three primary types of estrogen formulations that exhibit different pharmacodynamics and activity at the □ and □ estrogen receptors: 17□-estradiol (= estradiol), ethinylestradiol (EE) found in most COCs, and conjugated equine estrogens (CEE). Only estradiol can be reliably measured by clinical assays, being the natural endogenous hormone. CEE contains a mixture of various xenoestrogenic compounds purified from pregnant mare urine, and EE is a synthetic analogue that has long been used in COCs. EE interacts with both □ and □ estrogen receptors, irreversibly inhibiting CYP enzymes involved in steroid metabolism and activating the renin-angiotensin system, resulting in a mechanism of action that diverges from normal physiology and that necessitates regular blood pressure monitoring (65). The COC is also inferior to HRT in respect of bone health in women with POI (66). Therefore, HRT based on 17□-estradiol (available in the form of tablets, patches, spray or gel) is now the preferred form, as per all current guidance (1-3), with data from both menopausal and transgender females indicating a lower rate of thrombosis, especially when administered transdermally (1). Hence, routine use of COC as a first-line form of HRT is no longer recommended unless there is a real risk of unwanted pregnancy and other forms of contraception are not acceptable (1-3). In this case, the SfE recommends one of the newer estradiol-based COCs that have the additional advantage of only a few blank days, rather than the traditional "pill-free week" during which zero estrogen is administered (1).

Progestins

Progesterone is required for endometrial protection in women with a uterus who have completed puberty, and a variety of progestins can be administered systemically in a sequential or continuous combined manner, or as an intrauterine system (IUS). Long-acting progestin contraceptive implants or depot injections could probably provide adequate endometrial protection as part of a continuous combined HRT regimen, but are unlicensed for this purpose. Progestins should be prescribed at the lowest dose that achieves endometrial protection, evidenced by the lack of unscheduled bleeding. This is because prolonged use of combined HRT in postmenopausal women confers a higher risk of breast cancer (greater with continuous combined than sequential), whereas that risk is much lower in hysterectomized women on estrogen monotherapy (1). Nevertheless, prolonged HRT use in women of premenopausal age with FH does not increase the risk of breast cancer above baseline for a eugonadal female (22,67). It has been plausibly suggested that the progestin dose should be adjusted in proportion to the estradiol dose, so that estradiol doses exceeding 2 mg orally or via gel, 100 mcg patches, or 3 sprays (4.59 mg) may require higher progestin doses than in standard preparations (22), but evidence is lacking (1).

All three guidelines (1-3) favor micronised progesterone (oral or vaginal; 100-200 mg daily for the first 12-14 days of each calendar month, or 100 mg daily taken continuously), or its stereoisomer dydrogesterone (oral; 10 mg daily for the first 12-14 days of each calendar month, or 5-10 mg daily taken continuously), as being metabolically neutral, improving sleep quality and potentially mitigating breast cancer risk due to pro-apoptotic and more antiproliferative effects on breast tissue (68-70). However, a levonorgestrel 52 mg IUS (approximately 21 mcg/day steady state release over 5 years) provides the best endometrial protection and, due to lesser systemic absorption, is likewise anticipated to have a lower associated breast cancer risk than older, more androgenic and procoagulant progestins, such as norethisterone acetate (NEA) and MPA (1). Moreover, for a female with disability, in whom it has not proven possible to avoid distressing cyclical or unscheduled bleeding, the insertion of a levonorgestrel IUS under general anesthetic can be transformative of quality of life. Nevertheless, despite the overall advantages of micronised progesterone or its stereoisomer dydrogesterone for most women, NEA in a continuous-combined regimen provides the next best progestin for endometrial protection after the levonorgestrel IUS and, when administered transdermally in the form of combined patches with estradiol, may also avoid the prothrombotic effect of oral NEA.

Cautions and contraindications

A wide range of medical conditions are listed as contraindications to HRT (or COC in eugonadal women)

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(71), based on studies predominantly using oral CEE in postmenopausal women or EE-based COC in younger women. Therefore, multidisciplinary discussion may be necessary with other specialists (e.g., Medical and surgical Oncologists and Neurologists, Hematologists, Stroke Physicians and Cardiologists) and of course the patient herself. To this end, it is useful to first remind all parties that, unlike perimenopause, there is no long-term treatment alternative to HRT and no valid or reasonable non-treatment strategy for FH. Second, that modern transdermal estradiol plus "neutral" progestins have a negligible prothrombotic action compared with historic CEE plus MPA regimens, with good evidence for this both from older postmenopausal women and younger transgender females (1). Finally, it may be necessary to focus the minds of colleagues by posing the direct question: *"if this were a young women with regular periods, would your usual standard of care for treating [migraine with aura, stroke, venous thromboembolism (VTE), meningioma, hepatic adenoma, obesity, diabetes, major surgery or a strong family history of breast cancer, etc.] comprise precautionary medical or surgical oophorectomy or anti-estrogen treatment?".* From this analysis, it becomes clearer that, for women with FH below the age for usual menopause, HRT is only contraindicated in two conditions: past or current breast cancer and active endometrial cancer.

For eugonadal women with BRCA1 or BRCA2 mutations, a risk-reducing bilateral salpingo-oophorectomy after completion of childbearing around age 45 years (the age threshold for early menopause) is recommended to significantly reduce the risk of ovarian, fallopian tube, breast and peritoneal cancers. Subject to patient choice, only the most severe BRCA1 mutations, causing complete loss or major disruption of protein structure of function, would prompt consideration of earlier oophorectomy (down to age 35 years), especially as prophylactic bilateral mastectomy more effectively reduces the risk of aggressive triple negative breast cancer (72). Therefore, younger women with FH who are BRCA carriers should not be routinely denied HRT, particularly as many will have already experienced years of untreated estrogen deficiency. It would be ideal to make such decisions after consulting with oncology colleagues.

Oncology guidance also suggests that vaginal estrogen is contraindicated in women with a history of breast cancer, but this is based entirely on precautionary principles and with no direct evidence of harm. Indeed, as systemic absorption is negligible (73) and no impact on breast cancer-specific mortality has been identified (74), the SfE supports the use of vaginal estrogen in FH, where breast cancer has been treated with curative intent and there are sexual or urogenital symptoms; especially in women taking tamoxifen (rather than aromatase inhibitors) or having ER-negative disease (1).

In the context of migraine with aura, stroke, angina, inherited procoagulant disorder, VTE (or strong family history thereof), obesity, type 2 diabetes, dyslipidemia, or cigarette smoking, oral estrogen and androgenic progestins are strongly discouraged, and transdermal estradiol with oral micronised progesterone, dydrogesterone or levonorgestrel IUS are instead recommended (1); if necessary, with the addition of long-term anticoagulation as per Hematologist advice. In relation to myocardial infarction, the SfE (1) suggests pausing HRT for 6 months if tolerated. This recommendation was based on the HERS study (75), albeit this was done with a prothrombotic HRT regimen based on CEE plus MPA.

HRT treatment: doses, monitoring and timelines

There are no licensed HRT products specifically developed for younger women with FH. All standard HRT preparations, whether at low, intermediate or higher dose, were formulated as the lowest effective doses to achieve suppression of vasomotor symptoms in the majority of symptomatic postmenopausal women, and not to maintain long-term bone, muscle, sexual, urogenital, or cardiovascular health in younger women with FH over a period of up to four decades, and this is where registry data relating to transgender women can help fill gaps in our knowledge. All women of reproductive age experiencing hypogonadism for six months or more should have a baseline assessment of BMD and identification of any additional risk factors for low bone mineral density, with the findings informing the frequency of any future DXA scans (1).

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HRT in postmenopausal women achieves effective fracture risk prevention even at standard doses, with the benefits comparable to those of bone-specific drugs, which cannot anyway be prescribed open-endedly due to diminishing benefit and greater side-effect profile beyond the authorized period. Therefore, except under exceptional circumstances (and subject to adequate calcium and vitamin D intake), HRT is considered the only recommended treatment for the prevention or treatment of osteoporosis and for fracture prevention in women with FH up to the normal age for menopause (1). Replacement can typically be continued to the normal menopausal age or beyond, depending on BMD and estrogen-deficiency symptoms and considering patient preference based on personalized counselling. Thereafter, bone management mirrors that in a woman who has reached the menopause at an expected age. However, women who experienced prolonged gaps in HRT are recommended to continue until the upper limit of normal age at menopause (55-56 years), rather than the median age (51 years).

Some clinicians continue to recommend adjusting HRT doses based on patient symptoms or BMD and discourage monitoring serum estradiol concentrations, and the International POI guidance broadly supports this position, albeit suggesting that target serum estradiol level 200-400 pmol/L might be appropriate (2). In contrast, guidance for transgender women (76) mandates adjusting estradiol doses to achieve serum levels harmonized to the mid-follicular range for healthy young women (typically 300-600 pmol/L). The latest International Turner syndrome guidance (3) also recommends adjusting the final HRT dose to achieve serum levels very similar to those of the general population (350-550 pmol/L). The SfE's guideline committee concluded that there was currently insufficient evidence to recommend whether routine testing of serum estradiol versus non-testing achieved better efficacy and safety outcomes in women with FH (1), but nevertheless identified circumstances in which measuring levels was likely to be beneficial, including the persistence of symptoms despite reasonable dose-adjustments, failure of BMD to improve on serial DXA scanning, or when adherence was doubtful, and identified either 350-550 or 300-600 pmol/L as being reasonable target ranges. However, compliance with treatment and correct use of medication should be ascertained prior to adjusting the dose of estradiol. Evaluation of endometrial thickness might be needed to evaluate vaginal bleeding, but should not be done on a routine basis (1). Adjusting the estradiol prescription to achieve these target ranges will require, however, doses that are 50-100% higher than the highest "standard" menopause HRT in around 50% of women (77).

Table 1 provides an overview of various 17□-estradiol preparations along with their equivalent dosages.

Adverse symptoms related to HRT typically resolve in the first three months of treatment and include bleeding, headaches, breast tenderness, nausea,

Table 1. Estrogen presentations and adverse effects

Intake	Presentation				Adverse effects
Oral	Tablets of 1 and 2 mg				Weight gain, nausea, vomiting, breast tenderness, headache, increased risk of VTE and gallstones, higher TG, increased thyroid binding globulin.
Approximate equivalence to transdermal	1.5 mg/day				
Monitoring method	Bloods 4 hours post-dose				
Transdermal	Patch (mcg/day)	Gel sachet (mg/day)	Gel pump (0.75 mg/ actuation)	Spray (1.53 mg/ actuation)	Neutral effect on blood lipids, thyroid and blood clots. May cause skin irritation.
Approximate equivalences	75 mcg/24 h	1 mg/day	2 actuations	3 actuations	
Monitoring method	Blood after 48 hours and prior to new patch	Bloods 4-6 hours after application and no gel on the arms		Blood 2-8 hours post-application; avoid sample from application site	

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fatigue and mood changes. It should be noted that the use of HRT does not increase the risk of breast cancer before the age of natural menopause (67).

HRT protocols for induction of puberty

Females presenting with absent or incomplete puberty require a highly specific therapeutic approach in order to achieve optimal breast and uterine development according to genetic potential, using incremental doses of estradiol monotherapy (rather than immediate full-dose estradiol + progestin hormone replacement – HRT) at the outset, and with the introduction of a progestin to confer long-term endometrial protection potentially delayed until both of these parameters have plateaued at a satisfactory level. In any case, longitudinal evaluation of uterine development through sonography provides reliable information on endometrial thickness as well as the uterine configuration, dimensions and volume. Starting these patients too early on full dose combined HRT (or COC) results in a smaller final uterine volume and final breast development that may never surpass Tanner B3 (3,4,11,12,78).

Options for achieving parenthood

It is important to inform women that HRT does not serve as a method of contraception. While fertility is reduced in the vast majority of patients, it is crucial to discuss and prescribe contraceptive options for those wishing to avoid pregnancy and, if other options such as levonorgestrel IUS are not acceptable, an estradiol-based COC could be used as an alternative to conventional HRT.

Fertility restoration is significantly influenced by the underlying cause of hypogonadism. In cases of HA, a comprehensive approach that includes proper nutrition, stress management, physical activity in moderation, and psychological intervention, such as cognitive behavioral therapy, is often deemed most effective. While implementing lifestyle changes can be challenging, they are often the ideal course of action and may successfully restore fertility in these patients. If lifestyle modifications are not achieved and a hypogonadal state persists for over 6 to 12 months, a discussion regarding HRT should be made. Although leptin has shown promise in restoring ovulation in certain women affected by HA (59) natural cycle monofollicular gonadotropin ovulation induction (GnOI) or pulsatile GnRH if available, is generally considered the primary treatment approach when behavioral strategies are unsuccessful (79), and is of course first line for women with organic central FH. Other things being equal, the cumulative likelihood of achieving pregnancy over the course of 3–6 cycles of GnRH parallels that of normally fertile couples, after which assisted reproduction techniques (ART) can be deployed. Crucially, a low AMH or antral follicle count in a woman with central FH should not be considered pathognomonic of a low ovarian reserve (rather as expected for unstimulated granulosa cells) and should not deter GnOI or ART. However, for women with panhypopituitarism and especially with vasopressin deficiency (a surrogate marker for oxytocin deficiency), the risk of pregnancy and labor are high, and thus specialist MDT oversight is required throughout pregnancy (80), much as for women with TS.

In TS (and other forms of POI), oocyte donation is usually necessary to achieve pregnancy. However, additional factors that may influence fertility or pregnancy outcome should always be investigated before proceeding to treatment, such as male sperm, tubal and uterine integrity and other external factors. In TS, no treatment should be offered until a comprehensive cardiovascular assessment has been undertaken, due to the heightened risk of aortic dissection in pregnancy (3).

CLOSING REMARKS

In conclusion, a serum estradiol concentration persistently < 200 pmol/L and/or FSH > 25 IU/L in the presence of amenorrhea and relevant clinical features is consistent with FH, even when another potential cause for amenorrhea is present or has been proposed. HRT is recommended for all women with FH of premenopausal age, including those with a reversible cause, if they are experiencing sustained amenorrhea. Ascertaining the likely etiology of FH, especially distinguishing between central FH and POI, is critical to ensure appropriate investigation and management, including accurate exposition of fertility options. HRT

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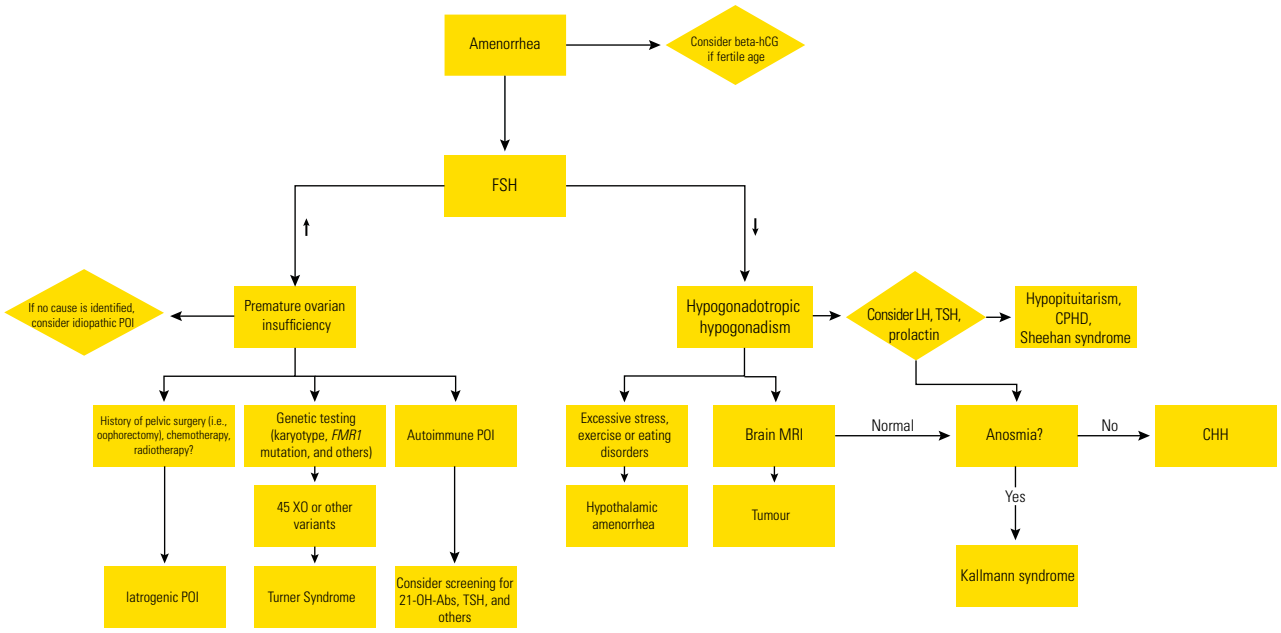


Figure 1. Suggested flowchart for investigation and management.

based on native 17β-estradiol should be prescribed in preference to synthetic or equine estrogens and, in women with a uterus, in combination with micronised progesterone, dydrogesterone or levonorgestrel IUS. HRT aims to provide physiological estrogen replacement to young women with FH, and so significantly higher doses of estradiol may be required than are contained in standard preparations formulated for natural postmenopause, and with no arbitrary limits placed upon the duration of HRT up to the normal age range for menopause (**Figure 1**).

There is no evidence that HRT increases risk of breast cancer (above being female) in young women with FH. Neither thrombotic risk factors (e.g., obesity, smoking, migraine aura) or events (stroke, angina, myocardial infarction), family history, nor genetic tumor predisposition (e.g., BRCA 1 and 2 mutations) should be reasons to deny HRT to a younger woman with FH, although HRT should ideally be paused for 6 months following MI. However, in these circumstances, transdermal routes of estradiol administration should be used first-line.

Guidelines are discordant as to whether serum estradiol levels should (International Turner) or should not (International POI) be measured routinely as part of routine treatment monitoring, with the Society for Endocrinology unable to make a firm recommendation either way based on current evidence. However, if testing is done, then an estradiol concentration in the 350-550 pmol/L range as per Turner's guidance would appear reasonable. Levonorgestrel IUS or 17β-estradiol-based contraceptives are ideal for women with reversible FH wanting contraception. Women with FH should have an assessment of BMD and identification of any additional risk factors for low bone mineral density. GnOI is recommended as the first line fertility therapy for women with central forms of FH.

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special issue
Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

invited review

The impact of thyroid disorders on the gut microbiome: emerging mechanisms and clinical relevance

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ABSTRACT

The thyroid-gut axis represents a dynamic interaction between the intestinal microbiota and thyroid function, with growing evidence linking gut dysbiosis to thyroid diseases. The gut microbiome, comprising over 100 trillion microorganisms, influences immune modulation, iodine metabolism, and thyroid hormone regulation. Short-chain fatty acids, produced by beneficial gut bacteria, support immune homeostasis and thyroid function, while pathogenic bacteria and lipopolysaccharides trigger inflammatory pathways that impair thyroid activity. Alterations in gut microbiota composition have been associated with autoimmune thyroid diseases, including Hashimoto's thyroiditis and Graves' disease. Dysbiosis increases intestinal permeability, antigen exposure, and immune activation, exacerbating thyroid autoimmunity. A reduction in short-chain fatty acids-producing bacteria weakens immune tolerance, promoting inflammatory cytokine release and autoantibody production. Recent studies highlight microbial metabolites such as tryptophan derivatives and their role in immune regulation. Gut dysbiosis is also implicated in thyroid nodules and cancer. Decreased butyrate-producing bacteria and increased inflammatory bacterial taxa have been observed in thyroid malignancies. Microbiota influence iodine and selenium bioavailability, essential for thyroid hormone synthesis, and modulate sodium-iodide symporter expression, affecting thyroid cancer response to radioactive iodine therapy. Microbiome-targeted interventions, including probiotics, prebiotics, dietary modifications, and fecal microbiota transplantation, may restore microbial balance, enhance immune regulation, and improve thyroid treatments. This review synthesizes our current understanding of the thyroid-gut axis, indicating that the intestinal microbiota and its metabolites may act directly or indirectly on the thyroid gland, highlighting potential clinical implications and paving the way for therapeutic strategies targeting the intestinal microbiota.

Keywords: Gastrointestinal microbiome; thyroid diseases; fatty acids, volatile

INTRODUCTION

The alimentary tract creates a connection between the external environment and the body, and within it, there is a complex polymicrobial ecology that exerts an important influence on health and disease (1). A microbiome is a collection of microorganisms that plays a crucial role in immune development, so that any alteration in its homeostasis (dysbiosis) can cause and aggravate several diseases (2). It has individual characteristics; thus, it can be said that it confers individual signatures that may vary according to personal and environmental specific conditions applying for a given individual.

The association between alterations in the intestinal microbiota and thyroid diseases has gained prominence in recent years, due to the belief that it may play a fundamental role in the development and/or progression of thyroid diseases (3). This, in turn, encompasses a range of disorders, including autoimmune diseases and cancer, which not only impact metabolic regulation but also have significant implications for general health and well-being (4). In view of this, the interaction between the thyroid gland and the gut has emerged as an area of substantial interest in endocrinology (5), becoming a growing field of study, with research revealing the complex connection between the microbiota and the endocrine system (4).

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This review explores recent advances in the gut microbiome's role in thyroid diseases, focusing on its influence on autoimmune conditions like Hashimoto's thyroiditis (HT) and Graves' disease (GD), as well as its broader impact on non-autoimmune disorders, including thyroid nodules and cancer. By combining current knowledge on this topic, we aimed to enhance the understanding of the thyroid-gut axis, providing a theoretical basis for future studies and a new perspective for the potential implementation of microecological treatment strategies for thyroid diseases.

THYROID-GUT AXIS

It has been estimated that the microbes in our bodies collectively comprise up to 100 trillion cells, most of which reside in the intestine. This observation suggests that they may encode one hundred times more genes than our own genome. Regarding the intestinal microbiota, it appears to be a tapestry of approximately 1,000 distinct bacterial species (6). Taxonomically, the phyla Firmicutes and Bacteroides predominate, constituting 70% to 75% of the gut microbiome (3). A high degree of gut microbiome diversity is crucial for maintaining overall health, as it supports immune function, nutrient absorption, and metabolic balance, and is strongly associated with reduced risks of chronic diseases and improved well-being. Several factors influence the composition of the microbiota, with four main components being highlighted: intrinsic factors related to the microbiome, such as composition, age dependency, and the presence of diseases; environmental factors, including local environment and vertical transmission; lifestyle factors, encompassing diet, medication usage, culture, and physical activity; and host genetics, involving body mass index, adipose tissue body topographical distribution, adaptive and innate immunity, and sex (7).

Beneficial bacteria from the phyla *Bifidobacterium* and *Lactobacillus* produce short-chain fatty acids (SCFAs) that are crucial for immunity regulation but also for the maintenance of thyroid hormone balance, while preserving the integrity of the intestinal barrier (8). In contrast, harmful bacteria, such as Bacteroides, Proteobacteria, and Actinobacteria, disrupt the balance of SCFAs by decreasing their production and promoting inflammation, impacting thyroid function. **Table 1** provides a concise overview of this influence on thyroid diseases.

There is a positive correlation between butyrate concentration, a SCFA, and the number of regulatory T cells (Tregs), which are key mediators of immune tolerance, as well as with lower concentrations of pro-inflammatory Th-17 cells. This is supported by observations that germ-free (gf) mice show impaired immune cell maturation due to the lack of microbial stimulation to the immune system (9). Treg cells, characterized by the expression of CD4, CD25, and the forkhead box P3 (Foxp3) transcription factor, are reported to aid in maintaining immune self-tolerance and suppressing autoreactive T and B cells through cell-to-cell contact or the secretion of regulatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). Additionally, a reduction in propionic acid also contributes to the imbalance between Tregs and Th17 cells (3).

Table 1. Comparison of intestinal microbiome patterns in individuals without thyroid disease, those with autoimmune thyroid disorders, and those with thyroid nodules and thyroid cancer

Parameter/bacterial group	Healthy individuals	Autoimmune thyroid diseases	Thyroid nodule	Thyroid cancer
Global diversity	High species diversity	Reduced diversity compared to healthy controls	Moderate reduction in diversity, but with variability	Discordant data: decreased diversity, possibly similar or even more pronounced than in autoimmune disease (28-31)
Firmicutes: Bacteroidetes	Relatively balanced	Possible dysregulation in the *Firmicutes: Bacteroidetes* ratio (increased *Bacteroidetes* and/or decreased *Firmicutes*)	Scarce data	Variable pattern. Increase in *Bacteroidetes* and decrease in *Firmicutes*
Short-chain fatty acid production	Normal	Reduction	Slightly reduced (few conclusive studies)	Generally reduced

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The thyroid gland requires iodine as an essential micronutrient for the synthesis of thyroid hormones. Absorption of this mineral from the gastrointestinal tract and its transfer to the thyroid gland constitutes the main pathway for iodine uptake in humans, but also selenium absorption is modulated by gut microbiota (9). In this context, intestinal microorganisms play a crucial role in the regulation of iodine metabolism in different manners. Thus, LPS and SCFAs released by the gut microbiota influences thyroid iodine metabolism by altering the expression and activity of the sodium-iodine symporter (NIS), as speculated in current research (10). But LPS also modulates thyroid homeostasis through a dual action on thyroid-stimulating hormone (TSH): by increasing gene expression of thyroglobulin (Tg) and NIS through the activation of TSH as demonstrated in a rat thyroid cell line (FRTL-5) (11) during infection, LPS or LPS-induced proinflammatory cytokines exert a direct action to stimulate the synthesis of deiodinase type II (D2) in the hypothalamus and anterior pituitary, thus facilitating the conversion of thyroxine (T4) to triiodothyronine (T3), which inhibits the production of TRH at the hypothalamus as well as TSH at the pituitary gland. D2 activity in the hypothalamus is linked to metabolic regulation, particularly in adaptive thermogenesis. By increasing local T3 levels, D2 influences energy expenditure and metabolic rate, which are critical for maintaining homeostasis. This activation of D2 has an important role in mediating the adaptation to central hypothyroidism that can occur during infection (12).

The intestinal microbiota plays a significant role in modulating thyroid function through various microbial mechanisms. Dysbiosis, characterized by an imbalance in microbial composition, leads to the deterioration of the intestinal barrier, increasing its permeability. This allows antigens to enter the circulation and activate the immune system, provoking the release of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) (13). This activation can trigger a cascade of inflammatory responses which, if persistent, may culminate in chronic inflammation. Chronic inflammation, in turn, can induce cellular stress in the thyroid gland, activating stress pathways and resulting in the production of reactive oxygen species (ROS). This cellular stress may cause DNA damage and provoke changes in thyroid follicular cells (3). Furthermore, the inflammation and immune activation associated with increased intestinal permeability can impact the production and regulation of thyroid hormones, disrupting the normal feedback loop of the hypothalamic-pituitary-thyroid axis (H-P-T) and leading to hormonal imbalances (14).

Furthermore, SCFAs play a critical role in regulating the expression of the NIS, particularly butyric acid. It acts by inhibiting histone deacetylase, which in turn promotes the reexpression of NIS in thyroid cancer cells, leading to redifferentiation and enhanced iodine uptake. Given this, it can be interpreted that modulating SCFA levels may increase the sensitivity of tumor cells to radioactive iodine by promoting histone acetylation and enhancing NIS expression. However, further investigation is necessary (10).

Therefore, it is understood that the diversity and composition of the microbiome can also affect the bioavailability of iodine and selenium. Furthermore, it has been observed that in inflammatory bowel disease (IBD), there is a reduction in the diversity of the intestinal microbiota and a lower abundance of *Firmicutes* and *Bacteroidetes*, making poor iodine absorption a common consequence of IBD, and vice versa, suggesting a reciprocal relationship (9). **Table 2** summarizes the key points of these elements and their relationships with the gut microbiome in the context of thyroid diseases.

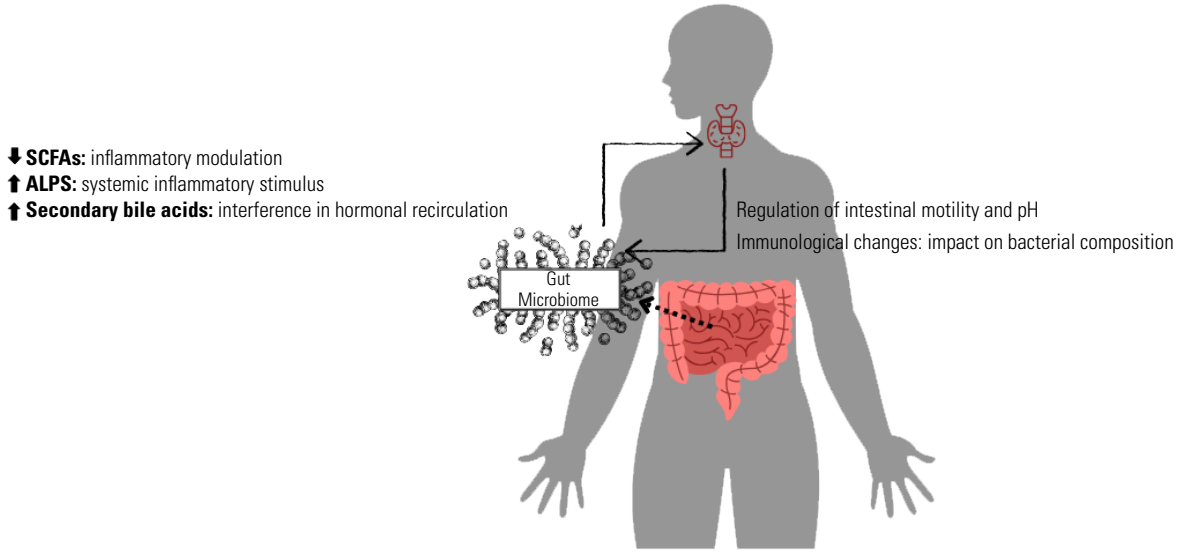
An additional point of fundamental relevance is the fact that the intestine plays another vital role as host to 70% of the body's immune tissue, called gut-associated lymphoid tissue (GALT) (15). Gut-associated lymphoid tissue stores immune cells, such as T and B lymphocytes, which attack and produce antibodies against antigens. This supports the idea that a healthy gut microbiota can influence the immune system and has a significant impact on thyroid function (3). **Figure 1** provides a visual synthesis of the mechanisms by which alterations in the gut microbiome can exert effects on the thyroid gland, and vice versa.

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Table 2. Interaction between the elements and nutrients involved in thyroid diseases and the gut microbiome

Element/nutrient	Mechanism of action	Relationship with the gut microbiome
Sodium/iodide symporter	Transports iodine into thyroid cells along with sodium, a process dependent on concentration gradients	By influencing iodine absorption, gut dysbiosis can impair its bioavailability, impacting NIS function. Alterations in the microbiome can directly affect the expression of NIS in the thyroid
Iodine	Iodine, in the thyroid, is organified and incorporated into the synthesis of thyroid hormones	The gut microbiome can affect iodine absorption. It also influences the intestinal microbiota through its effect on the immune system
Selenium	Cofactor in enzymes such as deiodinase, responsible for the conversion of T4 to T3 Immunomodulator	The gut microbiome can influence selenium absorption, and its deficiency may exacerbate autoimmune thyroid disorders, as it has antioxidant and anti-inflammatory properties

NIS: sodium-iodide symporter.



SCFA: short chain fatty acid; LPS: lipopolysacharides.

Figure 1. Relationships between the thyroid gland and the gut microbiota.

IMPACT OF MICROBIOTA ON AUTOIMMUNE THYROID DISEASES

Autoimmune thyroid disease (AITD) is the most common thyroid disorder, its two extremes being HT and GD (16). Some studies have reported its connection with the intestinal microbiota, however, the mechanisms of the complex intestine-thyroid axis have not yet been fully elucidated (17,18). In any case, it is speculated that intestinal microbiota dysbiosis in these diseases occurs through different mechanisms, such as bacterial overgrowth, overactivation of the inflammasome, increased intestinal permeability, alteration of microbiota metabolites, and immune homeostasis (13). In short, the changes observed indicate a potential breakdown in metabolic pathways and immunological balance, which may be relevant to the pathogenesis of AITD. These findings emphasize the significant role of gut microbiota in the development and progression of these pathological conditions (19).

Short-chain fatty acids, through their interaction with G protein-coupled receptors on leukocytes and intestinal epithelial cells, can inhibit AITD (20). In individuals with autoimmune primary hypothyroidism, a decrease in SCFA-producing bacteria leads to SCFAs decreased levels, exacerbating damage to the intestinal barrier and increasing serum LPS levels, which in turn can activate the immune system triggering the release of inflammatory mediators (21). Short-chain fatty acids reduction influences Tregs contributing to a Th1/Th2 imbalance, thus increasing the production of pro-inflammatory cytokines, such as interferon-gamma (IFN-γ) and TNF-α (22). The enhancement of this kind of immune response contributes to the

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breakdown of immunological tolerance and the generation of autoantibodies (3).

A significantly reduced proportion of circulating CD4 + Foxp3 + Treg cells has been observed in patients with recently diagnosed GD. This decrease in Treg cells may be partially explained by the increased apoptosis of these cells, as a higher number of apoptotic cells has been detected in the thyroids of patients with AITD. Furthermore, the proportion of Treg cells was inversely correlated with thyroid-stimulating antibody (TSAb) activity, suggesting that the deficiency of Treg cells in patients with GD may compromise their ability to inhibit the production of autoantibodies by B cells. Additionally, there is an increase in Th17 cells and elevated levels of IL-17 mRNA expression. Thus, it is proposed that the imbalance between Th17 and Tregs plays a crucial role in the pathogenesis of GD (23).

Advances in cellular immunology have ushered in a new era in exploring the mechanisms of diseases related to the immune system. It has been demonstrated that Th17 lymphocytes and their transcription factor are elevated in patients with AITDs; however, this increase is significantly more pronounced in patients with HT compared to those with GD. Therefore, it is speculated that Th17 plays a critical role in the pathogenesis of HT. Interestingly, unlike in GD, the differences in Tregs and their transcription factor were not significant between patients with Graves' orbitopathy (GO) and healthy controls. Thus, it is suggested that Th17 has a critical influence on the development of GO, while Tregs primarily participate in the pathogenesis of GD. Ultimately, a disruption of the Th17/Treg balance occurs in AITDs (24).

Furthermore, a Mendelian randomization study, aiming to explore causality using statistics from several genome-wide association studies (GWASs) of gut microbes and fecal/circulating metabolites to assess potential causal associations of gut microbes and metabolites with AITD, highlighted the role of gut flora-related metabolites in the circulation, such as tryptophan, whose derivatives can interact with transcription factors such as nuclear factor-kappa B (NF-κB), estrogen receptor, and are capable of activating regulatory feedback loops highly relevant to immunoregulation. Also, circulating 3-indole glyoxylic acid in plasma showed a significant pathogenic role in AITD (16).

In turn, a meta-analysis (13) reported that the ratio of Firmicutes and Bacteroidetes of patients with AITD showed a lower level than their healthy counterparts. A random-effect model indicates that these patients have a significant increase in pathogenic bacteria together with a decreased proportion of beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*, these latter having anti-inflammatory effects. Another hypothesis on the relationship that the microbiota plays in the progress of thyroid autoimmunity is molecular mimicry, since the antigenic properties of proteins from certain intestinal bacteria can link TPO and TG, which are among the most relevant targets in the development of these diseases. It is hypothesized that genetic predisposition to AITD and/or intestinal epithelium penetration by α-1,6-glucan are required for triggering/acceleration or prevention/abrogation of AITD by bifidobacteria through molecular mimicry mechanism (25).

A field of continuous interest and progress in recent years is GO. Recently, a study (26) suggested that a possible increase in intestinal permeability is an aggravating factor for orbital inflammation and, therefore, for the differentiation of myofibroblasts and fibrosis. In view of this, intestinal permeability was assessed by measuring serum lipopolysaccharide-binding protein (LBP), zonulin, TLR5, and TLR9 ligands, and biopsies from the orbital tissue were studied. It was found that GO patients had significantly higher serum LBP concentrations than healthy controls, as well as circulating zonulin, TLR5, and TLR9 ligands, inferring that increased intestinal permeability was accompanied by enhanced expression of genes involved in immune cell infiltration and encoding key proteins for immune cell adhesion at the orbital tissue. Macrophage influx was positively linked to the extent of T cell influx and fibroblast activation within GO-affected orbital tissues. Equally important, serum LBP levels significantly correlated with the abundance of specific intestinal *Gram*-negative bacteria, linking the gut to local orbital inflammation.

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IMPACT OF MICROBIOTA ON THYROID NODULES AND CANCER

The development of thyroid nodules is multifactorial, involving genetic predisposition, environmental exposures, and hormonal factors. It is already known that the risk of thyroid cancer arising within a nodule is influenced by various factors; however, there is growing interest in the influence of the intestinal microbiome in the context of thyroid nodules (3).

Studies show a significant increase in the relative abundance of *Neisseria* and *Streptococcus* and a notable decrease in microbes such as *Butyricimonas* and *Lactobacillus* in patients with thyroid nodules (27). Furthermore, the reduction in the metabolic pathways responsible for producing the SCFA butyrate, along with an upregulation of amino acid biosynthesis pathways, as a consequence of the disruption of intestinal microbial metabolism that may stimulate nodule development (28). Some studies have suggested that LPS may exert a direct effect on thyroid cells, influencing their growth and function, and potentially leading to nodule formation through (29). Moreover, the impact of the intestinal microbiome on thyroid nodules generation and growth can be explained by its ability to modulate the production of cytokines such as IL-1β, IL-6, and TNF-α, which are known to influence the proliferation of thyroid cells (30).

Regarding thyroid cancer, the role of the intestinal microbiome in its pathophysiology is also an emerging area of research, especially considering that it is the most common endocrine malignancy, with globally increasing incidence in recent decades (31). There is no doubt that evidence points to a fundamental interaction between the intestinal microbiota and the thyroid gland; however, the literature presents some discrepancies concerning the nature of this interaction. While some studies have indicated that patients with thyroid cancer show higher intestinal microbiota richness and diversity compared to a control group of healthy individuals (32,33), other studies report a significant decrease (34,35). Despite these contradictory findings, more data seem to support a decline in the abundance of SCFA-producing bacteria in patients with thyroid cancer (10), suggesting that this reduction are associated to disease progression (36).

A recent Mendelian randomization study (36) – a novel statistical approach that allows researchers to assess causal relationships in potential exposure-outcome pathways – indicated that an increased abundance of *Butyrivibrio*, *Fusicatenibacter*, *Oscillospira*, *Ruminococcus* 2, and *Terrisporobacter* may contribute to a higher risk of thyroid cancer, whereas elevated levels of *Olsenella* and *Ruminococcaceae UCG-004* were associated with a reduced risk. In this way, the study offered genetic evidence supporting the existence of a gut-thyroid axis, emphasizing the strong correlation between the intestinal microbiota and thyroid cancer.

The complex interaction between the thyroid and the gut becomes even clearer when one recognizes that it is bidirectional, as the thyroid and/or its treatment can also affect the composition and activity of the intestinal microbiome. A pilot study (37) reported a significant decline in the *Firmicutes-to-Bacteroides* ratio following radioactive iodine (I131) therapy in patients who had undergone total thyroidectomy for papillary thyroid cancer. In addition, it was noted that *Dorea* (a butyric acid–producing genus) was significantly less abundant prior to treatment in patients who showed a lower response post-I131, suggesting its potential pathogenic importance and its predictive value (37,38).

CLINICAL PERSPECTIVES

The integration of microbiome-based therapies with traditional treatments represents a paradigm shift in many fields and also in thyroid disease management. Personalized approaches, tailored to an individual's gut microbiota composition, could potentially optimize therapeutic outcomes and minimize adverse effects. For example, dietary interventions aimed at restoring microbial balance, such as the elimination of gluten in patients with celiac disease or non-celiac wheat sensitivity, have shown promising results in alleviating thyroid dysfunction (9). Similarly, the use of synbiotics – combinations of probiotics and prebiotics – may offer synergistic benefits in modulating the gut-thyroid axis (39).

As previously commented, the role of gut microbiota in thyroid cancer is an area of growing interest. Dysbiosis has been associated with an increased

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abundance of carcinogenic and inflammatory bacterial strains, which may contribute to tumorigenesis (40). For instance, certain bacterial taxa, such as *Ruminococcaceae UCG004* and *Streptococcaceae*, have been implicated in thyroid cancer progression through mechanisms involving immune modulation and metabolic pathway alterations, thus decreasing the gut content of these specific strains may potentially be of benefit for thyroid cancer patients. Additionally, gut microbiota can influence the efficacy of radioactive iodine therapy by modulating the expression of NIS, which facilitates iodine uptake in thyroid cancer cells; thus, microbiota-derived metabolites like SCFAs can enhance the sensitivity of tumor cells to radioactive iodine, potentially improving treatment outcomes.

The modulation of gut microbiota through probiotics, prebiotics, and fecal microbiota transplantation (FMT) has shown promise in managing thyroid disorders. Specific probiotic strains, such as *Lactiplantibacillus plantarum 299v* and *Bifidobacterium longum*, have been demonstrated to restore microbiota balance, improve intestinal barrier function, and reduce systemic inflammation (3). These probiotics can enhance the effects of conventional treatments, such as levothyroxine (L-T4) therapy for hypothyroidism, by optimizing absorption and stabilizing the required dosage of L-T4. However, other studies have suggested that probiotics, generally containing *Bifidobacterium* spp. and *Lactobacillus* spp., have not been able to alter susceptibility or improve hypothyroidism in patients with HT. Interactions between probiotics, L-T4 therapy and H-P-T were examined, leading to the conclusion that probiotics are unlikely to be beneficial in the treatment of patients with TH (41). This finding is particularly noteworthy given that significantly lower levels of *Lactobacillus* spp. have been identified in patients with thyroid nodules and thyroid cancer, suggesting a link between the absence of this genus and thyroid disease. Nonetheless, it is possible that the duration of treatment was too short to achieve a significant change in microbiota composition (7,41).

Fecal microbiota transplantation has emerged as a potential therapeutic option in GD. By recalibrating gut microbiota, FMT can influence neurotransmitter activity and trace element metabolism via the gut-brain and gut-thyroid axes, offering a holistic approach to disease management (3). However, while these interventions hold promise, further large-scale clinical trials are needed to establish standardized protocols and validate their efficacy across diverse patient populations.

The gut microbiota plays a crucial role in modulating selenium bioavailability, which is essential for the synthesis of selenoproteins, including glutathione peroxidases and iodothyronine deiodinases, enzymes that are critical for thyroid hormone metabolism (39). Dysbiosis in the gut microbiota has been shown to impair selenium absorption, leading to reduced selenoprotein activity, which in turn affects thyroid hormone conversion and increases susceptibility to thyroid dysfunction (42). Studies indicate that certain gut bacteria, such as *Lactobacillus* and *Bifidobacterium* species, can enhance selenium bioavailability, thereby protecting thyroid hormone homeostasis and reducing the risk of hypothyroidism (43). Reduced gut microbial diversity has been associated with altered selenium metabolism, leading to suboptimal thyroid function due to impaired conversion of T4 to the biologically active T3 hormone (44). Therefore, targeting dysbiosis for rebalancing the specific microbiome strains involved in selenium malabsorption may be crucial for preservation of thyroid function through maximizing selenium bioavailability in patients in which this mineral is given as therapeutic supplementation for AITD.

Future research should focus on elucidating the specific mechanisms underlying the thyroid-gut axis, including the role of microbial metabolites like SCFAs and bile acids in thyroid hormone metabolism. Advanced techniques, such as metagenomic sequencing and metabolomic profiling, can provide deeper insights into the complex interactions between gut microbiota and thyroid function. Additionally, longitudinal studies are needed to assess the long-term effects of microbiota-modulating interventions on thyroid health.

CONCLUSIONS

The thyroid-gut axis highlights the profound impact of gut microbiota on thyroid function and disease. From autoimmune disorders to thyroid cancer, dysbiosis plays an important role in disease pathogenesis and

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progression. Therapeutic strategies targeting the gut microbiota, such as probiotics, fecal microbiota transplantation, and dietary interventions, offer promising avenues for improving patient outcomes. As research in this field continues to evolve, the integration of microbiome-based therapies into clinical practice holds the potential to revolutionize the management of thyroid diseases, paving the way for more personalized and effective treatments.

By leveraging the insights gained from the thyroid-gut axis, clinicians can adopt a more holistic approach to thyroid care, addressing not only the gland itself but also the intricate microbial ecosystem that influences its function. This paradigm shift underscores the importance of considering the gut microbiota as a key player in thyroid health and disease, opening new frontiers in endocrinology and personalized medicine.

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special issue
Voices of Endocrinology: contemporary insights in endocrine and metabolic disorders

invited review

Supplements for bone health

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ABSTRACT

Bone health is influenced by a dynamic interplay of genetic, hormonal, and environmental factors, with nutrition playing a vital role throughout life. This review consolidates the current evidence on the roles of essential micronutrients, specifically calcium, vitamin D, vitamin K, magnesium, and phosphorus, in skeletal metabolism and integrity. Calcium and vitamin D, the most extensively studied, have been shown to reduce bone loss and fracture risk, particularly in institutionalized individuals or those with deficiencies, while evidence is less consistent in the general population. Although vitamin K, magnesium, and phosphorus are important for bone physiology, the clinical evidence supporting their supplementation is either limited or context dependent. Additionally, this review explores the current status of micronutrient intake in Brazil and discusses potential risks associated with excessive or inappropriate supplementation, such as cardiovascular issues and mineral metabolism disturbances. An individualized, evidence-informed approach may be beneficial in optimizing bone health while minimizing adverse effects.

Keywords: Bone health; supplementation; vitamin D; vitamin K; magnesium; phosphorus

INTRODUCTION

Bone health is determined by a complex interplay of genetic, hormonal, and environmental factors, with nutrient intake representing an important contributor to skeletal integrity. Calcium and vitamin D are well-established for maintaining bone mass and reducing fracture risk, particularly in deficient or high-risk populations, whereas evidence supporting the roles of vitamin K, magnesium, and phosphorus is more limited and population specific.

This review has three primary objectives: (1) to delineate the physiological functions of calcium, vitamin D, vitamin K, magnesium, and phosphorus in bone metabolism; (2) to summarize current dietary intake recommendations and evaluate the Brazilian context; (3) to synthesize evidence from meta-analyses and systematic reviews regarding their impact on bone health. Additionally, potential adverse effects related to excessive or inappropriate supplementation are discussed.

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CALCIUM

Physiological role in bone tissue

Calcium is the most abundant mineral in the human body, playing an essential role in bone formation and regulating various intracellular processes, including cell growth and division, blood coagulation, and muscle contraction (1). The majority of the body's calcium is stored in the skeleton, and daily absorption depends not only on dietary intake but also on physiological mechanisms that regulate calcium distribution and homeostasis. This regulation is mediated through three primary processes: bone resorption, intestinal absorption, and renal reabsorption orchestrated by hormones such as parathyroid hormone (PTH), vitamin D, calcitonin, and fibroblast growth factor 23 (FGF-23). Serum calcium levels, the calcium-sensing receptor, and local regulatory mechanisms in bone, intestine, and kidney ensure calcium availability for physiological functions and skeletal maintenance (1).

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A decline in serum calcium stimulates PTH secretion, which increases bone resorption and promotes the conversion of vitamin D to its active form, calcitriol, thereby enhancing intestinal calcium absorption and reducing renal excretion. Conversely, elevated serum calcium levels suppress PTH secretion through negative feedback, leading to decreased bone resorption and reduced calcium reabsorption in the kidneys (1,2). Through these coordinated actions, calcitriol plays a central role in maintaining calcium balance and supporting bone strength. FGF-23, produced by osteocytes and osteoblasts in response to high phosphate, reduces renal phosphate reabsorption and inhibits calcitriol synthesis, indirectly modulating intestinal calcium uptake (3). **Figure 1** illustrates the interactions among the main regulators of mineral metabolism.

Within bone tissue, calcium provides structural stability and resistance to mechanical stress while regulating the balance between incorporation into the bone matrix and release into the circulation (4,5). Bone remodeling, coordinated by osteoblasts, osteocytes, and osteoclasts, ensures daily calcium turnover and maintains skeletal integrity. Insufficient calcium availability can disrupt this balance, leading to bone loss and increased fracture risk, whereas adequate intake supports bone mass maintenance and densification (5).

Adequate dietary calcium intake, particularly from dairy sources, is crucial for peak bone mass acquisition during growth and for preserving bone strength throughout life, reducing age-related bone loss and fracture risk (6).

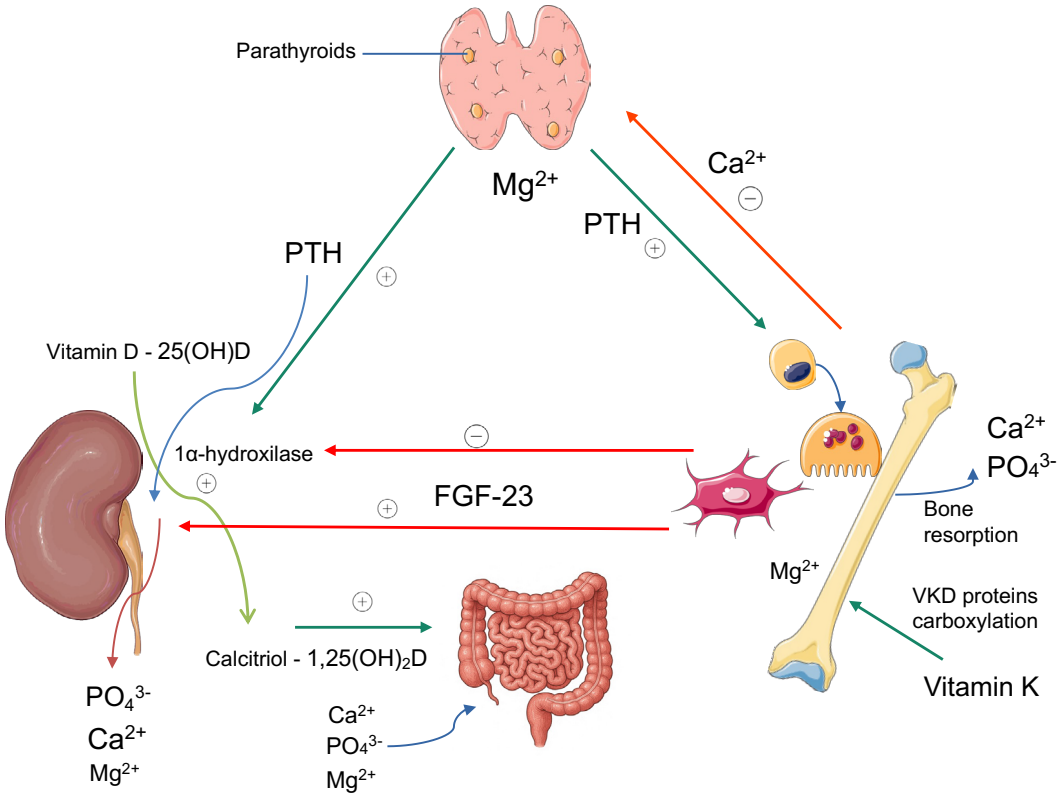


Figure 1. Interactions among the main regulators of mineral metabolism. Parathyroid hormone (PTH), 1,25-dihydroxyvitamin D [1,25(OH)$_2$D or calcitriol], and fibroblast growth factor 23 (FGF-23) act together to maintain calcium (Ca^{2+}), phosphate (PO_4^{3-}), and magnesium (Mg^{2+}) homeostasis. PTH stimulates bone and renal reabsorption of Ca^{2+} and Mg^{2+} and induces 1α-hydroxylase, which converts 25(OH)D into calcitriol. Calcitriol, in turn, enhances intestinal absorption of Ca^{2+}, PO_4^{3-}, and Mg^{2+}. FGF-23 decreases renal PO_4^{3-} reabsorption and inhibits 1α-hydroxylase activity. Magnesium modulates PTH secretion and action, acts as a cofactor for enzymes involved in vitamin D activation, and contributes to osteoblastic function and bone mineralization. Vitamin K promotes the carboxylation of vitamin K–dependent (VKD) proteins, which are essential for bone mineralization and integrity. This representation was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

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Recommended daily intake of calcium

Humans rely on a daily intake of dietary calcium, which is essential for maintaining physiological functions and skeletal health. Calcium requirements vary depending on the balance between bone formation and resorption, as well as renal and other systemic losses (1). Calcium is absorbed throughout the intestinal tract, primarily in the duodenum and jejunum. The fraction absorbed depends on daily intake and is higher when habitual intake is low. During periods of increased demand — such as growth, pregnancy, and lactation — intestinal absorption capacity can increase significantly, reaching up to 60% (7). In children and adolescents, calcium retention rises linearly with intake due to both increased absorption and reduced bone resorption; however, absorption declines with aging (8).

Calcium absorption occurs via two main mechanisms: (1) active transcellular transport in the duodenum and jejunum, and (2) paracellular transport throughout the small intestine. The active mechanism plays a particularly important role during low calcium intake, whereas passive diffusion (paracellular transport) predominates with higher intake, accounting for only 8–23% of total absorption. In the duodenum, where vitamin D receptors (VDRs) are abundant, active transport relies on the activation of VDRs and the expression of calcium transport proteins. The active form of vitamin D, $1,25(OH)_2D$, primarily regulates active transport but also influences paracellular absorption (1).

Reference values for daily calcium intake vary by age, sex, and life stage. For individuals over 19 years of age, recommendations vary from 1000 to 1300 mg per day, depending on the guidelines adopted (9). Many national recommendations align with those of the Institute of Medicine of the National Academy of Sciences (IOM/NAM), which bases intake values on available evidence quality and quantity. For infants (0–6 and 6–12 months), Adequate Intake (AI) reflects average intake in healthy populations due to limited data. From age one onwards, Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) are defined: EAR meets the needs of 50% of healthy individuals, while RDA, derived from EAR, covers nearly all (97–98%) individuals. These values are based on calcium's effects on bone health (Table 1) (10).

Table 1. Dietary reference values (mg/day) for calcium according to the Institute of Medicine of the National Academy of Sciences (10)

Age	AI	EAR	RDA	UL
Infancy to adolescence				
0–6 months	200	-	-	1000
6–12 months	260	-	-	1500
1–3 years		500	700	2500
4–8 years		800	1000	2500
9–18 years		1100	1300	3000
Women				
19–50 years		800	1000	2500
Post-menopause (51+ years)		1000	1200	2000
During pregnancy/lactation (14–18 years)		1100	1300	3000
During pregnancy/lactation (19–50 years)		800	1000	2500
Men				
19–70 years		800	1000	2500
≥ 70 years		1000	1200	2000

AI: adequate intake; EAR: estimated average requirement; RDA: recommended dietary allowance; UL: tolerable upper intake level.

Sources of calcium

For most individuals, milk and dairy products remain the primary dietary sources of calcium due to their high mineral content and widespread consumption. Alternative sources include dark green leafy vegetables, such as kale, and certain seafood, particularly specific fish species; however, larger quantities of these foods are generally required to meet recommended intake levels (11). The Brazilian Food Composition Table, developed by the University of São Paulo, provides detailed data on the calcium content of various food items (Table 2) (12).

Bioavailability factors

Calcium bioavailability, or the fraction of ingested calcium absorbed by the body, is influenced by several dietary and physiological factors (13). Absorption is facilitated by adequate vitamin D levels, gastric acidity, lactose, and non-digestible oligosaccharides (14,15). Diets high in protein, particularly from animal sources, may enhance fractional calcium absorption, partially compensating for increased urinary calcium excretion (16,17).

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Table 2. Calcium content in selected foods (mg/100g)

Category	Food	Calcium (mg/100g)
Dairy products	Parmesan cheese	1050
	Mozzarella cheese	774.55
	Minas cheese (Brazilian fresh cheese)	1020
	Whole milk powder	887.53
	Whole UHT milk	107.74
	Skimmed UHT milk	134.61
	Whole plain yogurt	207.04
Fish/eggs	Canned sardines in oil	393.37
	Cooked salmon	28.76
	Boiled chicken egg	43.72
Vegetables	Raw collard greens	208.43
	Cooked spinach	66.74
	Cooked broccoli	56.83
	Raw watercress	129.77
	Raw arugula	107.28
Legumes	Cooked carioca beans	106.24
	Cooked soybeans	70.81
	Cooked lentils	19
Nuts/seeds	Raw almonds	269
	Raw sesame seeds	825.45
	Raw Brazil nuts	162.63
Processed soy	Tofu	80.76
Cereals/grains	Enriched wheat flour	16.03
	Sliced bread	129.22
	Rolled oats	49.81
Fruits	Banana	221.99
	Orange	29.93
	Strawberry	15.40

Source: Adapted from Brazilian Food Composition Table (version 7.2) (12).

Conversely, several dietary components may reduce calcium bioavailability. Phytic acid, found in fiber-rich foods and cereals, and oxalic acid, present in spinach, chocolate, carrots, sweet potatoes, and cola beverages, are both known to interfere with calcium absorption (18). Additionally, agents such as proton pump inhibitors, cholestyramine, tetracycline, and iron supplements may impair calcium bioavailability by reducing intestinal absorption. These agents, therefore, should not be administered concomitantly with calcium (19).

Considering both content and bioavailability, milk and dairy products should remain the primary recommended sources of calcium, while alternative sources and supplements can be used when dietary intake is insufficient. Supplementation is generally recommended at 500–600 mg per day, preferably in combination with vitamin D (20).

Calcium supplements

Supplementation is particularly indicated for patients at high risk of calcium and vitamin D deficiency and for those undergoing osteoporosis treatment (21). When pharmacological calcium supplements are required, they should be consumed with meals to improve tolerance and enhance absorption (22).

Common formulations include calcium carbonate, calcium citrate, calcium citrate malate, and tricalcium phosphate, each with distinct elemental calcium content, absorption characteristics, and clinical considerations (Table 3).

Table 3. Comparative overview of calcium supplement formulations: elemental content, clinical considerations, and potential adverse effects

Formulation	Elemental Ca (%)	Recommended Use/Dose	Advantages	Potential Limitations/ Adverse Effects
Calcium carbonate	40	Typically 500–600 mg/day, with meals	High elemental calcium content; widely available; cost-effective	Gastrointestinal intolerance; reduced absorption in achlorhydria, atrophic gastritis, or bariatric surgery; may increase kidney stone risk
Calcium citrate	24.1	500–600 mg/day; can be taken with or without food	Well absorbed regardless of food or gastric acidity; safer in achlorhydria or post-gastric surgery	Slightly lower elemental calcium content
Calcium citrate malate	23	500–600 mg/day	Higher bioavailability; reduced GI side effects; minimal interaction with other nutrients; preserves absorption of zinc, magnesium; lower nephrolithiasis risk	Less widely available; moderate elemental calcium
Tricalcium phosphate	37.5	500–600 mg/day; useful for elderly with low dietary phosphorus or intolerance to carbonate/citrate	Moderate elemental calcium; phosphate supplementation	Contraindicated in hyperphosphatemia, chronic kidney disease, or hypoparathyroidism

Source: Adapted from the literature: (18,20,23–29).

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This comparative overview allows clinicians to select the most appropriate formulation based on patient-specific factors, including tolerance, comorbidities, and dietary intake.

Brazilian calcium intake scenario

In a population-based study conducted across 150 municipalities in Brazil's five regions, calcium intake was assessed among men and women aged 40 years and older. The results indicated that residents of the North region had the highest average intake (454 mg/day), irrespective of socioeconomic status. Overall, the average calcium intake for the Brazilian population was approximately 400 mg per day (30). However, these estimates may be underestimated due to potential biases inherent in cross-sectional dietary recall methods.

A cross-sectional survey of adolescents aged 15–18 years living in São Paulo revealed that 97% of participants did not meet the recommended daily calcium intake, with an average intake of approximately 700 mg per day (31).

Furthermore, an analysis of data from a population survey in São Paulo showed a declining trend in average calcium intake with increasing age, while higher educational levels correlated with greater mineral consumption. The lowest averages were observed among adult women, whereas adolescent males presented the highest values. Despite variations across groups, the most significant finding was the high prevalence of inadequate calcium intake, reaching 85% among adult men and 99% among elderly women (32). It is important to note that these results may also be affected by underreporting associated with dietary recall bias.

Lastly, data from a systematic review analyzing studies conducted since 2010 in 74 countries indicate that in Brazil, the average daily calcium intake among adults, both men and women, is approximately 505 mg per day (33). These findings reinforce the scenario of inadequate calcium consumption across different regions, age groups, and sexes, suggesting a possible association with the increasing prevalence of osteoporosis in the country.

Evidence from meta-analyses and systematic reviews

A 2002 meta-analysis evaluated the effect of calcium supplementation on the prevention of osteoporosis in postmenopausal women. This analysis included 15 randomized clinical trials with a total of 1806 participants, comparing calcium supplementation to standard dietary calcium intake. Results indicated that calcium supplementation was more effective than a placebo in reducing bone loss after two or more years of treatment. However, evidence for fracture reduction, particularly concerning non-vertebral fractures, was limited (34).

A 2007 meta-analysis by Tang and cols. (35) examined the use of calcium supplementation, either alone or in combination with vitamin D, to prevent fractures and bone loss in individuals aged 50 years or older. Findings suggested that supplementation correlated with a 12% reduction in the risk of fractures of all types. Additionally, there was a decrease in the rate of bone mineral density (BMD) loss by 0.54% at the hip and 1.19% at the spine. Daily doses of ≥ 1200 mg of calcium and ≥ 800 IU of vitamin D were linked to better outcomes. Therefore, evidence suggests a modest benefit of calcium use (alone or with vitamin D), particularly in older or deficient individuals, as part of a preventive strategy for osteoporosis in individuals aged ≥ 50 (35).

Notably, evidence indicates that calcium from dietary sources may have more favorable effects on bone health in postmenopausal women, possibly due to a more beneficial influence on estrogen metabolism compared to calcium from supplements. This aligns with the notion that calcium's source may play a crucial role in modulating hormonal effects and maintaining bone health (36).

Conversely, a clinical trial involving participants in the Women's Health Initiative examined the effect of calcium and vitamin D supplementation on fracture risk among postmenopausal women (24). The results indicated that supplementation had a more significant impact in specific subgroups, such as women with low calcium and vitamin D intake, older women, and those with osteoporosis or low BMD. These groups

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experienced a reduced risk of fractures, particularly hip fractures. However, despite the benefits observed in these subgroups, supplementation did not substantially impact fracture risk in the overall study population, highlighting that the effects were confined to women with specific characteristics. An increased risk of kidney stones was also observed (24).

Similarly, a longitudinal observational study using data from the Study of Women's Health Across the Nation found that calcium supplementation was associated with a lower rate of BMD loss at the femoral neck and lumbar spine among middle-aged women, particularly during the premenopausal phase. However, no reduction in fracture risk was observed among supplement users, underscoring the strategy's limitation for preserving BMD rather than preventing fractures (37).

A 2023 systematic review reached a similar conclusion, assessing the effects of calcium and vitamin D supplementation on BMD in premenopausal women. This review included randomized clinical trials comparing calcium, vitamin D, or both with a placebo. Results indicated that supplementation did not lead to clinically significant differences in total hip or lumbar spine BMD compared to placebo. The authors concluded that calcium and vitamin D supplementation, whether alone or combined, is not recommended as a public health intervention to improve BMD in healthy premenopausal women and is unlikely to provide benefits in fracture prevention (38).

A recent systematic review suggested that calcium supplementation for fracture prevention is more effective when combined with vitamin D, mainly in reducing hip fractures among elderly and institutionalized individuals at risk of nutritional deficiencies. This combined supplementation produces a synergistic effect on intestinal calcium absorption and reverses secondary hyperparathyroidism, especially when vitamin D levels are below 10 ng/mL (39).

Side effects and adverse events

Hypercalcemia, or elevated serum calcium levels, may occur as an adverse effect of calcium supplementation, particularly when taken in high doses. In such instances, acute toxicity may develop, ranging from mild to severe hypercalcemia. Mild hypercalcemia is often asymptomatic, while moderate hypercalcemia may also be asymptomatic or present with nonspecific symptoms such as decreased appetite, nausea, vomiting, constipation, abdominal pain, dry mouth, and excessive thirst. In cases of severe hypercalcemia, neurological symptoms may emerge, including confusion, delirium, and coma, potentially progressing to death if not properly treated (40).

The tolerable upper intake level (UL) establishes thresholds above which nutrient intake may increase the risk of adverse health effects. These values should not be considered recommended intake targets. Excessive calcium intake through a habitual diet is rare and more commonly associated with supplement use (**Table 1**) (10).

Calcium supplements, particularly calcium carbonate, are known to cause gastrointestinal side effects such as constipation and flatulence, which are generally regarded as mild discomforts. However, these adverse effects are common and significantly contribute to poor treatment adherence (41). A 2019 meta-analysis summarized these symptoms, which include constipation, abdominal cramps, bloating, upper gastrointestinal events, and diarrhea. Furthermore, increased hospital admissions for acute abdominal symptoms were reported in groups treated with calcium, suggesting that these more serious gastrointestinal events may outweigh the benefits of calcium supplementation for fracture prevention (41,42).

The association between calcium supplements and the risk of nephrolithiasis (kidney stones) remains controversial. Supplement use may increase urinary calcium excretion, thereby elevating the risk of stone formation (24,43,44). However, other studies have found no significant increase in nephrolithiasis among individuals who use calcium supplements (45-47). Notably, adequate dietary calcium intake has been linked to a lower risk of kidney stone formation, as calcium from food binds to oxalate in the intestine, reducing its absorption and urinary excretion, which are two of the main risk factors for stone formation (44,48). Therefore, dietary calcium protects against stones, while supplemental calcium may increase the risk of nephrolithiasis.

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Calcium supplementation and cardiovascular risk

A growing body of evidence has examined the potential cardiovascular risks associated with calcium supplementation across diverse populations and study designs. Table 4 summarizes the main findings from clinical trials, meta-analyses, cohort studies, and guideline statements addressing this issue, highlighting the heterogeneity of results and the influence of factors such as dosage, co-administration with vitamin D, and underlying comorbidities.

Although the current data do not allow for a definitive consensus on the cardiovascular effects of calcium supplementation, the absence of robust, well-powered clinical trials limits more precise

Table 4. Evidence on cardiovascular risks associated with calcium supplementation

Study Type/ Population	Intervention/ Comparison	Main Findings	Conclusions/Observations	References
Patients with CKD	Calcium supplements	Increased arterial calcification	Suggests potential cardiovascular risk; prompted investigation in other populations	(49,50)
Randomized placebo-controlled trial (women)	Calcium vs placebo	Higher incidence of MI in the calcium group	Secondary analysis; calcium group had more baseline risk factors (smoking, dyslipidemia, hypertension)	(51)
Meta-analysis (15 trials)	Calcium without vitamin D	Higher relative risk of MI	Indicated increased cardiovascular risk, particularly for MI	(52)
Women's Health Initiative calcium and vitamin D trial	Initiation of supplementation during follow-up	Increased MI risk, independent of dose (< 500 mg/day or ≥ 1000 mg/day)	Adverse effect not dose-dependent	(53)
Swedish cohort (median follow-up: 19 years)	Dietary and supplemental calcium intake	Nonlinear association between calcium intake and mortality: increased risk with < 600 mg/day and ≥ 1400 mg/day	Higher mortality from ischemic heart disease; greatest risk in women with high dietary intake plus supplements; no association with stroke	(54)
Prospective cohort (n = 23,980; mean follow-up: 11 years)	Calcium supplements alone	Increased MI risk	Risk highest among users taking calcium without other micronutrients	(55)
Subanalysis of RCT (elderly women)	1200 mg/day calcium vs placebo	No significant difference in CV events or MI	Suggests no increased cardiovascular risk at this dosage	(56)
Pooled analysis (older adults)	Calcium + vitamin D vs vitamin D alone	Reduced mortality with combined supplementation	Protective effect observed only with calcium + vitamin D	(57)
Critical review of major meta-analyses	Various RCTs	Significant methodological limitations	Trials not designed for CV endpoints; inconsistent dosage, duration, and co-administration with vitamin D	(58)
Observational studies	Dietary vs supplemental calcium	Dietary calcium not associated with increased CV risk; supplemental calcium potentially harmful	Adverse cardiovascular effects appear confined to supplemental forms	(55,59,60) (61)
Clinical guideline (NOF & ASPC, 2016)	Dietary and supplemental calcium (with/without vitamin D)	No significant increase in CV, cerebrovascular, or mortality risk up to 2000 mg/day	Recommended intake ≤2000 mg/day, consistent with IOM/NAM	(10,62)
Meta-analysis (2021; 13 RCTs)	Dietary calcium 700–1000 mg/day or 1000 mg/day supplement	An increased risk of cardiovascular and coronary disease by 15% in healthy postmenopausal women.	Reinforces concerns about excessive supplementation	(63)
American College of Cardiology (2021)	Proposed mechanisms	Transient serum calcium elevations may activate coagulation, enhance smooth muscle contractility, and promote vascular calcification	Mechanistic rationale for accelerated atherosclerosis	(64)
UK prospective cohort (n = 434,374)	Habitual calcium supplement use	Higher incidence of CV events and mortality among diabetics; no association in non-diabetics	Diabetes-related insulin resistance and calcium dysregulation may increase susceptibility to CV outcomes	(65)

CKD: chronic kidney disease; MI: myocardial infarction; CV: cardiovascular; RCT: randomized controlled trial; NOF: National Osteoporosis Foundation; ASPC: American Society for Preventive Cardiology; IOM/NAM: Institute of Medicine/National Academy of Medicine; UK: United Kingdom.

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conclusions. Nevertheless, based on available findings, it is recommended that calcium intake be prioritized through dietary sources, with supplementation reserved for insufficient dietary intake. Furthermore, high-dose supplementation should be avoided, particularly in individuals at increased cardiovascular risk, such as those with diabetes, where adverse effects appear more pronounced.

VITAMIN D

Physiological role in bone tissue

To elucidate the interaction between the vitamin D axis and bone tissue, it is essential to recognize that the principal objective of mineral homeostasis is to maintain serum calcium concentrations within a tightly regulated physiological range. This regulation is of critical importance, as calcium plays a vital role in various physiological processes, including hemostasis, synaptic transmission, and muscle contraction (66).

Systemic calcium balance, defined as the difference between dietary calcium intake and daily losses through feces, urine, and sweat, governs this interaction. In states of negative calcium balance, compensatory homeostatic mechanisms are activated to preserve normocalcemia. A key adaptive response is upregulation of 1α-hydroxylase activity, resulting in increased synthesis of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the biologically active form of vitamin D (**Figure 1**). This secosteroid hormone acts on bone tissue by stimulating osteoclastic bone resorption and inhibiting extracellular matrix mineralization (67).

In addition to bone tissue, several other organs integral to calcium homeostasis (e.g., the intestinal epithelium, renal tubular cells, and parathyroid glands) express the VDR. Notably, the effects of vitamin D on bone physiology are primarily mediated through systemic endocrine mechanisms, rather than direct activation of VDRs within bone tissue itself (68).

Positive calcium balance

A positive calcium balance develops when calcium intake is normal or low–normal, provided adequate levels of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] are present. Under these conditions, vitamin D contributes to bone homeostasis predominantly through indirect mechanisms, particularly by enhancing intestinal calcium absorption. Although direct actions of vitamin D on osteogenic cells have been demonstrated in *in vitro* and *in vivo* studies, the precise underlying mechanisms remain incompletely understood (67,68).

Activation of the VDR in intestinal epithelial cells upregulates genes encoding proteins involved in both pathways of calcium transport, as detailed in the "Calcium" section. With respect to direct effects on bone tissue, VDR expression is most prominent in osteoblasts and osteocytes, although it is also present at lower levels in chondrocytes and osteoclasts (69). Evidence supporting the effects of vitamin D on these cells during positive calcium balance derives primarily from transgenic mouse models, in which VDR is either overexpressed or selectively deleted in specific bone cell populations. **Table 5** summarizes the principal findings from these studies.

Negative calcium balance

Negative calcium balance occurs when intestinal calcium absorption is insufficient to meet physiological demands. This condition may result from decreased VDR activity or may develop even when VDR expression is normal. Severe vitamin D deficiency and vitamin D-dependent rickets or osteomalacia are disorders associated with diminished VDR-mediated

Table 5. Bone-related outcomes in transgenic mouse models with cell-specific VDR gene modifications

VDR modification	Target cell type	Bone outcomes
Deletion	Osteoblast precursors	No changes in serum markers (calcium, PTH, phosphate, 1,25$(OH)_2$D) or trabecular bone mass
Deletion	Immature osteoblasts	Increased trabecular bone mass due to reduced RANKL production
Deletion	Mature osteoblasts and osteocytes	No differences in trabecular or cortical bone mass compared to the control group
Overexpression	Mature osteoblasts	Increased cortical and trabecular bone mass
Deletion	Osteoclast precursors	No changes in bone metabolism

Source: adapted from literature (70–73).

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activity. In such conditions, the synthesis of all components essential for intestinal calcium absorption is impaired (67,74).

Proper VDR expressions in the distal nephron, along with PTH activity at this site, is critical for adequate renal calcium reabsorption. This process closely resembles the active transcellular calcium transport found in the intestinal epithelium. Therefore, in states of negative calcium balance due to reduced vitamin D action, the compensatory mechanism of enhanced renal calcium reabsorption is compromised, despite elevated PTH levels (i.e., secondary hyperparathyroidism). In bone tissue, high PTH stimulates the production of receptor activator of nuclear factor κB ligand (RANKL) by osteoblasts; however, bone resorption is not significantly increased because VDR signaling in osteoclasts is impaired. Vitamin D activity in osteoclasts is likely necessary for full induction of osteoclastogenesis. The cumulative outcome of these processes is hypocalcemia, which leads to impaired bone matrix mineralization characteristic of osteomalacia (75).

Recommended daily intake of vitamin D

In 2011, the IOM/NAM established dietary reference intakes for vitamin D for the general population (**Table 6**). They defined the minimum daily nutritional intake required to prevent vitamin D deficiency, which is characterized by serum 25-hydroxyvitamin D [25(OH)D] levels below 20 ng/mL (76). Thirteen years after the release of the IOM/NAM report, the Endocrine Society continues to endorse these recommendations, specifically for individuals aged 19–74 years (77).

However, certain at-risk populations may benefit from achieving serum 25(OH)D levels above 30 ng/mL, which requires vitamin D intake exceeding the amounts recommended by the IOM/NAM. This need is highlighted in a joint position statement from the Brazilian Society of Endocrinology and Metabolism and the Brazilian Society of Clinical Pathology and Laboratory Medicine (78). Older adults are especially susceptible to vitamin D deficiency, a condition associated with increased risks of falls, secondary hyperparathyroidism, and fractures.

Based on several studies that evaluated clinical outcomes related to serum 25(OH)D levels (e.g., PTH suppression, fracture incidence, sarcopenia, muscle weakness, and risk of fall) the position statement supports a target 25(OH)D range of 30–60 ng/mL in individuals over 65 years of age to mitigate the adverse health outcomes linked to serum levels below 30 ng/mL. Other clinical conditions may also benefit from maintaining serum 25(OH)D within this range, including osteoporosis, osteomalacia, osteogenesis imperfecta, hyperparathyroidism, sarcopenia, recurrent falls, CKD, malabsorption syndromes, liver failure, anorexia nervosa, and cancer (78).

The Endocrine Society adheres to the IOM/NAM vitamin D intake recommendations for individuals aged 19–74 years. However, the two organizations differ in their approach for persons aged 75 years and older. The Endocrine Society recommends empirical vitamin D supplementation for healthy individuals aged 75 years and above, based on evidence suggesting a reduced risk of mortality. For this demographic, the recommended average supplemental dose is 900 IU daily (77).

Table 6. Dietary vitamin D recommendations for preventing hypovitaminosis D. No specific intake recommendation has been established for infants under 1 year of age

Age group or condition	Recommended daily intake	Tolerable upper intake level
1–3 years	600 IU	2500 IU
4–8 years	600 IU	3000 IU
9–70 years	600 IU	4000 IU
>70 years	800 IU	4000 IU
Pregnant and lactating women	600 IU	4000 IU

Brazilian scenario of vitamin D intake

Vitamin D possesses unique characteristics compared to other nutrients discussed in this paper. Its supply to the body is partly provided through dietary intake of cholecalciferol, obtained mainly from animal sources, and, to a lesser extent, ergocalciferol, derived predominantly from fungi, algae, and plants. Both forms serve as substrates for the hepatic enzyme 25-hydroxylase, which converts them into 25-hydroxyvitamin D (25(OH)D), a serum marker that reflects the body's vitamin D stores. However, dietary intake contributes only about 20% of the total supply. Unlike other nutrients addressed here, the primary source of vitamin D

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is endogenous cutaneous synthesis of cholecalciferol through sun exposure, accounting for approximately 80% of the substrate required for 25(OH)D production (79). Thus, vitamin D status is influenced by both dietary intake and the degree of sun exposure.

The typical Brazilian diet is not rich in vitamin D, as foods with substantial amounts of cholecalciferol or ergocalciferol are limited (80). Two Brazilian surveys assessed nutrient intake, including vitamin D, in a combined sample of 77,493 individuals. The average daily vitamin D intake among adolescents, adults, and older adults varied by 2.0–2.4 μg/day (80–96 IU), 1.7–2.2 μg/day (68–88 IU), and 1.5–2.0 μg/day (60–80 IU), respectively. Among all nutrients evaluated, vitamin D had the highest prevalence of inadequate intake (99.4–100%) (81). **Table 7** summarizes the vitamin D content of the primary dietary sources of this nutrient (82).

Table 7. Vitamin D content per serving size

Food	Serving size	Vitamin D content
Sun-dried mushrooms	100 g	1600 IU ergocalciferol
Fresh mushrooms	100 g	100 IU ergocalciferol
Cod liver oil	1 Tablespoon	1360 IU cholecalciferol
Wild salmon	100 g	600–1000 IU cholecalciferol
Farmed salmon	100 g	100–250 IU cholecalciferol
Canned sardines	100 g	300 IU cholecalciferol
Canned tuna	100 g	230 IU cholecalciferol
Egg yolk	1 Unit	20 IU cholecalciferol
Cooked beef liver	100 g	15 IU cholecalciferol

Evidence from meta-analyses and systematic reviews

A systematic review and network meta-analysis underlying the Endocrine Society's osteoporosis guidelines evaluated the effects of various interventions on fracture risk. Compared to placebo, the combination of vitamin D and calcium resulted in a 19% relative risk reduction in hip fractures. For non-vertebral fractures, vitamin D alone reduced the risk by 56% compared to placebo (83,84).

Another meta-analysis found that combined vitamin D and calcium supplementation reduced the risk of hip fractures by 16–33%, and the risk of any fractures by 5–19%. However, variations in study populations, vitamin D dosages, and methods within this and other meta-analyses prevent definitive conclusions (85).

Bouillon and cols. reviewed randomized clinical trial data regarding the impact of vitamin D supplementation on a range of outcomes. The most substantial bone health benefits were observed in individuals with vitamin D deficiency. Conversely, administering high intermittent doses of vitamin D to sufficient individuals was associated with decreased BMD and an increased risk of falls and fractures (86).

In summary, the correlation between serum vitamin D levels and the risk of falls and fractures exhibits a U-shaped distribution, whereby both vitamin D deficiency and vitamin D excess are associated with increased risk of these outcomes. The most robust evidence for benefit from vitamin D supplementation, namely improvement in bone mineral density and reduction in falls and fractures, would be for individuals with adequate calcium intake, vitamin D doses between 800 and 2000 IU per day, elderly individuals (over 70 years of age), and individuals with vitamin D deficiency (87).

Side effects and adverse events

As discussed in the physiology section, the human body has mechanisms to maintain serum calcium levels within a narrow range. Because vitamin D enhances intestinal calcium absorption, renal tubular calcium reabsorption, and bone resorption, hypercalcemia is a potential adverse effect of its use. Nevertheless, the therapeutic index of vitamin D formulations, including cholecalciferol, ergocalciferol, and calcifediol, is broad. In individuals without predisposing risk factors for hypercalcemia, serum 25(OH)D levels above 150–200 ng/mL are generally necessary to induce toxicity. This effect is partially mediated by vitamin D catabolic enzymes, which protect against intoxication (88).

Cases of exogenous vitamin D intoxication have been reported following ingestion of cholecalciferol, ergocalciferol, calcifediol, calcitriol, vitamin D analogs, and even topical application of vitamin D analogs for psoriasis (e.g., calcipotriol) (88). Among currently available vitamin D formulations, the 1α-hydroxylated compounds (calcitriol, alfacalcidol, and eldecalcitol) carry higher risks of hypercalcemia, hypercalciuria,

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and ectopic calcification. Their use is therefore limited to specific indications such as hypoparathyroidism and renal osteodystrophy. However, most reported cases of vitamin D intoxication since 2010 have been related to inappropriate prescribing of cholecalciferol, unauthorized high-dose cholecalciferol prescriptions, and the use of unregulated products (79).

The duration of vitamin D intoxication correlates with the half-life and lipophilicity of the compound involved. The half-lives of cholecalciferol, calcifediol, and calcitriol are approximately 2–3 months, 2–3 weeks, and 15 hours, respectively (89). Accordingly, intoxication with calcitriol often resolves more rapidly, whereas that caused by calcifediol or cholecalciferol can persist for weeks to months (88). Clinical manifestations of vitamin D intoxication are diverse, primarily related to hypercalcemia as detailed in the "Calcium" section.

The management of vitamin D intoxication involves restricting the intake of calcium-rich foods (limiting consumption to 400 mg/day or less) and vitamin D, avoiding sun exposure or using sunscreen when exposure cannot be avoided, increasing fluid intake, and reducing the consumption of oxalate-containing foods (90). These initial measures may not always suffice to resolve symptoms and hypercalcemia associated with vitamin D intoxication. Additional interventions, as detailed in **Table 8**, should be implemented according to the severity of the condition (91).

VITAMIN K

Physiological role in bone tissue

The initial association between vitamin K and skeletal biology originated from observations of bone malformations in newborns whose mothers had taken the vitamin K antagonist warfarin during pregnancy (92). Vitamin K refers to a family of lipophilic molecules characterized by a common 2-methyl-1,4-naphthoquinone ring structure (92,93). Among these, phylloquinone (vitamin K1) is the primary dietary source and is found in vegetables (e.g., spinach and broccoli), fruits (e.g., kiwi and avocado), and plant oils (e.g., soy and canola) (94). Another form, menaquinones (MK or vitamin K2), is predominantly synthesized by bacteria and is present in foods such as meat, cheese, and fermented products (93). Menaquinones can also be produced by the intestinal bacterial flora. The MKs are subdivided into 13 subtypes, MK-2 through MK-14; except for MK-4, all can be synthesized in the human gut (95). The main characteristics of the commercially available forms of vitamin K2 are summarized in **Table 9**. Vitamin K1 is mainly involved in the production of coagulation factors and can be converted into vitamin K2 by gut flora. During this conversion, some forms of MK generate menadione as an intermediate molecule (95).

As a fat-soluble vitamin, vitamin K from dietary sources requires normal pancreatic function and the presence of bile salts for intestinal absorption, after which it is transported in chylomicrons through

Table 8. Management strategies for vitamin D intoxication.

Intervention	Mechanism of action	Dose	Onset of action	Duration of effect	Comments
0.9% Sodium chloride	Corrects hypovolemia (primary treatment goal). Increases urinary calcium excretion	4–6 L/day (200–300 mL/hour)	Hours	During infusion	Caution in elderly patients and/or those with acute kidney injury and/or heart failure
Loop diuretics	Increases urinary calcium excretion	40–160 mg/day	Hours	During treatment	Initiate only after correction of hypovolemia. Early use may worsen hypercalcemia
Glucocorticoids	Decrease intestinal calcium absorption; reduce $1,25(OH)_2D$ production; activate 24-hydroxylase	Prednisone (1 mg/kg/day)	2–5 days	Days to weeks	Side effects include hyperglycemia, immunosuppression, and myopathy
Bisphosphonates	Inhibit bone resorption	Pamidronate (90 mg + 0.9% saline 250 mL); Zoledronic acid (4 mg infusion)	24–72 hours	2–4 weeks	Contraindicated in patients with a glomerular filtration rate < 35 mL/min/1.73 m^2

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Table 9. Characteristics of commercially available forms of vitamin K2

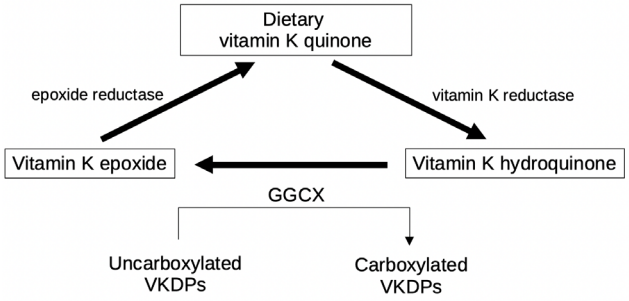
MK subtypes	Characteristics
MK-4	Short-chain MK; shorter half-life; main form of vitamin K in the human body; can be produced from vitamin K1; not produced by human gut flora
MK-7	Long-chain MK; longer half-life; found in natto (fermented soy beans), chicken, pork, beef and cheese

Source: Adapted from the literature (95,98,99).

the lymphatic system (96). Vitamin K1 is primarily delivered to the liver, where it mainly facilitates the carboxylation and activation of coagulation factors. The longer side chains of vitamin K2 result in greater stability, allowing these forms to circulate in the bloodstream longer than vitamin K1 (97).

Vitamin K1, MK-4, and MK-7 are also commercially produced via fermentation or chemical synthesis and are available over the counter (100). Despite these sources, vitamin K is efficiently recycled during the gamma-carboxylation process, which reduces the dietary requirement for this vitamin (92). **Figure 2** presents the vitamin K cycle.

The two main forms of vitamin K (phylloquinone and menaquinones) function as cofactors for the enzyme carboxyglutamyl carboxylase, which catalyzes the carboxylation of protein glutamic acid residues, producing active gamma-carboxyglutamic acid (Gla) residues (101). Among the 17 vitamin K-dependent proteins, six are involved in bone metabolism: matrix Gla protein (MGP), periostin, growth arrest-specific protein 6, protein S, and osteocalcin (OC), the most abundant non-collagenous protein in bone (92,94). By carboxylating and thereby activating MGP and OC, vitamin K plays a significant role in maintaining bone strength (**Figure 1**).



GGCX: gamma-glutamyl carboxylase; VKDPs: vitamin K dependente proteins.

Figure 2. Vitamin K cycle.

Properly carboxylated Gla residues of OC bind to calcium ions in hydroxyapatite, facilitating adequate bone mineralization, while undercarboxylated forms (ucOC) exhibit reduced affinity for calcium and hydroxyapatite (94). OC is specifically expressed in osteoblasts, whereas MGP is synthesized by vascular smooth muscle cells, endothelial cells, chondrocytes, osteoblasts, and osteoclasts. The gamma-carboxylated form of MGP acts as an inhibitor of calcification, preventing both vascular calcification and mineralization by osteoblasts (94). A recent study using MG63 cell culture demonstrated that MGP also stimulates bone formation through the upregulation of the Wnt-beta-catenin signaling pathway (102).

Vitamin K further influences bone remodeling through carboxylation-independent mechanisms. For example, MK-4 is involved in SXR (steroid and xenobiotic receptor)-induced gene expression and the regulation of proteins such as matrilin-2 and tsukushi, which are associated with collagen quality and quantity, as well as CD14, which modulates the genetic transcription of osteoblastic markers and osteoclastogenesis (94,95). A Japanese study also suggests that vitamin K decreases activation of the RANK pathway and increases expression of osteoprotegerin, thereby promoting bone formation and reducing bone resorption (103). **Table 10** lists the effects of vitamin K on bone metabolism.

Table 10. Effects of Vitamin K on bone metabolism

Variable	Effects
Coenzyme for the GGCX	Suppresses bone resorption Increases osteoblast genesis
Gla osteocalcin formation	Regulates osteoclast formation Enhances osteoblast collagen accumulation
Gla-rich protein and periostin production	Decreases RANKL expression Increases osteoprotegerin expression
MGP maintains bone metabolism	Induces osteoclast apoptosis SXR signaling induces osteoblast differentiation

Source: Adapted from the literature (104).

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Both vitamin K1 and K2 deficiencies have been associated with an increased risk of fractures; however, vitamin K supplementation has not consistently demonstrated a protective effect across studies, as discussed below. One of the key challenges in conducting studies focused on bone or vascular health is the difficulty in accurately measuring plasma vitamin K levels, in addition to controlling for confounding variables such as blood lipid concentrations, the coexistence of chronic diseases, and the presence of inflammation (105). In this context, undercarboxylated protein levels can serve as indicators of low vitamin K concentrations and may even help to identify tissue-specific insufficiencies. For instance, levels of ucOC are considered a sensitive, indirect marker of vitamin K status in humans (95), while elevated levels of PIVKA-II are recognized as an indicator of hepatic vitamin K deficiency (106).

A meta-analysis including over 80,000 participants demonstrated that both low dietary intake and low circulating levels of vitamin K are associated with reduced BMD and an increased risk of fractures, particularly of the hip (107). Another investigation utilizing data from the Nurses' Health Study found that women who consumed less than 109 mcg of vitamin K per day had a higher risk of fractures (108).

Furthermore, a study involving male and female participants from the Framingham Heart Study identified an association between low dietary vitamin K intake and an elevated risk of hip fractures; this study also reported a link between low intake and decreased bone density in women (109).

Recommended daily intake of vitamin K

The recommended daily allowance of vitamin K is based on levels required to ensure normal blood coagulation (94). The Food and Agriculture Organization of the United Nations and the World Health Organization recommend 55 mcg/day for adult females and 65 mcg/day for adult males (110). The Food and Drug Administration recommends that adults consume 120 mcg of vitamin K daily (111), while the National Institutes of Health considers 120 mcg for males and 90 mcg for females to be adequate daily intakes (112). In Brazil, the National Health Surveillance Agency adopts 120 mcg per day as the general recommended daily value for food (113).

Nevertheless, studies focused on bone and vascular health suggest that higher daily intakes (exceeding even 156–250 mcg/day) may be necessary to prevent unfavorable outcomes (114,115). These findings indicate that subclinical deficiencies may impair vitamin K-dependent carboxylation before significant alterations in coagulation are observed (116). Thus, in situations of vitamin K deficiency, there appears to be preferential carboxylation of coagulation factors over extra-hepatic proteins (92).

Another notable finding is that plasma levels of K1 or MK-7 required to reduce ucOC increase with age. These requirements are higher in individuals over 70 years, a group that is also at increased risk for vitamin K-related vascular diseases, such as vascular calcifications, which have been associated with osteoporosis (106). The reason for this greater demand in older individuals remains to be clarified.

Brazilian scenario of vitamin K intake

The Brazilian Institute of Geography and Statistics conducted surveys on personal food consumption in Brazil, revealing insufficient vegetable consumption, which implies low vitamin K intake among the Brazilian population (117). Consistent with this finding, a cross-sectional study using 3-day nutritional records from 173 healthy individuals aged 21–81 years in São Paulo, Brazil, found that the median daily vitamin K intake for adults was 99 mcg/day, while the elderly population (older than 60 years) consumed 104 mcg/day (118).

In addition to dietary intake, the vitamin K content in vegetables depends on cultivation conditions. A study conducted by the School of Pharmaceutical Sciences of the University of São Paulo demonstrated significant variation in vitamin K concentrations between products grown in Brazil and those planted in the United States. For example, kale and arugula cultivated in Brazilian soil contain 245.52 and 259.11 mcg/100g, respectively, while their American counterparts contain 817 and 108.60 mcg/100g, respectively (119).

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Evidence from meta-analyses and systematic reviews

Although vitamin K deficiency has been substantially associated with reduced BMD and increased fracture risk, vitamin K supplementation has not demonstrated clear benefits or definitive evidence for preventing these outcomes. Variations in dosage, treatment duration, and forms of supplementation (K1, MK-4, MK-7) across studies likely contribute to the heterogeneity of results. Furthermore, a recent meta-analysis revealed that the anti-fracture effect of vitamin K was only observed in long-term observational studies with follow-up durations exceeding 10 years, indicating that follow-up duration is also a relevant factor (107). Nevertheless, vitamin K is widely prescribed in Japan as an approved medication for osteoporosis (95).

Vitamin K effects on bone mineral density

Studies about the effects of vitamin K, alone or in combination, on bone health have been published since the 60's. Since then, several randomized clinical trials (RCTs) using either vitamin K1 or vitamin K2 supplements have been conducted, however as discussed earlier, the results are still conflicting. Hu and cols. (120) conducted a meta-analysis with 10 RCTs that compared the effects of vitamin K taken with calcium to control groups taking only vitamin K, or only calcium or a placebo. Six trials were performed using vitamin K1 with doses ranging from 30mcg to 5mg per day, and 7 studies used vitamin K2, from 90 mcg to 45 mg. The meta-analysis included 1,346 participants who were followed for 6 months to 4 years, and they concluded that the combination was associated with increased lumbar BMD and reduced levels of ucOC. Other meta-analyses reached less conclusive results, like the one published by Huang and cols., which included 19 RCTs and 6759 postmenopausal women taking vitamin K2 supplements, whether MK-4 (1.5 to 90 mg/day) or MK-7 (100 to 360 mcg/day). They observed significant improvements in lumbar BMD among Japanese patients with osteoporosis; however, no significant changes were found in the non-osteoporotic group (121). There are also meta-analyses that did not observe significant changes in BMD, like the one conducted by Salma and cols. which incorporated studies from Asia, North America, Europe, and Africa, using vitamin K1 (100 mcg to 5 mg) or K2 (180 mcg to 45 mg) for 6–36 months, either as monotherapy or in combination (122).

Vitamin K effects on fractures

Few RCTs included fractures as an endpoint. In the meta-analysis conducted by Huang and cols. (121), the pooled analysis showed no significant differences in fracture incidence between patients who received and did not receive K2, although a subsequent sensitivity analysis demonstrated a significant benefit favoring vitamin K2 supplementation. Salma and cols. (122) described a decrease in the overall fracture risk in the group that received supplementation with vitamin K, mainly K2 forms in higher dosages, despite showing minimal impact on BMD, with higher doses of K2 forms exhibiting a more pronounced effect.

Vitamin K and bisphosphonates

There are only few studies exploring the association of vitamin K with bisphosphonate treatments. Moore and colleagues (123) conducted a trial involving 105 postmenopausal women with osteoporosis and low baseline vitamin K1 levels, all of whom were already receiving oral bisphosphonates, calcium, and/or vitamin D. Participants received either 1 mg/day of vitamin K1, 45 mg/day of MK-4, or placebo for 18 months. No significant differences in BMD were observed among the groups; however, vitamin K1 administration led to significant changes in bone turnover markers and hip geometry parameters, as assessed by hip structural analysis software (123). Kasukawa and cols. (124) evaluated the addition of vitamin K2 to risedronate in 101 postmenopausal women with osteoporosis. They found no difference in fracture incidence after 12 months with K2 use, but patients who experienced vertebral fractures had significantly higher levels of ucOC when treated with risedronate alone. **Table 11** summarizes the types and dosages of vitamin K used in the above-mentioned studies.

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Table 11. Vitamin K1 and vitamin K2 dosages and observed outcomes in the above-mentioned RCTs

	Dosages	Effects on BMD
Philoquinone (K1)	30 mcg – 10 mg	Increase in BMD, decrease in ucOC when used with calcium
Menatetrenone (MK-4)	1,5 mg – 90 mg	Increase in BMD in osteoporotic patients; reduced overall fracture risk
Menaquinone-7 (MK-7)	100 mcg – 10 mg	Increase in BMD in osteoporotic patients; reduced overall fracture risk

Source: Adapted from literature (120–122).

Side effects and adverse events

There is no known toxicity associated with dietary vitamin K. The synthetic derivative of vitamin K1, phytadione, is commercially available and can be administered orally, intramuscularly, subcutaneously, or intravenously. It is indicated for the treatment of coagulation disorders due to vitamin K deficiency. Synthetic vitamin K2 is also available for oral supplementation as MK. Vitamin K toxicity is extremely rare, but may result in hemolytic anemia, hyperbilirubinemia, and jaundice (125).

MAGNESIUM

Physiological role in bone tissue

Magnesium is an important cation in the human body, facilitating numerous essential enzymatic reactions (126–128). Approximately 60% of the body's total magnesium is stored in the bones, with about 30% of this pool available to regulate blood magnesium levels (127–131). Dietary magnesium is absorbed into the bloodstream primarily in the ileum through passive paracellular mechanisms dependent on claudins 2 and 12, as well as active transcellular mechanisms dependent on transient receptor potential cation channel subfamily M members 6 and 7 (TRPM6 and TRPM7). Calcitriol (the active metabolite of vitamin D) and inulin (a non-absorbable oligosaccharide synthesized by certain plants) can enhance intestinal magnesium absorption (126,127,130–132). Absorption is also influenced by factors such as estrogen, intestinal lumen pH, FGF-23, PTH, insulin, epidermal growth factor (EGF), and the intestinal microbiota (130). (**Figure 1**).

Renally, 95–97% of filtered magnesium is reabsorbed in the thick ascending limb of the loop of Henle, a process dependent on claudins 16, 19, and 10b, and in the distal convoluted tubule, through TRPM6 and TRPM7. Several factors stimulate renal magnesium reabsorption, including PTH, calcitriol, insulin, metabolic alkalosis, EGF, inulin, sodium-glucose cotransporter 2 inhibitors, amiloride, and triamterene (126,130,132,133). Conversely, reabsorption is inhibited by alcohol, insulin resistance, hypercalcemia, metabolic acidosis, hypokalemia, hypophosphatemia, thiazide and loop diuretics, calcineurin inhibitors, cisplatin, cetuximab, erlotinib, and various genetic disorders (126,130,133).

Plasma magnesium homeostasis is maintained by the balance between intestinal absorption, bone storage, and renal excretion (130). As magnesium is predominantly intracellular, only about 1% resides in plasma; thus, serum measurements may not accurately reflect total body magnesium stores (128,130,132). Most clinical laboratories define the normal serum magnesium as 1.7–2.4 mg/dL (0.7–1.0 mmol/L). Potential laboratory interferences include hypoalbuminemia, sample hemolysis, and the use of anticoagulants such as ethylenediaminetetraacetic acid (130).

Hypomagnesemia may result from inadequate dietary intake, alcoholism, gastrointestinal malabsorption, intestinal dysbiosis, type 2 diabetes, and the use of proton pump inhibitors, diuretics, H_2 blockers, antihistamines, antibiotics, antivirals, antiepileptics, immunosuppressants, or chemotherapy agents (126,130,134). Hypomagnesemia is typically asymptomatic; however, potential manifestations include muscle weakness, cramps, and fatigue. Severe deficiency may lead to seizures and arrhythmias (126,130).

In cases of moderate or severe hypomagnesemia, both PTH levels and renal calcium reabsorption decrease, resulting in hypocalcemia (129,130,134,135). Mild hypomagnesemia, in contrast, can stimulate PTH secretion (133,135). When hypermagnesemia reduces PTH levels and induces hypercalciuria, it also leads to hypocalcemia (129,133,135). Both hypo- and hypermagnesemia appear to be detrimental to bone health (131).

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Magnesium serves as a cofactor for alkaline phosphatase, which is indispensable for bone matrix synthesis and mineralization. Magnesium also promotes bone formation by stimulating osteoblast proliferation. Furthermore, it is necessary for enzymes involved in activating vitamin D and participates in maintaining calcium homeostasis (126–130,132,134). Osteoclastogenesis inducer IκB kinase is regulated by magnesium; thus, deficiency can facilitate osteoclast survival, proliferation, and differentiation (126).

Hypomagnesemia acts by reducing osteoblast numbers, triggering local inflammation in bone tissue, and enhancing osteoclast differentiation and activity. It also impairs the activation of vitamin D, whose active form is important for promoting osteoblast differentiation and proliferation, as well as for inhibiting osteoclast generation. Collectively, hypomagnesemia increases osteoclast activity while decreasing osteoblast activity, ultimately leading to elevated bone resorption (126–130,132,134).

An *in vitro* study by Mammoli and cols. (131) demonstrated that hypermagnesemia significantly reduces the expression of osteogenic genes *RUNX2* and *COL1A1* and is associated with diminished matrix calcification. Moreover, hypermagnesemia impaired protein kinase activity, which further promoted osteoclast differentiation and inhibited osteoblast differentiation. Overall, this study suggests that hypermagnesemia inhibits osteoblast differentiation while promoting osteoclast differentiation, thereby enhancing bone resorption.

Recommended daily intake of magnesium

The recommended daily allowance (RDA) for magnesium is 300–320 mg/day for adult women, 350–430 mg/day for adult men (126–128,130,134), and 350–360 mg/day for pregnant women (126).

The adequate intake (AI), the estimated average requirement (EAR), the recommended daily allowance (RDA), and the tolerable upper intake level (UL) for magnesium are detailed in **Table 12**. In pregnant women, the EAR for magnesium is between 290 and 335 mg/day and the RDA is between 350 and 400 mg/day. In lactating women, the EAR is between 255 and 300 mg/day and the RDA is between 310 and 360mg/day (136).

Table 12. Magnesium intake recommendations

Age	mg/day	
0 to 6 months	30	AI
7 to 12 months	75	
1 to 3 years	65	EAR
	80	RDA
	65	UL of supplementary magnesium
4 to 8 years	110	EAR
	130	RDA
	110	UL of supplementary magnesium
9 to 13 years	200	EAR
	240	RDA
Male		
14 to 18 years	340	EAR
	410	RDA
19 to 30 years	330	EAR
	400	RDA
≥ 31 years	350	EAR
	420	RDA
Female		
14 to 18 years	300	EAR
	360	RDA
19 to 30 years	255	EAR
	310	RDA
≥ 31 years	265	EAR
	320	RDA
> 8 years	350	UL of supplementary magnesium

Adequate intake (AI), estimated average requirement (EAR), recommended daily allowance (RDA), tolerable upper intake level (UL). Source: Adapted from the literature (136).

The richest dietary sources of magnesium include legumes, vegetables, nuts, seeds, and whole grains (**Table 13**) (126–128,130,134). Magnesium bioavailability can be reduced by food refining processes, cooking, and exposure to the herbicide glyphosate. Magnesium content in water varies substantially depending on the source (126,127). Organic magnesium salts (e.g., glycinate, lactate, citrate, gluconate, and aspartate) are absorbed more efficiently than inorganic salts (e.g., oxide, chloride, and carbonate) (130).

Low dietary magnesium intake can lead to hypomagnesemia, which treatment involves increasing magnesium intake through dietary sources or supplementation. In cases where oral supplementation fails to correct hypomagnesemia, intravenous magnesium replacement is indicated. Pharmacologic

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Table 13. Examples of commonly consumed foods and their approximate magnesium content per portion

Some examples of foods rich in magnesium	Approximate magnesium content (mg)
Spinach, cooked, 200 g	150
Pasta, whole grain, boiled, 200 g	90
Seeds (pumpkin seeds, sunflower seeds, and/or pine nuts), one tablespoon	55
Mixed nuts, one handful	55
Peanuts, one handful	55
Red kidney beans, boiled, 100 g	50
Banana, a middle-sized	40
Bread, whole grain, one slice	25

Source: Adapted from the literature (134).

interventions such as amiloride, triamterene, inulin, and sodium-glucose cotransporter 2 inhibitors may also be employed (130).

Brazilian scenario of magnesium intake

The prevalence of hypomagnesemia is 3–10% in the global population, 10–30% among individuals with type 2 diabetes, 10–60% in hospitalized patients, and exceeds 65% in patients admitted to intensive care units (130).

Pinheiro and cols. conducted the BRAZOS study analyzing mineral and vitamin intake in a Brazilian population over the age of 40 using a 24-hour dietary recall questionnaire. 80% of the participants had an inadequate dietary magnesium intake. Magnesium intake was measured in individuals with and without fragility fractures (**Table 14**), and the difference was statistically significant for women but not for men (**Table 14**). As for regional disparities in magnesium intake, the only statistically significant finding was a higher magnesium intake among participants with fragility fractures in the northern region of Brazil (30).

In northeastern Brazil, a study involving pregnant women reported a prevalence of magnesium deficiency (defined as <1.8 mg/dL) of approximately 50% (137). Another study, Hermes Sales and cols., found that over 80% of the São Paulo population has inadequate dietary magnesium intake (**Table 14**) (138).

The study by Varly-Jr and cols. consisted of two food records covering the last 30 days of 32,749 individuals in two consecutive years (2008 and 2009) and two 24-hour dietary recalls of 44,744 individuals in another two consecutive years (2017 and 2018). Regarding magnesium intake, a deficiency of more than 50% was found in adolescents and more than 60% in adults and the elderly (**Table 14**) (81).

Rodrigues et. al conducted a cross-sectional survey of adolescents aged 15–18 years living in São Paulo revealed that more than 70% of participants did not meet the recommended daily magnesium intake (**Table 14**) (31).

Table 14. Magnesium observed intake in Brazilian studies

			Mean observed intake
Pinheiro and cols.	With history of fragility fracture	Men	244
		Women	196
	Without history of fragility fracture	Men	201
		Women	189
Hermes Sales and cols.	Men	**Years old**	
		14-18	225.2
		19-30	256.8
		31-50	249.4
		51-70	239.1
		≥ 71	237.1
	Women	14-18	199.2
		19-30	196.4
		31-50	193.7
		51-70	188.3
		≥ 71	184.0
Verly-Jr and cols.	**2008-2009**		
	Men	Adolescents	285.8
		Adults	310.0
		Elderly	285.3
	Women	Adolescents	244.3
		Adults	240.8
		Elderly	232.4
	2017-2018		
	Men	Adolescents	273.3
		Adults	304.7
		Elderly	275.7
	Women	Adolescents	229.7
		Adults	232.8
		Elderly	225.5
Rodrigues and cols.	Adolescents		243.91

Source: Adapted from the literature (30,31,81,138).

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Evidence from meta-analyses and systematic reviews

Dominguez and cols. (132) conducted a meta-analysis investigating the association between serum magnesium levels and fracture incidence. Their findings revealed a statistically significant association between low serum magnesium levels and an increased risk of fractures (relative risk = 1,579; 95% confidence interval = 1,216–2,051; *p*-value = 0.001). Although the authors considered the overall number of participants adequate, they noted several limitations incluinding the small number of eligible studies, the fact that all those eligible studies were observational, and the fact that half of those studies involved patients undergoing hemodialysis (132).

Another meta-analysis by Groenendijk and cols. (134) examined the relationship between magnesium intake (from supplements and food) and various bone parameters, including BMD (total body, lumbar spine, femoral neck, and hip), bone turnover markers, and fracture risk (total and hip). The only parameter suitable for meta-analysis was the association between magnesium intake and hip BMD, for which a positive association was identified ($p < 0.05$). Limitations of this Groenendijk and cols. study also consist of the small number of eligible studies included and the fact that most of them were observational.

Sari and cols.'s meta-analysis considered nine randomized controlled trials, but no significant correlation was found between oral magnesium supplementation and fracture incidence. Limitations include the fact that the follow-up time of eligible studies varied considerably and there was considerable heterogeneity between the effect sizes across eligible studies (139).

There is a meta-analysis of randomized clinical trials in hemodialysis patients, which analyzes the correlation between magnesium supplementation and serum calcium, phosphorus, and PTH levels and carotid intima-media thickness. However, no research has been conducted on the relationship between magnesium supplementation and bone parameters or fractures (140).

Reviews by Fatima and cols., Rondanelli and cols. and Liu and cols. discuss the interaction of magnesium with bone physiology agents (see section "Physiological role in bone tissue") and suggest that hypomagnesemia may have a potentially negative effect on bone health (126,128,129). However, to date, there are only a few meta-analyses on magnesium and its relationship with bone parameters or fractures. There is no solid evidence from randomized controlled clinical trials to support magnesium supplementation for fracture prevention.

Side effects and adverse events

Hypermagnesemia is a rare condition that predominantly occurs as a result of kidney failure, particularly in association with the use of magnesium-retaining medications (128,130,133). Hypermagnesemia is usually asymptomatic; however, possible symptoms include diarrhea, nausea, and fatigue (130,133). In severe cases, symptoms may include lethargy, hypotension, urinary retention, respiratory depression, and bradycardia (133). An Italian study reported a prevalence of hypermagnesemia of 1.78% among hospitalized patients, defining hypermagnesemia as a serum level > 3.8 mg/dL (141).

The treatment of hypermagnesemia involves discontinuing all exogenous sources of magnesium. In severe cases, treatment options include administration of calcium gluconate, loop diuretics, and intravenous normal saline. Hemodialysis is reserved for cases of severe hypermagnesemia that do not respond to other measures, particularly in patients with advanced renal dysfunction (133).

In conclusion, magnesium is a cation that the human body cannot synthesize and must obtain through dietary sources. Its potential importance for bone health highlights the need for adequate intake and appropriate clinical management, as well as further studies on the subject, particularly longitudinal studies.

PHOSPHORUS

Physiology and homeostasis of phosphorus

Phosphorus is a highly reactive chemical element that combines with oxygen under physiological conditions. In the human body, phosphorus predominantly exists as organic or inorganic phosphate (Pi) (142). Its most common natural form is pentavalent, combined with

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oxygen as the phosphate ion (PO_4^{3-}) (136). Phosphorus is an essential component of the bone mineral matrix. In adults, approximately 85% (around 700 g) of total body phosphorus is stored in bone tissue (143). Bones and teeth serve as the primary reservoirs of phosphorus in humans, where it is present as calcium phosphate crystals (apatite); the remainder is distributed among soft tissues and the extracellular fluid (ECF) (144). In soft tissues, phosphorus exists as soluble phosphate ions, and it is also present in lipids, proteins, carbohydrates, and nucleic acids in the form of ester or anhydride bonds, where it functions as a modulator of enzymatic activity (143).

Under physiological conditions, plasma phosphate concentration is maintained by a dynamic interplay among dietary intake (with efficient intestinal absorption), renal excretion (modulated by renal tubular reabsorption), and bone remodeling. (**Figure 1**). This regulatory system is governed by endocrine mechanisms involving FGF-23, PTH, and the active form of vitamin D, 1,25-dihydroxyvitamin D [calcitriol, $1,25(OH)_2D$] (145).

Phosphate is provided through the diet as either inorganic salts or organic phosphate compounds, which can be hydrolyzed by intestinal alkaline phosphatases or bacterial phytases. Inorganic phosphate is absorbed in the intestine by two primary pathways: the transcellular pathway, mediated by active transport through sodium-dependent transporters such as PiT1, PiT2, and NaPi-IIb, located in the luminal membrane of small intestinal enterocytes, and the paracellular pathway, which appears to be independent of both dietary phosphorus intake and calcitriol levels (142,146).

Approximately 15% of total body phosphorus is stored in soft tissues, primarily in the liver and skeletal muscle. Phosphate uptake by muscle is stimulated by insulin via the PiT1 and PiT2 transporters. In the liver, phosphate plays a crucial role in metabolic processes, including glycolysis and phospholipid synthesis (142). Skeletal muscle functions as the main storage site of phosphorus in soft tissues, mainly as adenosine triphosphate and phosphocreatine (144). Adequate Pi levels are essential for muscle energy metabolism (147), and deficiency may result in myopathy, which is reversible with phosphate supplementation, as observed in osteomalacia related to vitamin D deficiency or tumor-induced osteomalacia (142,144). Beyond its structural role, phosphate acts as a signaling molecule in bone remodeling, influencing osteoblast and osteoclast activity through local pathways involving sclerostin, RANKL, and osteoprotegerin (142,148,149). It is estimated that approximately 180 mg of Pi are deposited through bone formation, and an equal amount is mobilized via resorption every 24 hours (144).

The kidneys are the primary regulators of plasma phosphate concentration. About 80% of filtered phosphate is reabsorbed in proximal tubules via NaPi cotransporters, a process modulated by FGF-23, PTH, and calcitriol (144,150). This process depends on the GFR and the tubular maximum capacity for phosphate reabsorption (TmPi) (151,152).

The maximum tubular reabsorption rate of Pi (TmPi) can be clinically assessed using fasting blood and urine samples collected over 1–2 hours, with a mid-interval blood draw. Calculations involve formulas that incorporate plasma and urinary Pi and creatinine concentrations (144,153). The fractional excretion of Pi can also be expressed relative to creatinine clearance to evaluate urinary phosphate loss (154). In adults, TmPi/GFR (maximum tubular phosphate reabsorption capacity adjusted for GFR) is calculated using the Walton and Bijvoet nomogram (155) or the Kenny and Glen algorithm (153,156) (**Table 15**). Reference values for TmPi/GFR in adults range from 0.8 to 1.35 mmol/L of glomerular filtrate (153).

Phosphate homeostasis is regulated by an endocrine axis primarily composed of the hormones FGF-23, PTH, and $1,25(OH)_2D$. Under physiological conditions, FGF-23 is produced by osteocytes and

Table 15. Renal parameters for the evaluation of phosphate reabsorption and excretion

Fractional excretion of phosphate	$FEPi\ (\%) = [(Pi_u \times Cr_p) / (Pi_p \times Cr_u)] \times 100$
Tubular reabsorption of phosphate (TRPi)	$TRP = 1 - FEPi$
Tubular maximum reabsorption rate per GFR (TmPi/GFR)	If $TRP < 0.86$: $TmP/GFR = TRP \times Pi_p$ If $TRP > 0.86$: $TmPi/GFR = \alpha \times Pi_p$ $\alpha = 0.3 \times TRP / (1 - [0.8 \times TRP])$

Pi_u: Urinary phosphate; Cr_p: plasma creatinine; Pi_p: plasma phosphate; Cr_u: urinary creatinine.
Source: Based on the literature (144,154,156).

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osteoblasts in response to high phosphorus intake, elevated serum phosphate levels, and increased concentrations of $1,25(OH)_2D$ (145). Acting on the renal proximal tubule through the FGFR–Klotho receptor complex, FGF-23 decreases the activity of sodium–phosphate cotransporters (NaPi-IIa and NaPi-IIc), thereby reducing phosphate reabsorption and enhancing urinary excretion (144,153). Additionally, FGF-23 suppresses renal 1α-hydroxylase, limiting the synthesis of $1,25(OH)_2D$, and induces 24-hydroxylase, which catalyzes the degradation of both 25(OH)D and $1,25(OH)_2D$, collectively reducing intestinal absorption of calcium and phosphate (153,157). Conversely, reduced extracellular phosphate inhibits FGF-23 secretion, which favors an increase in TmPi and enhances intestinal phosphate absorption, thereby contributing to the maintenance of normophosphatemia (144).

PTH is secreted in response to hypocalcemia and/or elevated serum phosphate. It stimulates the production of $1,25(OH)_2D$ and may also induce FGF-23 secretion. In cases of hyperphosphatemia, circulating levels of both PTH and FGF-23 increase, acting on the kidneys to downregulate the expression of the NaPi-IIa and NaPi-IIc cotransporters. This process reduces phosphate reabsorption capacity and promotes phosphaturia. Conversely, during hypophosphatemia, increased synthesis of $1,25(OH)_2D_3$ stimulates the intestinal expression of the NaPi-IIb cotransporter, enhancing the efficiency of dietary phosphate absorption (158).

Recommended daily intake of phosphorus

A typical diet generally provides sufficient phosphorus, making dietary phosphate deficiency unlikely under most circumstances (159). Dietary phosphate exists in two primary forms: organic and inorganic (158). Organic phosphate from plant sources is mainly present as phytates, while animal-derived phosphate is bound to proteins. The most significant source of Pi is the addition of Pi salts as food additives (142).

Approximately 30% of dietary phosphorus is derived from meats (animal tissues) and vegetables, another 30% comes from dairy products, with about 70% of this being Pi, and the remaining 40% originates from phosphate added as food additives, processed foods, and dietary supplements (144,160).

Phytate (inositol hexakisphosphate), found in plants, is rich in phosphorus and is more prevalent in vegetarian diets. However, the bioavailability of phosphorus from phytate is low in humans, as plant-derived phytase is inactivated by cooking, and the human intestinal tract expresses negligible levels of endogenous phytase activity (144,158,161). Interestingly, the gut microbiota in individuals who consume high-phytate diets (e.g., vegetarians) is more effective in degrading phytate. This suggests that the microbiome can adapt to dietary environments and that diet may modulate bacterial metabolic activity (161).

In addition to naturally occurring food phosphorus, total dietary phosphorus intake is significantly influenced by phosphate-containing additives, which are widely used as preservatives and flavor enhancers in ultra-processed foods, fast foods, and soft drinks. Because these additives are rich in highly bioavailable phosphate salts and have become increasingly common, the actual percentage of absorbable phosphate has risen considerably in recent years, often exceeding dietary recommendations, particularly in industrialized nations (158,162).

The RDA for phosphorus in adults is 700 mg/day, and the EAR is 580 mg/day (136). The tolerable UL is 4000 mg/day (163), although some evidence suggests that such a high intake may contribute to the development of bone and cardiovascular diseases (144,158). **Table 16** presents the usual mean daily phosphorus intake, EAR, RDA, and UL by sex and age group.

The RDA for phosphorus in pregnant and lactating women up to 12 months postpartum is 1250 mg for those aged 14–18 years and 700 mg for those aged 19–50 years (164,166). Among infants, dietary phosphorus intake varies based on the food source. Phosphorus bioavailability is highest in human milk (85–90%), intermediate in cow's milk (72%), and lowest in soy-based formulas (~59%) due to the presence of phytic acid. Although human milk contains less phosphorus, infant formulas compensate for lower absorption rates by providing higher

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Table 16. Usual mean daily phosphorus intake and dietary reference intake guidelines (EAR, RDA, and UL) by sex and age. Values are given in mg/dL

Sex and age	Usual phosphorus intake	EAR	RDA	UL
Men				
1–3	1030 ± 26.3	380	460	3000
4–8	1145 ± 27.4	405	500	3000
9–13	1321 ± 35.4	1055	1250	4000
14–18	1681 ± 61.5	1055	1250	4000
19–30	1656 ± 53.4	580	700	4000
31–50	1727 ± 25.0	580	700	4000
51–70	1492 ± 30.0	580	700	4000
≥ 71	1270 ± 27.6	580	700	3000
Women				
1–3	1030 ± 26.3	380	460	3000
4–8	1145 ± 27.4	405	500	3000
9–13	1176 ± 57.5	1055	1250	4000
14–18	1067 ± 29.8	1055	1250	4000
19–30	1120 ± 40.8	580	700	4000
31–50	1197 ± 25.0	580	700	4000
51–70	1106 ± 34.0	580	700	4000
≥ 71	985 ± 28.8	580	700	3000

EAR: Estimated average requirement; RDA: recommended dietary allowance; UL: tolerable upper intake level. Source: Adapted from the literature (10,163–166).

concentrations of phosphorus, calcium, and other minerals, thereby resulting in greater overall mineral absorption (136). Nevertheless, the lower phosphorus intake from human milk may be advantageous, as it helps decrease fecal pH and inhibits the proliferation of pathogenic microorganisms in the distal gut, while also safeguarding the immature renal system of the newborn (136,167–169).

Brazilian scenario of phosphorus intake

A Brazilian analysis using data from the National Dietary Survey (2008–2009; 2017–2018) evaluated phosphorus intake across different age and sex groups: 1,094.6–1,081.9 mg for male adolescents, 1,167.0–1,153.4 mg for adult men, and 1,036.6–977.1 mg for older men; and 977.1–924.6 mg, 928.9–878.9 mg, and 877.3–811.2 mg for female adolescents, adults, and older adults, respectively. Despite these relatively high mean intakes, the study found that more than half of Brazilian adolescents had phosphorus intake below the EAR, reflecting the higher physiological requirements during adolescence and explaining the prevalence of inadequacy in this age group (81).

Over the past decade, phosphorus consumption in Brazil has risen. The proportion of ultra-processed foods in total energy intake increased from 18.7% to 19.7% between 2008 and 2018, alongside higher sugar, fat, and sodium intake and reduced consumption of nutrient-dense foods (170). Many of these products contain phosphate-based additives with nearly complete intestinal absorption, substantially increasing total phosphorus exposure and potentially disturbing mineral homeostasis (171, 172).

In a cross-sectional study among manufacturing workers in Northeastern Brazil, frequent consumption of processed meat products - such as sausages, mortadella, hamburgers, and nuggets containing mechanically separated meat - was associated with higher intakes of energy, fat, sodium, and phosphorus, and lower intake of minimally processed foods (173). Among adolescents, regular intake of soft drinks, fast foods, and other ultra-processed products was linked to poorer overall diet quality and greater exposure to phosphate additives (174).

This pattern aligns with evidence from the NOVA food classification system, which associates higher consumption of ultra-processed foods with poorer overall nutrient profiles, characterized by increased exposure to industrial additives and reduced intake of nutrient-dense foods (170). Collectively, these findings indicate that excessive phosphorus intake from additive-rich, ultra-processed foods represents an emerging nutritional and metabolic concern in the Brazilian population (171). In light of the increasing share of ultra-processed foods in the Brazilian diet, enhanced monitoring of phosphate additives should be considered a nutritional priority. This recommendation is consistent with recent European frameworks, such as the *Nordic Nutrition Recommendations 2023*, which emphasize the high bioavailability of phosphorus additives and the current lack of comprehensive data on their intake and long-term health implications (175).

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Scientific evidence

Phosphorus deficiency is rare in the individuals with normal renal function and adequate dietary intake. Homeostatic mechanisms involving renal excretion and endocrine regulation (FGF-23, PTH, and vitamin D) maintain serum phosphate within narrow physiological range. Deficiency typically occurs only in specific pathological contexts, such as chronic malnutrition, severe gastrointestinal disorders, or inherited renal phosphate-wasting syndromes (145,176). However, acute increases in inorganic phosphate intake, particularly from additives, can transiently elevate plasma phosphate and alter calcium–phosphate and PTH dynamics even in healthy adults (177).

In randomized cross-over trials involving healthy young adults, short-term loading with inorganic phosphate for five days led to significant increases in plasma phosphate and FGF-23 concentrations, even in the context of preserved renal function (178). Similarly, controlled experimental studies demonstrate that short-term ingestion of phosphorus-based food additives increases circulating FGF-23, osteopontin, and osteocalcin, while decreasing sclerostin, representing early endocrine and skeletal responses even in individuals with normal kidney function (179).

The balance between calcium and phosphorus intake plays a fundamental role in bone mineralization and remodeling, as both minerals are major components of the hydroxyapatite matrix and tightly regulated by endocrine and renal mechanisms (180). Experimental and clinical evidence indicates that diets with a disproportionate calcium-to-phosphorus (Ca:P) ratio, particularly those with excessive phosphorus relative to calcium, can disrupt mineral homeostasis, stimulate secondary hyperparathyroidism, and compromise skeletal integrity (180,181). Experimental studies demonstrate that high phosphorus intake can impair skeletal microarchitecture. In rats with normal renal function, Fernández-Villabrille and cols. demonstrated that chronically elevated dietary phosphorus intake induced significant bone deterioration, with a particular impact on trabecular bone microstructure (182). Rizzoli and cols. emphasize that high phosphorus intake combined with insufficient calcium increases parathyroid hormone concentrations and bone resorption, a condition frequently observed in Westernized diets rich in processed foods (180). Likewise, Takeda and cols. highlighted that the widespread use of phosphate additives markedly elevates dietary phosphorus exposure, lowering the Ca:P ratio, and poses risks to bone mineralization (181). These findings indicate that maintaining an adequate Ca:P ratio, through limiting additive-derived phosphorus and ensuring sufficient calcium intake, constitutes a nutritional strategy to preserve bone structure and mineral homeostasis (180-182).

Phosphate excess also contributes to cardiovascular injury through direct effects on vascular smooth muscle cells (VSMCs), thereby driving medial arterial calcification and loss of elasticity (183). In parallel, phosphate retention induces a compensatory increase in FGF-23, which acts directly on cardiomyocytes and promotes pathological left ventricular hypertrophy independent of kidney function (184). Collectively, these mechanisms show how phosphate excess and FGF-23 dysregulation act synergistically to drive vascular and cardiac damage (183-184). **Table 17** summarizes the main dietary sources of phosphorus and highlights the potential health risks associated with excessive intake.

Side effects and adverse events

Phosphorus disorders

In adults, normal plasma Pi levels range from 2.5 to 4.5 mg/dL (0.81–1.45 mmol/L) (**Table 18**) (144,150). A diurnal variation in plasma phosphate concentration is observed, ranging from 0.6 to 1.0 mg/dL, with a nadir occurring around 11:00 am and a peak at approximately 12:30 am (187,188). In children, phosphate concentrations are higher due to a greater maximum tubular reabsorption capacity (TmPi), which decreases with age until adult reference values are reached (144). In adults, serum phosphate levels tend to decline with advancing age, reflecting changes in renal tubular phosphate reabsorption (189).

Proper regulation of phosphorus metabolism is essential throughout life, as imbalances can result in hyperphosphatemia or hypophosphatemia, which are frequently associated with severe clinical manifestations (144,145). Chronic hypophosphatemia may lead

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Table 17. Main dietary sources of phosphorus and potential risks of excessive intake

Category	Examples/Main foods	Bioavailability/Chemical form	Evidence and potential health risks
Unprocessed and minimally processed foods	Milk, yogurt, white cheese, eggs, fresh meat, fish	Organic phosphate bound to proteins; moderate bioavailability (approximately 40–60 %)	Adequate intake balanced with calcium maintains bone and mineral homeostasis.
Plant sources (legumes, nuts and whole grains)	Beans, lentils, soybeans, peanuts, cashews, oats, whole wheat, brown rice	Organic phosphate in phytates; low bioavailability (< 40%)	High plant intake rarely causes excess phosphorus (P); lower absorption than animal sources.
Processed meats and sausages	Ham, sausage, mortadella, nuggets, industrial hamburgers	Inorganic phosphate additives; high bioavailability (approximately 80–100%)	Major contributors to excessive phosphorus intake; inorganic additives are rapidly absorbed and stimulate FGF-23 secretion, bone remodeling, and vascular calcification.
Cola-type soft drinks & phosphoric acid beverages	Cola, energy drinks, industrial soft drinks	Inorganic phosphate additives; high bioavailability (approximately 80–100%)	Observational data show lower bone mineral density in women with frequent cola intake, although findings were inconsistent across populations.
Ultra-processed foods	Sliced bread, processed cheese, condensed milk, fast food, frozen meals	Mix of highly bioavailable phosphate additives	Primary dietary source of inorganic phosphate additives. Highly absorbable phosphorus increases serum phosphate, PTH, and FGF-23. Chronic intake promotes endothelial dysfunction, vascular calcification, and bone remodeling alterations.

Source: Adapted from literature (142,176,185,186).

Table 18. Reference ranges for serum phosphate

Age (years)	Males		Females	
	mmol/L	mg/dL	mmol/L	mg/dL
1–4	1.39–1.74	4.3–5.4	1.39–1.74	4.3–5.4
5–13	1.19–1.74	3.7–5.4	1.29–1.68	4.0–5.2
14–15	1.13–1.52	3.5–5.3	1.13–1.58	3.5–4.9
16–17	1.0–1.52	3.1–4.7	1.0–1.52	3.1–4.7
≥18	0.81–1.45	2.5–4.5	0.81–1.45	2.5–4.5

Reference values for patients under 12 months of age have not been established.
Source: Adapted from the literature (145,190).

to musculoskeletal disorders, such as delayed bone mineralization (rickets in children and osteomalacia in adults), as well as proximal muscle weakness (144). Additional manifestations include respiratory muscle weakness, bone pain and loss, neuropathy, cardiac dysfunction, and hematologic and neurologic abnormalities (142,191). Persistent hypophosphatemia affects multiple systems, including skeletal, muscular, and dental, ultimately compromising physical function and quality of life (145). Conversely, acute hyperphosphatemia may be associated with hypocalcemia; if chronic and uncontrolled, it can lead to vascular and soft tissue calcifications, increasing the risk of necrotic skin lesions, cardiac arrhythmias, and phosphate crystal deposition in joints, tendons, and eyes (192). **Table 19** summarizes clinical conditions and pathophysiological mechanisms associated with phosphorus disorders.

Hypophosphatemia is defined as a serum phosphate level below 2.5 mg/dL in adults and below 4.0 mg/dL in children (179). It can be classified as moderate (0.3–0.65 mmol/L [1–2.5 mg/dL]) or severe (< 0.3 mmol/L [< 1.0 mg/dL]). In contrast, hyperphosphatemia is defined by plasma phosphate levels > 1.46 mmol/L (4.5 mg/dL) and is considered severe when levels exceed 14 mg/dL (187,188).

Mild to moderate hypophosphatemia can be managed with oral supplementation of sodium phosphate and potassium phosphate (187,193), which are typically compounded in specialized pharmacies in Brazil due to their limited availability in standard pharmacies. The therapeutic dose should aim for at least 1 g/day (15 mg/kg) and may be increased to up to 3 g/day in cases of severe phosphate depletion (187,193). Common adverse effects include diarrhea and gastrointestinal irritation, especially when doses exceed 1 g. To improve tolerability, the total daily dose should be divided into three or four administrations (187).

In cases of severe hypophosphatemia or when clinically significant symptoms are present (e.g., cardiac, respiratory, or neurological manifestations), intravenous phosphate replacement is indicated. It should be initiated in the emergency setting with continuous monitoring. Intravenous administration should be performed using either 0.9% sodium chloride or 5%

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Table 19. Clinical conditions and pathophysiological mechanisms associated with serum phosphorus disorders

Chronic Hypophosphatemia	
Clinical Disorder	**Pathophysiological Mechanism**
Primary or secondary hyperparathyroidism	Reduced TmPi (tubular maximum phosphate reabsorption); elevated PTH
Phosphorus deficiency or use of phosphate binders	Reduced dietary intake and bioavailability
X-linked hypophosphatemic rickets/osteomalacia (PHEX mutation)	Reduced TmPi; elevated FGF-23
Tumor-induced osteomalacia (FGF-23-producing tumor)	
Autosomal dominant hypophosphatemic rickets/ osteomalacia (FGF-23 mutation)	
Autosomal recessive hypophosphatemic rickets/ osteomalacia (DMP1 mutation, ENPP1 mutation)	
Intravenous iron administration	
Fibrous dysplasia/McCune-Albright syndrome (GNAS1 gain of function)	
Hypercalciuric hypophosphatemic nephrolithiasis	Reduced TmPi; decreased NaPi2a and NHERF1 expression
Hyperphosphatemia	
Clinical Disorder	**Pathophysiological Mechanism**
Chronic kidney disease	Decreased glomerular filtration rate (GFR); phosphate retention
Hypoparathyroidism	Decreased PTH; increased TmPi
Familial hyperphosphatemic tumoral calcinosis	Genetic mutations in FGF-23, Klotho, or GalNt3
Rhabdomyolysis	Extensive muscle injury with massive phosphate release

NaPi2a: Sodium-dependent Phosphate Transporter 2A; NHERF1: Na^+/H^+ Exchanger Regulatory Factor 1.
Source: Adapted from the literature (144,145).

dextrose solutions; lactated Ringer's solution should be avoided due to the risk of calcium phosphate precipitation (187,193). Serum phosphate, calcium, and magnesium levels should be monitored every 6 hours during parenteral therapy to detect complications, including rebound hyperphosphatemia, hypocalcemia, and hypomagnesemia (187). A commonly used protocol involves infusing 4.5 mmol/h over 3 hours, with a maximum dose of 90 mmol over 24 hours. Alternatively, 0.08 mmol/kg may be administered over 6 hours for acute cases and 0.16 mmol/kg over 6 hours for chronic depletion states, which are generally more resistant to correction (187).

Management of hyperphosphatemia should focus on treating the underlying cause, such as intravenous volume resuscitation in cases of rhabdomyolysis or tumor lysis syndrome. In patients with CKD and mild, asymptomatic hyperphosphatemia, dietary phosphate restriction and intestinal phosphate binders containing aluminum, calcium, or magnesium are recommended. In severe cases, hemodialysis or peritoneal dialysis provides rapid and effective correction of hyperphosphatemia and associated symptomatic hypocalcemia (187).

CONCLUSION

Taken together, these micronutrients each play distinct yet interconnected roles in bone health. Evidence from randomized controlled trials supports the combined use of calcium and vitamin D in older adults and individuals with deficiency, as this strategy effectively reduces fracture risk. In contrast, the roles of vitamin K and magnesium remain promising but inconsistent, emphasizing the need for further well-designed randomized trials to clarify their clinical benefits. Phosphorus deficiency is uncommon in healthy adults; however, excessive intake — particularly from processed foods — may contribute to adverse metabolic and vascular outcomes. Whenever possible, dietary sources should be prioritized, reserving supplementation for populations at risk or with confirmed deficiencies. A concise overview of the supporting evidence and clinical considerations is provided in **Table 20**.

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Table 20. Summary of evidence, clinical recommendations, and adverse effects of key micronutrients in bone health

Nutrient	Strength of Evidence	Clinical Recommendations	Adverse Effects/Risks
Calcium	High (multiple meta-analyses and RCTs)	Supplementation recommended for individuals with low intake or osteoporosis risk, preferably in combination with vitamin D	Gastrointestinal discomfort, hypercalcemia, nephrolithiasis, possible increased cardiovascular risk in those with adequate dietary intake
Vitamin D	High (consistent RCTs and meta-analyses)	Combined calcium + vitamin D supplementation reduces fracture risk in older adults and deficient populations; monitoring advised in high-dose regimens	Hypercalcemia, hypercalciuria, toxicity with inappropriate use
Vitamin K	Moderate to low (heterogeneous clinical trials)	Evidence suggests potential skeletal benefits, but current data are inconsistent; further RCTs required before recommending routine supplementation	Generally safe; possible interaction with some anticoagulants (e.g., warfarin)
Magnesium	Moderate to low (observational and limited interventional studies)	Maintain adequate dietary intake; supplementation may be beneficial in individuals with low intake or deficiency	Diarrhea, gastrointestinal discomfort; toxicity rare, usually in renal impairment
Phosphorus	Moderate to low (strong physiological rationale; limited clinical data)	Deficiency is uncommon; supplementation reserved for specific conditions (e.g., hypophosphatemia). Excess intake from processed foods should be avoided	Hyperphosphatemia, vascular calcification, secondary hyperparathyroidism, especially in renal disease

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