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Diagnosis and therapeutic approach to bone health in patients with hypopituitarism

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Abstract
The results of many studies in recent years indicate a significant impact of pituitary function on bone health. The proper function of the pituitary gland has a significant impact on the growth of the skeleton and the appearance of sexual dimorphism. It is also responsible for achieving peak bone mass, which protects against the development of osteoporosis and fractures later in life. It is also liable for the proper remodeling of the skeleton, which is a physiological mechanism managing the proper mechanical resistance of bones and the possibility of its regeneration after injuries. Pituitary diseases causing hypofunction and deficiency of tropic hormones, and thus deficiency of key hormones of effector organs, have a negative impact on the skeleton, resulting in reduced bone mass and susceptibility to pathological fractures. The early appearance of pituitary dysfunction, i.e. in the pre-pubertal period, is responsible for failure to achieve peak bone mass, and thus the risk of developing osteoporosis in later years. This argues for the need for a thorough assessment of patients with hypopituitarism, not only in terms of metabolic disorders, but also in terms of bone disorders. Early and properly performed treatment may prevent patients from developing the bone complications that are so common in this pathology. The aim of this review is to discuss the physiological, pathophysiological, and clinical insights of bone involvement in pituitary disease.

Keywords Hypopituitarism · Bone mineral density · Bone remodeling · Fractures · Hormone replacement

Among many factors contributing to bone health, hormonal status is a mainstay of skeletal development, bone tissue maintenance and adequate bone turnover (BT). Impairment of bone structure and metabolism may lead to bone strength deterioration, decline of bone mineral density (BMD) and bone quality, resulting in fractures, finally [1]. There are numerous well known bone effects of pituitary hormonal hyperfunction, like in hyperprolactinemia, hypercortisolism and acromegaly, but they are present in hypopituitarism, too [1, 2]. Hypopituitarism, especially growth hormone deficiency (GHD) and hypogonadism, are well known causes of secondary osteoporosis [1–7].

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Osteoporosis is a disease characterized by the impairment of bone density as well as bone microarchitecture, resulting in increased risk of fractures. The classic definition of osteoporosis according to World Health Organization (WHO) is based on BMD measurement using dual-energy X-ray absorptiometry (DXA) [8]. Osteoporosis is diagnosed when BMD at the hip or lumbar spine is less or equal to 2.5 standard deviations (SDs) below the mean BMD of a young adult reference population (*T-score*). As these definitions are applicable for postmenopausal women and men ≥ 50 years of age, younger subjects and subjects with secondary osteoporosis are defined with the *Z-score* (i.e., the number of SDs from age-matched controls) of ≤ -2.0, an indication of osteoporosis or low bone mass [9]. However, in patients with secondary osteoporosis bone quality is more affected than bone quantity and fractures may occur even when BMD remains within normal reference range. Most of osteoporotic fractures occur in patients with T-score better than −2.5 [10]. The recent conclusion from International Osteoporosis Foundation (IOF) and the European Society

for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) suggested the need for separate diagnostic and intervention thresholds [11]. BMD alone is less sensitive in evaluating fracture risk than algorithms, such as The Fracture Risk Assessment Tool (FRAX) which involve other fracture predictors in addition to BMD. Many other factors contribute to fracture risk, such as falls, frailty, presence of former fractures, parental hip fracture, tobacco and alcohol use, inflammatory and endocrine diseases. Focusing only on BMD leads to delay in treatment. To help clinicians decide whether to initiate antiosteoporotic drugs, algorithms like FRAX were designed. However, they are not validated in hypopituitarism. Another problem is that FRAX should be only used in patients between 40 and 90 years of age, while patients with hypopituitarism often younger. Therefore, the stratification of fracture risk and therapeutic decisions have to be individualized in patients with hypopituitarism. It is important to examine patients in search for osteoporotic fractures even with normal BMD results, especially when clinical suspicion exists (for example loss of height, pain). Morphometric vertebral fractures assessment (VFA) is considered the most reliable in the fracture's examination in pituitary diseases [12], but spine X-ray might be also sufficient. Adequate hormone replacement therapy is crucial to maintain bone health in hypopituitary patients. However, in some cases at high fractures risk, also additional antiosteoporotic treatment is needed.

1 Bone health diagnostics

Abnormalities in pituitary hormonal activity may lead to bone health impairment. Therefore, it is of great importance to use proper tools for fracture risk assessment in such conditions, which are intercurrent with predominant deterioration in bone quality [1]. Numerous methods of bone structure assessment have been applied in the studies of endocrine patients. The utilization of appropriate methodologies is essential to discern the intricate relationship between pituitary hormonal abnormalities and their impact on bone health, thereby advancing our understanding of the multifaceted interplay between endocrine function and skeletal integrity.

1.1 Bone structure assessment

1.1.1 Bone densitometry

Bone densitometry is a standard tool to diagnose osteoporosis, but also to monitor the disease and efficacy of therapies [13]. The gold standard for this purpose is DXA, which is used to measure BMD of different areas. Notably, the region of the proximal femur composed mostly of cortical bone is particularly important, as the femoral neck and total hip BMDs are the recommended parameters for diagnosing osteoporosis, while fracture risk is determined by the femoral neck *T-score*. The BMD of the lumbar spine area (L1-L4) composed of trabecular bone is susceptible to potential inaccuracies in spine densitometric results readings due to prior vertebral body fractures (discerned through lumbar spine measurements) or advanced degenerative changes in the spine, encompassing vertebral bodies and facet joints. Therefore, the femoral neck BMD is used for calculating fracture risk. Diverse scientific entities across different nations have established therapeutic thresholds predicated on the BMD *T-score*, with approximately 52 national guidelines disseminated across 36 countries [14–20]. As delineated in the introductory section, the validation of osteoporotic fracture risk assessment tools remains unexplored in the context of hypopituitarism. Furthermore, pituitary diseases frequently manifest in males below 50 years of age and premenopausal women, thereby complicating the diagnosis of osteoporosis solely based on BMD [1].

1.1.2 Trabecular bone score

The trabecular bone score (TBS) index is derived through a grayscale analysis of DXA scans specifically focused on the lumbar spine. This innovative technology facilitates a comprehensive assessment of bone microarchitectural texture, thereby proving to be instrumental in the evaluation of bone quality [21]. TBS serves as a gray-level textural metric, extracted from the two-dimensional DXA image of the lumbar spine. It encapsulates the average rate of pixel gray-level variations within the DXA image. A heightened TBS value signifies superior bone structure, contrasting with a diminished TBS value that indicates compromised microarchitecture prone to fractures [22]. The utility of DXA images extends beyond the mere calculation of BMD or TBS. A non-invasive technique known as 3D-SHAPER utilizes these images to conduct a detailed analysis of the proximal femur, encompassing the calculation of both cortical and trabecular microarchitecture [23].

1.1.3 "Classical" computed tomography

In the historical context, computed tomography (CT) utilizing X-ray technology, providing cross-sectional imaging for distinct visualization of both cortical and trabecular bone structures, had been previously employed for the evaluation of lumbar spine bone architecture [2, 24]. However, this measurement modality has fallen out of routine clinical practice due to its prohibitively high cost and the potential

risk of subjecting patients to excessive X-ray radiation, rendering it less feasible in contemporary healthcare settings.

1.1.4 High-resolution peripheral quantitative computed tomography

Due to its inherently two-dimensional nature, BMD measurement using DXA exhibits notable limitations, offering insufficient insights into bone quality. These constraints inherent to DXA assessments can be effectively addressed through the utilization of high-resolution peripheral quantitative computed tomography (HR-pQCT) performed at the distal radius and tibia. HR-pQCT, as a three-dimensional noninvasive imaging modality, enables the comprehensive evaluation of volumetric bone density and microarchitecture within both cortical and trabecular bone compartments. Despite its potential advantages, HR-pQCT has not attained widespread adoption as a standard diagnostic procedure, particularly in patients with pituitary disorders. This limited uptake is attributed to factors such as elevated cost and restricted accessibility, thereby impeding its routine application in clinical settings [25–28]. The challenges associated with HR-pQCT implementation underscore the ongoing considerations surrounding cost-effectiveness and resource availability in medical diagnostics, particularly in the context of specialized patient populations.

1.1.5 High-resolution cone-beam computed tomography

High-resolution cone-beam computed tomography (HR-CBCT) stands as a potential substitute for HR-pQCT in the imaging of bone extremities. Distinguished by a more expansive field of view and swift acquisition capabilities, HR-CBCT offers notable advantages. However, it is imperative to acknowledge a drawback associated with this modality - specifically, a diminished image contrast owing to the presence of artefacts [29, 30]. Despite its advantageous features, the consideration of artefact-related challenges emphasizes the nuanced evaluation required when opting for HR-CBCT in comparison to HR-pQCT, thus underlining the ongoing quest for imaging modalities that balance efficiency and precision in musculoskeletal assessments.

1.1.6 Quantitative ultrasound

In the field of diagnosing bone health, the clinical significance of ultrasound extends beyond the conventional measurement of BMD, encompassing parameters reflective of bone strength. Metrics such as the speed of sound (SOS) and broadband ultrasound attenuation (BUA) are pivotal data points that hold diagnostic relevance for various bones, including the heel, patella, tibia, fingers (phalanges), and contribute to the predictive assessment of fracture risk [31, 32]. These parameters are derived through Quantitative Ultrasound (QUS) techniques, providing valuable insights into bone health by offering nuanced information beyond traditional BMD assessments [33]. The utilization of ultrasound-based measurements, with a focus on QUS-derived data, signifies a broader perspective in bone health diagnostics, enabling a comprehensive evaluation that extends beyond the conventional BMD-centric approaches.

1.1.7 Radiofrequency echographic multi-spectrometry

Radiofrequency echographic multi-spectrometry (REMS) emerges as a non-ionizing technology integral to osteoporosis assessment. Operating through the scrutiny of radiofrequency (RF) signals generated from ultrasound spectra acquired during an echographic scan, REMS is specifically applied to lumbar vertebrae or the femoral neck. The software autonomously identifies regions of interest (ROI) by cross-referencing acquired images with matrices of RF signals. Subsequently, the ROI RF signals undergo a comparative analysis with reference models sourced from a dedicated database, facilitating correlation with pathological or normal conditions. Notably, REMS possesses the capability to differentiate among trabecular bone, cortical bone, and cartilage. Each outcome is categorized within the Osteoporosis Score and subsequently recalibrated into BMD values, yielding *T-score* and *Z-score* results. Given the absence of specific patient preparation requirements and the expeditious nature of the examination procedure lasting only a few minutes, coupled with the portability of the handheld device, REMS is positioned as an innovative tool for osteoporosis screening. Noteworthy evaluations have characterized REMS as precise and comparable to BMD results derived from DXA [34, 35]. This underscores the potential of REMS as a viable alternative, offering efficiency and accuracy akin to established methodologies such as DXA in the landscape of osteoporosis assessment.

1.1.8 Bone microindentation

Reference point indentation involves the insertion of a probe through the skin and periosteum of the proximal tibia, followed by indentation testing. The resultant measurement, termed the bone material strength index (BMSi), serves as an indicator of the resistance to microfracture propagation, with higher BMSi values reflecting increased resistance [36]. Despite its potential, comprehensive investigations into the associations between BMSi and other bone measures remain limited [22, 37]. The intricate connections and correlations between BMSi and various parameters related to bone health warrant further exploration and in-depth

examination to enhance our understanding of the clinical implications of this novel measurement methodology.

1.1.9 Vertebral fractures

Vertebral fractures (VFs) on X-ray, serving as the quintessential hallmark of osteoporosis, stand out as the most prevalent fragility fractures encountered in clinical practice [38]. Remarkably, over 50% of VFs manifest without overt clinical symptoms in common osteoporosis, but probably also in case of hypopituitarism with growth hormone deficiency (GHD). The characterization of VFs involves the delineation of the vertebral body through the allocation of six points to articulate its three-dimensional structure. Employing a morphometric approach, VFs are stratified into mild, moderate, and severe categories based on a height ratio decrease, primarily discerned through spinal X-ray images, although images obtained by DXA of the spine may also serve this purpose [27, 38, 39]. Several authors underscore the significance of VFs as an early manifestation of compromised bone health in the context of pituitary hyperfunction [1, 40]. In contemporary medical discourse, the meticulous evaluation of VFs has assumed a pivotal role in defining the status of bone health in secondary osteopathies. Moreover, recent investigations posit that traditional methods employed for BMD assessment may prove insufficient in the context of pituitary-induced secondary osteoporosis [1, 40]. Consequently, the imaging of VFs is now recommended, particularly within centers of excellence specializing in pituitary tumors (PTCOEs) [41–43]. It is noteworthy, however, that these innovative tools are still undergoing rigorous testing, particularly in the realm of secondary osteopathies [1], thereby emphasizing the dynamic nature of advancements in diagnostic practices within the field of osteoporosis.

1.2 Bone markers

Bone formation markers encompass enzymes and proteins generated by osteoblasts at different stages of their development, providing insights into diverse aspects of osteoblast function. For instance, during bone formation, osteoblasts secrete the precursor procollagen molecule, a vital component of the bone matrix, represented by type I collagen. Conversely, degradation products of type I collagen are released during bone resorption. Noteworthy bone formation markers include osteocalcin (OC), bone-specific alkaline phosphatase (BALP), and procollagen type I N propeptide. In contrast, markers of bone resorption encompass carboxyl-terminal cross-linking telopeptide of type I collagen (CTX) in serum, collagen type I cross-linked N-telopeptide (NTX), and tartrate-resistant acid phosphatase (TRAP) [44]. Current guidelines advocate procollagen type I N propeptide and CTX as reference markers for bone formation and resorption, recommended for routine clinical use in monitoring osteoporosis treatment with bone-active drugs [45, 46]. Biochemical markers of bone turnover also offer insights into potential skeletal disorders concurrent with abnormal pituitary function.

In patients with secondary osteoporosis, certain abnormalities may be associated with an underlying condition, necessitating specific tests to exclude secondary osteoporosis. These tests include erythrocyte sedimentation rate (ESR), complete blood count (CBC), protein electrophoresis, serum activity of alkaline phosphatase (ALP), creatinine, parathyroid hormone (PTH), 25(OH)D3, calcium and phosphate concentrations. Additionally, a 24-hour urinary calcium excretion test is recommended [44, 47].

Recent advancements introduce novel biochemical markers such as the wingless (Wnt) signaling pathway and modulators like sclerostin (SOST) and Dickkopf (DKK)-1, expanding the scope beyond classical bone turnover markers. Furthermore, microRNAs (miRNAs), small noncoding RNAs, have emerged as potential markers of bone turnover in osteoporotic patients. Interestingly, miRNA expression is influenced by canonical Wnt signaling in osteoblasts, mediating intercellular signaling between bone cells. The expression of the osteoclast differentiation inhibitor osteoprotegerin (OPG) further regulates osteoclastic bone resorption [33, 48–51]. These advancements underscore the evolving landscape of biochemical markers, enriching the understanding of bone health in various contexts, including postmenopausal osteoporosis and pituitary disorders.

1.3 Perspectives on bone health evaluation

The extensive exploration of genetic factors through genome-wide association studies has unveiled over 500 susceptibility loci associated with traits related to osteoporosis. Additionally, numerous loci have been discovered to correlate with BMD and the occurrence of osteoporotic fractures [52, 53]. Beyond the genetic realm, the human gut microbiome has emerged as a potential influencer of bone metabolism, actively regulating the production of insulin-like growth factor 1 (IGF-I) [54]. The integration of artificial intelligence and machine learning technologies [55–57] holds promising prospects for a more profound investigation into osteoporosis. These advanced methodologies can be employed to predict crucial indicators such as BMD or fracture risk, serving as invaluable tools for automatic segmentation in clinical applications. The convergence of genetics, microbiome research, and cutting-edge technologies exemplifies the multidisciplinary approach undertaken to unravel the complexities of osteoporosis, providing

avenues for enhanced diagnostic precision and therapeutic strategies.

1.4 Bone health diagnosis - conclusions

Due to the constrained predictive capacity of DXA-derived BMD assessments, there is a burgeoning interest in the application of morphometric VFA for bone health diagnosis in individuals with pituitary disorders. Novel approaches for evaluating bone quality have recently surfaced as supplementary tools in the postprocessing of DXA images. Additionally, the exploration of new circulating markers holds promise for predicting the fracture risk associated with pituitary disease, thereby presenting an intriguing avenue for enhanced fracture risk assessment in this specific clinical context. The continuous evolution and integration of these diverse methodologies underscore the comprehensive and multidimensional approach adopted to refine the diagnosis and risk assessment of bone health in individuals with pituitary ailments.

2 Growth hormone deficiency

2.1 Growth hormone and insulin growth factor-1 and their influence on bone metabolism

Growth hormone (GH) and IGF-I are pivotal in the regulation of bone metabolism, exerting pleiotropic effects, that connect both bone formation and bone resorption. GH has a significant direct effect on bones through its influence on skeletal cells, but much of its action is exerted through IGF-I. IGF-I is produced mainly in the liver in the response to GH stimulation, but it can also by synthesized locally in various cells. The amount of IGF-binding protein (IGFBP) regulate the availability and activity of IGF-I and they may either enhance or inhibit the actions of IGF-I [58]. The activation of chondrocytes within epiphyseal growth plates of children is crucial in promoting linear bone growth, while heightened activity of osteoblasts contributes to increased bone formation. During the prepuberty period, GH and IGF-I play key roles in stimulating both bone growth in length and maturation of the skeletal structure. Subsequently, during the adolescence and young adulthood, these hormones impact on the achieving peak bone mass (PBM). Following this phase, GH and IGF-I take part in the regulation of bone turnover and affecting the maintenance of bone mass. The anabolic effects of GH and IGF-I manifest through the stimulation of osteoblast proliferation, differentiation, and the formation of the bone matrix. Conversely, these growth factors also stimulate the resorption activity of osteoclasts, contributing to the dynamic process of bone remodeling [59]. IGF-I plays an important role in promoting osteoclastogenesis by inducing the synthesis of the receptor activating nuclear factor κB ligand (RANK-L), a key factor in the formation and activation of osteoclasts. This action enhances the bone resorption process. Conversely, GH acts as a counterbalance by increasing the production of OPG, an inhibitor that limits the formation and activation of osteoclasts, which result in decreased bone resorption [60, 61]. An *in-vitro* study demonstrated that IGF-I inhibits the expression of OPG while increasing RANK-L expression, which further support its role in augmenting osteoclastogenesis. Interestingly, when recombinant IGF-I was administered to postmenopausal women for a year, a significant 20% reduction in serum OPG concentration was noted. Researchers posit that the influence of IGF-I on bone tissue resorption is mediated through its modulation of the OPG/RANK-L system [62]. In contrast, GH stimulates osteoblast to express and secrete OPG, contributing to the inhibition of osteoclast activity. This dynamic interaction between GH and IGF-I, together with their influence on the OPG/RANK-L system, highlights their complex involvement in the regulation of bone remodeling and ensuring skeletal integrity [63].

In summary, an activated somatotropic axis increases bone formation and resorption, ultimately increasing bone turnover and remodeling. However, it is noteworthy that bone formation tends to dominate over resorption in this process [60, 61]. Patients with GHD may have mild skeletal, intestinal, and renal resistance to the action of PTH [64, 65]. Additionally, disruptions in the circadian rhythm of PTH, have been observed in individuals with GHD. These factors potentially may have influence on bone remodeling [1]. It is known that IGF-I is also synthesized in many peripheral tissues, acting as a local growth factor, whose synthesis and function are regulated by various hormones and growth factors [1]. Notably, in chondrocytes, the synthesis of IGF-I is governed by GH, while in osteoblasts, PTH controls its synthesis [66, 67]. . IGF-I has been identified as a mediator of some of the anabolic effects of PTH in bone, regulating the impact of PTH on cell proliferation. Survival transcription of IGF-I in osteoblasts is enhanced by estrogens and attenuated by glucocorticoids [68–70]. Furthermore, thyroid hormones, especially T3 (triiodothyronine), increase the synthesis of IGF-I by osteoblasts and reciprocal the relationship in which IGF-I may, in turn, mediate the anabolic effects of T3 in bone [58, 71, 72].

2.2 The influence of GH deficiency on bone

GHD is recognized for its significant impact on bone health, and it results in the reduction of BT, impaired growth in children and lower bone mass. Reduced bone density, in turn, leads to an elevated risk of fractures in adults. Particularly,

noteworthy is the observation, that patients with childhood-onset growth hormone deficiency (CO-GHD) not only have shorter stature but also and their bones are much smaller in volume and size. This characteristic anatomical difference can be reflected in the underestimation of the BMD [61, 73–75]. The deteriorated bone quality in patients with GHD further compounds their susceptibility to fractures. The risk is 5–7 times higher, regardless of the coexistence of dysfunctions in other tropic axes of the pituitary gland. This underscores a huge impact of GHD on skeletal health, emphasizing the importance of early diagnosis and intervention to mitigate the long-term consequences on bone structure and risk of fractures [1, 76].

Fractures are common and affect over 30% of untreated patients in both sexes, even among in these patients with normal BMD [77]. The current classification of GHD distinguishes between patients with CO-GHD and adult-onset growth hormone deficiency (AO-GHD) [78]. The clinical manifestation of GH deficiency depends on the age at which it occurs. Patients with GHD beginning in childhood primarily exhibit growth disorders, short stature, and craniofacial abnormalities. Conversely, AO-GHD is characterized by changes in body composition, including an increase in total body fat and a decrease in lean body mass and bone mass. Thus, in the long term, adult patients with GHD face with long term risks such as cardiovascular complications, fragile fractures, and impaired quality of life [1–3, 12]. The impact of GHD on the bone status is influenced by coincidence of insufficiency of other pituitary axes. So, treatment of GHD is essential to alleviate these disturbances and improve the overall well-being of affected individuals.

GH replacement therapy has demonstrated positive effect on growth in GHD children and has been shown to increase BMD. This particularly helps to achieve the PBM and maintain it during the transition from adolescence to adulthood in patients with persistent GHD [79]. Many studies support the idea that GH replacement may effectively reduce risk of fractures associated with GHD [77, 80, 81]. What is important to note, in addition to its impact on bone health, GH replacement therapy affects another critical factor – sarcopenia, which is an important risk factor for falls and fractures. Research has shown that GH replacement therapy plays a role in preserving the muscle strength [82]. This preservation of muscle strength is associated with a reduction in falls, which indirectly contributes to reducing of fractures. Therefore, beyond its effect on bone density, GH replacement therapy proves valuable in reducing the risk of fractures by improving both bone health and muscle strength. In this indirect way it also reduces the risk of fractures.

2.2.1 Childhood-onset growth hormone deficiency

The treatment of growth hormone deficiency in childhood involves the administration of exogenous GH with the primary objective of maximizing linear growth. The aim is to help the patient attain their full potential height in adulthood [4]. Historically, GH treatment was often discontinued once the expected growth was achieved. In recent years, it is increasingly recognized that GH administration has significant effects beyond promoting linear growth. There is a growing understanding that persistent GHD can result in enduring abnormalities in adults, affecting factors such as bone mass, muscle strength and body composition. Research shows that these parameters can be positively influenced by continuing GH administration during the critical period between reaching final growth and attaining full maturity, called the transition period. Therefore, an evolving approach is to expand GH treatment beyond the achievement of expected height to address and improve various aspects of health and well-being during the transition period [83].

Continuing GH treatment in young adults, who were treated for CO-GHD proves to be beneficial for BMD in adulthood. Studies indicate that in patients with CO-GHD, the continuation or resumption of GH treatment for two years in patients after completing growth, induced a significant increase in BMD compared to untreated patients [84]. This treatment has a greater impact on the increase in BMD in the vertebrae than in the femur. A 24-month course of GH treatment in this group of patients has been associated with an estimated 3.5% increase in lumbar spine BMD compared to the control group [85]. Some studies indicated 4–10% increase in BMD [86]. The PBM is typically reached within 1–7 years after the end of growth phase [87, 88]. In adolescents and young adults with CO-GHD, a decrease in BMD and cortical bone thickness was observed, after discontinuation of recombinant human growth hormone (rhGH) therapy. Consequently, it led to an increased risk of fractured bones [80, 85]. However, restarting therapy with rhGH, initially caused a slight decrease in BMD and then a significant increase in BMD compared to the untreated group has been observed [85].

2.2.2 Adult-onset growth hormone deficiency

Untreated GHD in adults is associated with reduced BT and diminished BMD. However, treatment causes an increase in BT, which is reflected in an increase in BMD and bone mineral content (BMC), along with heightened the activity of BT markers [87, 89, 90]. Historically, studies revealed that GH therapy led to the increase in BMD and BMC for the first 7 years of treatment, followed by a stabilization phase

[91–94]. Subsequent studies challenged this notion and revealed that the increase was noticeable for over a decade, with the peak increase in BMD and BMC at the femoral neck occurring after 5–7 years of treatment [95]. Elbornsson et al. demonstrated a persistence of increased BMD and BMC for the total body and the lumbar spine over 15 years. However, at the femoral neck, a decline was noted after 7 years of treatment [96]. In another study Appelmann-Dijkstra et al. observed a constant increase in BMD and BMC of the lumbar spine over 15 years of rhGH treatment, reaching a peak after 5–7 years, with the greatest impact seen in men. Surprisingly, there were also no changes in BMD at the femoral neck, contrary to expectations based on age-related decline. This suggest that, beyond its effect on BMD of lumbar spine, rhGH replacement therapy positively impact on the femoral neck [87]. In 2014, Kuzma and colleagues assessed TBS in AGHD patients undergoing rhGH replacement therapy. The authors showed a significant 4% increase in TBS after 24 months ($p = 0.02$), suggesting a positive effect of rhGH on bone quality. However, it was noted that this increase in TBS was lower than the increase in BMD. This emphasizes the multifaceted and lasting effects of GH therapy on bone health in adults with GHD [97]. Another study, included 18 patients with AO-GHD, did not confirm a significant effect of GH therapy on bone microarchitecture. In this study, patients initially had an average TBS value within the normal range. However, after 7 years of treatment, the TBS values decrease insignificantly, while there was a simultaneous significant increase in BDM at the lumbar spine ($p = 0.01$) [98]. Further research on this group of patients is needed to assess the usefulness of TBS in this group of patients. It could help to understand how GH therapy may influence on different aspects of bone health in AO-GHD.

2.3 Factors influence on the bone density and risk of fractures in patients with GHD

The impact of rhGH replacement therapy on bone remodeling follows a two-phase pattern. Initially, rhGH exerts a maximum effect on bone resorption (after approximately 3 months) followed by a subsequent focus on bone formation (after approximately 6 months). Nevertheless, bone formation phase persists for a longer duration [1, 93, 94]. Several factors have the negative impact on BMD values in patients with GHD. These include young age at onset of the disease, the severity GHD and an extended period without GHD treatment [2, 3, 25]. Additionally, studies also highlight that the coexistence of the gonadotropic axis insufficiency and the lack of adequate hormonal replacement have a detrimental impact on BMD. Moreover, excessivewith glucocorticoids and/or L-thyroxine doses, along with prematurely discontinuing rhGH treatment in children and young adults before reaching PBM, has been associated with the same negative effect on BMD [58, 99–101]. In the context of CO-GHD, vertebral BMD experiences notably reduced with approximately one-third of adult's patients exhibiting a *T-score* of −2.5 SD or less [101, 102]. In patients with AO-GHD, vertebral *T-scores* typically register at −1 SD or higher [103–110]. The varying degrees of bone loss may be the consequences of the longer duration of the disease and the inability to attain PBM if GH deficiency commenced in childhood [1, 111, 112]. The age of onset of GH deficiency in AO-GHD also plays a crucial role in determining the degree of bone loss and thus the BMD value. If the onset of the disease is below the age of 30, there is a more significant reduction in bone mass [89, 105, 110]. On the other hand, the BMD of GHD patients over the age of 55 is often comparable to those healthy controls. So, both the duration and the age of onset of growth hormone deficiency in adults significantly influence the degree of bone loss and consequently BMD values [89, 104, 105].

A pivotal study in the analysis of the influence of various factors on the risk of fracture and BMD among individuals with hypopituitarism and GHD involved the analysis of data from a large-scale pharmacoepidemiological survey (the Pharmacia & Upjohn International Metabolic Database [KIMS]). These data was analyzed and compared with information derived from a control population, sourced from the European Vertebral Osteoporosis Study [EVOS]). The KIMS cohort, included 2,084 patients (1,112 men and 972 women) with various types of pituitary diseases, and the EVOS group consisted of 1,176 people (581 men and 595 women). The groundbreaking results of this study highlighted the increased risk of fractures in patients with GHD, revealing a 2.66 times higher risk compared to the EVOS population without GHD. They also observed that AO-GHD patients had a higher risk of fractures than patients with CO-GHD, which was consistent with previous results [80, 113, 114]. Additionally, they did not notice any effect of hormonal replacement with L-thyroxine, estrogens, testosterone, or steroids on the risk of fractures. Moreover, the fracture rates in patients with isolated GHD were found to be comparable to those in patients with multiple pituitary hormone deficiencies. Interestingly, higher risk of fractures was observed in men with diabetes insipidus, but the proportion of patients with low BMD remained consistent between the diabetes insipidus and non-diabetes insipidus group (14% vs. 13%). Furthermore, the incidence of fractures in KIMS was found to be independent of body mass index (BMI) and country of origin. On the other hand, an association was noted between smoking and a higher incidence of fractures within this group cohort. This research was the first large-scale analysis, which support the hypothesis of an increased fractures in adult patients with hypopituitarism

and GHD. Importantly, the increased risk appears to be specifically linked to GHD itself rather than being influenced by other pituitary hormone deficiencies or the use of replacement therapies [80]. The meta-analysis presented by Barake et al. showed a beneficial effect of rhGH therapy on BMD in adults. This analysis suggested that the effectiveness of rhGH therapy is modified by sexr age, and treatment duration. The meta-analysis proposed that sexplays a role in the observed effect, because women require higher doses of GH replacement compared to men. It is interesting to note that the necessity for sex-dependent dosing was not included in all studies selected for the meta-analysis. Even in cases where higher doses of rhGH were administered to women, the change in BMD remained more pronounced in men This nuance underscores the complexity of the relationship between sex, growth hormone replacement, and its impact on bone health in adults [115–118]. Appelman et al. showed the BMD increase in the lumbar spine in men as well as in women during the first 5 years of rhGH treatment. Then, the increase was still observed in men, but in women, BMD decreased toward baseline values. The response of bone to rhGH therapy is known to vary, with sex-specific differences being a significant factor in this response [87]. Notably, estrogens play crucial role in mediating regulatory interactions occur between the gonads and the GH axis. The use of estrogen-based drugs may affect metabolic health by influencing the GH axis and the effects depend on the route of administration and are particularly relevant for patients with pituitary disease. A study by Holmer et al. revealed sex-specific differences in fracture risk among patients with GHD and increased risk of facture in CO-GHD women. This was due to simultaneous GH replacement and hormone replacement therapy using oral contraception. This was a consequence of the interaction between estrogens and the GH-IGF-I axis. The same study demonstrated a lower risk of fracture in men with AO-GHD, which was associated with adequate testosterone replacement. The degree of suppression of IGF-I secretion and stimulation of GH secretion during therapy depends on the dose and strength of oral estrogen. Importantly, oral estrogens were found to increase the synthesis of IGF-BP, leading to a decrease in the bioavailability and effectiveness of the reduced IGF-1 concentration [119]. This effect was not observed with transdermal estrogen replacement therapy in postmenopausal women. Because oral estrogens antagonize and eliminate the beneficial effect of rhGH therapy, female patients require higher doses of rhGH, while those using transdermal estrogen may require lower doses, similar to those used by men [120, 121]. To optimize GH replacement therapy, it is crucial to consider parenteral administration of estrogen in women with hypopituitarism. This approach helps mitigate potential interference with the therapeutic benefits of rhGH, providing a more effective and tailored treatment strategy. This recommendation is also very important for many patients with hypopituitarism who are not treated with GH. In women with hypopituitarism, especially when their IGF-I levels are already low, the use of oral estrogen therapy exacerbates a further decrease, intensifying the degree of GHD [120, 121]. It is noteworthy that even in women with pituitary diseases who do not have somatotropic axis hypofunction, oral estrogen therapy can lead to a reduction in IGF-I concentration. This may contribute to a loss of fat-free mass and an increase in fat mass. Thus, women with sufficient GH levels are also susceptible to the harmful effects of oral estrogen therapy. This cautionary note, regarding the route of estrogen therapy is applicable to all women with pituitary diseases, especially those with GHD. The authors highlight that women with hypopituitarism, who require estrogens should be treated with transdermal formulation [122].

The perspectives on the simultaneous use of rhGH therapy and antiresorptive therapy on the increase in BMD and the risk of fractures are not clear. The first study showed that the addition of oral bisphosphonates to a stable, constant dose of rhGH has a positive effect on the BMD at the lumbar spine. Moreover, the combined therapy was associated with a reduction in the activity of bone markers in patients with GHD and osteoporosis. This suggests a potentially synergistic effect of these therapy on bone health [123]. Next, Biermasz et al. observed a significant increase in BMD at the lumbar spine during the first 4 years of rhGH treatment. After 4 years, there was no increase in BMD in patients who continued rhGH as monotherapy. However, after adding alendronate to the therapy, a rapid and sustained increase in BMD was observed. This effect was noted to persist for at least 3 years after the addition of alendronate. Importantly, the increase in BMD associated with the combined therapy (rhGH and alendronate) was linked to a low incidence of vertebral fractures [124]. These findings suggest that while rhGH treatment initially enhances BMD, the response may plateau over time. However, the combination of rhGH with an antiresorptive agent, such as alendronate, appears to reinvigorate the positive effects on BMD, offering a potential strategy for prolonged bone health in patients undergoing GH replacement therapy.

In contrast to some studies suggesting a positive impact of combining rhGH therapy with bisphosphonates on BMD, another study presented a different perspective. It was shown that adding bisphosphonates to the rhGH treatment did not have any beneficial effect on the increase in BMD. This study was the first to demonstrate, during long-term rhGH replacement therapy, that the concomitant use of bisphosphonates did not provide any additional beneficial effect on BMD. However, the research highlighted that the treatment protocol included bisphosphonates, calcium and vitamin D

was not used according to a standard protocol. Additionally, in many studies that assessed the impact of long-term rhGH replacement on the skeletal system, information on the use of bisphosphonates was often not available. This lack of standardization in the administration of supportive treatments can have impact on the outcomes. Therefore, assessing the benefits of the combined use of bisphosphonates and rhGH should be the subject of future research [87].

2.4 Recombinant human growth hormone replacement therapy

The dose of GH should be selected individually to obtain optimal results with good treatment tolerance. The recommended starting dose of GH therapy is based on age, sex and some specific conditions. Starting dose for patients under 60 years is 0.2–0.4 mg/day and 0.1–0.2 mg/day in patients over 60 years of age. It should be remembered that GH secretion is higher in women than in men. Proposed starting doses of rhGH are 0.2 mg/day for adolescents' men and 0.3 mg/day for young women, and 0.1 mg/day for older people. In adolescents with severe GHD after completion of therapy promoting growth, intermediate doses (between pediatric and adult) are recommended [125].The dose of GH should be gradually increased, with a target to maintain IGF-I level below the upper limit of normal. If side effects occur, a reduction in dose may be necessary. Additionally, women undergoing oral estrogen replacement therapy, typically require higher doses of GH compared to eugonadal women and men. After initiating GH treatment, it is advisable to reassess the doses of L-thyroxine and/or hydrocortisone in patients who were previously treated with these medications. It is also recommended to reevaluate the adrenocorticotropic and thyrotropic axis in patients previously diagnosed with isolated GHD if symptoms indicating the failure of these axes appeared during rhGH therapy [125, 126]. These facts highlight the importance of personalized dosing and continuous monitoring to optimize the effectiveness and safety of GH treatment.

3 Hypogonadotropic hypogonadism

3.1 Impact of sex steroids on skeletal growth and maintenance

Sex steroids play a crucial role in skeletal growth and maintenance, PBM formation, and bone density maintaining throughout the entire reproductive period. Estrogen as well as androgen receptors were discovered in different human bone cells. In general, reproductive hormones activate bone remodeling, inhibit bone resorption, and stimulate bone formation. Declining estrogen levels during menopause, lead to accelerated BMD loss which is also observed in women with hypoestrogenism at reproductive age. Decrease of testosterone (T) is also associated with lowering of BMD in men with hypogonadism of all causes. Sex steroids influence bone metabolism at various stages of life through a number of different mechanisms [1, 127–130].

3.2 Sex hormones during the puberty and adulthood

Reproductive hormones, including estrogen and T, play a crucial role in the growth and development of the human skeleton. The critical period for establishing a strong musculoskeletal system is childhood and puberty as nearly 95% of the skeletal bone mass is acquired by the age of 18 years [127]. There are two distinct phases of rapid skeletal growth – the first two to three years of life and the period from the onset of puberty to early adulthood. Before puberty, there are only slight differences in skeletal features between both sexes. However, during and after puberty, sexual dimorphism becomes evident, influenced largely by sex hormones and accumulating throughout the pubertal phase [128–130]. At the end of skeletal growth, males typically attain a higher PBM, larger bone size and greater height compared to females [128–130].

Sex hormones play the crucial role in three processes essential for proper skeletal development and maintenance: longitudinal growth, appositional growth, and the resorption of the endosteal surface leading to the expansion of the marrow cavity. These processes exhibit sexual dimorphism [131, 132]. Estrogens regulate longitudinal bone growth through a biphasic mechanism. In the early stages of puberty, typically low levels of estrogen promote linear growth in both sexes by interacting with the GH/IGF-I axis. As puberty progresses, estrogen levels increase, impeding longitudinal growth in both sexes. This inhibition mainly occurs through the direct suppression of chondrocytes at the growth plate level, although central estrogen signaling might also be involved [132–135]. Estrogens also play a vital role in the longitudinal bone growth in males, as evidenced by the notably tall stature observed in males with estrogen deficiency resulting from estrogen receptor defects or aromatase deficiency. Multiple lines of evidence suggest that estradiol, produced through the aromatization of T, is the most important sex steroid in men, responsible for the achievement of PBM and ensuring skeletal maintenance throughout the lifespan. While androgens exert a less potent influence on the bone growth, they contribute partly through the stimulation of GH/IGF-I [130, 132]. Results of studies concerning the skeletal effects of androgens in women are contradictory. However, complete androgen insensitivity in

women leads to reduction in BMD in comparison to healthy females and males, which might support the beneficial effects of androgens on bones [136, 137]. Estrogens exhibit a positive association with bone mineralization and a negative with endosteal circumference. In contrary, T promotes the increase of bone area at both trabecular and cortical sites, along with periosteal expansion [138].

The timing of puberty is also very important with most data supporting the concept of an 'adolescent window', a specific timeframe in which periosteal bone acquisition peaks [88, 139–143]. This is evident in patients with delayed puberty, where impaired PBM is observed due to transient hypogonadism in adolescence. Finkelstein et al. found that men with pubertal delay exhibited significantly lower lumbar and radial areal BMD (aBMD) [139]. Yap et al. revealed that impaired periosteal expansion was observed in men with delayed puberty although adult BMD at the lumbar spine and femoral neck were in normal reference ranges [140]. A reduced PBM was also observed in women with delayed puberty and amenorrhea. Notably, an earlier onset of puberty by up to one year was associated with almost 5% greater bone mineral content and 2.5% greater BMD in comparison to bone parameters in girls with a later onset of puberty [142].

The central role of estrogens and androgens in bone acquisition and maintenance becomes evident later in life when decline in estrogen levels in postmenopausal women and androgens in elderly men leads to loss of bone mass and strength and contributes to the development of osteoporosis.

There are many mechanisms underlying the effects of sex hormones on bone metabolism. Estrogen receptors α and β (ERα, ERβ) and androgen receptor (AR) have been found in various cell lines throughout the differentiation process from precursors to osteoblasts and osteoclasts [132]. Deleting ERα either from mesenchymal progenitors or from osteoblast progenitors led to a significant decrease in periosteal apposition and cortical bone mass [144]. Studies involving mice with the deletion of ERα, AR, or both receptors have suggested that both ERα and AR contribute to periosteal bone accrual in males [145]. The deletion of AR from the entire mesenchymal lineage had no effect on cortical bone mass, indicating that androgens' effects on this compartment are indirect. In contrast, direct actions of androgens on cancellous bone are observable [132]. Estrogens as well as androgens exert a suppressive effect on bone resorption by hindering the differentiation of osteoclasts and shortening their lifespan, primarily through the induction of apoptosis [132, 144]. Estrogen exerts a partial inhibition of osteoclast activity partly by regulation of vascular endothelial growth factor production which is essential for angiogenesis during bone development [146]. Additionally, sex steroids play a role in reducing apoptosis of osteoblasts and osteocytes. Estrogen induces secretion of OPG and leads to the inhibition of osteoclast maturation. It is also able to prevent osteoblast apoptosis by inhibiting the decrease of B-cell lymphoma 2 in osteoblasts [147, 148]. Recent findings suggest that estrogens mitigate bone resorption by the stimulation of the Wnt signaling, a negative regulator of osteoclastogenesis, in osteoclasts [149]. Similarly, in vitro studies suggest that T or dihydrotestosterone act directly on osteoclast progenitors and mature osteoclasts to inhibit osteoclastogenesis and stimulate apoptosis [148, 150]. T in adult males decrease IGFBP-4 which has inhibitory effects on osteoblast differentiation and increasing IGFBP-2 and IGFBP-3 which stimulate this process [150, 151].

In summary, androgens are mainly responsible for the bone size expansion whereas estrogens for skeletal mineralization. Part of androgens in males is converted in peripheral tissues to estrogens and therefore it is difficult to estimate the exact contribution of individual types of sex hormones to the skeletal development.

3.3 Sex hormones and GH/IGF-1 crosstalk

An interaction of sex hormones with GH-IGF-I axis also plays an important role in the skeletal growth and maintenance although the exact mechanism of this interaction is still under research. Puberty is the developmental period in which the GH-IGF-I axis plays the most important role although sex hormones affect GH secretion also during adulthood [132]. During puberty, in both sexes not only amplitude but also duration of GH secretory peaks and IGF-I concentration rise [152]. Many studies suggested an important role of estrogens and androgens in modulating GH spikes and estrogens and GH in determination of IGF-I secretion [131]. Moreover, GH secretion pattern is sexually dimorphic which is determined as early as in perinatal period by testosterone peaks. In mice treated by estrogens IGF-I increase while in male animals ER-knockout or aromatase-knockout or treated by aromatase inhibitors, IGF-I decrease. Androgenic stimulation seems to have no effect on IGF-I secretion which further support the notion that the main factor contributing to IGF-I secretion is androgen aromatization to estrogens [152, 153].

3.4 Prolactin and bone changes during hyperprolactinemia

It is well-known observation that increased prolactin (PRL) levels are responsible of decreased bone mass mainly by the impact on pulsatile gonadotropin releasing hormone (GnRH) secretion and concomitant hypogonadotropic hypogonadism. However, in patients with prolactinomas without subsequent hypogonadism, increased bone loss was

also observed which could suggest that PRL exerts a direct effect on bone metabolism [76, 154, 155]. Indeed, PRL receptors were found on osteoblasts [154, 156]. PRL impact on skeleton is dose-dependent, with elevated levels favoring bone resorption over formation [157]. The intensity of bone resorption correlates with PRL level – concentrations between 100 and 500 ng/ml induce bone resorption mainly by the stimulation of osteoclastogenesis through RANK-L upregulation whereas levels > 1000 ng/ml are associated with the inhibition of osteoblastogenesis and bone formation [157]. PRL indirectly controls osteoclast activity through stimulation of cytokines secretion by osteoblasts (RANK-L, TNF-α, IL-1 and cyclooxygenase-2) and inhibition of OPG levels [154]. However, high levels of PRL can also suppress the differentiation of osteoblasts as well as their osteocalcin and ALP secretory functions in vitro [154, 158]. Despite these observations, direct effects of hyperprolactinemia on skeletal metabolism are difficult to separate from the action of PRL-mediated hypogonadism. 80% of prolactinoma males had osteopenia or osteoporosis at lumbar spine with limited reduction in femoral BMD which could suggest an earlier and more severe damage of trabecular than cortical bone [159, 160]. 22% of premenopausal women with prolactinoma had decreased DXA *Z score* prevalently at lumbar spine which was more pronounced in amenorrheic vs. eumenorrheic patients [159, 160].

The age of onset of hyperprolactinemia is also important as hyperprolactinemia may impair attainment of PBM in young patients. Childhood-onset may have reduced BMD vs. adult onset prolactinoma patients [161]. Data about the influence of hyperprolactinemia on fracture frequency is ambiguous. Results of The Prolactin, Epidemiology, Audit and Research Study did not show increased fracture rate in patients with prolactinoma [162]. In two separate cross-sectional studies conducted on females and males with prolactinoma, the occurrence of morphometric VFs was studied. Morphometric VFs were identified in 32.6% of patients, mainly in postmenopausal women who exhibited a higher prevalence of VFs in comparison to control women of similar age [163]. In males with prolactinoma, 37.5% of patients had morphometric VFs, representing a five-fold higher rate compared to age matched controls. Both females and males with VFs showed significantly lower BMD *T-score* than non-fractured prolactinoma patients [7]. Women with morphometric VFs were significantly older and with longer duration of disease and exhibited higher serum PRL levels than non-fractured counterparts [163]. Male patients with morphometric fractures also had longer duration of disease as compared to non-fractured patients without a relevant impact of hypogonadism, and no significant differences in serum T were found between fractured and non-fractured men [7]. This finding could suggest that, in both sexes, the excess of PRL per se may contribute to an increased fracture risk. The authors suggested that hyperprolactinemia and a hypogonadal state might act synergistically in causing bone damage in patients with prolactinoma. According to current guidelines, not all patients with prolactinoma must be treated with dopamine agonists [164]. Moreover, bone protection is not currently part of the gold standard of the treatment. Anyway, treatment with dopamine agonists in case of prolactinoma was associated with normalization of BT markers as well as normalization of serum PRL and gonadal function [165, 166]. Despite the increase in BMD during the treatment with dopaminergic drugs, BMD did not reach the values typical for control subjects [159–161]. It might seem that the improvement of BMD was more linked to the recovery from hypogonadism, than to PRL normalization. A higher prevalence of morphometric VFs was noted in untreated compared to cabergoline-treated male and female prolactinoma patients. However, even with treatment, VFs remained more frequent in the latter group than in age-matched controls. The reduction in VFs prevalence in treated prolactinoma patients is attributed to the improvement in BMD resulting from the restoration of gonadal function and amelioration of bone quality due to decreased PRL levels. Both factors contribute to a decreased incidence of VFs in treated prolactinoma patients [7, 163]. According to current guidelines, eumenorrheic premenopausal women without galactorrhea, as well as postmenopausal women with microprolactinoma, are not good candidates to treatment with dopaminergic agents. Instead, they are recommended only for follow-up to avoid potential tumor enlargement [164]. Neither osteoporosis nor fractures were included in the guidelines among potential indications to treatment with dopamine agents, but it seems reasonable based on the evidence of detrimental influence of hyperprolactinemia on the skeleton particularly in high-risk categories such as postmenopausal women or elderly men. On the other hand, data concerning the effect of low levels of PRL on bones in humans is not available since the occurrence of low levels of PRL in hypopituitarism is very low and usually is accompanied by low levels of gonadotropin and sex hormones.

3.5 Hypogonadotropic hypogonadism and bone changes

The causes of hypoestrogenism and low T level include central (hypogonadotropic) hypogonadism. Hypogonadotropic hypogonadism may be congenital or acquired. Congenital causes include idiopathic hypogonadotropic hypogonadism and Kallman's syndrome. Acquired causes of hypogonadotropic hypogonadism include organic pituitary lesions and the consequences of their surgical treatment or radiation

therapy as well as ischemic pituitary necrosis, primary empty sella syndrome, and systemic infiltrative diseases causing accumulation of pathological deposits in pituitary gland. Excessive exercise or weight loss induce acquired functional hypothalamic hypogonadism in young women without organic lesion of hypothalamic-hypophyseal region although such functional changes of pituitary function can be observed also in young men [1]. There is evidence indicating that patients with hypogonadotropic hypogonadism exhibit lower BMD compared to those with primary hypogonadism. This is inconsistent with the experimental evidence that low FSH values may be protective for bone loss caused by sex steroid deficiency. Tritos et al. evaluated the skeletal impact of untreated hypogonadism in patients with AO-GHD. The patients with hypogonadism were older and had lower IGF-I levels, as well as reduced BMD in the lumbar spine and femoral neck, in comparison with patients without hypogonadism. However, the prevalence of fragility fractures was high in untreated GHD, regardless of the presence of hypogonadism. In other studies, fragility fractures were more frequent in patients with multiple pituitary hormone deficiencies in comparison to patients with isolated GHD [167].

Replacement treatment with sex steroids is recommended to improve skeletal health [126]. Treatment increased BMD, and improved trabecular structure and bone mechanical properties, whereas the impact of therapy on fracture risk is still unknown [126]. In a cross-sectional study performed in 89 hypopituitary patients (25 with preserved gonadal function, 29 with hypogonadism in adequate replacement therapy with testosterone or estrogens, and 35 with untreated hypogonadism) a high prevalence of VFs was associated with untreated GHD and was not influenced by treatment of hypogonadism [168]. Comparable results were provided by Tritos et al., who evaluated the prevalence of clinical fractures in untreated GHD patients with or without hypogonadism [167].

3.5.1 Congenital hypogonadotropic hypogonadism

Congenital hypogonadotropic hypogonadism (CHH) is an early form of hypogonadism with isolated sex steroid deficiency and no other pituitary hormones deficiencies, which makes it a very good model to examine the effects of sex steroids deficiencies on skeleton in men. CHH is a rare condition with prevalence 1:4,000 to 1:10,000 [169]. In comparison to age-matched controls, men with CHH have lower lumbar and radius BMD before as well as after growth plate closure with both areal and volumetric bone density reduction [5, 6, 170]. Studies concerning the concentration of bone turnover markers brought inconsistent results – some patients had low-turnover osteoporosis whereas the others had increased levels of markers of bone formation and resorption [171].

Results of the study of Antonio et al. showed that BMD partially improves following the initiation of T replacement therapy (TRT) in men with CHH [169]. Data from observational and intervention studies indicate that bone loss occurs when testosterone levels drop below 200 ng/dL (7 nmol/L) [139, 172]. Despite continuous TRT over several years, most patients did not reach a normal *T-score*. The authors assumed that a possible cause of the limited overall impact of long-term TRT on bone density could be the relatively late age at which TRT was started. In several previous studies an inverse correlation between age of initial TRT and total femur and lumbar BMD has been reported [5, 6, 169]. However, in a case series of 6 CHH patients who were diagnosed after 40 years of age and had never received TRT, BMD was not different between the untreated men compared to age- and BMI-matched CHH patients who had started treatment before age 25, although lumbar and femoral BMD in both groups was lower than expected for their age [173]. A delay in treatment initiation, resulting in starting TRT only at an adult age, can have lasting negative effects on BMD in later life. In Antonio et al. study, patients remain in the osteopenic/osteoporotic range, despite achieving the T concentration threshold. This could indicate that long-term TRT is insufficient to restore BMD to a normal level [169]. Similar results were obtained in other studies where despite initial improvement of lumbar and femoral BMD, long-lasting bone mineral deficit was still observed [5, 174]. It also seems that continuous TRT is necessary to maintain its beneficial effects on bones as cessation of therapy can lead to a sharp decrease in lumbar and femoral BMD [6]. The inability to achieve normal BMD in CHH patients even despite long-term TRT might be the result of limited bone formation during adolescence which means that there is an irreversible loss of bone potential. It seems that untreated hypogonadism during puberty and early adulthood not only prevents achievement of PBM but also increases the lifetime risk of an osteoporotic fracture [175]. It is possible that initiating treatment during adolescence has the potential to prevent a BMD deficit in later life, but larger prospective studies are needed to investigate this [169].

It is not possible to precisely distinguish whether T itself or the estradiol (E2) derived from aromatization, is responsible for the anabolic effects of TRT on bone. The changes of bone formation and resorption markers followed physiologic T and E2 replacement have shown the role of estrogen as the main regulator of bone resorption, while bone formation was maintained by both estrogen and T.

3.5.2 Functional hypothalamic amenorrhea

Functional hypothalamic amenorrhea (FHA) is a common cause of secondary amenorrhea in premenopausal, young, or adolescent women without organic or anatomical disease of hypothalamic-pituitary-ovarian (HPO) axis. This condition is responsible even for 20–30% of all secondary amenorrhea [176]. FHA is characterized by irregular or absent menses due to abnormalities in GnRH secretion and thus low levels of gonadotropin and severe hypoestrogenism. Main causes are conditions leading to low body weight such as anorexia nervosa, excessive physical training, stress, or a combination of these factors. Prolonged estrogen deficiency has detrimental effects on various body systems, particularly the skeleton. This is especially crucial during adolescence, as estrogen deficiency can lead to decreased BMD and an increased risk of fractures, both in the short term and later in life [176]. Prolonged hypoestrogenism contributes to changes in aBMD, bone microarchitecture, and bone strength, all of which lead to increased fracture risk. The duration of amenorrhea which aligns with the duration of hypogonadism, and the age of menarche serve as predictors of the extent of bone impairment [176]. Recent findings reveal that around 52% patients with anorexia nervosa (AN) have an aBMD *Z-score* < -1 at one or more sites, with the trabecular bone being the most affected [177, 178]. In AN, the achievement of peak bone mass is hindered. Studies using HRpQCT and microfinite element analysis (μFEA) have highlighted alteration in both cortical and trabecular volumetric BMD (vBMD), bone geometry, and microarchitecture in patients with AN [179–181]. All these bone changes are associated with a higher risk of fractures in adolescents and adult women with AN compared to controls [179, 180, 182]. Similarly, in oligo/amenorrheic athletes, BMD, bone microarchitecture and strength undergo alterations due to the coexistence of factors such as low caloric intake, increased metabolic demands, hypoestrogenism, and changes in other hormones like IGF-I, other gonadal steroids, cortisol, and adipokines [176]. Hypogonadal athletes exhibit lower spine, hip, and whole body aBMD compared to eumenorrheic athletes [183, 184]. Fractures, particularly stress fractures, are more frequent among oligo/amenorrheic athletes than eumenorrheic athletes and non-athletes [183, 184].

The initial approach to enhance bone density in adolescent and adult women with FHA involves lifestyle modification, especially the restoration of menstrual cycles and achieving a normal weight. Additionally, it is important to supplement vitamin D and ensure sufficient calcium intake. Factors such as undernutrition, malabsorption, and stress-induced elevation of cortisol levels may contribute to the low BMD associated with FHA; however, estrogen levels play a pivotal role. A serum E2 level of 40–50 pg/ml or higher is necessary for physiological bone metabolism. Most studies on FHA have reported E2 levels below 20 pg/ml. Despite this, numerous studies have indicated a lack of a protective effect of combined oral contraceptives (COCs) on bone health [185, 186]. One possible explanation is the suppression of IGF-I, an osteoanabolic hormone, by oral estrogens due to hepatic first pass metabolism [125]. In contrast, transdermal 17β-E2 in replacement doses does not suppress IGF-I [125, 182]. In randomized clinical trials, 12- or 18-months treatment with transdermal 17β-E2 in adolescents with AN and oligo/amenorrhea athletes was effective in increasing lumbar and femoral BMD *Z-scores*, although BMD typical for healthy age-matched population was not achieved [178, 182]. Lack of complete recovery is probable caused by alterations in other hormones that may have an impact on bone health. The impact of estrogen replacement on fracture risk in women with FHA remains unclear. According to the guidelines of the Endocrine Society, the short-term utilization of transdermal 17β-E2 with cyclic oral progestin is considered a reasonable option for adolescents and women with FHA with sustained amenorrhea despite attempting lifestyle modification [187]. The method of estrogen administration can also influence bone metabolism, extending its effects to IGF-I. Replacement with transdermal E2, leading to elevated E2 levels, has been associated with increases in BMD, and a reduction in factors inhibiting osteoblastic activity, such as SOST and brain-derived neurotrophic factor [182]. In contrast, COCs, compared to transdermal formulations, resulted in a significant rise in sex hormone binding globulin levels, accompanied by a subsequent decrease in levels of free and bioavailable sex hormones [182]. These mechanisms collectively contribute to the efficacy of transdermal estrogen formulation in enhancing bone density. In a study comparing estradiol valerate to ethinyl estradiol in oral contraceptive pills with the same progestin, the estradiol valerate group exhibited less pronounced FSH suppression, associated with higher estradiol levels, suggesting more positive effects of natural estradiol on bone mass [188]. Women with FHA typically have lower levels of testosterone compared to control groups. However, in a study where transdermal testosterone was given in replacement doses (versus placebo) to adult women with AN, no increases in BMD were observed, despite an initial increase in bone formation markers [189]. Limited studies have explored the use of anti-resorptive medications in FHA. In one randomized controlled study involving adult women with AN, risedronate was linked to a modest but significant increase in BMD (2–3%) at the lumbar spine and hip. Another study in adolescents with AN found that alendronate led to a slight increase only at the femoral neck [189, 190]. Given the extended half-life of bisphosphonates,

caution is advised in women during their reproductive years. Data on the efficacy of denosumab in patients with AN are currently unavailable. Limited studies have investigated the impact of osteoanabolic drugs on bone outcomes in FHA, but the results are inconclusive. Current guidelines discourage the use of denosumab, metreleptin, and androgens to improve bone outcomes in FHA [176]. For adult patients with FHA, the guidelines suggest short-term use of teriparatide as an option in those with delayed fracture healing and very low BMD [187].

In summary, data from many studies indicate that central hypogonadism significantly affects BMD in most patients. The monitoring of mineral turnover and BMD, as well as the treatment with sex steroids specifically to improve bone health, should be an essential part of the control especially of young patients with hypopituitarism.

4 Secondary (central) adrenal insufficiency

4.1 Effects of glucocorticoids on bone

Glucocorticosteroids (GC) influence bone health directly through effects on bone cells, but also indirectly due to actions on calcium balance, gonadotropins level and muscle function. In case of physiological endogenous GC secretion, this effect is predominantly positive. GC are important hormonal players of bone development and metabolism, particularly stimulating bone formation. Endogenous GC influence also bone tissue maintenance during bone remodeling [10]. The negative effect of GC prevails, when there is a significant increase in serum GC concentrations, but also in case of 11β-hydroxysteroid dehydrogenases (11β-HSDs) overexpression, which locally increases the ratio of active to inactive form of GC in osteoblasts [10, 191]. Therefore, the action of GC on bone is variable, depending mostly on cortisol serum level, but also factors modifying their action, like age of the patient, and local activity of 11β-HSDs.

4.1.1 Endogenous glucocorticoids action - skeletal development and changes during aging

In physiological conditions, GC are involved in bone health particularly through their direct influence on osteoblasts, whilst their effect on osteoclasts appears less important. GC play crucial role in osteoblasts differentiation of mesenchymal cells through Wnt/βcatenin pathway and this effect seems dose-dependent. In case of GC deficiency, Wnt/βcatenin is down-regulated, and mesenchymal progenitors differentiate into adipocytes. However, with GC concentration increasing, the effect on Wnt signaling changes, resulting in inhibition of osteoblasts differentiation, which is a key factor of glucocorticoid-induced osteoporosis (GIOP). This bimodal action of GC on Wnt expression in osteoblasts may partially explain such variable, dose-dependent action of GC on bone [11].

Physiological GC action is an important signal for osteoblastogenesis and inhibition of chondrogenesis during cranial development. It has been shown, that transgenic mice with lack of GC presented phenotype with hypoplasia, sustained sutures, osteopenia, and increased amount of cranial cartilage [12]. Due to their effect on osteoblasts, endogenous GC participate also in growth and maintenance of long bones. Moreover, in mice with the disruption of GC signaling, the adverse effect on vertebral trabecular and femoral cortical bone parameters were observed. The influence of sex hormones on GC action in vertebral bones was also suggested [192].

Aging in humans is related to a decreased negative feedback response of the HPA axis to circulating cortisol. It may be associated with age-related reduction of brain glucocorticoid receptor density, caused by multiple stress challenges during lifetime. Therefore, older people are characterized by more pronounced cortisol serum increase after stressful situation. Consequently, tissues are exposed to higher circulating cortisol concentration [191, 193]. In addition to that, also the activity of 11β-HSD1 in skin and osteoblasts increases, leading to locally stronger GC action in those tissues. The age-related increase of 11β-HSD1 expression was reported in vertebral bone. The significance of this phenomenon remains unclear, but some authors reported that in elderly population the concentration of evening salivary cortisol was higher in comparison to younger controls, moreover it correlated negatively with BMD [194].

4.1.2 The effects of therapeutic glucocorticoids on bone

The negative action of GC excess on bone is well known, mainly through the adverse effect on bone formation. Severe inhibition of osteoblasts function is crucial in GIOP pathophysiology, and includes suppression of osteogenesis due to promotion of mesenchymal cells differentiation towards adipocytes, as well as reduction in maturation, lifespan, and function of bone-forming cells [195]. Moreover, hypercortisolemia stimulates apoptosis of osteocytes and leads to reduction of bone hydration and mineralization around osteocytes, a phenomenon called ”osteocytic osteolysis” [196]. Those microarchitectural changes may result in increased fracture risk with inadequate reduction of BMD.

The osteoclasts activity increases at the beginning of GC therapy which is accompanied by a rise of serum markers of bone resorption. However, osteoclasts differentiation is inhibited during prolonged treatment with high doses of GC [11, 197, 198]. Therefore, during long-lasting

hypercortisolemia, the suppression of bone formation dominates in the clinical picture.

There are also many indirect mechanisms in which GC affect bone health. Hypercortisolemia leads to muscle fiber atrophy and a significant decrease in myogenesis, which results in sarcopenia and reduced muscle strength. This is an important risk factor of falls and fractures, followed by the deterioration of bone strength through mechanical loading. Some studies suggest also that GC reduce bone vascularity and bone hydration, affecting bone quality [199].

GC excess leads also to hypogonadism, which negatively affects bone health. GC decrease the response of gonadotropins after GnRH as well as their action in males and females, consequently reducing gonadal sex steroids secretion [200]. In context of patients with hypopituitarism is seems very important to properly replace sex hormones. Another important influence of GC on bone is mediated through calcium metabolism and PTH action. GC increase the availability of PTH receptors on bone-forming cells and have a synergistic effect on PTH-related bone resorption. Hypercortisolemia predisposes also to a negative calcium balance via reduced intestinal absorption and increased renal excretion [200].

4.2 The influence of secondary adrenal insufficiency on bone

It is very difficult to assess the effect of isolated secondary adrenal insufficiency (SAI) on bone. The most common reason for isolated SAI is prolonged use of exogenous GC, which causes also GIOP. The diseases which are treated by long-term GC therapy are often inflammatory and can also influence bone health. Other causes of isolated ACTH deficiency are rare. Endogenous SAI is most commonly accompanied by other pituitary deficits, in particular GHD and hypogonadism, therefore the clinical picture is a result of all those hormonal deficiencies. It is also important, that both hypo- and hypercortisolemia may predispose to functional and transient GHD – the phenomenon of dual-phase and dose-dependent influence of GC on GH [201]. There are also different preparations of GC replacement, having variable effect on bone. Also, the action of GC on bone is modified at a tissue level and through expression of 11β-HSDs, which regulates the local conversion between the active cortisol with the inactive cortisone.

The GC replacement therapy with currently available GC preparations does not sufficiently reflect physiological cortisol production and there are periods of both hypo- and hypercortisolemia. Therefore, patients with SAI are at risk of osteoporosis due to hypopituitarism and GC deficiency and also periods of overtreatment with GC during replacement therapy. SAI may affect bone health mainly due to their effect on bone-forming cells [10]. In adults with GHD, additional SAI was independently associated with decreased BMD at the lumbar spine [28]. However, the European Adrenal Insufficiency Registry showed that 12.6% of patients with adrenal insufficiency receive more than 30 mg of hydrocortisone daily [202]. Consequently, we can suspect that overtreatment in patients with SAI is probably an important problem, strongly affecting bone health. It has been shown that iatrogenic hypercortisolemia in patients with hypopituitarism and untreated GHD may increase risk of VF [203].

4.3 Glucocorticoid replacement therapy and bone

There data regarding the effect of GC replacement therapy on bone health in patients with SAI is scarce, because most researchers focused on other pituitary deficits. There are more studies concerning GC replacement therapy in primary adrenal insufficiency, however Addison`s disease is a distinct disease entity with other aspects influencing bone health (for example lack of mineralocorticoids, higher doses of GC used in therapy, mostly autoimmune etiology). According to some reports, primary adrenal insufficiency predisposes to a decrease of BMD at the femoral neck and lumbar spine, especially when patients receive dexamethasone and prednisolone rather than hydrocortisone in their replacement therapy [204]. Moreover, some authors showed that in morphometric examination, Addison`s patients had more VFs than controls, while their BMD was not significantly lower. It highlights the fact, that BMD alone is not a proper predictor of fracture risk in patients with adrenal insufficiency [205]. Additionally, in a Swedish population-based cohort study, hip fractures were significantly more common in patients with Addison`s disease in comparison to controls, and the risk was particularly increased in younger females [206].

In SAI, many mechanisms of GC effect on bone health would be similar to Addison`s disease, but coexisting deficits of other pituitary hormones probably has significant impact on general fracture risk. In the retrospective analysis of patients with AO-GHD without previous GH replacement, untreated hypogonadism and SAI were independent predictors of worse BMD at the lumbar spine [167]. In a group of 51 hypopituitary males with AO-GHD, Mazziotti et al. have shown that overreplacement with cortisone and increased urinary cortisol excretion were associated with higher prevalence of VFs. However, this was seen only in patients with untreated GHD, because in patients receiving GH replacement therapy the risk of VFs was not increased, suggesting the protective role of GH during hypercortisolemia [203]. Recently, the same author has shown, that in the opposite disease – acromegaly, the existence of SAI was independently associated with higher prevalence of VFs

during follow up. This association was showed only in a group with active acromegaly, and it was independent of previous fractures. Authors concluded that overtreatment with GC was a possible explanation [207]. Those studies highlight the interplay between the growth hormone and GC action on bone, indicating that both GH deficit and excess are unfavorable to bones especially in patients with hypoadrenalism.

There is no reliable clinical nor biochemical marker of adequate GC dosage in adrenal insufficiency, therefore many patients may be overtreated. Many studies have shown, that even subclinical hypercortisolemia is detrimental to bone, leading to increased prevalence of VFs. It is only partially explained by decrease of BMD, therefore the impairment of bone quality probably plays pivotal role. Some studies have shown a reduction in OC level as a marker of reduced bone formation in subclinical hypercortisolemia. BMD is lower typically in spine, to a lesser degree in cortical bone tissue [208]. It stays in agreement with the pathophysiology of GIOP, where bone formation is mostly injured (see above). TBS is a novel diagnostic marker of bone microarchitecture, correlating with many trabecular parameters, which may be more suitable than BMD in evaluating fracture risk in hypercortisolemia. Studies showed that TBS value was lower in patients with endogenous Cushing`s syndrome in comparison to controls and was associated with the duration of hypercortisolemia [209]. Eller-Vainicher et al. investigated TBS in mild autonomous cortisol secretion and demonstrated that the TBS decrease correlated with the cortisol excess and the severity of fractures, and that TBS was a better risk fracture predictor than BMD [210]. In patients with primary adrenal insufficiency, TBS did not differ between subjects with hypoadrenalism vs. controls, but correlated negatively with disease duration and age [211]. To our best knowledge, there is no data on TBS in SAI and this topic appears to be an interesting direction of future studies.

To improve GC replacement therapy, new drugs formulations like dual-release hydrocortisone have been developed. They were aimed to better mimic the physiological cortisol daily rhythm and simultaneously reduce the total GC dose. In a study comprising 14 hypopituitary patients (including SAI and GHD) switched into dual-release hydrocortisone, there was a significant improvement of BMD at the lumbar spine and hip after 2 years of observation [156]. Despite important limitations (small number of patients and only 2 subjects treated with rhGH), those results are very promising and suggest beneficial effect of dual-release hydrocortisone on bone health in SAI. From the patients perspective, the significant drawback of new hydrocortisone formulations is the higher price in comparison to older drugs, as well as limited availability in many countries. Also, in cases of post-surgical or other potentially transient pituitary insufficiency, SAI replacement with modified-release hydrocortisone is not recommended due to the unavailability of lower doses. The beginning of the treatment with new GC formulations may be considered when SAI lasts more than a year [212].

5 Secondary (central) hypothyroidism

5.1 Thyroid hormones, thyrotropin and their receptors

Thyroid-stimulating hormone (thyrotropin, TSH) produced by the anterior pituitary thyrotropic cells stimulates the secretion of thyroid hormones (triiodothyronine - T3; thyroxine - T4). T3 is the active hormone produced by the thyroid gland and by peripheral deiodination of T4. Thyroid hormones play physiological stimulatory effects on metabolism in many organs and tissues including bone, influencing bone remodelling and bone mineralization. Normal thyroid status during childhood and adolescence is mandatory for skeletal growth and attaining of expected PBM. Serum levels of free T3 (fT3) and free T4 (fT4) reflect thyroid normal and disturbed function [213–215]. The thyroid hormones action is mediated by thyroid hormone receptors (TR), which are encoded by *THRA* and *THRB* genes. Each of TR owns a few subtypes: TRα1, TRα2, TRβ1 and TRβ2 [216–219]. They are localized mainly on thyrocytes, but also on other human tissues and cells including osteoblasts [215]. Bone expression of TRs reflects direct influence of thyroid hormones. T3 stimulates osteoblast proliferation and differentiation as well as the expression of bone matrix proteins by increasing expression of various proteins, such as OC, osteopontin, type I collagen, ALP, IGF-I, IGFBP-2, and IGFBP-4. The activating enzyme type 2 iodothyronine deiodinase is expressed in osteoblasts [213, 215, 220]. Osteoblasts and chondrocytes exert the expression of both TRα and TRβ, but concentration of TRα1 is more than ten times greater than TRβ1, and thus TRα1 is as a main functional mediator of T3 action in bones [216, 217, 219, 221–224]. Dysfunction or deficiency of TRα causes growth retardation, delayed bone age, disturbed bone mineralisation and decreased BMD. T3 regulates the chondrogenesis and bone mineralisation [219]. T3 stimulates the interleukins IL-6 and IL-8, intensifies the effects of IL-1 and IL-6, augments the synthesis of osteocalcin, collagen type 1, increases proliferation, differentiation and apoptosis of osteoblasts [225, 226]. Experimental studies presented T3 anabolic action in bone during skeletal development but catabolic effects in adult bone [223, 227]. Thyroid hormones excess can promote bone loss by increasing bone resorption [228]. T3 may also potentiate osteoblast responses to PTH by modulating expression of the PTH receptor [229, 230]. Osteoclasts express both thyroid

hormone receptors mRNAs, but there is no evidence for functional receptors expression in these cells [216]. IGF-I synthesis by osteoblasts is increased by thyroid hormones and IGF-I can mediate T3 anabolic actions in bone [71]. TSH can act directly on bone cells possibly modulating the skeletal effects of thyroid hormones too. Some pre-clinical and clinical studies shown ability of TSH to inhibit osteoclastogenesis and bone resorption [1]. The receptors for TSH (TSHR) are located on thyroid follicular cells, but also in osteoblasts and osteoclasts. Some data suggest that TSH may be considered as a negative regulator of bone turnover [216, 217]. Its direct action on bone tissue cells leads to enhanced bone remodelling and osteoporosis [231, 232].

5.2 The influence of clinically overt hypothyroidism on bone

Hypothyroidism is characterized by general slowing of metabolism, also bone metabolism [233]. In patients with each form of hypothyroidism, there is a decrease of both bone formation by osteoblasts and bone resorption by osteoclasts, causing finally decrease of BT. The effect is delay of bone remodelling cycle, causing a net increase in bone mineralization and BMD without a change in bone volume [215]. The slowing of bone metabolism is shown in bone histomorphometry and by decrease of BT markers. The severity of bone disease relates to the degree of the thyroid hormone deficit. In severe hypothyroidism, activation frequency is very low and the number of bone multicellular units (BMU) operating at a given moment is low [233]. In every BMU, bone resorption rate is low and final depth of resorption cavity is decreased. Untreated hypothyroidism in children leads to growth retardation or even growth arrest, disturbances of endochondral ossification, delayed bone age and persistent short stature [225, 234, 235]. In some studies patients with overt hypothyroidism had low levels of bone resorption markers [236–239]. The bone formation is also slow (low bone formation rate, longer bone formation period) and operates on a smaller bone formation surface in few previously created BMUs (due to low activation frequency) [233, 240]. In most, but not all, studies performed in patients with overt hypothyroidism, serum concentrations of bone formation markers, mainly OC are decreased [241]. In general, bone formation processes are slowed by 50%, bone resorption ones - by 40% [242]. In the groups of subjects with hypo-, eu- and hyperthyroidism, BT markers correlated positively with concentrations of total and free thyroid hormones [236, 237, 243], which may explain the differences between the studies. Indeed, decreased BT markers activity were observed mainly in groups with severe hypothyroidism, but not in patients with moderately decreased thyroid hormones levels [241]. The calcium urinary excretion is reduced, serum OC level and ALP activity are decreased, but serum PTH and vitamin D concentrations can be elevated. It is assumed that hypothyroidism is related with increased risk of fractures, although their mechanism remains unclear [242].

5.3 Levothyroxine replacement therapy in hypothyroidism

Each form of hypothyroidism, including secondary (central) hypothyroidism, requires sufficient replacement with levothyroxine (L-T4) in doses efficacious to maintain serum fT4 levels in the middle to upper half of the reference range, whereas TSH is not useful to choose the appropriate L-T4 replacement dose. The predicted L-T4 doses in central hypothyroidism reach 1.6 µg/kg/day on average, based on the evidence that this hormone dose was associated with an improvement in several clinical endpoints of central hypothyroidism [244–246]. It is noteworthy, that higher L-T4 doses may cause skeletal fragility, as in hyperthyroidism or when TSH suppression is desired because of differentiated thyroid carcinoma (DTC) surgery [242]. On the contrary to primary hypothyroidism, TSH cannot be used to monitor replacement therapy of central hypothyroidism and to determine the adequacy of L-T4 dosage [126]. So, overtreatment of central hypothyroidism may often occur, especially when other pituitary hormones deficiencies coexist. GH status is a major determinant of thyroid hormone biological effects by stimulating the deiodination of T4 in active T3 [247, 248]. Mazziotti et al. reported in the post hoc analysis of a study in GHD patients, high prevalence of radiological VFs in patients receiving L-T4 doses > 1.3 µg/kg/day [249]. Such an association was more significant in patients with treated GHD, consistent with the physiological concept that peripheral activation of T4 in T3 is stimulated by rhGH and treatment of GHD may favor higher exposure of peripheral tissues to thyroid hormones [1]. Hanna et al. observed no evidence for a difference in BMD in patients receiving replacement doses of L-T4 irrespective of the hypothyroidism etiology [250]. Leger et al. documented that LT4 replacement therapy among children with congenital hypothyroidism is not detrimental to the skeletal mineralization [251]. Tuchendler et al. noted that newly diagnosed hypothyroidism in premenopausal women (average age 33.37 ± 10.8 yrs) did not have an influence on BMD [252]. Vestergaard et al. observed a temporary increase in fracture risk within the first 2 years after diagnosis of primary idiopathic hypothyroidism. The fracture risk was mainly increased in the age group above 50 years, and the increased risk was limited to the forearms [253]. Another study of the same author showed an increase in the risk of any fracture within the first 10 years after a diagnosis of hypothyroidism, with no

effect of L-T4 replacement on fracture risk [254]. Gonzalez-Rodriguez et al. did not find any association between hypothyroidism and decreased BMD or VFs and nonvertebral fractures among 400 women suffering from hypothyroidism [255].

5.4 The influence of suppressive doses of levothyroxine on bone

Suppressive doses of L-T4 are administered in patients with DTC as a complementary treatment after thyroidectomy and radioactive iodine therapy. Although an endogenous hyperthyroidism is a risk factor of secondary osteoporosis, the effects of supraphysiological doses of L-T4 on bone are still under discussion [256, 257]. Uzzan et al. performed a meta-analysis (by pooling standardized differences, using a fixed effect model) of 41 published controlled cross-sectional studies (including 1250 patients) concerning the impact of thyroid hormones therapy on BMD. They found out that for lumbar spine and hip (as for all other sites), suppressive thyroid hormones therapy was associated with significant bone loss only in postmenopausal women, but not in premenopausal ones [258]. The available evidence suggests that premenopausal women on chronic TSH suppressive treatment with L-T4 do not have adverse effects on BMD. On the contrary, postmenopausal women on TSH suppressive doses of L-T4 are at risk of bone loss, particularly, when osteopenia or osteoporosis are already present. Finally, a very recent meta-analysis study on the influence of TSH suppression on BMD in patients with DTC suggested a possible association between L-T4-mediated TSH suppression and the lower BMD in postmenopausal women, but not in premenopausal women and men [259]. Similar bone effects of L-T4 overtreatment in central hypothyroidism are possible, especially when replacement monitoring is based on the TSH values, only.

In summary, hypothyroidism in any form may cause skeletal fragility influencing bone metabolism, but it is not easy to demonstrate a significant correlation between hypothyroidism and BMD or fractures owing to the small number of studies and discordant results of clinical studies published to date. Although L-T4 treatment has been associated with an increase in fractures in some studies, there have been no long-term prospective follow-up studies of patients with untreated hypothyroidism [260–262]. Therefore, the bone health of patients with hypothyroidism should be based on the sufficient hormonal replacement, beyond that evaluated and managed according to general osteoporosis guidelines [2, 263, 264].

6 Summary

The impact of hypopituitarism on bone health is not uniform, as various forms of hypopituitarism occur. During the childhood and adolescence failure of all pituitary axes can cause harmful effects on bone. Later in the adult life, after attaining the PBM, the most detrimental consequences are due to gonadotropin/gonadal and GH/IGF-I axes hormonal hypofunction. The early and sufficient rhGH and/or sex steroid hormones replacement is crucial. On the other hand, adrenocorticotropin or thyrotropin deficiencies seem not to be as harmful, as possible overreplacement using L-T4 or GCs. In general, first step in the maintaining of bone health and prevention of possible fractures represents proper hormone replacement therapy controlling hormonal dysfunctions. Another important issue are universal bone health recommendations like adequate calcium and vit. D intake, regular physical activity, falls prevention. When above-mentioned solutions fail, proven antiosteoporotic therapy may be necessary.

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