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Role of bisphosphonates in osteoporosis caused by adult growth hormone deficiency

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ABSTRACT In recent years, growth hormone and insulin-like growth factors have become key regulators of bone metabolism and remodeling, crucial for maintaining healthy bone mass throughout life. Studies have shown that adult growth hormone deficiency leads to alterations in bone remodeling, significantly affecting bone microarchitecture and increasing fracture risk. Although recombinant human growth hormone replacement therapy can mitigate these adverse effects, improving bone density, and reduce fracture risk, its effectiveness in treating osteoporosis, especially in adults with established growth hormone deficiency, seems limited. Bisphosphonates inhibit bone resorption by targeting farnesyl pyrophosphate synthase in osteoclasts, and clinical trials have confirmed their efficacy in improving osteoporosis. Therefore, for adult growth hormone deficiency patients with osteoporosis, the use of bisphosphonates alongside growth hormone replacement therapy is recommended.

KEY WORDS growth hormone; adult growth hormone deficiency; osteoporosis; bisphosphonates; insulin-like growth factor 1; skeleton

双膦酸盐在成人生长激素缺乏所致骨质疏松症中的作用

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[摘 要] 近年来，生长激素和胰岛素样生长因子已成为骨代谢和重塑的关键调节剂，对于生命各阶段健康骨量的维持均至关重要。研究表明，成人生长激素缺乏会引发骨重塑变化，显著改变骨微结构并增加骨折风险。虽然重组人生长激素替代疗法可以减轻这些负面影响，提高骨密度并降低骨折风险，但其治疗骨质疏松症的效果，特别是对于已有生长激素缺乏症的成年人，似乎有限。双膦酸盐通过抑制破骨细胞中的法尼醇焦磷酸合酶起抗骨吸收的作用，临床试验已证实其可有效改善骨质疏松。因此，对患有骨质疏松的成人生长激素缺乏症患者，建议在使用生长激素替代疗法的同时使用双膦酸盐。

[关键词] 生长激素；成人生长激素缺乏症；骨质疏松症；双磷酸盐；胰岛素样生长因子1；骨骼

Growth hormone deficiency (GHD) in adults often results from various organic pituitary disorders that arise during adulthood. These include pituitary tumors, radiation therapy, traumatic brain injury, surgical interventions, and subarachnoid hemorrhage. Additionally, GHD might persist from childhood into adulthood. In adults, GHD manifests as reduced growth hormone (GH) production and secretion, leading to either complete or partial GH insufficiency. This condition triggers multiple metabolic disturbances, notably in bone metabolism[1]. A critical consequence of adult GHD is the marked reduction in bone mineral density (BMD), a key measure of bone strength and health. This reduction substantially elevates fracture risk in affected individuals. The GH-insulin-like growth factor 1 (IGF1) axis plays a vital role in maintaining skeletal physiological balance, influencing bone growth and maturation during adolescence and sustaining bone mass in adulthood[2]. It is crucial for bone remodeling and metabolism[3]. GH, secreted by the pituitary gland, promotes IGF1 synthesis in the liver and other tissues. IGF1's systemic and local actions, along with the autocrine and paracrine functions of osteocyte-produced IGF binding proteins (IGFBP), contribute to the GH-IGF1 axis's complex impact on bone. This intricacy is evident in the axis's comprehensive effect on bone health. Individuals with GHD often experience reduced BMD and bone mineral content (BMC)[4], heightening fracture risk. Treatment with recombinant human growth hormone (rhGH) can improve BMD, thereby reducing fracture risk in this group[5]. However, compared to other osteoporosis treatments, rhGH therapy yields a relatively modest increase in BMD[6]. Clinical trials in osteoporotic patients revealed no significant fracture risk difference between those treated with GH and those who were not, suggesting that GH replacement therapy alone might be inadequate for adult growth hormone deficiency (AGHD) patients with concurrent osteoporosis[7]. Consequently, integrating GH replacement therapy with other anti-osteoporotic drugs is often advisable.

Antiresorptive medications have become the predominant treatments for osteoporosis, working by inhibiting osteoclast activity and thereby slowing bone remodeling and resorption[8]. Among these, bisphosphonates have shown efficacy in clinical trials. They act by inhibiting farnesol pyrophosphate synthase in osteoclasts, a key component of their antiresorptive effect[9]. Additional factors include their affinity for hydroxyapatite and their distribution and retention in the skeleton. Dosing schedules for bisphosphonates vary: oral alendronate and risedronate are taken weekly, oral ibandronate monthly, and intravenous zoledronate annually[10-11]. In AGHD with osteoporosis, concurrent bisphosphonate medication is suggested due to the limited impact of GH replacement therapy alone[12]. However, questions remain about the optimal timing, choice, and duration of combination therapy, as well as its safety and effectiveness. This review focuses on the pathophysiological, clinical, and therapeutic aspects of bisphosphonates in AGHD patients with osteoporosis.

1 Physiological actions of GH-IGF1 axis on skeleton

Pituitary dwarfism was one of the first conditions for which GH was proposed as a treatment in 1958[4]. GH, a 191-amino acid single-chain polypeptide, is regulated by a negative feedback loop: Somatostatin inhibits its secretion, while growth hormone-releasing hormone (GHRH) stimulates production[13]. In healthy individuals, peak GH production occurs during slow-

wave sleep[14-15]. GH production is enhanced by fasting, but declines with age[16]. The binding of GH to its receptor enables IGF1 production, allowing GH to exert both direct and indirect effects. GH activation activates tyrosine kinase enzymes[15]. A significant number of growth hormone receptors (GHR) are present in skeletal muscle, liver, adipose tissue, heart, pancreas, kidney, gastrointestinal tract, and lungs. Receptor activation by a ligand is essential for signaling. This leads to receptor dimerization and cellular uptake, initiating Janus tyrosine kinase 2 activation. This triggers phosphorylation of both the extracellular GHR and the internalized protein. The signal transducer and activator of transcription (STAT) plays a key role in GH signaling[17-18]. GHR also interacts with the insulin receptor signaling pathway, phosphorylating insulin receptor substrates (IRS) -1, -2, and -3[19]. Direct interaction between GHR and IGF-I receptor (IGF-IR) is a possible regulatory mechanism in GH signaling, allowing it to function even without binding IGF[20]. Other pathways in GH signaling involve the expression of p90rsk and c-fos, as well as the activation of mitogen-activated protein kinases (MAPKs) via protein kinase C (PKC) [21-22]. These pathways include the expression of p90rsk and c-fos.

The body equires IGF1 for GH to fulfill its function. IGF1 can be sourced from either the liver or bone cells. In bone cells, osteoblasts are primary in IGF1 synthesis. Several tissues, including muscles and bones, synthesize and release paracrine IGF1 in response to GH. Circulating IGF1, predominantly produced by hepatocytes, activates IGF1 receptors, facilitating GH's anabolic effects[23]. The activity of IGF1 is thought to be controlled by proteins known as IGFBP-1 through -6. IGFBP-3, in particular, regulates active IGF1 availability by creating a ternary complex with IGFBP-3 and an acid-labile component, binding up to 75% of circulating IGF1. Individuals with GH insensitivity frequently have shorter body lengths at birth, resulting in shorter statures throughout development and maturity[24]. This is notably evident in patients with Laron syndrome, resulting from *GHR* gene mutations that impair longitudinal bone growth due to reduced IGF1 or IGFBP-3 synthesis. In GH-resistant mice, cortical bone traits and markers of periosteal and endosteal bone formation are significantly reduced[25]. This observation extends to various bone formation assessments. Furthermore, osteoblast-derived IGF1 is hypothesized to significantly contribute to bone tissue's anabolic response to parathyroid hormone (PTH) [3, 26]. Evidence from several studies supports this hypothesis. PTH induces osteoblasts to produce collagen, alkaline phosphatase (ALP), and osteocalcin. "Osteoblast activation" encompasses osteoblast proliferation, differentiation, and survival, in addition to the aforementioned functions[27-29]. Both glucocorticoids and 1, 25-dihydroxy vitamin D3 are known to inhibit IGF1 production. This discussion highlights the GH-IGF1 axis's role in bone physiology, particularly its impact on IGF1 production and bone health. Future studies should further investigate this axis to reveal new therapeutic avenues for bone disorders and to understand its variable effects across different demographics.

2 Effects of GH deficiency on skeleton

Reduced osteoblast osteogenesis[30] is a significant factor in the slower bone turnover observed in individuals with GHD compared to healthy counterparts. Bone biopsies from adult males with GHD show decreased osteoid and mineralizing surfaces, along with reduced bone formation rates[31]. Patients with GHD exhibit lower BMD, with greater severity in cases of pronounced hormone deficiency or when GHD results from pituitary radiation therapy or surgery for Cushing's disease[32]. The skeletal effects of GHD are more prominent in younger individuals, likely due to declining GH synthesis and secretion with age. As a result, children with GHD typically have lower BMD, whereas adults with GHD often display normal BMD levels[33]. Significant reductions in cortical area and thickness have been observed using high-resolution peripheral quantitative CT (HR-pQCT) at the radius and distal tibia, and 3D dual energy X-ray absorptiometry (DXA) at the hip in individuals with GHD, irrespective of its onset in childhood or longstanding presence[34-35]. A decrease in trabecular thickness in cancellous bone is also noted. However, if GHD develops after peak bone mass is achieved, it may not significantly impact bone microarchitecture[36]. In postmenopausal women, IGF1 blood levels and osteoprogenitor cell activation decrease with age, regardless of osteoporosis development[37-38],

showing a strong correlation between BMD and IGF1 levels. This section highlights how GHD compromises skeletal health, particularly by reducing osteoblast activity and BMD, especially in cases of severe deficiency or early onset. The data reveal a more substantial impact in younger individuals and varied effects across age groups. Future research should focus on understanding the long-term skeletal outcomes of GHD in all age groups and developing interventions, with an emphasis on early detection and treatment.

3 Role of GH replacement therapy on GHD-related bone disfunction

GH replacement therapy in individuals with GHD increases muscle mass and decreases fat[39]. Increases in skeletal muscle mass and strength are observed after 6 months of rhGH therapy[40]. GHD patients undergoing GH replacement therapy experience accelerated bone remodeling; however, changes in bone resorption precede increases in bone formation[41]. Blood biochemical markers for bone formation and resorption, such as the C-terminal cross-linking telopeptide of type I collagen, respond dose-dependently following rhGH administration[42]. Findings from prospective, long-term studies align with those from randomized controlled trials. Two studies[43-44] showed that up to 15 years of GH replacement therapy led to an approximate 10% increase in male lumbar spine BMD. However, the modest increase in femoral neck BMD following GH replacement was not fully sustained at the study's end[44]. Some evidence suggests concerns about potential fracture risk with GH replacement, but these have only been assessed retrospectively. Large-scale observational study[45] indicated that male patients receiving GH replacement therapy for juvenile or adult-onset GH insufficiency do not exhibit an increased fracture risk. The study monitored 832 individuals with GHD undergoing replacement therapy over a median duration of 5–15 years, categorized based on symptom onset.

Men and women get different effects from GH injections on BMD. According to a meta-analysis[46] of randomized studies on GH replacement treatment, only men experienced an increase in BMD in the lumbar spine and femoral neck. Longitudinal studies[43-44] lasting up to 15 years revealed comparable findings, emphasizing the stability of these findings. To reach the same IGF1 levels as those on transdermal estrogen, women on oral estrogen replacement therapy require greater growth hormone doses[47]. Oral estrogen directly reduces the liver's IGF1 stores[48]. This sexually dimorphic effect was observed even with adequate GH replacement[44, 49]. While some studies may have administered insufficient GH doses to women, others have provided adequate dosages. The BMD response to GH varies based on the cause of hypopituitarism, GHD severity, and pre-treatment BMD levels. A study[50] found that patients with Cushing's syndrome or prolactinomas exhibited slower BMD improvements post-treatment compared to those with non-functioning pituitary adenomas. A meta-analysis[46] showed that patients with more severe GHD and lower baseline BMD experienced more significant increases in femoral neck BMD with GH therapy.

The potential increase in BMD following rhGH replacement is relatively modest compared to other osteoporosis treatments. BMD typically increases significantly between 12 and 18 months and remains elevated for up to 4 months after starting rhGH replacement[51-56], with an estimated annual growth rate of about 1%. The long-term sustainability of these BMD improvements is not yet clear. For comparison, BMD in the lumbar spine increases by 9% after 3 years of alendronate therapy, an oral bisphosphonate, equating to a rate of 3% per year. Currently, the effectiveness of rhGH replacement therapy in treating osteoporosis remains inconclusive[57]. By comparison, alendronate sodium has been proven to reduce the risk of vertebral and hip fractures in postmenopausal osteoporosis patients by 48%[17]. However, recent study[7] indicates that growth hormone therapy does not significantly impact the incidence of fractures. This raises the question of whether combining bisphosphonates with rhGH replacement therapy affects BMD. This section reviews the efficacy of GH replacement therapy for GHD-related skeletal diseases, focusing primarily on its improvement of muscle mass and BMD, particularly in men. However, these improvements in BMD are not significantly beneficial compared to other osteoporosis therapies and also exhibit gender differences. Future research should focus on the long-term effectiveness and

safety of GH therapy in various populations and consider its combination with other treatments (such as bisphosphonates) to optimize the potential for improved skeletal health outcomes in GHD patients.

4 Bisphosphonates

4.1 Mechanisms of the action of bisphosphonates

Since the 1990s, bisphosphonates have been effectively used to treat osteoporosis in both women and men, marking a significant advancement in the field. These drugs are known for reducing bone resorption and have been proven effective in treating osteoporosis and related conditions[58-60]. The Food and Drug Administration (FDA) has approved bisphosphonates for various indications, including postmenopausal osteoporosis, steroid-induced osteoporosis, chemotherapy-related osteoporosis, Paget's disease, and osteoporosis associated with bladder cancer. However, they are not approved for treating osteogenesis imperfecta or preventing glucocorticoid-induced osteoporosis in children or adults. Bisphosphonates are considered a first-line treatment for osteoporosis. They have a structure similar to pyrophosphates but with greater stability, which has led to their widespread use. These drugs work by binding to bone and inducing apoptosis in osteoclasts, thereby inhibiting bone resorption and increasing BMD. They bind with hydroxyapatite to effectively prevent bone loss; during bone resorption, the released bisphosphonates inhibit osteoclast activity[59, 61-62].

Bisphosphonates are divided into 2 categories based on their chemical structure: nitrogen-containing (NBPs) and non-nitrogen-containing (NNBPs). NBPs, such as alendronate, risedronate, ibandronate, pamidronate, and zoledronate, inhibit farnesyl pyrophosphate synthase in the mevalonate pathway, disrupting protein prenylation and causing abnormalities in the cytoskeleton of osteoclasts, thereby reducing their activity. In contrast, NNBPs like etidronate, clodronate, and tiludronate, have a different mechanism of action, interfering with cellular metabolism by substituting ATP with a terminal pyrophosphate, thus inducing osteoclast apoptosis. Bisphosphonates can be administered either orally or via intravenous injection. Oral administration is preferred, but intravenous injection is an alternative in case of adverse reactions such as difficulty swallowing, abdominal pain, nausea, bloating, constipation or diarrhea, acid reflux, taste distortion, esophageal ulcers, and gastritis. Rare side effects, such as atypical femoral fractures and osteonecrosis of the jaw, can be managed by reducing the dosage or altering the dosing schedule. Despite common side effects, bisphosphonates are still considered an ideal choice for the early treatment of osteoporosis when administered correctly.

4.2 Effects of bisphosphonates on GHD-related osteoporosis

The role of bisphosphonates in managing osteoporosis associated with AGHD warrants detailed exploration due to the complex interplay between GH and bone metabolism. While bisphosphonates are well-established in the treatment of osteoporosis by enhancing bone strength and reducing fracture risks, their specific impact in the context of AGHD remains less clear. Research by Jakob et al.[60] is instrumental in underscoring the potential synergistic effects of bisphosphonates when used alongside rhGH. Their findings suggest that combining bisphosphonates with rhGH significantly improves bone health outcomes in adults with concurrent osteoporosis and GHD. This combination therapy appears to augment the anabolic effects of GH on bone, thus enhancing overall treatment efficacy. In a randomized trial examining individuals with low GH levels, both osteoporotic and non-osteoporotic subjects received 4 years of GH supplementation. For osteoporotic patients, this regimen was supplemented with an additional 3 years of alendronate sodium treatment. The study observed no significant disparity in lumbar spine BMD between the osteoporotic and non-osteoporotic groups. However, it did note a gender-related difference in BMD outcomes, with men exhibiting higher bone mineral density than women[63].

Further supporting this notion, another study[44] indicated that patients receiving both bisphosphonates and GH supplementation exhibited significant improvements in lumbar spine BMD compared to those treated with GH alone. This finding points to the added

benefits of bisphosphonates in enhancing the bone-strengthening effects of GH therapy in AGHD-related osteoporosis. Researches[64-65] also contribute to understanding the multifaceted impact of bisphosphonates on bone turnover and PTH sensitivity in AGHD patients. These studies, along with other studies, delineate the nuanced effects of bisphosphonates on skeletal health in the context of GHD. Despite these promising insights, the current literature presents some inconsistencies and lacks a comprehensive overview of the role of bisphosphonates in AGHD-related osteoporosis. Table 1 lists the advantages and disadvantages of GH therapy and bisphosphonate therapy. Future research is imperative to elucidate the differential effects of various bisphosphonates, assess their long-term safety, and evaluate their efficacy across diverse patient populations with AGHD. Such research endeavors[66-67] are crucial for gaining a more thorough understanding of bisphosphonates' therapeutic potential in this specific context.

In summary, while existing studies indicate a positive role of bisphosphonates in conjunction with GH supplementation for treating AGHD-related osteoporosis, a more detailed and consistent body of research is needed for a clearer understanding and better clinical guidance.

Table 1 Comparison of growth hormone therapy and bisphosphonate therapy in treating growth hormone deficiency-related bone conditions

Treatment method	Advantages	Disadvantages
Growth hormone therapy	1) Increases bone density and muscle mass 2) Improves muscle strength and body composition 3) Significant increase in lumbar spine bone mineral density in some studies	1) Bone formation increase often lags behind bone resorption 2) Limited improvement in femoral neck bone mineral density in long-term studies 3) Unclear effect on reducing fracture risk
Bisphosphonate therapy	1) Significantly improves bone mineral density in osteoporosis 2) Reduces risk of non-vertebral and vertebral fractures 3) Effective in adults with growth hormone deficiency and osteoporosis	1) Potential side effects with long-term use 2) May not be suitable for certain patients (e.g., severe renal impairment) 3) Effectiveness may depend more on duration compared to growth hormone therapy

5 Conclusion

Recent clinical research suggests that individuals with GHD-related osteoporosis might benefit from an additional dose of bisphosphonates alongside their GH supplementation. Further research, conducted over longer periods and with larger population samples, is necessary to explore the potential supplemental benefits of bisphosphonates in conjunction with rhGH in reducing the heightened risk of fractures associated with GHD.

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