Review Article

Effect of growth hormone to spinal growth and recombinant human growth hormone to scoliosis

Cheng Luo[1#], Shuping Liu[1#], Yanyan Li[1], Qiong Wu[1], Qing Liu[1], Danxia Peng[1], Shu Han[1], Xuan Xu[1], Jie Wen[2]^

[1]Department of Children's Medical Center, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, China; [2]Department of Pediatric Orthopedics, Hunan Provincial People's Hospital, the First Affiliated Hospital of Hunan Normal University, Changsha, China

Contributions: (I) Conception and design: C Luo; (II) Administrative support: X Xu, J Wen; (III) Provision of study materials or patients: S Liu; (IV) Collection and assembly of data: Y Li; (V) Data analysis and interpretation: Q Wu, Q Liu, D Peng, S Han; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Xuan Xu, MS. Department of Children's Medical Center, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, No. 61 West Jiefang Rd., Changsha 410005, China. Email: 1312558601@qq.com; Jie Wen, MD. Department of Pediatric Orthopedics, Hunan Provincial People's Hospital, the First Affiliated Hospital of Hunan Normal University, No. 61 West Jiefang Rd., Changsha 410005, China. Email: cashwj@qq.com.

Abstract: Growth hormone (GH) plays a key role in human growth and development. In addition to promoting height growth, GH affects bone metabolism, bone size, and bone mineral density (BMD) in children and adolescents by affecting bone formation and resorption. Among them, the effect of GH on spinal growth has been widely concerned. Scoliosis is a three-dimensional structural spinal deformity characterized by lateral curvature of one or more segments of the spine accompanied by vertebral rotation and sagittal imbalance. For children with growth hormone deficiency (GHD), whether GH supplementation leads to scoliosis is still controversial. In recent years, numerous scholars have conducted extensive research to investigate the correlation between recombinant human GH replacement therapy and scoliosis, yielding divergent findings with some even presenting contradictory results. This study aims to investigate the impact of GH on spinal growth and explore the association between recombinant human GH replacement therapy and scoliosis by comprehensively reviewing the effects of GH and insulin-like growth factors 1 (IGF-1) on bone metabolism, bone mass, as well as examining the consequences of GHD on bone health. Additionally, we aim to access the influence of recombinant human GH replacement therapy on adolescent idiopathic scoliosis (AIS).

Keywords: Growth hormone (GH); spinal growth; recombinant human growth hormone; insulin-like growth factors 1 (IGF-1)

Submitted May 10, 2024. Accepted for publication Sep 29, 2024. Published online Oct 28, 2024.
doi: 10.21037/tp-24-180
View this article at: https://dx.doi.org/10.21037/tp-24-180

^ ORCID: 0000-0002-5734-4678.

Introduction

Human growth hormone (GH) is a peptide hormone secreted by the anterior pituitary gland, which can promote protein synthesis, promote growth of internal organs and bones, affect mineral and fat metabolism, and play a key role in human growth and development. It is one of the most important endocrine hormones in individual growth and development. In addition to promoting growth, GH can also affect bone metabolism, bone size, and bone density in children and adolescents by regulating bone formation and absorption. Among them, the effect of GH on spinal growth has been widely concerned. In children with growth hormone deficiency (GHD), GH replacement therapy can improve adult height and increase adult bone mineral density (BMD). However, for children treated with GH, it remains controversial whether GH supplementation can cause spinal growth disorders, spinal fractures, or scoliosis. This study aims to review the related literature, summarize the effects of GH on spinal growth and development, and investigate whether recombinant human GH can cause spinal fractures and scoliosis.

Effects of GH and insulin-like growth factors 1 (IGF-1) on bone metabolism

GH is a single chain protein containing 191 amino acids, which is secreted by growth promoting cells in the anterior pituitary in a pulsating manner (1,2). GH mainly acts on its specific GH receptors or induces IGF-1, the synthesis of IGF-1 and insulin-like growth factor binding protein 3 (IGFBP-3) plays a role (3) in ultimately promoting growth metabolism (4). The effect of GH-IGF-1 axis on epiphyseal plates has been extensively studied, and it has a pleiotropic effect on bone, affecting bone formation and bone resorption (5). Both GH and IGF-1 receptor can exist in bone (6), the interaction of GH with IGF-1 in regulating somatic cell growth has been studied for many years in different models (7). The results show that mice disrupting the genes regulating IGF-1 deletion resulted in significant intrauterine growth retardation. The IGF-1 mainly affects the proliferation and hypertrophy of chondrocytes. However, GH has dual effects on the proliferation and hypertrophy and generation of chondrocytes (8). *In vitro*, GH exerts a direct stimulatory effect on osteoblast differentiation and proliferation, as well as chondrocyte pre-proliferation (9-11). In addition to the direct effects of GH, the endocrine IGF-1 secreted by the liver into the systemic circulation and the locally synthesized paracrine IGF-1 are also closely related to bone metabolism. The IGF-1 hormone stimulates the proliferation of osteoblasts and enhances bone formation, while also mitigating osteoblast apoptosis and facilitating chondrocyte differentiation (12). According to data obtained from animal models, mice deficient in the GH receptor and IGF-1 gene had a greater reduction in bone length than mice deficient in both genes alone, suggesting that both GH and IGF-1 play an important role in bone biology (13). GH also regulates the secretion of parathyroid hormone (PTH) in the whole body, activated osteoblasts through the PTH/PTH-related protein receptor (14), and it has the potential to enhance hematopoiesis by activating the IGF system (IGF-2, IGFBP-1, IGFBP-2, and IGFBP-3) and hematopoietic growth factors [granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF)] in osteoblasts (15). GH also induces phosphate retention and enhances the 1a hydroxylation of 25-hydroxyvitamin D through direct renal effects, thereby facilitating the promotion of intestinal calcium absorption (16,17). In addition, thyroid hormone and estradiol can also stimulate the expression of IGF-1 in osteoblasts, while glucocorticoids can inhibit it (*Figure 1*).

Effects of GH and IGF-1 on bone mass

In Sim's animal studies, mice with GH receptor knockout had reduced cortical bone but retained trabecular bone mass (18). Some mouse studies involving specific deletion of IGF-1 gene have confirmed that the cortical bone mass of these mice is also reduced (19,20), indicating that GH and circulating IGF-1 also play an important role in regulating cortical bone mass. Conversely, transgenic overexpression of IGF-1 in osteoblasts results in augmented trabecular volume, whereas targeted deletion of the IGF-1 gene in osteoblasts leads to diminished trabecular volume and mineralization, indicating a pivotal role for paracrine IGF-1 in regulating trabecular bone mass (21,22).

Effects of GHD on human bone and spine

Effects of GHD on bone

GH is an important systemic regulator of longitudinal bone growth in childhood. In addition to the clear role of GH in promoting linear growth, both GH and IGF-1 affect bone turnover, bone size, and BMD in childhood and

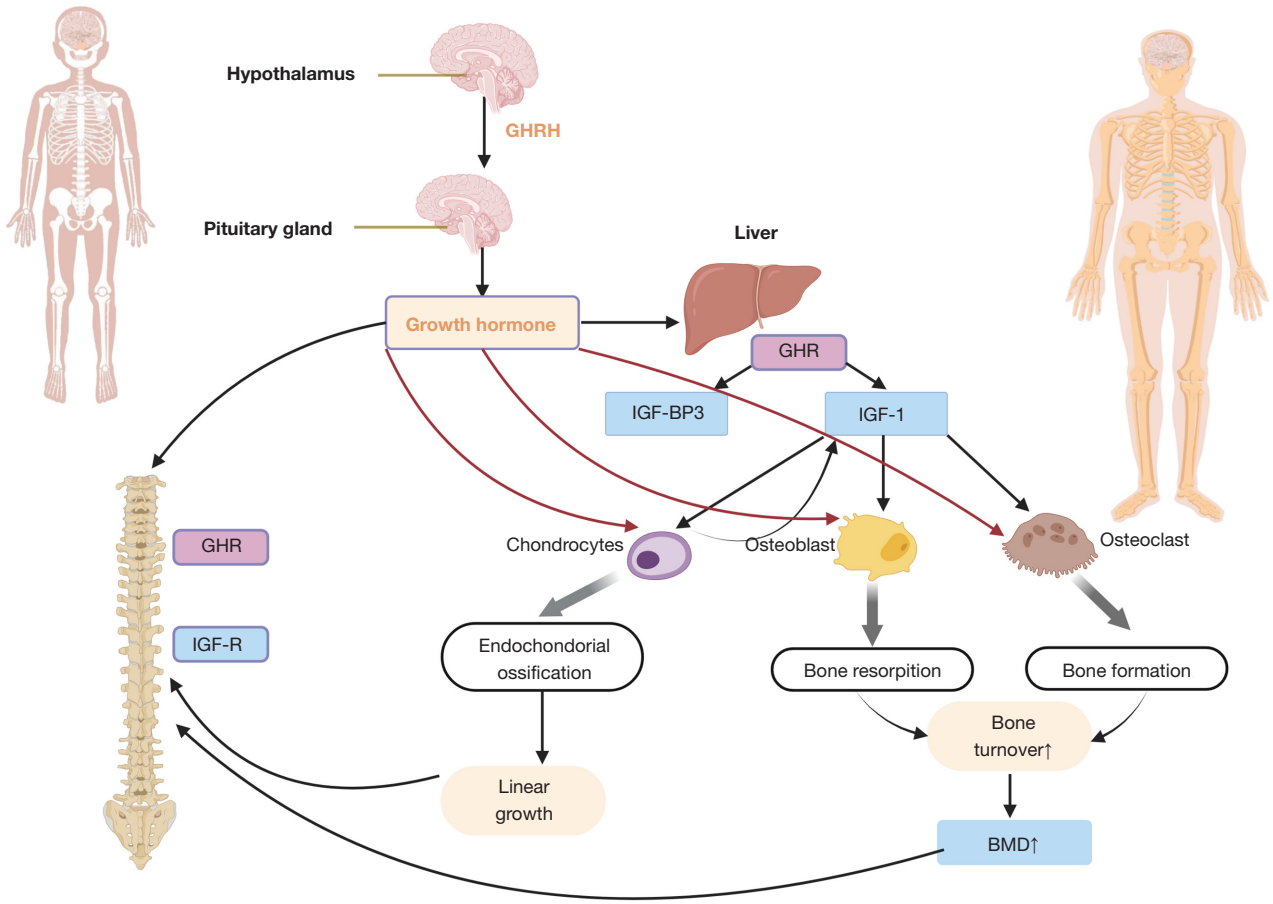

Figure 1 Effects of growth hormone and IGF-1 on bone metabolism, in addition to the clear role of GH in promoting linear growth, both GH and IGF-1 increase (↑) bone turnover, bone size, and BMD in childhood and adolescence. GHRH, growth hormone releasing hormone; GHR, growth hormone receptor; IGF-1, insulin-like growth factors 1; IGF-R, insulin-like growth factors receptor; IGF-BP3, insulin-like growth factors-binding protein 3; BMD, bone mineral density.

adolescence (23). GH also plays a major role in peak bone mass accumulation and bone preservation in children and adolescents (24-26). Bouillon's study showed that GHD patients who did not receive GH treatment in childhood showed significant decrease in adult height but with retained trabecular bone mineral content (BMC). Localized BMD also decreased significantly (27). However, Fors *et al.* reported that GHD patients treated with GH during childhood had normal bulk BMD. Levels of biochemical markers of bone formation were lower in the GH-deficient group than in the GH-adequate and healthy controls. After GH therapy was discontinued in adolescents treated with GH to final height or near final height, the BMC and BMD of adolescents in the GHD group and GH adequate group continued to increase (28).

In adults with GHD, low bone mass is considered to be a feature of the disease, and osteopenia is an important surrogate indicator of fracture risk in clinical practice. A retrospective study by Mukherjee *et al.* has shown an increased incidence of fracture in untreated adults with GHD (29). A study has shown that bone turnover in GHD patients caused by adult hypopituitarism is decreased according to the results of bone biomarker and histopathologic data analysis (30). Shalet *et al.* designed a 2-year, multicenter prospective study to evaluate the optimal GH replacement dose in young adults with childhood onset GHD. In this study, 128 patients were randomly assigned to receive an adult dose of GH replacement (12.5 Ig/kg/day), a child dose of GH replacement (25 Ig/kg/day), or no treatment at all. After 1 year, bone turnover markers

were significantly reduced in the untreated group and significantly increased in the treated group, and after 2 years, total BMC was significantly higher in the treated group without a significant dose effect, suggesting that the adult dose regimen is ideal for sustained bone mass accumulation after linear growth is complete. If GH therapy is terminated after reaching a lifetime high in adulthood, it may eventually lead to lower BMD in adulthood as the bone remodeling cycle progresses in the absence of GH (31).

Effects of GH on spinal growth

GH is not only associated with reduced growth rate, but also plays an important role in bone mass acquisition in children and adolescents. GHD can lead to a decrease in peripheral and axial BMD (32). Holmes *et al.* reported in their study that the median BMD z score in the lumbar spine and forearm of adult GHD patients was significantly lower (33). A cross-sectional study by Mazziotti *et al.* suggests that untreated GHD may lead to an increased risk of spinal radiological malformations in adult patients, and that recombinant human GH (rhGH) therapy may be effective in reducing this risk (34). A study by Baroncelli *et al.* showed that treated GHD adolescents had increased lumbar BMD area and lumbar BMD volume after reaching their final height and stopping GH therapy, but compared to the control group, They delayed the time and reduced the mean value of the lumbar peak BMD (pBMD) area and the lumbar pBMD volume, suggesting that GH plays a role in obtaining lumbar BMD after the final height of GHD patients, suggesting that GH therapy should be continued until lumbar pBMD is achieved (35).

Effect of rhGH replacement therapy on adolescent idiopathic scoliosis (AIS)

Scoliosis is a three-dimensional structural spinal deformity characterized by lateral curvature of one or more segments of the spine accompanied by vertebral rotation and sagittal imbalance. AIS is the most common form of scoliosis. According to epidemiological studies, 1–2% of adolescents suffer from AIS (36). AIS has a significantly increased probability of scoliosis in adolescence (10–15 years old), which is related to the rapid growth rate during the peak growth period of adolescence (37,38). Scoliosis not only has a huge physical impact on patients, it can also cause psychological problems and seriously reduce quality of life.

At present, the etiology of scoliosis has not been fully elucidated, but growth state, genetic abnormality, hormone imbalance, neuromuscular development abnormality, etc., are widely believed to be related to the occurrence of scoliosis (39). GH plays a key role in human growth and development, and rhGH has been widely used clinically to treat GHD and idiopathic short stature (ISS) (40). However, in the process of rhGH treatment, it has been found that it has an impact on bone, endocrine, glucose and lipid metabolism, fluid retention and secondary tumor, etc. (41,42). Some studies have shown that rhGH causes rapid bone growth, which may lead to scoliosis (43,44). Long-term use of rhGH may increase the degree of scoliosis in children with scoliosis at baseline, with clinical manifestations of aggravation of scoliosis deformity and significant changes in appearance, as well as imaging manifestations of increased Cobb Angle or increased parietal translation (45). However, with the deepening of research and the increase of clinical statistics, some scholars have found that rhGH treatment only leads to the progression of scoliosis, but does not lead to an increase in the incidence of scoliosis (46-48). But this conclusion is still controversial. Recently, Park *et al.* conducted a comprehensive analysis on 1,128 patients with ISS. The study revealed that the incidence of new scoliosis during GH treatment was found to be 3.7%, which is comparable to the prevalence observed in the general population. Furthermore, no significant association between the development of scoliosis and either the type or duration of rhGH treatment was identified in this investigation (49).

In order to explore the relationship between idiopathic scoliosis and GH therapy in children with short stature, scholars Mijin Park *et al.* observed subjects diagnosed with short stature and receiving GH therapy for at least 1 year and found that after GH therapy, Height, standard deviation score of height, IGF-1 and IGFBP-3 ($P<0.001$) were significantly increased. However, there was no significant difference in mean Cobb angle and incidence of scoliosis before and after 1 year of treatment. The findings suggest that although GH treatment increases height and growth rate, it is not associated with the development or exacerbation of idiopathic scoliosis (50). Hong *et al.* conducted a cross-sectional and retrospective cohort study to investigate the radiological prevalence of scoliosis in children with ISS, as well as the impact of GH therapy. The results suggest that the risk of scoliosis development in ISS children is higher than that in control group. In children with ISS and without pre-existing scoliosis, treatment with GH significantly augmented the susceptibility to scoliosis

development and necessitated orthotic intervention. In patients with idiopathic dwarf and scoliosis at baseline, GH therapy does not increase the risk of scoliosis progression, the need for a brace, or surgery (51). Some scholars evaluated short stature patients [GHD, small for gestational age (SGA), ISS and Turner syndrome (TS)] for up to 3 years, and found that the height standard deviation score (HtSDS) increase was higher in children with GHD. No harmful side effects requiring discontinuation of treatment were observed in the majority of children during the observation period (52). The research by Al Shaikh *et al.* shows that among 73 children with GHD, ISS, short stature homeobox-containing (SHOX) gene mutation, and SGA who received GH treatment, their height was significantly improved, and the treatment was relatively safe (53). Grootjen *et al.* (54) also reported that 8 years of GH therapy did not demonstrate any deleterious effects on the prevalence and severity of scoliosis in children with Prader-Willi syndrome (PWS) prior to reaching 11 years old. A survey by van Bosse *et al.* (55) on PWS showed that for every month of delay in the start of GH treatment in children with PWS, the risk of needing scoliosis surgery increased by 0.7%. According to the study of Murakami *et al.*, scoliosis did not occur in PWS children without scoliosis after GH treatment, which may be related to the improvement of paravertebral muscular dysplasia in PWS children with GH treatment (56). The research findings by Nakamura *et al.* (57) indicate that there was no statistically significant difference in the prevalence of scoliosis between PWS patients treated with GH and those not receiving raw GH treatment. However, it was observed that GH administration significantly enhanced lumbar bone density (Z score) in individuals with PWS. For PWS patients, GH therapy may be an effective treatment to reduce the incidence of osteoporotic fractures in PWS patients. Early treatment with GH is necessary.

Conclusions

GH is essential for normal growth during childhood and adolescence. For children with GHD, whether GH supplementation can cause spinal growth disorders, spinal fractures, or scoliosis remains controversial (*Table 1*). Overall, the question of whether rhGH use causes scoliosis remains unclear, which requires more comparative studies with larger cohorts of long-term follow-up. In the process of GH treatment, it is recommended to strengthen safety monitoring, the changes in the spine should be strictly evaluated and monitored by professional doctors, and attention should also be paid to regular review, which helps

Table 1 Research on rhGH therapy and scoliosis

Author	Year	Findings
Ziv-Baran *et al.* (43)	2023	rhGH treatment was associated with an increased risk to be diagnosed with adolescent scoliosis in males. Scoliosis development should be monitored appropriately in rhGH recipients
Griffero González *et al.* (52)	2024	Significant increased height in children with GHD, ISS, SHOX mutation and SGA, highlighting the importance of early treatment of GHD and ISS, and the treatment was relatively safe
Al Shaikh *et al.* (53)	2020	Children with GHD, SGA, ISS and TS exhibited significant increases in HtSDS when treated with rhGH for 3 years. The HtSDS gain was higher in children with GHD compared to other groups
Hong *et al.* (51)	2023	The controllability of scoliosis in children with idiopathic short stature following treatment with growth hormone was deemed manageable. However, meticulous attention should be given by physicians to the evaluation of spinal curves in these individuals
Park *et al.* (50)	2022	Although GH treatment in short children increased height and growth velocity, it was not associated with development or aggravation of idiopathic scoliosis
Park *et al.* (49)	2021	De novo scoliosis developed in 3.7% of patients, while scoliosis progressed in 16.4% during rhGH treatment. However, neither the types nor duration of rhGH treatment had a significant impact on scoliosis development or progression in patients with ISS
Grootjen *et al.* (54)	2021	Eight years of GH treatment has no adverse effect on the prevalence and severity of scoliosis in children with PWS until 11 years of age. As BMADLS SDS is inversely associated with Cobb angle, it is pivotal to optimize the BMD status in children with PWS

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Findings
Maghnie *et al.* (44)	2022	Data from KIGS, the largest and longest-running international database of children treated with rhGH, demonstrate the safety profile of rhGH and its efficacy in promoting short-term height gain as well as adult height improvement across both GHD and non-GHD conditions
Yun *et al.* (46)	2017	The radiographic examination revealed that growth hormone therapy for idiopathic short stature had an impact on the progression of scoliosis Cobb angle and apical vertebral translation in the coronal plane
Danowitz *et al.* (40)	2022	GH therapy is expensive, pediatric population almost tripled from 2001–2016 over the past 35 years. Treatment efficacy in such conditions is variable and generally less than in patients with GHD, and unresolved safety concerns require on-going scrutiny
Di Felice *et al.* (37)	2018	During growth, idiopathic scoliosis tends to progress in a high percentage of cases. The progression rate varies according to the age at diagnosis, with infantile scoliosis being the most unpredictable
Divall *et al.* (41)	2013	rhGH therapy has had an exemplary track record of safety and efficacy. Practitioners who prescribe rhGH be provided with solid data regarding the long-term safety issues and patients be adequately informed of the benefits and risks related to therapy
van Bosse *et al.* (55)	2020	Childhood risk is 70% or higher until skeletal maturity, exhibiting a bimodal age distribution with one peak occurring before the age of 4 and another approaching adolescence. A comprehensive comprehension of the risks associated with surgical intervention in pediatric patients diagnosed with PWS is crucial and will be thoroughly discussed
Yakar *et al.* (20)	2002	Normal postnatal growth and development in these animals may be due to normal free IGF-1 levels (from as yet unidentified sources), although the role of autocrine/paracrine IGF-I has yet to be determined
Murakami *et al.* (56)	2012	Total paravertebral muscle area and prolonged asymmetry were identified as potential prognostic indicators for progressive scoliosis in patients with Prader-Willi syndrome undergoing growth hormone therapy
Nakamura *et al.* (57)	2014	Among patients with PWS, 61.5 % had low BMDs. GH administration significantly improved the lumbar BMD. There were no statistically significant differences in the prevalence of scoliosis among patients who received GH treatment compared to patients who did not

rhGH, recombinant human growth hormone; GHD, growth hormone deficiency, ISS, idiopathic short stature, SHOX, short stature homeobox-containing gene; SGA, small for gestational age; TS, Turner syndrome; HtSDS, height standard deviation score; PWS, Prader-Willi syndrome; IGF-1, insulin-like growth factors 1; BMADLS, bone mineral apparent density of lumbar spine; SDS, standard deviation score; BMD, bone mineral density; KIGS, The Kabi/Pfizer International Growth Database.

doctors adjust the treatment plan according to the problems in the treatment.

Acknowledgments

Funding: This study was supported by Changsha Soft Science Project (No. 2022-24).

Footnote

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-180/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-180/coif). All authors report that this study was supported by Changsha Soft Science Project (No. 2022-24). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Cummings DE, Merriam GR. Growth hormone therapy in adults. Annu Rev Med 2003;54:513-33.
2. Molitch ME, Clemmons DR, Malozowski S, et al. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1587-609.
3. Møller N, Jørgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev 2009;30:152-77.
4. Akanji AO, Smith RJ. The insulin-like growth factor system, metabolic syndrome, and cardiovascular disease risk. Metab Syndr Relat Disord 2012;10:3-13.
5. Giustina A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. Endocr Rev 2008;29:535-59.
6. Parker EA, Hegde A, Buckley M, et al. Spatial and temporal regulation of GH-IGF-related gene expression in growth plate cartilage. J Endocrinol 2007;194:31-40.
7. Lee HY, Jang HR, Li H, et al. Deletion of Jazf1 gene causes early growth retardation and insulin resistance in mice. Proc Natl Acad Sci U S A 2022;119:e2213628119.
8. Liu H, Davis T, Duran-Ortiz S, et al. Growth hormone-receptor disruption in mice reduces osteoarthritis and chondrocyte hypertrophy. Geroscience 2024;46:4895-908.
9. Kassem M, Blum W, Ristelli J, et al. Growth hormone stimulates proliferation and differentiation of normal human osteoblast-like cells in vitro. Calcif Tissue Int 1993;52:222-6.
10. Chihara K, Sugimoto T. The action of GH/IGF-I/IGFBP in osteoblasts and osteoclasts. Horm Res 1997;48 Suppl 5:45-9.
11. Barnard R, Ng KW, Martin TJ, et al. Growth hormone (GH) receptors in clonal osteoblast-like cells mediate a mitogenic response to GH. Endocrinology 1991;128:1459-64.
12. Conover CA. In vitro studies of insulin-like growth factor I and bone. Growth Horm IGF Res 2000;10 Suppl B:S107-10.
13. Lupu F, Terwilliger JD, Lee K, et al. Roles of growth hormone and insulin-like growth factor 1 in mouse postnatal growth. Dev Biol 2001;229:141-62.
14. Lv Z, Zhang J, Liang S, et al. Comparative study in estrogen-depleted mice identifies skeletal and osteocyte transcriptomic responses to abaloparatide and teriparatide. JCI Insight 2023;8:e161932.
15. Zhang J, Hu Y, Cai W. Bone metabolism factors in predicting the risk of osteoporosis fracture in the elderly. BMC Musculoskelet Disord 2024;25:442.
16. Bikle DD, Sakata T, Leary C, et al. Insulin-like growth factor I is required for the anabolic actions of parathyroid hormone on mouse bone. J Bone Miner Res 2002;17:1570-8.
17. Gertner JM, Horst RL, Broadus AE, et al. Parathyroid function and vitamin D metabolism during human growth hormone replacement. J Clin Endocrinol Metab 1979;49:185-8.
18. Sims NA, Clément-Lacroix P, Da Ponte F, et al. Bone homeostasis in growth hormone receptor-null mice is restored by IGF-I but independent of Stat5. J Clin Invest 2000;106:1095-103.
19. Yakar S, Canalis E, Sun H, et al. Serum IGF-1 determines skeletal strength by regulating subperiosteal expansion and trait interactions. J Bone Miner Res 2009;24:1481-92.
20. Yakar S, Rosen CJ, Beamer WG, et al. Circulating levels of IGF-1 directly regulate bone growth and density. J Clin Invest 2002;110:771-81.
21. Zhang M, Xuan S, Bouxsein ML, et al. Osteoblast-specific knockout of the insulin-like growth factor (IGF) receptor gene reveals an essential role of IGF signaling in bone matrix mineralization. J Biol Chem 2002;277:44005-12.
22. Zhao G, Monier-Faugere MC, Langub MC, et al. Targeted overexpression of insulin-like growth factor I to osteoblasts of transgenic mice: increased trabecular bone volume without increased osteoblast proliferation. Endocrinology 2000;141:2674-82.
23. Baroncelli GI, Bertelloni S, Sodini F, et al. Acquisition of bone mass in normal individuals and in patients with growth hormone deficiency. J Pediatr Endocrinol Metab 2003;16 Suppl 2:327-35.
24. Saggese G, Baroncelli GI, Bertelloni S, et al. The effect of long-term growth hormone (GH) treatment on bone mineral density in children with GH deficiency. Role of GH in the attainment of peak bone mass. J Clin Endocrinol Metab 1996;81:3077-83.
25. Attie KM. The importance of growth hormone replacement therapy for bone mass in young adults with growth hormone deficiency. J Pediatr Endocrinol Metab 2000;13 Suppl 2:1011-21.
26. Wydra A, Czajka-Oraniec I, Wydra J, et al. The influence

of growth hormone deficiency on bone health and metabolisms. Reumatologia 2023;61:239-47.
27. Bouillon R, Koledova E, Bezlepkina O, et al. Bone status and fracture prevalence in Russian adults with childhood-onset growth hormone deficiency. J Clin Endocrinol Metab 2004;89:4993-8.
28. Fors H, Bjarnason R, Wirént L, et al. Currently used growth-promoting treatment of children results in normal bone mass and density. A prospective trial of discontinuing growth hormone treatment in adolescents. Clin Endocrinol (Oxf) 2001;55:617-24.
29. Mukherjee A, Murray RD, Shalet SM. Impact of growth hormone status on body composition and the skeleton. Horm Res 2004;62 Suppl 3:35-41.
30. Sartorio A, Conti A, Monzani M, et al. Growth hormone treatment in adults with GH deficiency: effects on new biochemical markers of bone and collagen turnover. J Endocrinol Invest 1993;16:893-8.
31. Shalet SM, Shavrikova E, Cromer M, et al. Effect of growth hormone (GH) treatment on bone in postpubertal GH-deficient patients: a 2-year randomized, controlled, dose-ranging study. J Clin Endocrinol Metab 2003;88:4124-9.
32. Baroncelli GI, Bertelloni S, Sodini F, et al. Lumbar bone mineral density at final height and prevalence of fractures in treated children with GH deficiency. J Clin Endocrinol Metab 2002;87:3624-31.
33. Holmes SJ, Economou G, Whitehouse RW, et al. Reduced bone mineral density in patients with adult onset growth hormone deficiency. J Clin Endocrinol Metab 1994;78:669-74.
34. Mazziotti G, Doga M, Frara S, et al. Incidence of morphometric vertebral fractures in adult patients with growth hormone deficiency. Endocrine 2016;52:103-10.
35. Baroncelli GI, Bertelloni S, Sodini F, et al. Longitudinal changes of lumbar bone mineral density (BMD) in patients with GH deficiency after discontinuation of treatment at final height; timing and peak values for lumbar BMD. Clin Endocrinol (Oxf) 2004;60:175-84.
36. Trobisch P, Suess O, Schwab F. Idiopathic scoliosis. Dtsch Arztebl Int 2010;107:875-83; quiz 884.
37. Di Felice F, Zaina F, Donzelli S, et al. The Natural History of Idiopathic Scoliosis During Growth: A Meta-Analysis. Am J Phys Med Rehabil 2018;97:346-56.
38. Burwell RG. Aetiology of idiopathic scoliosis: current concepts. Pediatr Rehabil 2003;6:137-70.
39. Wang S, Qiu Y, Zhu Z, et al. Histomorphological study of the spinal growth plates from the convex side and the concave side in adolescent idiopathic scoliosis. J Orthop Surg Res 2007;2:19.
40. Danowitz M, Grimberg A. Clinical Indications for Growth Hormone Therapy. Adv Pediatr 2022;69:203-17.
41. Divall SA, Radovick S. Growth Hormone and Treatment Controversy; Long Term Safety of rGH. Curr Pediatr Rep 2013;1:128-32.
42. Sklar CA, Mertens AC, Mitby P, et al. Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 2002;87:3136-41.
43. Ziv-Baran T, Modan-Moses D, Zacay G, et al. Growth hormone treatment and the risk of adolescent scoliosis: A large matched cohort study. Acta Paediatr 2023;112:1240-8.
44. Maghnie M, Ranke MB, Geffner ME, et al. Safety and Efficacy of Pediatric Growth Hormone Therapy: Results From the Full KIGS Cohort. J Clin Endocrinol Metab 2022;107:3287-301.
45. Wang ED, Drummond DS, Dormans JP, et al. Scoliosis in patients treated with growth hormone. J Pediatr Orthop 1997;17:708-11.
46. Yun YH, Kwon SS, Koh Y, et al. Influence of growth hormone treatment on radiographic indices of the spine: propensity-matched analysis. J Orthop Surg Res 2017;12:130.
47. Day GA, McPhee IB, Batch J, et al. Growth rates and the prevalence and progression of scoliosis in short-statured children on Australian growth hormone treatment programmes. Scoliosis 2007;2:3.
48. Nagai T, Obata K, Ogata T, et al. Growth hormone therapy and scoliosis in patients with Prader-Willi syndrome. Am J Med Genet A 2006;140:1623-7.
49. Park SJ, Lee KH, Lee CS, et al. Impact of growth hormone treatment on scoliosis development and progression: analysis of 1128 patients with idiopathic short stature. J Pediatr Endocrinol Metab 2021;34:243-50.
50. Park M, Kim YJ, Oh KE, et al. The association between idiopathic scoliosis and growth hormone treatment in short children. Ann Pediatr Endocrinol Metab 2022;27:207-13.
51. Hong H, Pan X, Song J, et al. Idiopathic short stature and scoliosis in children treated with growth hormone. Bone Joint J 2023;105-B:439-48.
52. Griffero González M, González Navarrete D, Tolosa Navarro F, et al. Growth Hormone treatment in children with Growth Hormone deficiency, idiopathic short stature, SHOX gene mutation, small for gestational age and Turner syndrome. Andes Pediatr 2024;95:151-8.

53. Al Shaikh A, Daftardar H, Alghamdi AA, et al. Effect of growth hormone treatment on children with idiopathic short stature (ISS), idiopathic growth hormone deficiency (IGHD), small for gestational age (SGA) and Turner syndrome (TS) in a tertiary care center. Acta Biomed 2020;91:29-40.
54. Grootjen LN, Rutges JPHJ, Damen L, et al. Effects of 8 years of growth hormone treatment on scoliosis in children with Prader-Willi syndrome. Eur J Endocrinol 2021;185:47-55.
55. van Bosse HJP, Butler MG. Clinical Observations and Treatment Approaches for Scoliosis in Prader-Willi Syndrome. Genes (Basel) 2020;11:260.
56. Murakami N, Obata K, Abe Y, et al. Scoliosis in Prader-Willi syndrome: effect of growth hormone therapy and value of paravertebral muscle volume by CT in predicting scoliosis progression. Am J Med Genet A 2012;158A:1628-32.
57. Nakamura Y, Murakami N, Iida T, et al. Growth hormone treatment for osteoporosis in patients with scoliosis of Prader-Willi syndrome. J Orthop Sci 2014;19:877-82.

Cite this article as: Luo C, Liu S, Li Y, Wu Q, Liu Q, Peng D, Han S, Xu X, Wen J. Effect of growth hormone to spinal growth and recombinant human growth hormone to scoliosis. Transl Pediatr 2024;13(10):1849-1857. doi: 10.21037/tp-24-180