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REVIEW ARTICLE

Vitamin D and the growth hormone in Children with Short Stature: Review Article

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ABSTRACT

Background: The human development is a complicated process that is believed to be influenced by dietary, environmental, hormonal, and genetic factors. The main hormones involved in growth at every stage of development are growth hormone (GH) and its mediator, insulin-like growth factor 1 (IGF-1). On the other hand, vitamin D controls how calcium and phosphorus are metabolized, which is important for bone growth and mineralization. Despite a number of biochemical and clinical studies demonstrating a strong correlation, no scientific research has yet to elucidate their interaction, particularly in terms of how one malfunction impacts the other. The aim of this article was to assess the role of vitamin D in growth hormone deficiency and the effect of GH therapy on vitamin D.

Conclusions: vitamin D levels are often lower in the patients with GH deficiency (GHD) than in healthy children. This condition may exacerbate the metabolic risk of GHD, which is already known to exist.

Keywords: Growth hormone deficiency; vitamin D; insulin-like growth factor.

INTRODUCTION

Growth hormone (GH) is a growth-promoting hormone that also preserves lean body mass and muscle mass while decreasing fat mass, supports healthy bone development, normalizes metabolic parameters like lipid profile, and improves children's quality of life. Adolescents continue to develop somatically, and growth hormone (GH) has long-lasting impacts on metabolism and body composition that last into adulthood (1).

Because growth hormone (GH) is secreted in a pulsatile fashion, a decrease in tonic hypothalamic somatostatin secretion mediates its measurement, which necessitates repeated sampling every 5 to 20 minutes. Hormone secretion can be influenced by age, sex hormones, dietary state, and other variables. Hormone release can also be regulated by ghrelin, somatostatin, and GHRH, among other things (2).

The link between GH and IGF-1 is robust. IGF-1 production and secretion are regulated by growth hormone levels, and the latter can operate as a negative feedback loop to regulate growth hormone release from the pituitary gland (3).

Etiology of short stature:

Although there are numerous reasons for low stature, the most prevalent ones include idiopathic short stature, pathological causes, and normal variant short stature (NVSS). Constitutional delay of growth and puberty (CDGP) and familial short stature (FSS) are the two categories of NVSS, whereas pathological causes include endocrine abnormalities and syndromes, chronic diseases, skeletal dysplasia, metabolic diseases, and others (4).

Growth failure due to reduced pituitary gland GH synthesis is known as growth hormone deficit (GHD) in children. This condition can be acquired or congenital, and it can manifest alone or in conjunction with various pituitary hormone deficiencies. There is one patient with isolated GHD for every 4,000–10,000 live births, and there are several possible reasons of this condition (5).

Vitamin D metabolism

Vitamin-D (1, 25-dihydroxy cholecalciferol) reflects endogenous synthesis via UV light effect

as Vitamin D is activated in liver and kidney Under stimulation of PTH, IGF-I and low calcium or phosphorus levels. Vitamin D regulates calcium and phosphate homeostasis by stimulating intestinal trans-epithelial transport of them. Circulating 25-OH D3 is measured to assess vitamin D status. The vitamin D system makes sure that newly deposited bone and cartilage matrix mineralize (6).

Risk factor of vitamin D deficiency

A frequent condition known as vitamin D insufficiency is characterized by blood levels of less than 27.5 ng/ml of vitamin D. There are multiple pathways that could be linked to the difference in lipid profile and 25-(OH) D insufficiency (7). A child who is a vegetarian and does not get enough sunlight or vitamin D supplements is risky for low Vitamin D level and rickets as Diets devoid of animal fat tend to be poor in vitamin D because natural vitamin D intake is directly correlated with animal fat. (7).

Twenty to thirty percent of people in Europe and thirty to fifty percent of people in the United States suffer from vitamin D insufficiency, which is more prevalent worldwide in high- and low-latitude nations (8).

The vitamin D deficiency seen in people who live in Antarctica or submarines and who receive very little sun exposure, as well as in several Arabian countries, best illustrates the significance of skin-derived vitamin D3 production in preserving appropriate levels of vitamin D. For both adults and children, two hours of weekly sun exposure to the skin is probably enough to keep 25-OH D concentrations at normal levels (9).

Vitamin D and metabolic diseases

The effects study is still being done on how vitamin D affects metabolic diseases like diabetes, insulin resistance, and metabolic syndrome. Vitamin D deficiency cannot be completely ruled out as a contributing factor in either illness, given that GHD is linked to metabolic abnormalities and that the metabolic syndrome is linked to both 25-OH D3 and IGF-I levels (Figure 1) (10).

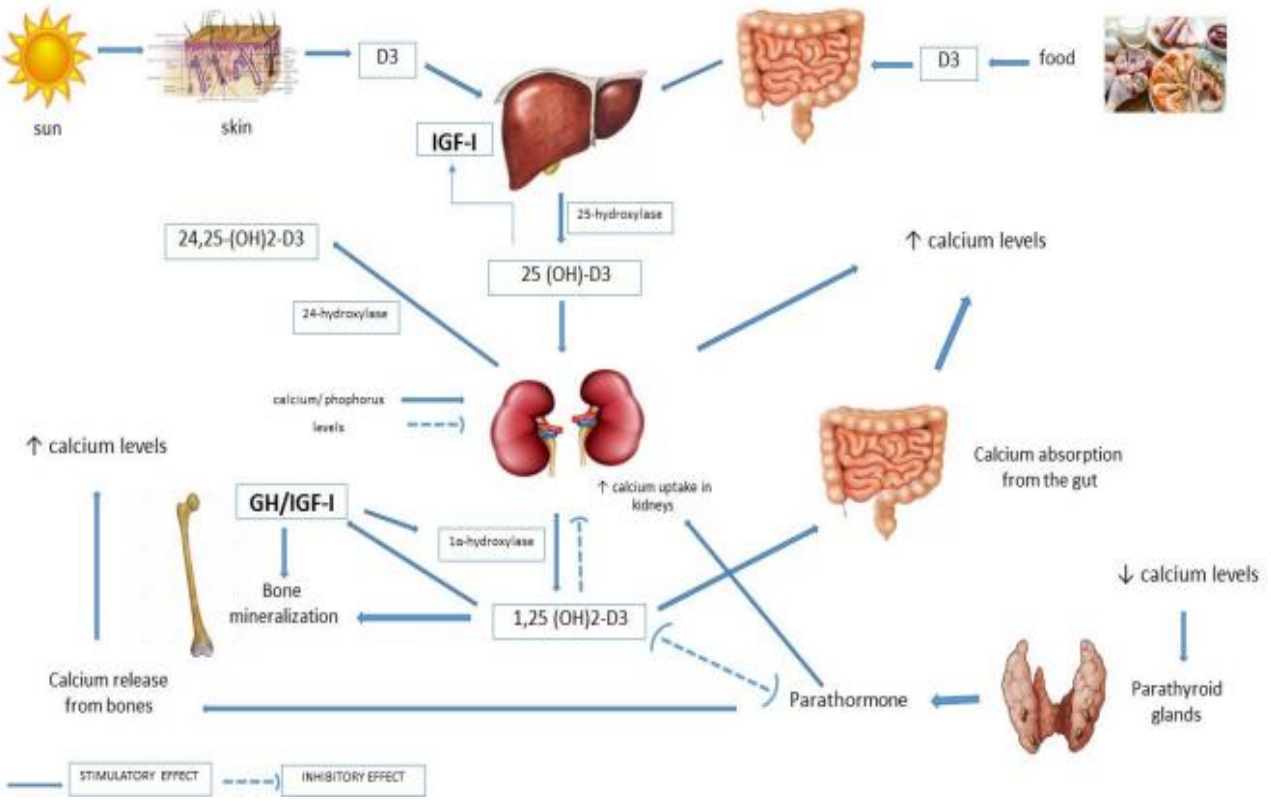

Figure 1: The relationship between vitamin D metabolism and the GH/IGF-1 axis (11).

GH/IGF-I and vitamin D:

Studies conducted in vivo and in vitro on adults and children have provided clear insights into the reciprocal link between vitamin D and IGF-I. It is unknown, though, if GH affects vitamin D and bone metabolism either directly or indirectly by producing more IGF-I. It is well established that IGF-I, independent of GH, directly increases kidney cells' in vitro synthesis of 1,25(OH)2-D3 (11).

Similar to this, GH appears to influence serum 1,25(OH)2-D3 in healthy individuals regardless of PTH levels in the blood, and IGF-I appears to be the mediator of this impact. Thus, an additional way that growth hormone (GH) may promote

increases in bone mass is via raising IGF-I levels, which in turn raise serum 1,25(OH)2-D3 (12).

A significant body of biological research has focused on the molecular interaction between vitamin D and the human GH/IGF-1 axis in recent years. According to this study, the presence or absence of vitamin D may have an impact on the expression of IGF-1 receptors in various organs as well as the hepatic synthesis of IGF-1 and IGFBP-3. Vitamin D and growth hormone metabolism are mutually reinforcing. Firstly, vitamin D supplements raise IGF-1 levels. Secondly, IGF-1 increases the 1α-hydroxylase enzyme's activity, which in turn regulates the kidneys' generation of vitamin D, also known as calcitriol or 1,25(OH)2D. Furthermore, GH itself directly stimulates the synthesis of 1,25(OH)2D. Additionally, it appears that GH and IGF-1 stimulate the activity of CYP27A1, a multifunctional cytochrome P450 enzyme that presents in hepatoblastoma cells, catalyzes the 25-hydroxylation of vitamin D, among other complex tasks (13, 14).

It appears that both the systemic and local levels are involved in how IGF-1 and vitamin D work. Indeed, recent studies have shown that bone and cartilage, as well as epiphyseal chondrocytes, are impacted by vitamin D, GH, and IGF-1. Specifically, an in vitro study showed that vitamin D may have a role in increasing the sensitivity of growth plate cells to GH and IGF-1; another study examined the possibility of mutual interference between IGF-1 and 25(OH)D on their respective receptors on epiphyseal chondrocytes (15, 16). The scientific community now has a better understanding of some of the effects of vitamin D deficiencies on the growth plate, thanks to some studies conducted on mice that had a targeted deletion of VDR. Specifically, it appears that a decrease in 1,25(OH)2D reduces the number and activity of chondroclasts/osteoclasts, cartilage calcification, and hypertrophic chondrocyte apoptosis. More specifically, it seems that a drop in 1,25(OH)2D lowers cartilage calcification, hypertrophic chondrocyte apoptosis, and the quantity and activity of chondroclasts/osteoclasts. These seem to be the bases of physiopathology underlying the skeletal changes seen in rickets patients. Nonetheless, it has been discovered in certain studies that the 1,25(OH)2D-induced proliferation of epiphyseal chondrocytes is mediated by locally produced IGF-1. The growth plate changes in children with rickets may be partially explained by the reduced levels of IGF-1 observed in vitamin D deficient patients (17).

The effect of GHD on vitamin D levels

On the other hand, it has also been shown that children with GHD have lower 1,25(OH)2-D3 or 25OH D3 levels [18]. Witkowska-Sędek et al. (18) examined GHD children, focused on the link between IGF-1 expressed in the SDS and 25(OH)D prior to the start of rhGH treatment and adjusted for bone age. There were 87–89% GHD individuals in this instance with 25(OH)D values at baseline < 30 ng/mL. The results showed a direct association between IGF-1 at baseline and 25(OH)D levels, with a prevalence among the GHD patients subgroup with 25(OH)D < 20 ng/mL.

Role of Vitamin D in GHD and effect of GH therapy on vitamin D

Vitamin D should be tested in children with GHD at diagnosis and during follow-up, as some studies have shown that hypovitaminosis D is common in these patients and may improve dramatically a year or more following GH medication. In addition to GH medication, children with GHD may benefit from vitamin D supplements, as shown by the relatively high prevalence of low 25(OH)D levels that persist after a year of GH treatment (19).

Wójcik and colleagues in 2018 examined GHD patients who were given rhGH. Keeping IGF-1 within the reference range and documenting any growth improvement during follow-up appointments permitted for the proper modulation of the rhGH dosage. it was possible to extrapolate an intriguing fact: even though all the participants had received rhGH treatment and 500–2000 IU of vitamin D3 per day, the majority of vitamin D deficiency affecting these patients (58%) who were mostly from metropolitan regions. Furthermore, this result was unaffected by the duration of the vitamin D administration (20).

In spite of certain investigations have demonstrated that GH treatment does not alter the organic content of vitamin D or its seasonal changes, at least not during the first few years of therapy. Nevertheless, a lack of vitamin D can influence how the body reacts to growth hormone therapy because vitamin D may reinforce the effects of GH therapy. Additionally, vitamin D status may have an impact on how much growth occurs during the first few years of GH treatment because patients with vitamin D deficiency grow at a significantly slower rate than those with vitamin D sufficiency, which is over 20 ng/ml (17).

Although in 2017 Witkowska-Sędek et al. additionally validated the potential contribution of vitamin D metabolites to the development processes. Because rhGH therapy stimulates IGF-1 secretion, it can raise bone turnover indices in

individuals with GHD who have low bone turnover. He suggested that there is association between two indicators of bone turnover, total alkaline phosphatase (ALP) and alkaline bone phosphatase (BALP), the levels of 25(OH)D, and the GH/IGF-1 axis in patients with GHD. The investigators reported hypovitaminosis in this group that was confirmed. The patients' improvement may have been attributed to receiving both a replacement treatment with rhGH and vitamin D supplementation. However. A reliable measure of bone turnover is BALP, which typically decreases in GHD patients and rises in response to rhGH treatment. The GH/IGF-1 axis has a significant influence on this parameter. Thus, the finding that vitamin D supplementation and this value were correlated in GHD patients receiving rhGH therapy validated the theory that vitamin D would enhance the effects of rhGH therapy (21).

The same authors study ICTP, a biochemical measure of bone resorption, as a potential predictor of the growth response in kids with GHD to rhGH therapy. Despite the fact that baseline serum 25(OH)D concentrations were not substantially low, every individual in the replacement therapy took a supplement containing 1000 IU of cholecalciferol every day. Therefore, the increase in growth rate observed in the first year of rGH therapy could have resulted from the action of GH by itself or in combination with vitamin D administration. The concentrations during the substitute treatment of ICTP and 25(OH)D values rose. The concentrations of 25(OH)D at 6 months from the start of therapy were connected with the ICTP values between 3 and 6 months of therapy, as well as a relationship between the serum 25(OH)D at baseline and the ICTP levels over the course of the first three months of treatment, as stated by the writers. This finding would make it clearer how important vitamin D is for bone turnover and how many patients with GHD undergoing rhGH must take it in order to support good growth (22).

Interesting data regarding vitamin D levels before and after substitutive treatment with rhGH in patients with GHD may be found in a study conducted by Ciresi and colleagues. They looked at the blood 25(OH)D levels at baseline and after 12 months of substitutive hormonal treatment in children with GHD separated into two groups in order to exclude vitamin D seasonal variability. Four out of five (75%) of the children with GHD in this study had low vitamin D levels (< 30 ng/mL), more frequently in the group that enrolled in the winter. Another interesting finding is the high frequency of normal 25(OH)D levels after a 12-month replacement therapy with rhGH. There was no association between the values in this experiment of 25(OH)D and IGF-1, Ca, P, and PTH. (23).

CONCLUSION

Patients with GH deficiency (GHD) typically have lower vitamin D levels than healthy children, and this condition may exacerbate the metabolic risk of GHD, which is already known.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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REFERENCES

1. Hauffa B, Touraine P, Urquhart-Kelly T, Koledova E. Managing transition in patients treated with growth hormone. Front. Endocrinol., 2017; 8, 346.
2. Ranke MB, Wit JM. Growth hormone —past, present and future. Nat. Rev. Endocrinol, 2018; 14(5), 285-300.
3. Li J, Zhang X, Xie S, Feng S, Niu M. Analysis of the Influence of High-Dose rhGH Therapy on Serum Vitamin D and IGF-1 Levels in School-Age Children with Idiopathic Short Stature. Evidence-Based CAM, 2021.
4. Rajput R, Rani M, Rajput M, Garg R. Etiological profile of short stature in children and adolescents. Indian J Endocrinol Metab, 2021; 25(3), 247.
5. Hage C, Gan W, Ibba A, Patti G, Dattani M, Loche S, et al. Advances in differential diagnosis and management of growth hormone deficiency in children. *Nat. Rev. Endocrinol, 2021; 17*(10), 608-624.
6. Rizzoli R. Vitamin D supplementation: upper limit for safety revisited? Aging Clin. Exp. Res., 2021; 33(1), 19-24.
7. Alia E, Kerr PE. Vitamin D: Skin, sunshine, and beyond. Clin. Dermatol., 2021; 39(5), 840-846.
8. Nouri Saeidlou S, Vahabzadeh D, Babaei F, Vahabzadeh Z. Seasonal variations of vitamin D and its relation to lipid profile in Iranian children and adults. *J Health Popul Nutr*, 2017; *36*(1), 1-7.
9. Luxwolda MF, Kuipers RS, Kema IP, Van der Veer E, Dijck-Brouwer DJ, Muskiet FA. Vitamin D status indicators in indigenous

populations in East Africa. *Eur. J. Nutr.*, 2013; *52*, 1115-1125.

10. Meng F, Bertucci C, Gao Y, Li J, Luu S, LeBoff MS, et al. Fibroblast growth factor 23 counters vitamin D metabolism and action in human mesenchymal stem cells. *J. Steroid Biochem. Mol. Biol.*, 2020; *199*, 105587.

11. Soliman AT, Al Khalaf F, AlHemaidi N, Al Ali M, Al Zyoud M, Yakoot K. Linear growth in relation to the circulating concentrations of insulin-like growth factor I, parathyroid hormone, and 25-hydroxy vitamin D in children with nutritional rickets before and after treatment: endocrine adaptation to vitamin D deficiency. *Metab.*, 2008; *57*(1), 95-102.

12. Ameri P, Canepa M, Fabbi P, Leoncini G, Milaneschi Y, Mussap M, et al. Vitamin D modulates the association of circulating insulin-like growth factor-1 with carotid artery intima-media thickness. *Atherosclerosis*, 2014; *236*(2), 418-425.

13. Ameri P, Giusti A, Boschetti M, Bovio M, Teti C, Leoncini G, et al. Vitamin D increases circulating IGF1 in adults: potential implication for the treatment of GH deficiency. Eur. J. Endocrinol., 2013a; 169(6), 767-772.

14. Esposito S, Leonardi A, Lanciotti L, Cofini M, Muzi G, Penta L. Vitamin D and growth hormone in children: a review of the current scientific knowledge. J. Transl. Med., 2019; 17, 1-18.

15. Ameri P, Giusti A, Boschetti M, Murialdo G, Minuto F, Ferone D. Interactions between vitamin D and IGF-I: from physiology to clinical practice. Clin Endocrinol. 2013b;79(4):457–63.

16. Fernández-Cancio M, Audi L, Carrascosa A, Toran N, Andaluz P, Esteban C, et al. Vitamin D and growth hormone regulate growth hormone/insulin-like growth factor (GH–IGF) axis gene expression in human fetal epiphyseal chondrocytes. Growth Horm IGF Res. 2009; 19(3), 232-237.

17. Durá-Travé T, Gallinas-Victoriano F, Moreno-González P, Urretavizcaya-Martinez M, Berrade-Zubiri S, Chueca-Guindulain MJ. Vitamin D status and response to growth hormone treatment in prepubertal children with growth hormone deficiency. J. Endocrinol. Invest., 2020; 43, 1485-1492.

18. Witkowska-Sędek E, Kucharska A, Rumińska M, Pyrżak B. Relationship between 25 (OH) D and IGF-I in children and adolescents with growth hormone deficiency. J Child Health Care., 2016; 43-49.

19. Hamza RT, Hamed AI, Sallam MT. Vitamin D status in prepubertal children with isolated idiopathic growth hormone deficiency: effect of growth hormone therapy. J Investig Med. 2018; 66:1–8.

20. Wójcik D, Krzewska A, Szalewski L, Pietryka-Michalowska E, Szalewska M, Krzewski S, et al. Dental caries and vitamin D3 in children with growth hormone deficiency. Medicine. 2018;97(8): e9811.

21. Witkowska-Sędek E, Stelmaszczyk-Emmel A, Majcher A, Demkow U, Pyrżak B. The relationship between alkaline phosphatase and bone alkaline phosphatase activity and the growth hormone/insulin-like growth factor-1 axis and vitamin D status in children with growth hormone deficiency. Acta Biochim Pol. 2018.

22. Witkowska-Sędek E, Stelmaszczyk-Emmel A, Kucharska A, Demkow U, Pyrżak B. Association between vitamin D and carboxy-terminal cross-linked telopeptide of type i collagen in children during growth hormone replacement therapy. Adv Exp Med Biol. 2018; 1047:53–60.

23. Ciresi A, Cicciò F, Giordano C. High prevalence of hypovitaminosis D in Sicilian children affected by growth hormone deficiency and its improvement after 12 months of replacement treatment. J Endocrinol Invest. 2014;37(7):631–8.

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