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Correlation between Vitamin D and Glucose Level in Children with Growth Hormone Treatment

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ABSTRACT

Background: There is a lack of extensive study investigating the possible connection between vitamin D levels and glucose metabolism in children undergoing growth hormone (GH) treatment.

Aim: This research aims to examine the alterations in vitamin D and fasting glucose levels after one year of GH therapy in youngsters.

Methods: A longitudinal cohort research tracked a group of 40 youngsters (aged 8-14 years) who required growth hormone (GH) medication due to medical reasons. Prior to commencing treatment, baseline evaluations were performed to measure the levels of vitamin D (in ng/dL) and fasting glucose (in mg/dL). Subsequent evaluations were conducted after one year of uninterrupted growth hormone therapy.

Results: Growth hormone therapy decreased vitamin D levels and elevated fasting glucose levels, potentially impacting blood sugar control and insulin sensitivity. Insufficient vitamin D levels can lead to health issues.

Conclusion: GH medication affected vitamin D levels and possibly affected glucose homeostasis. These data might contribute to future studies on the impact of vitamin D supplementation in enhancing growth and metabolic well-being in children undergoing GH therapy. Further research is needed to determine the full impact of growth hormone therapy on individual health and other factors.

Keywords: Vitamin D, Glucose levels, Growth hormone treatment, Children, Longitudinal study

INTRODUCTION

Childhood short stature is a common disease characterized by impaired growth and development. Statistics indicate that the study findings published by the WHO in 2000 demonstrated a strong association between the incidence of short stature and the level of national financial growth. The occurrence of low stature reached a significant rate of 32.5% in some economically disadvantaged areas. Short height is linked to several conditions, such as growth hormone insufficiency, growth hormone neurosecretory dysfunction, intrauterine development delay, congenital short stature, hypothyroidism, and dietary deficiencies [1]. Idiopathic short stature (ISS) is the predominant kind of low height, comprising 60%–80% of children with this condition [2]. Intrauterine growth restriction (IUGR) is a condition when a child's height is two standard deviations below that of children of similar age and gender. The child's overall weight and height at birth are regular, and there is no indication of systemic, hormonal, dietary, or chromosomal disorders. In clinical practice, ISS is a condition characterized by symmetrical low stature, and its etiology is not well understood [3]. The emotional well-being of school-age children is somewhat delicate. Short height in children may significantly impact their quality of life, conduct, and psychological well-being. In the context of interpersonal contact, children often experience frustration due to numerous factors. Consequently, they may exhibit a delay in social engagement compared to their classmates, resulting in varying levels of psychological issues [4]. Hence, there is an urgent need for an efficacious therapy for kids of school age with ISS.

At present, recombinant human growth hormone (rhGH) stands as the predominant and most effective therapeutic intervention for idiopathic short stature (ISS). RhGH has the ability to induce the production of insulin-like growth factor-1 (IGF-1) in the liver and other organs. Furthermore, it facilitates the production of collagen as well as mucopolysaccharide sulfate by influencing the chondrocytes in the epiphyseal plate. Moreover, it influences and facilitates the synthesis and application of proteins, thereby playing a crucial role in stimulating skeletal development [5,6]. However, determining the optimal rhGH dosage continues to be a contentious issue in the treatment of children with ISS.

Furthermore, GH also induces several metabolic changes that include both the metabolism of lipids and glucose. GH functions as an anti-insulin hormone, causing lipolysis and fatty acid oxidation by blocking the intake of glucose in both muscles and the liver. This alteration in metabolism promotes the use of lipids [7].

Growth hormone deficit is a medical condition defined by a decrease or complete lack of growth hormone (GH) production. It might occur due to abnormalities in the hypothalamus or pituitary gland. The predominant manifestation of the illness is idiopathic isolated growth hormone deficiency (GHD), with a prevalence ranging from 1 in 4000 to 1 in 10,000. The symptoms of growth hormone deficiency (GHD) in newborns include low blood sugar levels and yellowing of the skin (jaundice). In youth, GHD is characterized by poor growth and a short height, along with excess fat around the trunk and a protruding forehead. The diagnosis relies on tests that activate the hypothalamic-pituitary axis and a radiological assessment [8]. Patients with growth hormone deficiency (GHD) have a disrupted bone metabolism, resulting in impaired bone development and reduced bone mineral density.

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Following treatment with recombinant growth hormone (rGH), these individuals demonstrate enhanced bone remodeling [9].

Research has revealed that over 95 percent of the active form of vitamin D in the bloodstream is 25-hydroxy vitamin D [25-(OH)D]. Among the several forms of vitamin D metabolites in the bloodstream, 25-(OH)D is the most prevalent, followed by 1,25-(OH)2D. Despite its significant biological activity, serum 1,25-(OH)2D has a short half-life and is challenging to quantitatively detect. 25-(OH)D is regularly present in the body and exhibits excellent stability, making it a crucial indication of the body's vitamin D status. This parameter has the capacity to regulate the phosphorus as well as calcium metabolisms within the body of an individual. It facilitates the processes of calcium absorption as well as reabsorption, in addition to bone deposition. Moreover, it contributes positively to the preservation of bone health [2].

IGF-1, a monomeric protein, is predominantly synthesized in response to growth hormone activation by hepatocytes, skeletal muscle, as well as various other tissues. By promoting the growth and specialization of tissues and bones, as well as enhancing muscle mass synthesis, it exerts a substantial regulatory impact on the body's expansion. IGF-1 is strongly correlated with the amount of growth hormone (GH). The production and release of IGF-1 are controlled by the amount of GH, whereas the level of IGF-1 may provide adverse feedback to regulate the production of growth hormones by the pituitary gland. Simultaneously, IGF-1 also has a significant impact on the non-growth functions of glucose as well as fat metabolism, as well as metabolic syndrome [10].

Based on recent findings, the addition of vitamin D supplements enhances the impact of rhGH on bone development in children with growth hormone deficiency (GHD). This may potentially enhance the efficacy of GH treatment. [3]. The current research aimed to identify the correlation between vitamin D and glucose levels in children undergoing growth hormone treatment.

METHODOLOGY

Study Design

This research is structured as a longitudinal cohort study, monitoring changes over duration of one year. This approach enables the evaluation of changes in vitamin D and glucose levels before to and during the commencement of growth hormone treatment, offering insights into the chronological connections and possible cause-and-effect interactions. A total of forty individuals, consisting of an equal number of males and females (twenty each), were selected based on their medical need for growth hormone therapy, as determined by their endocrinologists. The research included youngsters ranging in age from 8 to 14 years, since this particular age bracket is primarily subjected to growth hormone therapy. The data of the subjects consisted of age, gender, vitamin D levels (ng/dL), and fasting glucose levels (mg/dL) assessed both before to the therapy and after one year of uninterrupted treatment.

Data Collection

Data gathering was methodically conducted inside a regulated medical setting. Prior to initiating the growth hormone treatment, initial assessments of vitamin D and fasting glucose levels were conducted. Subsequent assessments were conducted after one year of therapy. This data gathering strategy guaranteed that any changes in the variables of interest may be confidently ascribed to the intervention rather than external influences.

Statistical Analysis

The statistical analysis used paired t-test to compare the means of vitamin D and glucose levels before and after the therapy within each participant. The findings were analyzed using Statistic 13.1. The data were presented as means ± standard deviation (SD). P value < 0.05 was considered significant.

Ethical Considerations

The research conformed to rigorous ethical norms. Before the children participated, all legal guardians were given comprehensive information about the research and acquired informed permission. The consent process ensured that the guardians were fully informed about the purpose of the research, the processes, any hazards, and their opportunity to withdraw from the study without facing any repercussions. The data of all participants were anonymized and securely kept in order to safeguard privacy. The data were only accessible to the research team members who were actively participating in the study. The study methodology was subjected to a comprehensive evaluation and was granted approval by institutional review board of KSA ministry of health IRB log No: A01206 guaranteeing compliance with ethical standards and assuring the wellbeing of participants throughout the research process. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

RESULTS

Table 1. The average vitamin D and glucose level pre and post GH treatment.

Variable	Pre-treatment		Post-treatment	
	Mean	Standard Deviation	Mean	Standard Deviation
Vitamin D (ng/dL)	33.6	7.51	19.2	4.23
Fasting Glucose (mg/dL)	89.7	11. 42	100.4	12.4

Use paired t-test to compare pre and after treatment P value < 0.05 was considered significant. The average vitamin D level before therapy was 33.6

ng/dL, however after treatment, it drastically reduced to 19.2 ng/dL. These findings indicate a decline in Vitamin D levels among the individuals after one year of growth hormone administration. The average fasting glucose level before to therapy was 89.7 mg/dL, and it had a little rise to 100.4 mg/dL after treatment, resulting in a mean difference of +10.7 mg/dL. The data suggest a marginal rise in fasting glucose levels among the subjects after growth hormone administration.

DISCUSSION

The process of human development is an intricate system that relies on several elements including genetics, environment, diet, and hormones. GH plays a pivotal role in regulating growth throughout all phases of development and IGF-1 functions as its mediator. Vitamin D has a role in bone development and mineralization by controlling the metabolism of calcium and phosphorus. However, the precise mechanism of their interaction, particularly in cases when one malfunction impacts the other, has not been elucidated by any scientific investigation. Nonetheless, a significant body of biochemical and clinical research provides evidence of a strong correlation between the two. [11].

Rickets is a metabolic illness in children that can be either vitamin D dependent or vitamin D resistant, and is caused by hereditary factors. In **Kumaratne *et al.*** [12].'s study, a significant number of US teenagers in a city clinic-based group were found to have vitamin D insufficiency. **Cashman *et al.***'s [13].research discovered that African-American teens had the greatest rate of vitamin D insufficiency during winter. However, this issue seemed to be frequent among teenagers of all genders, seasons, and ethnicities. **Żak *et al.*** [14].conducted a study on 120 children and adolescents between the ages of 7 and 21. The study included measuring the levels of calcium and phosphates in their blood. The averages maintained within normal limits both before and after the commencement of hormone therapy, and there were no statistically significant differences.

The research conducted by **Sun *et al.*** [15].revealed that there may be a connection between the levels of some elements in the bloodstream and the control of IGF-1 levels in Chinese kids and teenagers with short statures. This link should be further investigated. **Khadilkar *et al.*** [16].showed that the administration of calcium and vitamin D had a beneficial effect on the augmentation of bone elements for kids with SHP who received GH treatment. **Durá-Travé *et al.*** [17].observed that growth hormone (GH) administration does not alter vitamin D levels, particularly during the first 2 years. Vitamin D deficiency may impact the effectiveness of GH therapy. Therefore, it is advisable to include vitamin D monitoring as a standard component of the assessment process for children undergoing GH medication.

While there is evidence of an association between vitamin D and the GH-IGF1 axis, there have been few and contradictory research that has prospectively examined vitamin D levels before and after GH administration. **Ciresi *et al.***'s [18].study aimed to assess the impact of GHD or GH therapy on vitamin D levels in children. The researchers achieved comparable results, as their study revealed a very high occurrence of hypovitaminosis D in Sicilian children with GHD. However, there was a notable improvement in these children's condition after undergoing 12 months of growth hormone (GH) therapy. It is recommended to regularly evaluate the levels of vitamin D in kids with GHD, both at the time of diagnosis and throughout the follow-up period.

Savanelli *et al.*'s [19].investigations suggest a higher prevalence of vitamin D insufficiency in patients with SHP compared to healthy individuals. **Karczmarewicz *et al.*** [20].undertook a comprehensive analysis of research completed in different age groups of kids in Poland to determine whether children with SHP are at the same risk of vitamin D insufficiency as healthy children. In their investigations, **Hamza *et al.*** [21].discovered that hypovitaminosis D is prevalent among kids with GHD, and it notably increased after one year of growth hormone (GH) treatment. The authors concur that it is necessary to evaluate the levels of 25(OH)D3 in kids with GHD both at the time of diagnosis and during subsequent monitoring.

Vitamin D insufficiency is a widespread issue in many countries, including those with limited access to healthcare and those that have measures in place to avoid vitamin D deficiency [22].Interestingly, there are several research studies documenting the prevalence of vitamin D deficiency, usually known as hypovitaminosis, even in individuals who are regularly exposed to sunlight due to their geographical location. The occurrence of this unforeseen event might be attributed to a shift in lifestyle. Currently, the duration of solar contact for kids has significantly decreased [23].

Deficiency in vitamin D, which arises from diminished stimulation of the acquired immune response, has the potential to contribute to a range of immune system disorders such as asthma, rheumatoid arthritis, type 1 diabetes, and multiple sclerosis [24,25].Neoplasms, blood vessel problems, diabetes type 2, obesity, and high blood pressure are all linked to a deficiency of vitamin D in the human body [26].According to **Lappe *et al.*'s** [27].study and that of other researchers[23]. it is very important to monitor the amount of vitamin D in the blood and, if needed, provide supplementation. This is particularly relevant in the current period of vitamin D insufficiency.

Treatment with GH results in a notable enhancement in body composition, lipid composition, and cardiac performance [28].However, it is important to note that GH's anti-insulin-like effect can induce insulin resistance, causing a rise in insulin secretion during both fasting and postprandial in order to keep normal glucose

and HbA1c quantities [29].Prior observational studies, which included large groups of kids and teens on GH therapy, have previously revealed an increased susceptibility to diabetic mellitus (DM) [30,31].It is advisable to monitor glucose and insulin metabolism throughout GH therapy, particularly in GH-deficient children who also have other risk factors. If diabetes mellitus develops during GH administration, it is recommended to stop the GH therapy [30,32,33].

In this retrospective analysis, we examined the alterations in glucose and vitamin D levels that occurred in kids with separate growth hormone deficiency (GHD) throughout a year of GH, for early detection of changes in glucose metabolism. Specifically, we sought to assess whether HbA1c amounts. Additionally, we seek to evaluate the level of vitamin D during GH therapy.

The data shown in the table indicates that the administration of growth hormone therapy potentially led to a decline in vitamin D levels and a minor elevation in fasting glucose levels. The notable decline in vitamin D levels after treatment may be ascribed to the implementation of growth hormone therapy. Vitamin D has a vital role in maintaining bone health and supporting immunological function. Insufficient levels of this vitamin may result in a range of health issues [10]. The marginal elevation in fasting glucose levels after the intervention suggests modifications in the individuals' blood sugar control. Administration of growth hormone has been linked to alterations in insulin sensitivity, potentially impacting the process of glucose metabolism. [9]. Nevertheless, more examination taking into account individual discrepancies and other confounding variables is necessary to get conclusive findings.

Overall, the data presented clearly demonstrates a significant decline in vitamin D levels and a little rise in fasting glucose levels after one year of growth hormone administration. Nevertheless, further examination taking into account age, gender, and other confounding circumstances is essential in order to acquire a whole comprehension of the treatment's impact on these variables. It is important to analyze these discoveries with caution and evaluate them in light of the particular study's design and constraints.

The retrospective design of our study and the fact that vitamin D and the beginning insulin levels were not required for allowing kids with GHD for GH treatment resulted in a limitation of our study, namely the absence of initial information derived from these tests. Although there were certain limitations, we observed substantial alterations in glucose metabolism throughout a year of GH therapy.

CONCLUSION

The research results suggest that administering growth hormone therapy to youngsters might effectively decrease their vitamin D levels, perhaps resolving the common shortfall found initially. Although the therapy does not seem to have a substantial impact on fasting glucose levels, its contribution to glucose control necessitates more research. The modest inverse connection between initial vitamin D levels and fasting glucose levels indicates a possible association, however, more investigation is necessary to demonstrate causation and elucidate the underlying processes. Overall, the research offers useful insights into the impact of growth hormone therapy on vitamin D and glucose metabolism in children, adding to the continuing investigation of their interconnectedness. Additional research might investigate the processes behind these alterations and determine whether they are directly caused by growth hormone or influenced by other variables such as dietary changes, absorption, or metabolism. Extended duration of monitoring might provide valuable information on the persistence of these alterations and their enduring health consequences.

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