Assement of Sclerostin and Some Biochemical Parameters in Growth hormone deficiency children

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Abstract

A healthy skeleton depends on the preservation and continuing renewal of bone tissue. Bone resorption and bone production are carefully balanced during the highly controlled process of bone remodeling. Sclerostin and other Wnt pathway inhibitors play critical roles in regulating bone formation and resorption since the Wnt signaling pathway is one of the most essential routes regulating bone metabolism. Researchs examining the role of sclerostin in children with growth hormone deficiency is scarce. The aim of this study is to find out the relationship between sclerostin and its role as an important bone marker with growth in toddlers with a deficit of growth hormone. In the study 120 children participated, including sixty patients and sixty controls. Sclerostin showed a significant decrease in the patients. Therefore, this study was conducted to provide a better knowledge of the factors that affect kids who lack growth hormone.

Keywords:GH, Sclerostin, Insulin, Vitamine D, Urea.

Introduction

Mesenchymal stem cells differentiate more favorably into osteoblasts when the Wnt pathway is activated, but chondrogenic and adipogenic differentiation is constrained. Additionally, it promotes the maturation of osteoblasts, boosts osteocyte survival, and prevents the formation of osteoclasts (Mach et al.,2019). Sclerostin functions as a hormone in addition to its function in bone and interacts with adipose tissue (Toro et al.,2021). Growth hormone (GH) is essential for organ development, cardiovascular health, cognition, metabolism, and bone formation in addition to supporting growth, the maintenance of a healthy body composition, and endocrine system health in general (Thornton et al.,2021). There are two key endocrine hormones that regulate metabolism, body composition, peak bone mass, and bone mineral density: growth hormone (GH) and insulin-like growth factor-1

(IGF-1). GH affects tissues, including bone, in a way that is both IGF-1-dependent and independent. (Liu et al.,2019). Elevated D3 influences osteoblast and osteoclast activity as well as calcium transport throughout the intestines, bones, and kidneys. Children or newborns may have rickets from a severe vitamin D shortage, and adults may develop osteomalacia, which is related to osteoporosis and an increased risk of fractures (Chang, 2019). For a number of reasons, vitamin D and calcium may affect the levels of sclerostin in the blood. Sclerostin is virtually entirely generated by osteocytes, which also express 1,25 dihydroxyvitamin D3 receptors Bone has a large number of osteoclasts, which can regulate bone production by modifying the Wnt signaling pathway (Cidem et al.,2015). Vitamin D and calcium are crucial for maintaining human bone health. (Abdullah et al.,2021, Alkabi et al.,2022). TNF-a is essential for the development of inflammatory osteoclasts and has an impact on the cells that produce osteoclasts, includes RANKL-expressing T cells, stromal cells, and macrophages that are capable of producing osteoclasts Additionally, TNF- increases the expression of sclerostin (Beak et al.,2014). Additionally, osteoclastogenesis during orthodontic tooth movement depends on tumor necrosis factor- (TNF-) (Ohori et al.,2019). TNF- directly increases RANKL expression in osteocytes and causes the development of osteoclasts (Marahleh et al.,2019). Additionally, GH causes temporary resistance to insulin's effects, which raises the level of insulin in the blood. Following GH injection, insulin synthesis is enhanced to counteract the rise in blood glucose levels. IGF-1 mimics the effects of insulin in the liver and skeletal muscles (Kim and Park, 2017). Sclerostin may be related to insulin and impact children's and adolescents' glucose consumption (Wedrychowicz et al.,2019). Urea and creatinine are crucial for assessing renal function. It has been noted that GH and IGF-1 lower hepatic urea genesis capacity and urea cycle enzyme gene expression. IGF-1 circulation is connected to urea production capability. One of the most powerful anabolic substances is growth hormone, and because of its anabolic effects on muscles, it can alter the quantity of serum creatinine (Davani et al.,2019). Sclerostin was discovered to have a direct impact on the metabolism of bone minerals in CKD patients (Fayed et al.,2022). Sclerostin levels in serum rise with the advancement of renal disease, reaching values that are many times greater than those in the general population of healthy people (Boltenstal et al.,2019). The purpose of this study is to investigate the impact of sclerostin on bone in individuals with growth hormone deficit and some biochemical characteristics for Iraqi children with growth hormone deficiency.

Materials and Methods:

Patients and control

This study was conducted in the Department of Pediatrics at the National Diabetes Center for patients enrolled in the Department of Pediatrics/National Diabetes Center whose parents consented to their participation in the study.. The study included (120) children between the ages of (4-12), of whom sixty suffer from growth hormone deficiency (37 males and 23 females) The diagnosis of GHD has been confirmed according to the person's medical history, physical and clinical examination as well as biochemical tests of the GH-IGF-1 axis and radiological evaluation of bone age estimated by x-ray of the left wrist and sixty healthy people were used as the control group. (36 male and 24 female).They had no history of/ or clinical features of short stature, no apparent abnormalities, and none of them had acute or chronic diseases.

Methods:

From each individual, Using disposable syringes, blood was extracted from a vein puncture and collected in a gel tube in the

amount of (5 2 ml). After an overnight fast, blood samples were taken between 8:00 and 11:00 in the morning. The blood sample was centrifuged at 1400 g for 10 minutes after collection. The finished serum was kept at -20 °C until analysis. The test for clonidine stimulation was determined between (8:00-11:00 am). Basal samples were obtained before the clonidine stimulation test and then clonidine administration orally (0.15 mg⁄m²), and samples were tested to estimate growth hormone at (1 hour and 1.5 hours). IGF-1 and GH can be measured quantitatively using a one-step sandwich chemiluminescence immunoassay approach. sclerostin was based on sandwich enzyme-linked immune-sorbent assay technology. The TNF alpha Human in vitro ELISA (Enzyme-Linked Immunosorbent Assay) kit from Abcam is made for measuring TNF alpha in supernatants and buffered solutions quantitatively. Human Insulin ELISA Kit is a Sandwich (quantitative) ELISA for the measurement of Human Insulin in Human Cell culture supernatant, Serum, Plasma samples. A two-step competitive immunoassay serves as the foundation for the Mini VIDAS 25-OH Vitamin D Total Assay architecture.

1. When vitamin D-specific antibody is coupled with alkaline phosphatase (ALP), serum or plasma 25(OH)D is released from its protein carrier (DBP).

2. The vitamin D analog coated-solid phase receptor is then exposed to the unbound ALP-antibody. After washing the solid-phase, the substrate reagent is introduced to start the fluorescence reaction.

Calcium, phosphor, urea and creatinine they are measured with a spectrophotometer.

Statistical analysis:

SPSS statistical software, version 26, was used to analyze the data. Independent-Samples Between the patient and control groups, Student t tests were used, and the results were expressed as mean standard deviation (SD).

Results:

Table 1 summarizes all anthropometric information collected from patients and control. The results showed a non-significant difference ($p>0.05$) In the median patient weight values. Age and Body mass index . While height resultsa highly significant ($p <0.01$).

Table 1. Anthropometric data of both patients and the matched group .

Anthropometric measurements	Mean ± SD		p-value
	Patients N=60	Control N=60	
Age (year)	11.05±2.33	9.35±3.52	0.1 NS
Weight (kg)	29.58±13.77	30.35±8.66	0.750NS
Height (cm)	125.96±24.86	107.11±13.54	0.0001**
BMI (kg/m2)	20.45±12.77	27.69±11.74	.963 NS

* Significant at ($p<0.05$), **:highly Significant at ($p<0.01$), NS: Non Significant($p>0.05$)

The information in table 2 displays the concentrations of GH and IGF-1 in the research groups. There were three ways to measure GH: Basal GH its measure directly and The findings were highly significant decreased ($p <0.01$). The second measurements of GH after 1 hour: its measure directly and The findings were highly significant decreased ($p <0.01$).The third measurements of GH after 1.30 hour: its measure directly and The findings were highly

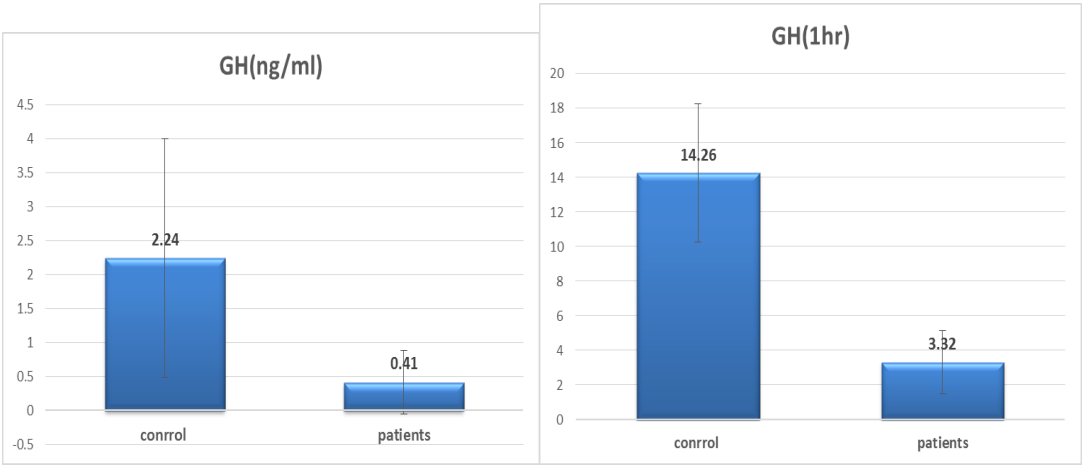
significant decreased (p <0.01). Regarding to IGF-1, the results revealed that there was significant decreased (P =**0.057**),), see figure 1.

Table 2. GH and IGF-1 values for the control group and patients.

Parameters	Mean ± SD		p-value
	Patients N=60	Control N=60	
Basal GH (ng/ml)	0.41±0.47	2.24±1.76	0.000 **
GH (ng/ml) after 1 hr.	3.32±1.18	1.77±1.20	0.000 **
GH (ng/ml) after 1.30hr.	14.26±4.00	7.11±3.31	0.000 **
IGF-1 (ng/ml)	131.02±71.22	235.40±65.77	0.057 *

* Significant at (p<0.05), **:highly Significant at (p<0.01), NS: Non Significant(p>0.05).

Figure 1: Diagram shows levels of GH and IGF-1 for patients and control groups.



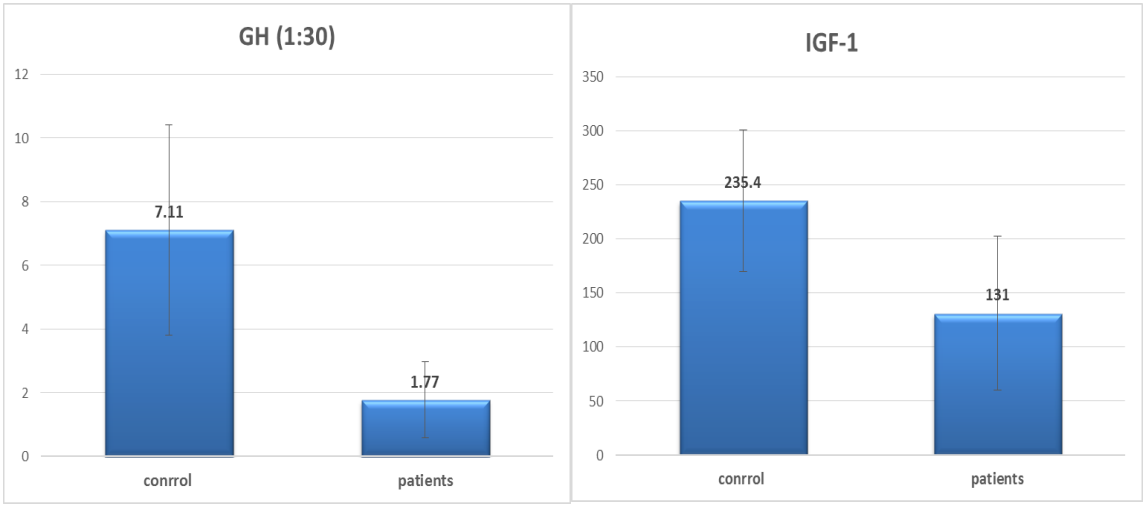


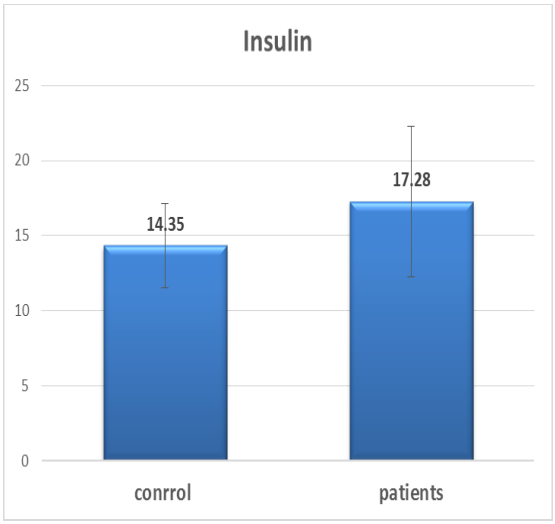
Table 3's data reveals insulin, TNF apha, vitamin D of GHD patients and control group , insulin shows highly significant increas ($p<0.01$). While TNF apha shows non-significant increas ($p> 0.05$). Vitamin D shows non-significant decreased ($p> 0.05$), see all data in figure 2.

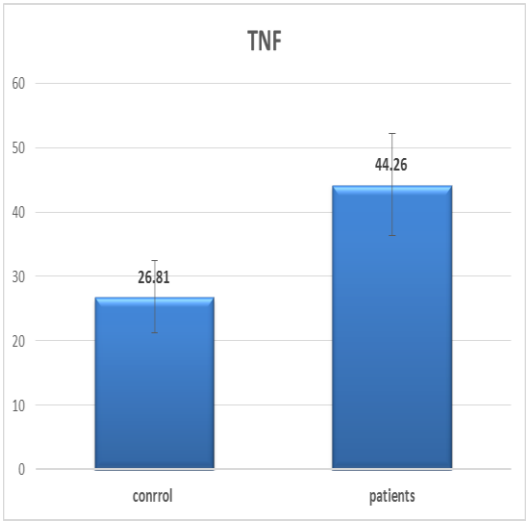
Table 3. levels of insulin, TNF apha, vitamin D for both patients and the control group

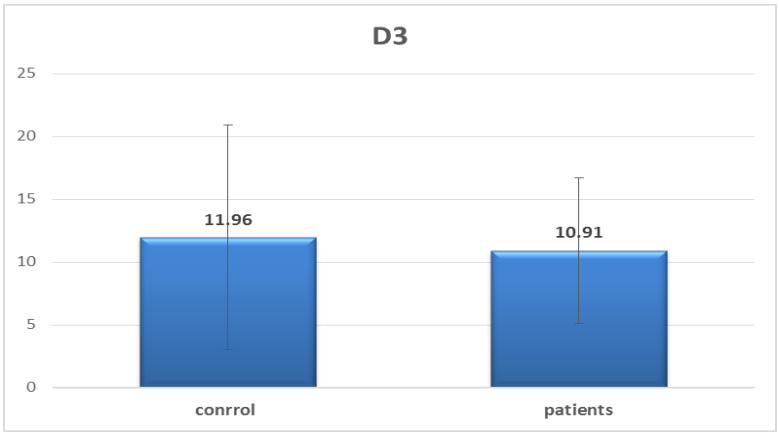
Parameters	**Mean ± SD**		**p-value**
	Patients N=60	**Control N=60**	
Insulin(µIU/mL)	17.28±5.02	14.35±2.79	**0.001****
TNF apha (pg/ml)	44.26±7.97	26.81±.64	**.466 NS**
Vitamin D (ng/dl)	10.91±5.80	11.96±8.94	**.282 NS**

* Significant at ($p<0.05$), **:highly Significant at ($p<0.01$), NS: Non Significant($p>0.05$).

Figure 2: Histogram shows Insulin,TNF-α and Vitamin D3 levels for patients and control groups.







In table 4 the results confirmed that there were non-significant increas ($p>0.05$) in urea, and also creatinin shows non-significant increas ($p>0.05$).

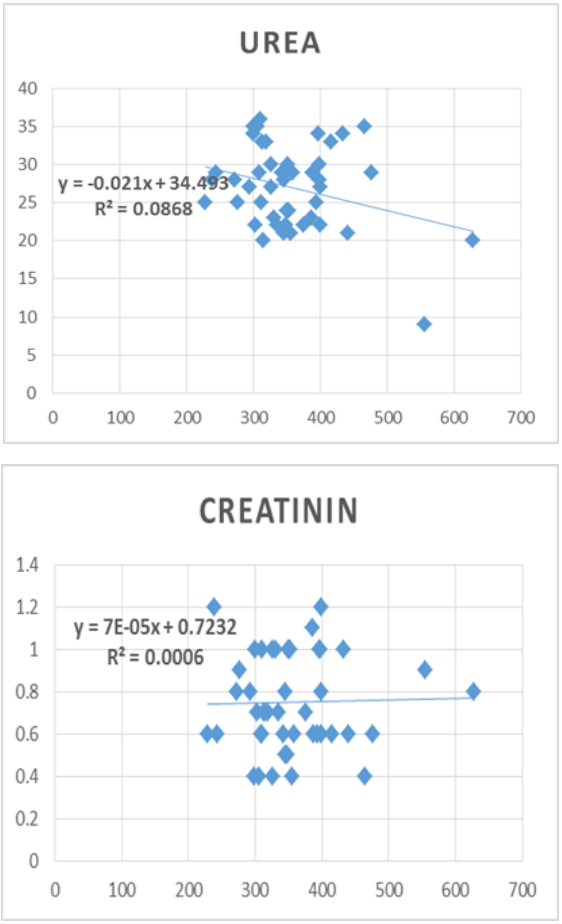
Table 4. Levels of urea and creatinin measured in GHD both patients and the control group

Parameters	Mean ± SD		p-value
	Patients N=60	Control N=60	
Urea(mg/dL)	27.00±5.44	25.60±4.36	.313
Creatinin(mg/dL)	0.74±0.22	0.73±0.21	.571

* Significant at (p<0.05), **:highly Significant at (p<0.01), NS: Non Significant(p>0.05).

A correlation study between sclerostin, urea and creatinin in children with growth hormone deficiency and control groups,a negative correlation was found between sclerostin and urea (-0.29,0.04) . A positive correlation was found between sclerostin and creatinin (0.02,0.87) see figure 3.

Figure 3: Correlation between sclerostin, urea and creatinin.



Levels of sclerostin, calcium, and phosphorous are shown in table 5's data. The findings indicate a significantly substantial decrease ($p<0.01$) in sclerostin. Calcium and phosphorous results show non-significant increas ($p>0.05$) .

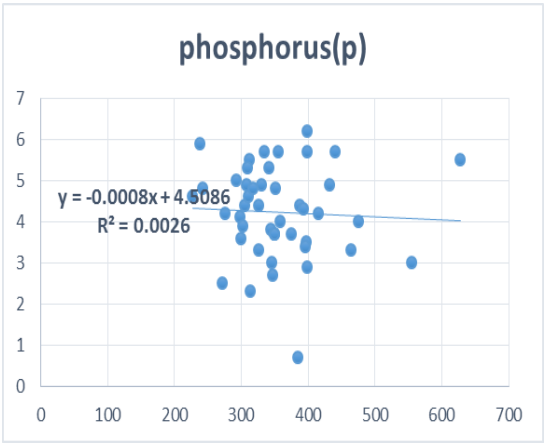
Table5. Levels of sclerostin, Calcium and phosphorous in GHD both patients and the control group .

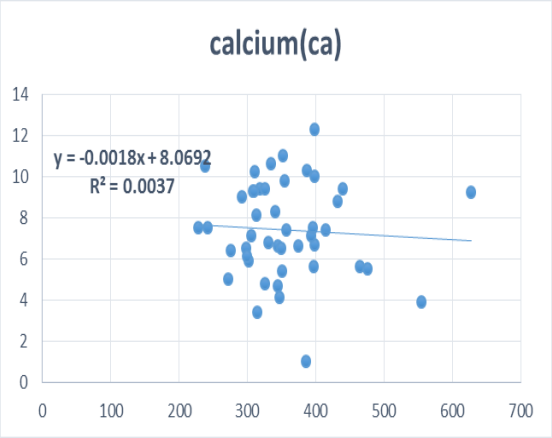
Parameters	Mean ± SD		p-value
	Patients N=60	Control N=60	
Sclerostin(pg/ml)	356.5±76.3	836.06±287.6	0.0001
Calcium(mg/dl)	7.41=±2.31	7.31±2.84	0.85
Phosphorous mmol/l)	4.24±1.11	4.05±1.51	0.5

* Significant at ($p<0.05$), **:highly Significant at ($p<0.01$), NS: Non Significant($p>0.05$).

A correlation study between sclerostin, calcium and phosphorous in children with growth hormone deficiency and control groups,a negative correlation was found between sclerostin, calcium and phosphorous (-0.06, 0.69), (-0.05, 0.73).

Figure 4: Correlation between sclerostin calcium and phosphorus.





Discussion:

To our knowledge, this is the first study to look at the serum concentrations of sclerostin for children with growth hormone deficiency in Iraq (and to some extent, the world, as we have not identified any prior studies finding sclerostin in GHD). Sclerostin it functions as a crucial bone homeostasis regulator by blocking the canonical Wnt-signaling pathway, and it contributes to the pathophysiology of numerous skeletal disorders. (Vasiliadis et al.,2022). Sclerostin early childhood, development Variations in sclerostin production during growth may be crucial in shaping cortical anatomy, according to the link between serum sclerostin levels and cortical porosity. Sclerostin levels rise with aging in adults, and men have higher levels than women. (Kimami et al.,2012). While sclerostin was studied in patients with acromegaly a study, active acromegaly patients had considerably greater serum sclerostin levels than healthy controls, and these levels corresponded with GH and IGF-1 levels (Uygur et al.,2021). İn another study patients with acromegaly had considerably lower levels of sclerostin than the control group in the study, which included patients with active acromegaly. (Halupczok et al.,2019). And in other research Serum sclerostin levels did not significantly differ between patients with active acromegaly. Increased bone remodeling has been linked to acromegaly, and this was validated by alterations in the indicators of bone turnover, calcium kinetics, and bone histomorphometry. (Giustina et al.,2008). Increasing osteoclastogenesis as a result of IGF-activation I's of RANK-L, a receptor activator of nuclear factor-B, is most likely the cause. (Mazziotti et al.,2019). In this study sclerostin showed highly significant decrease ($p < 0.01$) in patients with GHD in children, This study showed that the level of sclerostin in affected children differed from that of adults with acromegaly. Patients who lack sclerostin have larger bone mass and more bone growth (Kalr, 2019). In contrast, elevated sclerostin levels have a detrimental effect on bone, increasing its fragility. As a result, sclerostin antibodies are now used Serum to treat osteoporosis (Bandeira et al.,2017),(Bhattacharyya and Canalis, 2018). Serum sclerostin levels in healthy people are greater in men and rise for both sexes throughout adulthood. Higher serum sclerostin levels have been shown to increase the risk of fracture in some studies, but not in others, especially when they are combined with reduced bone mineral density (Clarke, 2013).

Regarding to the age, The current outcome matched that of the earlier investigation (Ciresi et al., 2007) which showed no statistically significant difference in the mean age between the GHD patients and the control group, a finding that could be explained by the similar age ranges of the subjects in the two groups. The weight's most recent results were

comparable to that of the study of (Lee et al., 2013; Ciresi et al., 2018) which revealed a non-significant difference in the weight between the patients and the control, while the current findings disagreed with (Ece et al., 2014), these inconsistencies can result from variations in the sample size, the nutritional state, and the way of life of the subjects. The results of the height were similar to the study done by (Bahrani et al., 2011), that reported a significant in the height in the patients compared to the control group, this finding might be explained by the fact that GHD, which drastically retards bone development, is the root cause of short stature (Correa et al., 2017). The present results of BMI were agreement with (Lee et al, 2013). They found no difference in the BMI between the patients and the control group that could be explained by the fact that the BMI was calculated using both weight and height (Kwon et al., 2017). Additionally, the majority of the patients in the current study were within the normal weight range. GH basl showed a significant in patients when compared to control the results presented are inagreement with a previous investigation by Thakur et al., that reported non-significant difference between basal GH levels in patients and control (Thakur et al.,2018), this might be caused by the growth hormone release, which is pulsated with diurnal fluctuation, under a negative feedback auto regulation loop, and may be influenced by a variety of circumstances. But in this study, when a difference between patients and healthy children is observed, it is regarded as proof that the disease has been correctly diagnosed, especially when the outcome occurs before clonidine provocation. Current results for levels of GH2 (after 1 hr.) and GH3 (after 1.5 hr.) correspond to the results reported in a previous study. Showed patients with GHD had significantly lower levels of IGF-1 in the blood compared to healthy controls, proving that IGF-1 was a trustworthy indicator of GH function and that it was influenced by a number of factors, such as age, gender, fasting status, and liver issues (Ciresi et al.,2014, 44. Al-gebori et al.,2020). GH and IGF-1 also enhance the skeleton by promoting the growth of healthy bone and decreasing bone breakdown. Vertebral fracture risk is increased by GH deficit (Pekkolay et al.,2020). Insulin had a significant increase in patients compared to healthy subjects, in contrast to previous research which showed that there was no significant difference between patients and healthy people, insulin effect on glucose homeostasis in patients with growth hormone deficiency (Stawerska and Tidblad, 2017). Increased ingestion of sweets and carbs causes the hormone insulin to be secreted more frequently, which causes fat to accumulate and the level of growth hormone to drop (Kim, 2017). Sclerostin is a bone-derived protein that interacts with insulin, and this interaction may be crucial in controlling children's and teenagers' glucose metabolism. The interaction between bone-derived sclerostin and glucose metabolism in young individuals seems to be unaffected by other bone- and fat-derived variables. Sclerostin's activity may result in reduced insulin resistance in young people with obesity. (Wedrychowicz et al., 2019). In this study,TNF-alpha are consistent with a previous study by Bozzola et al. Although there was no difference in the basal serum TNF-a levels of isolated GHD children and controls, researchers looked into the acute effect of rhGH on TNF-a. TNF-a levels significantly increased by 4 hours and decreased again for 24 hours after the first rhGH administration in isolated GHD children. A significant correlation was found between basal serum concentrations of GH and TNF-a (Bozzola et al., 1998). Baseline serum TNF-a concentrations in GHD were found not to differ significantly from controls (Dabrosin, 2020). Vitamin D shows non significant decrease in patiants when paralled to control. The high proportion of GHD patients who have hypovitaminosis D is the first important finding from the 13 research on the connection between vitamin D metabolism

and GHD in children. This condition is consistent with what adult investigations have shown to be important. For instance, Savanelli et al. found that 41 adult GHD patients had higher rates of vitamin D insufficiency than a control group. (Barrea et al., 2021). The findings, which were obtained in both adults and children, support the notion that the GH/IGF-1 axis and vitamin D function are inextricably linked, with the GH and consequent IGF-1 shortage that GHD sufferers experience playing a role in determining vitamin D deficiency (Esposito et al., 2019). As for urea and creatinine, it was observed that there was no significant difference for patients compared to healthy people, Regarding urea and creatinine levels, the current results are in line with a previous study's findings that showed no discernible changes in the levels of the waste products urea and creatinine between GHD patients and the healthy control group. (Ece et al., 2014). However, a prior study revealed that children with chronic renal insufficiency frequently have small stature (Huh et al., 2021). According to his study of(Graciolli FG et al. 2017) Sclerostin-positive osteocytes are more prevalent in CKD patients than in healthy individuals, which may be related to an increase in sclerostin production by osteocytes. Phosphorus, Low plasma levels of sclerostin are linked to proper phosphate alignment and vitamin D deficiency, although there was no noticeable difference between patients and healthy individuals (Pietrzyk et al., 2019). n a recent work, blood phosphate and sclerostin were assessed in patients with chronic kidney disease. We discovered a positive association between the two variables, suggesting that serum phosphate may be responsible for the early and significant elevation of sclerostin. due to the role sclerostin plays in decreased bone turnover (Pelletier et al., 2013). Calsium, it was noted that there was no discernible difference between patients and control, the results of this study do not match those of a previous study (vena et al 2013) Children with growth hormone deficiency (GHD) have been shown to have less bone mineral content. (Caputo et al., 2021). Vitamin D controls the metabolism of calcium and phosphorus, which contributes to the processes of bone formation and mineralization (Esposito et al., 2019). Calcium is the most vital mineral in the body and is responsible for the development and upkeep of the skeletal system, which is why calcium is the cause of bone strength, an osteoporosis that develops as a result of calcium shortage, causes physical and mental growth difficulties in children, and trouble moving are all symptoms of this illness (Raskh, 2020).

Conclusion:

In view of the results of the research this study concluded a complicated process including genetic, environmental, dietary, and hormonal components governs human growth.Growth hormone (GH) and its mediator, insulin-like growth factor 1 (IGF-1), are the primary hormones in engaged in growth at all stages of development (IGF-1).On the other hand, vitamin D controls the metabolism of calcium and phosphorus, which contributes to its role in the processes involved mineralization and bone formation. Knowing the strong connection between sclerostin and children with growth hormone deficit, as well as the critical role it plays in bone development and the connection between sclerostin and urea and the kidneys.

References

Compston, J.E.; McClung, M.R.; Leslie, W.D. Osteoporosis. Lancet 2019, 393, 364–376. [Google Scholar] [CrossRef] [PubMed]].

Delgado-Calle, J.; Sato, A.Y.; Bellido, T. Role and Mechanism of Action of Sclerostin in Bone. Bone 2017, 96, 29–37. [Google Scholar] [CrossRef]].

Carrillo-López, N.; Martínez-Arias, L.; Fernández-Villabrille, S.; Ruiz-Torres, M.P.; Dusso, A.; Cannata-Andía, J.B.;

Naves-Díaz, M.; Panizo, S. Role of the RANK/RANKL/OPG and Wnt/β-Catenin Systems in CKD Bone and Cardiovascular Disorders. Calcif. Tissue Int. 2021, 108, 439–451. [Google Scholar] [CrossRef] [PubMed]].

Mach, F.; Baigent, C.; Catapano, A.L.; Koskina, K.C.; Casula, M.; Badimon, L.; Chapman, M.J.; de Backer, G.G.; Delgado, V.; Ference, B.A.; et al. 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk. Atherosclerosis 2019, 290, 140–205. [Google Scholar] [CrossRef] [PubMed]

del Toro, R.; Cavallari, I.; Tramontana, F.; Park, K.; Strollo, R.; Valente, L.; de Pascalis, M.; Grigioni, F.; Pozzilli, P.; Buzzetti, R.; et al. Association of Bone Biomarkers with Advanced Atherosclerotic Disease in People with Overweight/Obesity. Endocrine 2021, 73, 339–346. [Google Scholar] [CrossRef] [PubMed]].

Thornton PS, Maniatis AK, Aghajanova E, Chertok E, Vlachopapadopoulou E, Lin Z, Song W, Christoffersen ED, Breinholt VM, Kovalenko T, Giorgadze E. Weekly Lonapegsomatropin in Treatment–Naïve Children With Growth Hormone Deficiency: The Phase 3 heiGHt Trial. The Journal of Clinical Endocrinology & Metabolism. 2021 Nov;106(11):3184-95.

Liu Z, Solesio ME, Schaffler MB, Frikha-Benayed D, Rosen CJ, Werner H, Kopchick JJ, Pavlov EV, Abramov AY, Yakar S. Mitochondrial Function Is Compromised in Cortical Bone Osteocytes of Long-Lived Growth Hormone Receptor Null Mice. Journal of bone and mineral research. 2019 Jan;34(1):106-22.

Chang SW, Lee HC. Vitamin D and health-The missing vitamin in humans. Pediatrics & Neonatology. 2019 Jun 1;60(3):237-44.

Cidem M, Karacan I, Arat NB, Zengi O, Ozkaya M, Guzel SP, Ozkan C, Beytemur O. Serum sclerostin is decreased following vitamin D treatment in young vitamin D-deficient female adults. Rheumatology international. 2015 Oct;35(10):1739-42.

Abdullah MA, Abdullah AH, Alfatlawi WR, Yahya CZ. A Comparative Study Of The Levels Osteoproteger In (OPG), Vitamin D, Parathyroid Hormone, And Estrogen Hormone Between Healthy Females And Breast Cancer Patients. NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO. 2021:62-76.

Alkabi HR, Alfatlawi WR, Aldabagh MA. Impact of Vitamin D Elements and Osteoporosis Factors in Postmenopausal Iraqi Women with T2DM. Journal of Applied Sciences and Nanotechnology. 2022;2(3).

Baek K., Hwang H.R., Park H.J., Kwon A., Qadir A.S., Ko S.H., Woo K.M., Ryoo H.M., Kim G.S., Baek J.H. TNF-alpha upregulates sclerostin expression in obese mice fed a high-fat diet. J. Cell Physiol. 2014;229:640–650. doi: 10.1002/jcp.24487. [PubMed] [CrossRef] [Google Scholar] [Ref list].

Ohori F., Kitaura H., Marahleh A., Kishikawa A., Ogawa S., Qi J., Shen W.R., Noguchi T., Nara Y., Mizoguchi I. Effect of TNF-alpha-Induced Sclerostin on Osteocytes during Orthodontic Tooth Movement. J. Immunol. Res. 2019;2019:9716758. doi: 10.1155/2019/9716758. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list]

Marahleh A., Kitaura H., Ohori F., Kishikawa A., Ogawa S., Shen W.R., Qi J., Noguchi T., Nara Y., Mizoguchi I. TNF-alpha Directly Enhances Osteocyte RANKL Expression and Promotes Osteoclast Formation. Front. Immunol. 2019;10:2925. doi:

10.3389/fimmu.2019.02925. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list].

Kim, S.-H. & Park, M.-J. Effects of growth hormone on glucose metabolism and insulin resistance in human. Ann. Pediatr. Endocrinol. Metab. 22, 145 (2017).

Wędrychowicz A, Sztefko K, Starzyk JB. Sclerostin and its association with insulin resistance in children and adolescents. Bone. 2019 Mar 1;120:232-8.

Davani-Davari, D., Karimzadeh, I. & Khalili, H. The potential effects of anabolic-androgenic steroids and growth hormone as commonly used sport supplements on the kidney: a systematic review. BMC Nephrol. 20, 198 (2019).

Fayed A, Abdulazim DO, Amin M, Elhadidy S, Samir HH, Salem MM, Abd ElAzim IM, El Hawary KE, El Din UA. Serum sclerostin in acute kidney injury patients. Nefrología (English Edition). 2022 Jan 1;42(1):50-5.

Boltenstål H, Qureshi AR, Behets GJ, Lindholm B, Stenvinkel P, D'Haese PC, Haarhaus M. Association of serum sclerostin with bone sclerostin in chronic kidney disease is lost in glucocorticoid treated patients. Calcified tissue international. 2019 Feb;104(2):214-23.

Vasiliadis ES, Evangelopoulos DS, Kaspiris A, Benetos IS, Vlachos C, Pneumaticos SG. The Role of Sclerostin in Bone Diseases. Journal of Clinical Medicine. 2022 Feb 2;11(3):806.

Kirmani S, Amin S, McCready LK, Atkinson EJ, Melton LJ, Müller R, Khosla S. Sclerostin levels during growth in children. Osteoporosis International. 2012 Mar;23(3):1123-30.

Modder UIL, Clowes JA, Hoey K, Peterson JM, McCready L, Oursler MJ, Riggs BL, Khosla S (2011) Regulation of circulating sclerostin levels by sex steroids in women and men. J Bone Miner Res 26:27–34.

Uygur MM, Buğdaycı O, Yavuz DG. Prevalence of vertebral fractures and serum sclerostin levels in acromegaly. Endocrine. 2021 Sep;73(3):667-73.

J. Halupczok-Żyła, A. Jawiarczyk-Przybyłowska, A. Zembska, M. Bolanowski (eds) Sclerostin and fracture risk assessment in acromegaly. 21st European Congress of Endocrinology (BioScientifica, 2019).

A. Giustina, G. Mazziotti, E. Canalis, Growth hormone, insulinlike growth factors, and the skeleton. Endocr. Rev. 29(5), 535–59 (2008).

G. Mazziotti, A.G.A. Lania, E. Canalis, Management of endocrine disease: bone disorders associated with acromegaly: mechanisms and treatment. Eur. J. Endocrinol. 181(2), R45–R56 (2019).

Klar RM . The induction of bone formation: the translation enigma. Front Bioeng Biotechnol.2018;6:74.. 12. Holdsworth G , Roberts SJ, Ke HZ. Novel actions of sclerostin on bone. J Mol Endocrinol.2019;62(2):R167–R185.

Bandeira L , Lewiecki EM, Bilezikian JP. Romosozumab for the treatment of osteoporosis. Expert Opin Biol Ther.2017;17(2):255–263.

Bhattacharyya S , Pal S, Chattopadhyay N. Targeted inhibition of sclerostin for post-menopausal osteoporosis therapy: a critical assessment of the mechanism of action. Eur J Pharmacol.2018;826:39–47.

Canalis E . Management of endocrine disease: novel anabolic treatments for osteoporosis. Eur J Endocrinol.2018;178(2):R33–R44.

Clarke BL, Drake MT. Clinical utility of serum sclerostin measurements. BoneKEy reports. 2013;2.

Pekkolay Z, Kılınç F, Gozel N, Önalan E, Tuzcu AK. Increased serum sclerostin levels in patients with active acromegaly. The Journal of Clinical Endocrinology & Metabolism. 2020 Mar 1;105(3):920-4.

Mazziotti, A.G.A. Lania, E. Canalis, Management of endocrine disease: bone disorders associated with acromegaly: mechanisms and treatment. Eur. J. Endocrinol. 181(2), R45–R56 (2019).

Ciresi A, Amato MC, Criscimanna A, Mattina A, Vetro C, Galluzzo A, D'Acquisto G, Giordano C. Metabolic parameters and adipokine profile during GH replacement therapy in children with GH deficiency. European journal of endocrinology. 2007 Mar 1;156(3):353-60.

Lee Y, Park J, Ryu C, Gang KS, Yang W, Park YK, Jung J, Hyun S. Comparison of biochar properties from biomass residues produced by slow pyrolysis at 500 C. Bioresource technology. 2013 Nov 1;148:196-201.

Ferraù F, Albani A, Ciresi A, Giordano C, Cannavò S. Diabetes secondary to acromegaly: physiopathology, clinical features and effects of treatment. Frontiers in endocrinology. 2018 Jul 6;9:358.

Yavuz S, Ece A. Mean platelet volume as an indicator of disease activity in juvenile SLE. Clinical rheumatology. 2014 May;33(5):637-41.

Joolaee S, Hajibabaee F, Peyrovi H, Haghani H, Bahrani N. The relationship between incidence and report of medication errors and working conditions. International nursing review. 2011 Mar;58(1):37-44.

Brand-Correa LI, Steinberger JK. A framework for decoupling human need satisfaction from energy use. Ecological Economics. 2017 Nov 1;141:43-52.

Lee Y, Park J, Ryu C, Gang KS, Yang W, Park YK, Jung J, Hyun S. Comparison of biochar properties from biomass residues produced by slow pyrolysis at 500 C. Bioresource technology. 2013 Nov 1;148:196-201.

Kwon T, Yoo SJ, Park CK, Lyoo YS. Prevalence of novel porcine circovirus 3 in Korean pig populations. Veterinary microbiology. 2017 Aug 1;207:178-80.

Thakur DS, Bhagwat NM, Bhide MM, Yerawar CG, Ghanekar GA, Sonawane AB, Chadha MD, Varthakavi PK. Clonidine stimulation test: Is single best time point, convenient yet efficacious. Indian J. Endocrinol. Metab. 2018 Jul;22(4):511.

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 Jul;37(7):631-8.

Al-gebori am, alosami mh, al-hashimi nh. prevalence of 25-hydroxy vitamin d deficiency and some biochemical parameters in iraqi patients with rheumatoid arthritis and their associations with disease activity. prevalence. 2020;13(4).

Stawerska, R., Smyczyńska, J., Hilczer, M. & Lewiński, A. Relationship between IGF-I concentration and metabolic profile in children with growth hormone deficiency: the influence of children's nutritional state as well as the ghrelin, leptin, adiponectin, and resistin serum concentrations. Int. J. Endocrinol. 2017, (2017).

Tidblad, A., Gustafsson, J., Marcus, C., Ritzén, M. & Ekström, K. Metabolic differences between short children with GH peak levels in the lower normal range and healthy children of normal height. Growth Horm. IGF Res. 34, 22–27 (2017).

Kim SH, Park MJ. Effects of growth hormone on glucose metabolism and insulin resistance in human. Annals of pediatric endocrinology & metabolism. 2017 Sep;22(3):145.

Wędrychowicz A, Sztefko K, Starzyk JB. Sclerostin and its association with insulin resistance in children and adolescents. Bone. 2019 Mar 1;120:232-8.

M. Bozzola, M. De Amici, M. Zecca, R.M. Schimpff, R. Rapaport, Modulating effect of human growth hormone on tumour necrosis factor-alpha and interleukin-1beta, Eur. J. Endocrinol. 138 (1998) 640–643.

Dabrosin N, Dabrosin C. Postmenopausal dense breasts maintain premenopausal levels of GH and insulin-like growth factor binding proteins in vivo. The Journal of Clinical Endocrinology & Metabolism. 2020 May 1;105(5):1617-28.

Barrea L, Muscogiuri G, Frias-Toral E, Laudisio D, Pugliese G, Castellucci B, Garcia-Velasquez E, Savastano S, Colao A. Nutrition and immune system: from the Mediterranean diet to dietary supplementary through the microbiota. Critical reviews in food science and nutrition. 2021 Oct 7;61(18):3066-90.

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. Journal of Translational Medicine. 2019 Dec;17(1):1-8.

Ece, A. et al. Kidney growth and renal functions under the growth hormone replacement therapy in children. Ren. Fail. 36, 508–513 (2014).

Huh K, Nah WH, Xu Y, Park MJ, Gye MC. Effects of recombinant human growth hormone on the onset of puberty, Leydig cell differentiation, spermatogenesis and hypothalamic KISS1 expression in immature male rats. The world journal of men's health. 2021 Apr;39(2):381.

Graciolli FG, Neves KR, Barreto F et al (2017) The complexity of chronic kidney disease-mineral and bone disorder across stages of chronic kidney disease. Kidney Int 91:1436–1446.

Pietrzyk B, Wyskida K, Ficek J, Kolonko A, Ficek R, Więcek A, Olszanecka-Glinianowicz M, Chudek J. Relationship between plasma levels of sclerostin, calcium–phosphate disturbances, established markers of bone turnover, and inflammation in haemodialysis patients. International Urology and Nephrology. 2019 Mar;51(3):519-26.

Pelletier S, Dubourg L, Carlier MC, Hadj-Aissa A, Fouque D. The relation between renal function and serum sclerostin in adult patients with CKD. Clinical Journal of the American Society of Nephrology. 2013 May 7;8(5):819-23.

Caputo M, Pigni S, Agosti E, Daffara T, Ferrero A, Filigheddu N, Prodam F. Regulation of GH and GH Signaling by Nutrients. Cells. 2021 Jun 2;10(6):1376.

Esposito, S., Leonardi, A., Lanciotti, L. et al. Vitamin D and growth hormone in children: a review of the current scientific knowledge. J Transl Med 17, 87 (2019). https://doi.org/10.1186/s12967-019-1840-4.

Raskh S. The importance and role of calcium on the growth and development of children and its complications. International Journal for Research in Applied Sciences and Biotechnology (IJRASB). 2020;7(6):162-7.