

## Correlation of Hepcidin with Some Biochemical Parameters in Iraqi Children with Growth Hormone Deficiency

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### Abstract

Hepcidin (Hep.) is a protein that maintains iron balance in the body. The Information about the role of Hep. in pathophysiology that is associated with growth hormone deficiency (GHD) is scarce. This study evaluates the correlation of Hep. with some biochemical parameters: Growth Hormone (GH), Insulin-Like Factor-1 (IGF-1), Iron, Vitamin D, Alkaline Phosphatase (ALP), Calcium, Phosphorous, and Ferritin in growth hormone deficient children. Children with GHD (60) and healthy volunteers (60) participated in this study, and their serum samples are collected from National Diabetes Center- Almustansiryia University from the period January to April 2022. Enzyme Linked Immune Sorbent Assay (ELIZA) is used to measure Hep. while Chemiluminescence immunoassay is to measure GH and IGF-1. Results demonstrate significant decrease of  $p < 0.01$  in the Hep. level in the sera of GHD patients when compared to healthy individuals, and iron levels increase. This can be explain the inverse relationship between hepcidin and iron. It is an important regulator of iron absorption, this mechanism through Hep. preventive any impact against anemia by increasing the bioavailability of (Fe). Therefore, this study is carried out to give a better understanding about the parameters that affect the children with GHD and Hep. that can be a dependable parameter for better management of those children.

**Keywords:** GHD, Hepcidin, IGF-1, Iron, Vitamin D.

### Introduction

Growth hormone (GH), which is a polypeptide hormone that is released by the anterior pituitary gland, is the main regulator of statutory growth during childhood and adolescence <sup>1</sup>. Growth hormone largely affects growth and development by activating the processes through insulin-like growth factor-1 (IGF-1) <sup>2</sup>. Growth hormone deficiency (GHD) is a medical condition that takes place due to a lack of growth hormone when it begins in childhood or infancy, and is characterized by several symptoms, especially the short stature. Until

now, the pathophysiology of this condition is not fully understood but it's clear that most of them have brain malformations <sup>3</sup>. The causes of this disorder are acquired or congenital as it may occur alone or in combination with other defects in the pituitary gland hormone <sup>4</sup>. The Investigations in the areas of neuroradiology, biochemistry, auxologic, and clinical practice are used to make diagnosis of growth hormone insufficiency. To validate GHD, provocative GH secretion assays with physiological/pharmacological stimuli are

necessary. To determine GH secretory state, the clonidine test (CT) is frequently performed<sup>5</sup>. Liver predominantly manufactures anabolic (IGF-1). Hormones is essential in controlling biological processes that are related to growth hormone (GH) such as insulin metabolism, cell division, reproduction, and apoptosis<sup>6</sup>. IGF-1 is principally composed of endocrine IGF-1 produced in the liver under GH stimulation as well as in target tissues in a paracrine/autocrine fashion<sup>7</sup>.

The amount of total body iron is determined by plasma iron concentrations and iron-regulatory hormone hepcidin. Hepatocytes release hepcidin, which regulates the activity of ferroprotein as a cellular iron exporter<sup>8</sup>. It is initially produced as a pro hepcidin that is released as a small peptide mainly from the liver<sup>9</sup>. Iron status affects the expression of hepcidin, as it rises when serum iron levels are elevated and liver iron reserves and falls when there is a deficit in iron<sup>10</sup>. There is a connection between growth hormone and iron as the latter is an important part of hemoglobin. The deficiency of iron is associated with stunting, developmental delays, and changes in immune processes beyond anemia. It is worth mentioning that iron and zinc compete with each other for the same digestive transport mechanisms when absorbing through the intestines. Growth is more closely connected with iron status than with zinc level<sup>11</sup>. In children with GHD, GH appears to have a unique effect on erythropoiesis that increases the level of Hb<sup>12</sup>. The Relationship between calcium and growth hormone GH and IGF-I is essential for adjusting Ca<sup>2+</sup> homeostasis, during the times of bone expansion. Calcium balance is significant for bone health and growth as calcium deprivation reduces mineralization and bone strength<sup>13</sup>. The early pubescent years for children is the crucial time

for the rapidly growing skeleton to calcify, since calcium is the primary mineral found in bone<sup>14,15</sup>. An adequate balance of phosphate is essential for healthy bone mineralization and linear growth<sup>16</sup>.

A functional GH/IGF-I axis is required for dietary phosphorus restriction to result in the proper synthesis of 1,25(OH)<sub>2</sub>D<sub>3</sub> as a feedback mechanism<sup>17,18</sup>. Moreover, vitamin D serves a variety of biological purposes and its significance is to be added to calcium metabolism and bone health, since vitamin D levels affects the function of GH/IGF-I axis. Insulin-like growth factor-1 (IGF-1) and IGFBP-3 (insulin-like growth factor-binding protein-3) synthesis and secretion in the liver may both increase in response to vitamin D<sup>15,17</sup>.

Vitamin D is involved in many gene expression processes and plays significant roles in calcium and phosphate metabolism<sup>19</sup>. Vitamin D also plays several crucial roles in the maintenance of the human pathophysiology, including maintaining strong bones, boosting immunity and preventing osteoporosis<sup>20</sup>. On the other hand, by increasing kidney both 1-hydroxylase activity, GH and IGF-1 enhance the renal production of the ability of kidneys to produce 1,25-(OH)<sub>2</sub>D (calcitriol), and blood level of vitamin D is thus impacted<sup>21-23</sup>. Certain Recent studies have revealed an inverse relationship between vitamin D concentrations (measured by serum 25(OH)D) and hepcidin concentration levels and a positive a connection between vitamin D concentrations and hemoglobin and iron concentrations<sup>24,25</sup>. The present study aims at the evaluation and studies the correlation of Hep. with some biochemical parameters: Growth Hormone (GH), Insulin-Like Factor-1 (IGF-1), Iron, Vitamin D, Alkaline Phosphatase (ALP), Calcium, Phosphorous, and Ferritin in children with growth hormone deficient.

## Materials and Methods

### Patients and control

This study is prepared in the Department of Pediatrics/National Diabetes Center. The subjects are selected from patients who are enrolled in the Department of Pediatrics/National Diabetes Center after their parents had agreed to their participation in the study. The criteria for selecting developmentally delayed subjects is according to the growth tables that are produced by the National Center for Health Statistics and the CDC's National Center for Chronic Disease Prevention and Health

Promotion (2000). (120) children between the ages of (4-12), of whom (60) suffer growth hormone deficiency (37 males and 23 females) are studied. 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. The radiological evaluation of bone age is estimated by x-ray taken for the left wrist. Clonidine is decided orally to stimulate the secretion of growth hormone. Growth hormone is three times measured: 15 minutes before

the implementation of clonidine (basal GH), 1 hour and 1.5 hours after the implementation of clonidine which is referred to as (GH2) and (GH3). Sixty (60) healthy individuals is the control group: (36 males and 24 females). Patients' records showed 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, (5\_2 ml) of blood through a vein puncture is taken via disposable syringes and then collected in a gel tube. Blood samples are collected between 8:00-11:00 am, after an overnight fasting. Blood samples are centrifuged at 3000 rpm for 10 minutes. The resulting serum is stored at -20 °C until the time of analysis comes. The test for clonidine stimulation is determined between (8:00-11:00 am). Basal samples are collected before the clonidine stimulation test and then clonidine administration orally (0.15 mg/m<sup>2</sup>) is done. The samples then are tested to estimate the growth hormone at (1 hour and 1.5 hours). IGF-1 and GH is measured quantitatively using a one-step sandwich chemiluminescence immunoassay approach <sup>26</sup>. Hepcidin is measured based on sandwich enzyme-linked immune-sorbent assay technology <sup>27</sup>. An automated instrument-based enzyme-linked

fluorescence immunoassay (ELFA) assay is applied to measure Ferritin (FER). A two-step competitive immunoassay serves as the foundation for the Mini VIDAS 25-OH is used to measure total Vitamin D Total Assay architecture.

1. Serum or plasma 25(OH)D is separated from its protein carrier (DBP) and then combined with vitamin D-specific antibody and conjugated to alkaline phosphatase (ALP).

2. Unbound ALP-antibody is then exposed to vitamin D analog coated-solid phase receptor. Solid phase is then washed, and substrate reagent is added to initiate the fluorescent reaction.

Alkaline Phosphite (ALP), Calcium, phosphor, and iron are measured with a spectrophotometer.

### Statistical analysis

The data is analyzed using SPSS statistical software, version 26. Independent-Samples Student test are performed between patients and control groups. The resulting values are expressed as mean ± standard deviation (SD). Pearson correlation coefficient is also carried out to determine the relationships between the study variables. The statistical tests are significant at p <0.05 and highly significant at p <0.01 with a confidence interval of 95%.

### Results and Discussion

Table 1 summarizes all anthropometric information of the studied groups. The age ranges are (11.05±2.33) and (9.35±3.52) for patients and the control group. Body mass index measurements

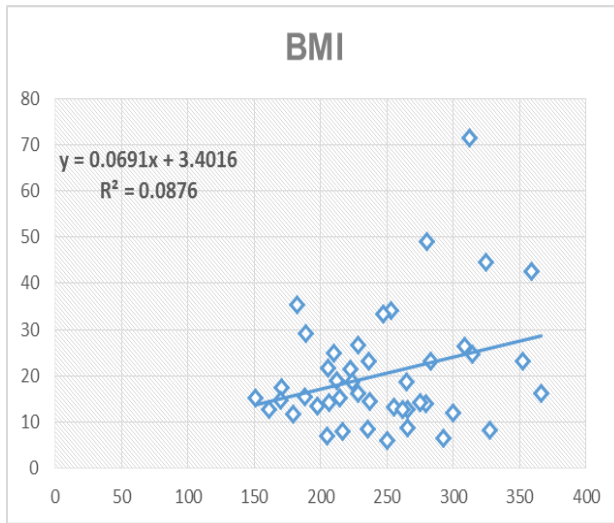
demonstrate non-significant difference (P=0.963) between patients (20.45±12.77) and the control group (27.96±11.74).

**Table 1. Anthropometric data of patients and control 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
BMI (kg/m <sup>2</sup> )	20.45±12.77	27.69±11.74	.963 NS

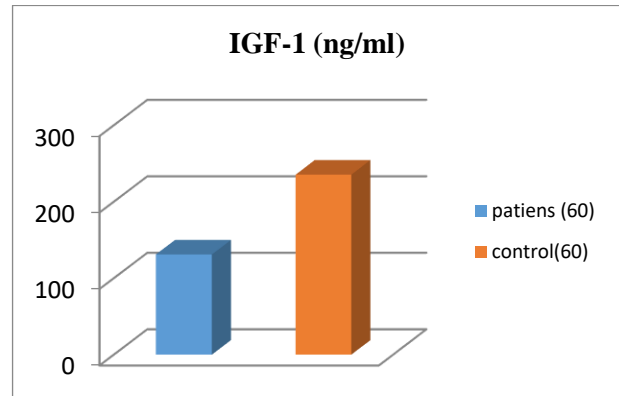
\* Significant at (p<0.05), \*: highly Significant at (p<0.01), NS: non-Significant (p>0.05).

A weak positive significant correlation is detected between Hep. and BMI in GHD children when it is compared to control (r=0.269), ( p=0.04) as it is shown in Fig.1

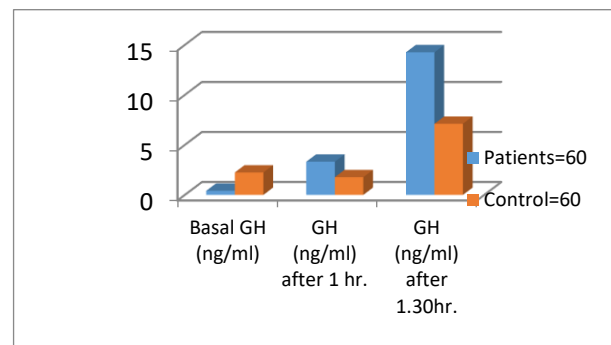


**Figure 1. Correlation between Hep. with BMI.**

The information in Fig. 2 displays the concentrations of GH and IGF-1 in the studied groups. There are three steps to measure GH: Basal GH is directly measured and the findings are significantly decreased ( $p < 0.01$ ) in patients in comparison to control ( $0.41 \pm 0.47$ ) and ( $2.24 \pm 1.76$ ) respectively. The second measurements of GH is done after 1 hour: it is directly measured and the findings are significant decreased ( $p < 0.01$ ) in patients in comparison to control ( $(3.32 \pm 1.18)$  and ( $1.77 \pm 1.20$ ) respectively. The third measurements of GH is done after 1.30 hour: it is directly measured and the findings are highly significant decreased ( $p < 0.01$ ) in patients in comparison to the control group ( $14.26 \pm 4.00$ ) and ( $7.11 \pm 3.31$ ) respectively. Regarding to IGF-1, the results revealed that there is a significant decrease of ( $P = 0.057$ ) in patients ( $131.02 \pm 71.22$ ) in comparison to the control group ( $235.40 \pm 65.77$ ).



**A**



**B**

**Figure 2. Levels of IGF-1 (A) and GH (B) in studied groups.**

The data as it is presented in table 2 shows hepcidin, iron and ferritin levels in the GHD patients and control group. There is a substantial decrease of ( $p < 0.05$ ) in hepcidin between patients ( $246.77 \pm 54.70$ ) and control ( $457.55 \pm 168.51$ ), ferritin shows significant decreased ( $p < 0.05$ ) in patients value ( $52.70 \pm 243.95$ ) compared to control value ( $114.45 \pm 366.82$ ), while iron levels are non-significantly ( $p > 0.05$ ) higher in patients ( $63.73 \pm 34.92$ ) in comparison to that ( $57.15 \pm 37.87$ ) of normal control group.

**Table 2. Levels of Hepcidin, iron and ferritin for patients and control group.**

Parameters	Mean $\pm$ SD		p-value
	Patients=60	Control=60	
Hepcidin (ng/ml)	246.77 $\pm$ 54.70	457.55 $\pm$ 168.51	0.03*
Iron (mg/dl)	63.73 $\pm$ 34.92	57.15 $\pm$ 37.87	0.278 NS
Ferritin (ng/ml)	52.70 $\pm$ 24.395	114.45 $\pm$ 36.682	0.015 **

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

In table 3, the results confirm that there is non-significant decrease ( $p > 0.05$ ) in the vitamin D3

levels between patients ( $10.91 \pm 5.80$ ) and control ( $11.96 \pm 8.94$ ) while ALP is significantly ( $p < 0.05$ )

decreased in patients (163.62±60.15) than that of the control group. (170.20±85.10) Phosphorous and calcium levels are non-significant lower ( $p > 0.05$ )

in patients (4.24±1.11), (7.41±2.31) respectively) than that (4.05±1.51),(7.31±2.84) respectively of the control group.

**Table 3. Levels of Vitamin D3, ALP, Phosphorous, and Calcium in patients and control.**

Parameters	Mean ± SD		p-value
	Patients=60	Control=60	
Vitamin D3 (ng/dl)	10.91±5.80	11.96±8.94	0.282 NS
Alkaline phosphatase (U/L)	163.62±60.15	170.20±85.10	0.012 *
Phosphorous(mmol/l)	4.24±1.11	4.05±1.51	0.156 NS
Calcium (mg/dl)	7.41±2.31	7.31±2.84	0.405 NS

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

## Discussion

As Hep. is the central regulator of systemic iron homeostasis, most studies are focused on its role in certain diseases like: Lung Cancer, Acromegaly, Atherosclerosis, and Kidney Disease. For this reason, this study may be the first study (at least in Iraqi children) investigates the significant role of Hep. in children who suffer GHD. This study hypothesized that in children with GHD hepcidin concentrations are decreased, in comparison to the case for children with normal GH. This may be due to the alteration in iron status and low grade of inflammation. As its previously explained in the results of this study, iron homeostasis is maintained by hepcidin through both local and systemic effects<sup>28,29</sup>. Body iron balance is maintained by certain sophisticated regulatory mechanisms. The lack of a regulated iron excretory mechanism means that body iron balance is controlled at the level of absorption from the diet, and thus the effects of hepcidin are demonstrated through its receptor, the cellular iron exporter ferroportin. Essential hepcidin regulators, and therefore of systemic iron homeostasis, include plasma iron concentrations, body iron stores, infection and inflammation, and erythropoiesis. Disturbances in the regulation of hepcidin contribute to the pathogenesis of many iron disorders: hepcidin deficiency causes iron overload<sup>30</sup>. According to the study by Troutt et al. in 2012, a reduction of hepcidin level following GH administration in GHD patients is detected, which is presumably due to the stimulating effect on erythropoiesis<sup>31</sup>. Methodologically, children administrated Clonidine orally to stimulate the secretion of growth hormone. The influence of GH

and IGF-1 on erythropoiesis has already been demonstrated on multiple levels. The process of erythropoiesis depends on the production of RBCs which relies on the bioavailability of Fe and erythropoietin stimulating proliferation and differentiation of erythroid progenitor cells. GH and IGF-1 stimulate growth of erythroid precursor cells in the presence of erythropoietin. Additionally, GH receptors are there in the bone marrow, and IGF-1 receptors are in located in erythrocytes. It has been hypothesized that the activity of GH is mainly mediated by IGF-1, which has a similar activity to erythropoietin and can act both directly, and also through the enhanced production of erythropoietin. In this study, no correlations between Hep., Fe, and ferritin is observed. It is known that the growth hormone (GH)-insulin-like growth Factor-I (IGF-I) axis regulates hematopoiesis<sup>32</sup>. As iron is a crucial part of hemoglobin, its lack is connected to stunting, developmental delay, and changes in immune processes that go beyond anemia<sup>33</sup>. Several researchers demonstrate that high levels of hepcidin produce hemochromatosis, or an overload of iron, whereas too little hepcidin causes Fe deficiency anemia<sup>34-36</sup>. Certain investigations study the impact of growth hormones on hepcidin levels and fetus iron metabolism in many diseases such as Acromegaly, but not in GHD patients. The results demonstrate that hepcidin is decreased in hepcidin in AG group, this might result in a higher bioavailability of iron and ferroportin, which will boost erythropoiesis that is given the role of hepcidin.

For the children's age, the results of the study reveal that they are of the same age range. This is rather significant to show a real comparison between patients and control groups. This study agrees with the previous one, which stated that the weight is lower in patients with growth hormone deficiency, for children, when compared to the one of the control group<sup>37</sup>. Body mass index show a non-significant decrease in patients when compared to the control group. The present BMI findings are in line with those of earlier researches, which found no statistically significant variations in BMI between patients and the control groups<sup>38,39</sup>. This findings may explained by the fact that weight and height are both included in the BMI, and they practically for both parameters. According to the study prepared by A. Amato et al. in 2010, weight loss among obese children is associated with lower hepcidin concentrations and a significant improvement in iron absorption, BMI reduces circulating hepcidin levels and increases iron absorption. This should, at least potentially, improve iron status<sup>40</sup>. GH basal show a significant decrease in patients when compared to the control group. According to Thakur et al, non-significant difference between basal GH levels in patients and control is detected<sup>29,41</sup>. This may be due to the growth hormone release, which is pulsated with diurnal variation, under a negative feedback auto regulation loop which may be affected by various factors. In this study, a difference between patients and healthy children is detected. It is considered an evidence of the diagnosis of the disease especially that the result is before provocation with clonidine. The results for levels of GH2 (after 1 hr.) and GH3 (after 1.30 hr.) correspond to the result that are reached by of Ciresi et al<sup>42</sup> that patients with GHD has significantly lower levels of GH and IGF-1 in the blood in comparison to that in healthy control groups. IGF-1 is a reliable measure of GH function and it is affected by certain variables, such as age, gender, fasting status, and liver problems. The interactions between vitamin D, GH, and IGF1 are also examined by Ciresi and Giordano<sup>43</sup>. GH directly impacts bone and vitamin D metabolism or whether

it does so indirectly through a rise in IGF-1 synthesis. When GH and IGF-1 are given together, healthy people have higher vitamin D concentrations. some researchers who suggest that treatment-related increases in IGF1 and GH levels do not significantly affect vitamin D concentration, as seen in individuals with acromegaly and GHD<sup>44</sup>. On the other hand, vitamin D appears to affect both children and adults' increased IGF1 production<sup>45</sup>.

A study shows that children with growth hormone deficiency often lack vitamin D and, this agrees with the results of the current study concerning the growth hormone. Infants with GHD often lack vitamin D, especially in winter, even in countries that get a lot of sun exposure. At childhood, a negative effect occurs during bone mineralization that is caused by incompetence D vitamin<sup>46</sup>. The growth skeletal depends mainly on GH/IGF-1 axis and vitamin D, nonetheless, the interplay between them is indistinct, particularly when dysfunction in one agitates the other. There is an initial view that explains the connection between GH and vitamin D activities in GHD observation of the patient that were subjected to GH replacement therapy. Recent investigations demonstrate a correlation between low levels of iron and low active form of vitamin D concentrations through the control of the hormone hepcidin in both in vitro and vivo tests. Regarding the correlation between vitamin D and Fe, iron levels may rise because vitamin D shows apparent direct and indirect reduction of hepcidin mRNA expression<sup>47-49</sup>. Hepcidin suppression is mediated by the increased cytokines and TNF- $\alpha$ , attenuating the hepcidin signaling in response to iron. In addition, an epigenetic suppression occurs at the hepcidin locus by histone deacetylase HDAC3<sup>50</sup>. During hypoxia related anemia, mediators such as PDGF-BB, which is released by different cell types, suppress hepcidin. Hepcidin levels are decreased by a special mechanism in low-risk myelodysplasia with ringed sideroblasts, a clonal disorder due to mutations of the spliceosome gene SF3B1<sup>51</sup>. Scientists revealed that iron accumulation in the mitochondria, could lead to ineffective erythropoiesis and systemic iron overload.

## Conclusion

This study found that decreased serum hepcidin concentrations in GHD children might be caused by different influences of various factors on hepcidin concentrations, when iron disorder is the

first one of which. The spectacular advances in understanding the regulation of iron metabolism and hepcidin allows a better understanding of erythropoiesis control, since together with

erythropoietin iron is a fundamental factor for erythroid cells maturation. The conditions that lead to anemia can be associated with high and low hepcidin levels. In both instances, contrasting hepcidin deregulation may ameliorate/ correct anemia in preclinical models, offering new tools

that are already or will be soon clinically explored for the treatment of specific anemia. Inflammations may be the second reason, and so this study suggests to evaluate another inflammatory parameter like: interleukins, CRP, and TNF to get the best understanding this case.

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## Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are our own. Besides, the Figures and images, which are not ours, have been given the permission for re-publication attached with the manuscript.

- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project is approved by the local ethical committee at University of Technology.

## Authors' Contribution Statement

N. F. A., W. R. A., A. M. A. and N. T. T contributed to the design and implementation of the

research, to the analysis of the results and to the writing of the research.

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## الهيبسيدين وبعض المتغيرات البيوكيميائية في الأطفال العراقيين الذين يعانون من نقص هرمون النمو

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### الخلاصة

الهيبسيدين هو بروتين يحافظ على توازن الحديد في الجسم . المعلومات حول دور الهيبسيدين في الفسيولوجيا المرضية المرتبطة بنقص هرمون النمو (GHD) شحيحة. تهدف الدراسة إلى تقييم ودراسة ارتباط الهيبسيدين ببعض المتغيرات الكيميائية الحيوية: هرمون النمو (GH) ، والعامل الشبيه بالانسولين 1- (IGF-1) ، والحديد ، وفيتامين د ، والفوسفاتيز القلوي (ALP) ، والكالسيوم ، والفوسفور ، والفيريتين في الأطفال الذين يعانون من نقص هرمون النمو . الأطفال المشاركون في الدراسة والذين هم من المصابون بنقص هرمون النمو 60 والمتطوعون الأصحاء (60) في هذه الدراسة ، وتم جمع العينات من المركز الوطني للسكري والغدد الصم - الجامعة المستنصرية من الفترة من يناير إلى أبريل 2022. تم استخدام فحص المواد الماصة المرتبطة بالإنزيم (ELIZA) لقياس Hep. و تم استخدام المقاييس المناعية الإشعاعية الكيميائية لقياس GH و IGF-1 ، وأظهرت النتائج انخفاضًا ملحوظًا  $p < 0.01$  في مستوى الهيبسيدين في مصل مرضى GHD مقارنة بالأفراد الأصحاء ، وزيادة مستويات الحديد ، وهذا يمكن أن يفسر العلاقة العكسية بين الهيبسيدين والحديد. وهو أهم منظم لامتناس الحديد ، وهذه الآلية تتم من خلال التأثير الوقائي للالتهاب ضد فقر الدم عن طريق زيادة التوافر الحيوي لـ (Fe). لذلك فإن هذه الدراسة التي أجريت لإعطاء فهم أفضل للمعلومات التي تؤثر على الأطفال المصابين بـ GHD و Hep. يمكن أن تكون معلمة يمكن الاعتماد عليها لإدارة أفضل لهؤلاء الأطفال.

**الكلمات المفتاحية:** نقص هرمون النمو ، الهيبسيدين ، عامل النمو الشبيه بالانسولين ، الحديد ، فيتامين د.