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Study the Adverse Impact of Iron Overload on Growth-related Functions of the Pituitary and Thyroid Glands in Iraqi Patients with Hemoglobinopathies

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Abstract:

BACKGROUND: Organ damage can happen because of iron buildup caused by hemoglobinopathies. Patients with hemoglobinopathies are at high risk of iron overload due to increased intestinal iron absorption, hemolysis, and frequent blood transfusions. An excessive amount of iron can hurt the pituitary and thyroid glands' growth-related hormonal processes. The bad effects of having too much iron have not been fully studied. This study aimed to investigate the impact of iron overload on these glands, particularly on their growth factors, thus providing valuable insights for improving the management and treatment.

MATERIALS AND METHODS: One hundred and forty people with hemoglobinopathies were part of a case–control study. A comparison group of 50 healthy people was also added. Measurements were made using standard methods to determine the levels of insulin-like growth factor-1 (IGF-1), growth hormone (GH), and insulin-like growth factor binding proteins (IGFBP). Iron, free triiodothyronine (FT3), free thyroid hormone (FT4), and thyroid-stimulating hormone (TSH) were examined.

RESULTS: The study found that the levels of GH, IGF-1, and IGFBP all dropped significantly ($P < 0.05$), but there were no significant changes in the levels of TSH, FT3, and FT4 ($P > 0.05$). On the other hand, compared to the control group, people with hemoglobinopathies had much higher ferritin levels.

CONCLUSIONS: The amounts of GH and IGF-1 went down. An excessive amount of iron can hurt the pituitary gland's growth-related hormonal processes. Due to iron poisoning, the cells that make GH were damaged, which led to hypopituitarism or slow growth.

Keywords:

Growth hormone, hemoglobinopathies, insulin-like growth factor-1, thyroid function tests

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Introduction

The production or shape of the hemoglobin molecule can go wrong in people with hemoglobinopathies, a group of genetic diseases. Sickle cell anemia, thalassemia, hemoglobin C disease, and hemoglobin S-C disease are all in this group. Sickle cell disease (SCD) and β-thalassemia are the most common types.[1] β-thalassemia is a blood disease that is passed down from parent to child. A sign of this condition is making very few or no beta-globin chains, which are a part of adult hemoglobin.[2] β-thalassemia comes in three different types: major, middle, and minor.[3] People with hemoglobinopathies need to get blood transfusions a lot, which can lead to iron buildup and organ damage.[1] People with this disease may have a number of

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hormonal problems, such as chronic anemia, hypoxia, and iron overload.[2,4] Thalassemia is the most common single-gene genetic disorder in Iraq. It affects the α-chain of hemoglobin and is a major health problem.[5,6] Because erythropoiesis and hemolysis do not work right, people with beta-thalassemia major (BTM) may have chronic anemia. Therefore, the patients' ability to stay alive depends on how often they get blood donations to keep their hemoglobin levels stable.[7] The World Health Organization says that about 1.5% of people in the world carry the gene for β-thalassemia.[8] The prevalence of β-thalassemia in Iraq was 3.5%.[9] Because of this, the body's ability to bind plasma-free iron is exceeded, which causes iron to build up in the main organs. People with BTM who cannot be treated with chelation will have problems with having too much iron, like not growing or failing multiple organs, this makes things hard for both patients and doctors.[10,11] A group of people with beta-thalassemia intermedia (BTI) are more likely to accumulate iron due to disease-related processes that are different from transfusional iron excess, even though their anemia is not serious enough to need regular treatments.[7] SCD, or SCD, is a type of hemoglobinopathy that is passed down from parent to child. It can be identified by the presence of hemoglobin S, it was caused by a single change in a gene. People who have SCD can get organ failure, hemolytic anemia, and vaso-occlusive events of small veins. A lot of blood transplants are used to treat anemia in people with SCD, which leads to iron buildup and organ damage caused by oxidative stress.[1,12] Hence, too much iron and problems with microcirculation are the main reasons why endocrine systems do not work right in people with hemoglobinopathy. The main goals of this study are to find out how having too much iron affects the pituitary gland and thyroid gland's ability to control growth hormones (GHs) in Iraqi patients with hemoglobinopathies.

Materials and Methods

One hundred and forty people with hemoglobinopathies were included in a case–control study. Fifty of them had beta thalassemia major, 40 had BTI, and 50 had sickle cell anemia. These people were between the ages of 5 and 18 years old. One more group, of 50 healthy people of the same age and gender, was also part of the study. Specialist doctors at the Center for Hemoglobinopathies in Basrah Governorate, Iraq, used clinical and laboratory tests to identify all of the patients in this study from October 2022 to July 2023. People who had other long-term illnesses or who were younger than 5 or older than 18 years old were not allowed to take part in the study. The e411 immunoassay tester (Cobas, Roche, Germany) was used to determine the levels of GH, IGF-1, TSH, FT3, FT4, and ferritin. The ELISA assay (China) was used to determine the amount of insulin-like growth factor binding proteins (IGFBP). The study was aware of and adhered to all privacy regulations, including obtaining permission after being informed and keeping data confidential.

Statistical analysis

Statistical analysis is commonly employed to analyze quantitative data, offering methods for describing data and making inferences for both continuous and categorical variables. This process involves collecting data to assess the relationship between two statistical datasets. In this study, all data are presented as frequencies and percentages. SPSS (version 26) (IBM corporation, Armonk, New York, United States) was used, applying the dependent *t*-test (two-tailed) and independent *t*-test (two-tailed) for variables with a normal distribution. For variables that did not follow a normal distribution, we utilized the Mann–Whitney *U*-test, the Wilcoxon test, and the Chi-square test. $P < 0.05$ was considered statistically significant.

Ethics approval

This research was approved by Al-Faiha'a Teaching Hospital, Al-Zehra'a Medical College, University of Basrah, and the Department of Basic Sciences, College of Dentistry, University of Basrah, Basrah, Iraq.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Results

Study the demographic characteristics of samples

Table 1 shows the basic information about the patients and the comparison group. It was not significant that the groups were different in terms of their mean ages or sexes ($P = 0.239$ and 0.839, respectively). The BMI of all the patient groups did, however, go down by a large amount.

Comparison of mean values of biomarkers between the control group and patients with hemoglobinopathies

There were big changes ($P < 0.05$) between the control group and the groups with hemoglobinopathies (SCD, BTM, and BTI) in the amounts of GH, IGF-1 binding protein, IGF-1, hemoglobin, and ferritin Table 2.

Comparison of mean values of biomarkers by sex among patients with hemoglobinopathies

Most of the molecular markers in Table 3 were not significantly different ($P > 0.05$) between male and female

Table 1: Demographic characteristics of controls and patients

Variable	Control (*n*=50), mean±SD	SCD (*n*=50), mean±SD	BTM (*n*=50), mean±SD	BTI (*n*=40), mean±SD	*P*
Age (years)	10.3±3.5	10.9±3.4	11.1±3.4	9.7±3.7	0.239
Gender, *n* (%)					
Males	24 (48)	23 (46)	27 (54)	21 (52.5)	0.839
Females	26 (52)	27 (54)	23 (46)	19 (47.5)	
BMI (kg/m^2)	20.8±2.5	17.3±6.1	18.1±7.6	15.8±2.5	<0.001

Statistical analyses=One-way ANOVA test and Chi-square test. Significant at *P*<0.05. BMI=Body mass index; SD=Standard deviation; SCD=Sickle cell disease; BTI=Beta-thalassemia intermedia; BTM=Beta-thalassemia major

Table 2: Comparison of means levels of biomarkers among patient and control groups

Variable	Control and SCA, mean±SD			Control and B-TM, mean±SD			Control and B-TIM, mean±SD		
	Control (*n*=50)	SCA (*n*=50)	*P*	Control (*n*=50)	BTM (*n*=50)	*P*	Control (*n*=50)	BTI (*n*=40)	*P*
Hb (g/dL)	11.5±1.49	9.2±1.34	<0.01	11.5±1.49	9.2±1.15	<0.01	11.5±1.49	9.0±1.68	<0.01
Urea (mg/dL)	20±8.33	17±5.44	0.275	20±8.33	17±6.74	0.613	20±8.33	16±5.36	0.232
Creatinine (mg/dL)	0.49 1±0.3	0.46 1±0.9	0.994	10.49±0.3	0.45±0.11	0.983	0.49±0.3	0.45±0.9	0.991
TSH (uIU/mL)	0.8±0.42	0.95±0.78	0.547	0.8±0.42	0.87±0.7	0.883	0.8±0.42	0.73±0.46	0.979
FT4 (Pmol/L)	16.3±3.55	16.8±4.5	0.795	16.3±3.55	16.6±3.8	0.987	16.3±3.55	14.6±4.0	0.821
FT3 (nmol/L)	4.6±1.04	4.6±1.05	0.995	4.6±1.04	4.4±1.01	0.664	4.6±1.04	4.3±0.94	0.503
GH (μIU/mL)	4.19±4.6	2.24±2.39	0.022	4.19±4.6	2.09±2.55	0.01	4.19±4.6	2.29±2.09	0.042
IGFBP (ng/mL)	5.288±0.402	2.48±0.376	<0.01	5.288±0.402	2.492±0.297	<0.01	5.288±0.402	3.548±0.329	<0.01
IGF-1 (ng/dL)	386±56.24	227±31.49	<0.01	386±56.24	226±32.25	<0.01	386±56.24	283±47.84	<0.01
Ferritin (ng/mL)	66.05±80.16	3637±1927	<0.01	66.05±80.16	3365±1760	<0.01	66.05±80.16	3794±2097	<0.01

Significant at *P*≤0.05. BTM=Beta-thalassemia major; BTI=Beta-thalassemia intermedia; SCD=Sickle cell disease; SD=Standard deviation; TSH=Thyroid stimulating hormone; FT4=Free thyroid hormone; FT3=Free triiodothyronine; GH=Growth hormone; IGFBP=Insulin-like Growth Factor Binding Proteins; IGF-1=Insulin-like growth factor-1; Hb=Hemoglobin; B-TIM=Beta-thalassemia intermedia

Table 3: Comparison of means values of biomarkers between males and females in patients with hemoglobinopathies

Variable	Males (*n*=71), mean±SD	Females (*n*=69), mean±SD	*P*
Hb (g/dL)	9.5±1.1	8.7±1.5	<0.01
Urea (mg/dL)	18.1±6.6	16.4±5.1	0.099
Creatinine (mg/dL)	0.46±0.07	0.46±0.1	0.823
TSH (uIU/mL)	0.8±0.6	0.9±0.6	0.457
FT4 (Pmol/L)	16.0±3.5	16.8±4.5	0.238
FT3 (nmol/L)	4.5±1.0	4.3±0.9	0.2658
GH (μIU/mL)	2.5±2.4	2.1±1.8	0.089
IGFBP (ng/mL)	2.782±0.62	2.798±0.553	0.874
IGF-1 (ng/dL)	243.3±51.02	242.7±37.94	0.929
Ferritin (ng/mL)	3384±1780	3792±1968	0.2

TSH=Thyroid-stimulating hormone; FT4=Free thyroid hormone; FT3=Free triiodothyronine; GH=Growth hormone; IGFBP=Insulin-like growth factor binding proteins; IGF-1=Insulin-like growth factor-1; SD=Standard deviation; Hb=Hemoglobin

patients with hemoglobinopathies. The only one that was significantly different was the amount of hemoglobin.

The correlations among biochemical parameters

Based on all the cases with hemoglobinopathies shown in Table 4, the relationships between the biomarkers are shown. TSH and IGF-1 had a strong negative relationship ($r = -0.372$; $P = 0.018$), and FT4 and Hb had a negative relationship ($r = -0.168$; $P = 0.047$). There was a strong positive association between IGFBP and IGF-1, on the other hand ($r = 0.509$; $P < 0.01$). There were no significant links between the other factors ($P > 0.05$).

Discussion

Hemoglobinopathies are genetic disorders that can lead to a wide range of systemic complications, including endocrine dysfunction. The relationship between hemoglobinopathies and endocrine diseases is significant due to the impact of chronic anemia, iron overload, and the overall metabolic stress; which causes increased morbidity and mortality in these patients.[13] Thalassemia and SCD do not favor men or women or a certain age group. This is shown by the fact that there were no major changes in the study groups' average ages or genders.

The decrease in BMI was significantly obvious in those children who had thalassemia or SCA because these groups severing from decrease level of GH and IGF-1, that play an important role in growth; this study was agree with previous studies.[14,15] In individuals with beta-thalassemia, and in all the text, endocrine and metabolic problems are rather frequent. As with other studies,[16-18] the amounts of GH, IGF-1, and IGFBP were lower in the BTM group than in the control group. A lot of people have problems with growth stunting. Hypoxia, chronic liver disease, iron overload, and changes in hormones (such as problems with GH release or its receptors, GH-IGF-1 axis imbalance, and hypothyroidism) are some of the things that could cause it.[16] People with thalassemia have problems with their GHs. This is because the pituitary gland is very stressed out from having too much iron.[17]

Table 4: Correlations among clinical and biochemical characteristics in all patients with hemoglobinopathies

Variables	Hb (g/dL)		TSH (mIU/mL)		FT4 (Pmol/L)		FT3 (Pmol/L)		GH (μIU/mL)		IGFBP (ng/mL)		IGF-1 (ng/dL)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Ferritin (ng/mL)	−0.143	0.379	0.04	0.806	0.116	0.475	0.043	0.793	−0.017	0.919	−0.017	0.919	−0.081	0.617
Hb (g/dL)	-	-	0.01	0.951	−0.168	0.047	0.232	0.149	−0.126	0.161	0.215	0.183	0.204	0.206
TSH (mIU/mL)			-	-	−0.108	0.507	−0.004	0.98	−0.028	0.334	−0.056	0.733	−0.372	0.018
FT4 (Pmol/L)					-	-	−0.009	0.956	−0.059	0.492	−0.016	0.924	−0.104	0.525
FT3 (nmol/L)							-	-	−0.098	0.549	0.079	0.627	−0.008	0.926
GH (μIU/mL)									-	-	0.003	0.984	0.066	0.164
IGFBP (ng/mL)											-	-	0.509	<0.01

r=correlation coefficient; significant at $P \leq 0.05$. Hb=Hemoglobin; TSH=Thyroid-stimulating hormone; FT4=Free thyroid hormone; FT3=Free triiodothyronine; GH=Growth hormone; IGFBP=Insulin-like growth factor binding proteins; IGF-1=Insulin-like growth factor-1

Several studies have shown that 53% of people with beta-thalassemia major have slow growth. A drop in the GH-IGF-1 pathway shows that growth is slowing down.[18,19] IGF-1 shortage was more common in BTM patients who also had problems with their hormones.[20] People with thalassemia major who get a lot of blood transfusions may have more free iron in their blood serum. After this, hydrogen peroxide changes into hydroxide ions (OH-), which makes reactive oxygen species (ROS) and oxidative stress worse. If there are a lot of ROS, they stop the production of IGF-1's mRNA. This causes muscle loss, sarcopenia, waste, and myopathy.[21] Because it controls many of the body's GH systems, IGF-1 is the main thing that changes bone growth. To guess how tall a young person with β-thalassemia major will be, IGF-1 levels can be used.[22] There were no big changes in the amounts of TSH, FT3, and FT4 between the control group and the BTM group. This might be because the patient groups were small or the patients were young, which causes the iron to deposit more quickly or for a shorter amount of time. Iron overload causes the thyroid gland to store too much iron, which leads to fibrosis of the glandular tissue and thyroid failure that gets worse over time until it becomes overt hypothyroidism.[23] In different countries, between 3.3% and 24.4% of people with thalassemia major also have hypothyroidism.[24] Primary hypothyroidism was found to be very common in some studies, with rates ranging from 17% to 18%. This study's results were the same as those of an earlier one.[16] However, they were not the same as those from another study.[24,25] GH, IGF-1, and IGFBP levels were also lower in the BTI group than in the control group, which was in line with what other studies[26,27] had found. Growth retardation, delayed puberty, hypogonadism, diabetes, and problems with the thyroid, parathyroid, and adrenal glands are some of the most common hormonal problems seen in BTI. It is very important to find and treat endocrine problems right away to lower the risk of later, permanent effects.[28] People with B-TIM may be short and have low IGF-1 levels because they have too much iron, serious anemia, or not enough GH. Release of the GH-IGF-1 axis.[23,27] The GHRH-GH-IGF-11 axis function has been looked at in many studies, and many short cases have shown that it is not working right.[1] It was said to be normal or slowed down, with a wide range of variations (8%–80%), in short-status people who had problems with their brain and/or pituitary gland.[29] The amounts of TSH, FT3, and FT4 in BTI were not significantly different from those in the control. The results of this study were similar to those of earlier ones.[27,28,30] GH, IGF-1, and IGFBP levels were lower in the SCA group than in the control group, this was similar with other studies.[30,31] It is also thought that in SCD, growth failure is caused by a hypermetabolic state and higher energy usage, which happen because of prolonged hemolysis. Research has shown that anemia, hemolysis markers, and not growing enough are all linked.[30] According to Mandese *et al*., these people with SCD have much lower levels of IGF-1 than people who naturally have growth delays. IGF-1 may not be being made properly because of a basic flaw in the axis.[32] There were no big changes in TSH, FT3, and FT4 levels between the SCD as thalassemia group and the control group. The findings of this study were similar to Ozen *et al*, and Soliman *et al*.[33,34] and different from Garadah *et al*.[35] There have been mixed results from tests on the thyroids of people with SCD. Several studies have shown that between 2% and 6% of people are diagnosed with hypothyroidism. In other studies, it was found that people with SCD had a stronger TSH reaction to TSH-releasing hormone than healthy people, which suggests that their thyroids were not working properly. The rate of both central and main hypothyroidism was higher in kids and teens with SCD (6%) according to a study. However, other investigations revealed that children with SCD had normal thyroid function.[33] The cause of thyroid dysfunction in SCD is unclear; however, the majority of afflicted individuals have had several transfusions, which is consistent with a serious iron overload. Autopsy studies in some cases revealed considerable iron accumulation in the thyroid gland, indicating that transfusional hemosiderosis and subsequent cellular damage to the thyroid gland may be the cause of primary thyroid failure.[34,36]

Conclusions

GHs and IGF-1 levels went down, but thyroid hormones (FT3 and FT4) levels stayed the same. IGF-1 is a better way to tell if someone is growing too slowly because they have too much iron, which means they need to get care at the right age. People with genetic blood diseases may have problems with the pituitary and thyroid glands' growth-related endocrine processes if they have too much iron. Iron toxicity damages the cells involved in the synthesis of TSH, free thyroxine (fT4), and IGF-1, leading to reduced levels of these hormones and subsequent hypothyroidism or growth retardation.

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Conflicts of interest

There are no conflicts of interest.

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