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Research Article:

Analysis of Some Regulatory Genes in Relation to Ferritin and Iron Metabolism among Thalassemia Patients in Mosul City

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Abstract

Background: α-thalassaemia is mostly caused by deletions in the alpha-globin gene complex, which result in either reduced or absent α-globin chain synthesis. β-globin chains are either absent or decreased in ß-thalassemia. Analyzing the regulatory genes (foxO1 and hepcidin) for iron and ferritin, in thalassemic patients was the goal of this study. **Methods:** Fifty individuals were selected for this study. Ten participants (5 females and 5 males) were healthy when they were recruited from general community and visited Al-Hadba'a Hospital (Mosul City) for blood withdrawal, while the forty patients (20 females and 20 males) have thalassaemia and ranged in age from 8 to 17. **Results:** Male participants had higher levels of iron and ferritin than female participants. Furthermore, there were notable differences in between male and female thalassaemic subjects. Additionally, ferritin and HbF were directly correlated with iron level and sex. Hepcidin expression analysis in healthy rather than thalassaemic participants found both down- and up-regulation; forkhead box O1 (foxO1) expression analysis demonstrated the reverse hemoglobin types pattern. **Conclusion:** In both thalassaemic and healthy subjects, gender was associated with the serum levels of iron, ferritin, and the genes that regulate them. Hepcidin and foxO1 synchronized with iron and ferritin in the human body.

1. Introduction

Among the common autosomal recessive disorders in human are α-and β-thalassaemias. The primary cause of alpha-thalassaemia is deletions in the alpha-globin gene complex, which results in decreased or absent α-globin chain synthesis. However, β-globin chains are either absent or decreased in beta-thalassaemia (1). The iron storage protein, ferritin, transports iron to locations where it is needed, stores it in a non-toxic form, and deposits it in a safe place. Serum ferritin levels are a direct indicator of the body's iron reserves, which are critical for the synthesis of red blood cells (2).

Iron overload can be noted by a high ferritin level. Disorders related to iron overload can also be detected by ferritin. Ferritin typically ranges between 15–310 and 12–150 ng ml−1 in males and females, respectively (3). Ferritin levels are significantly higher in individuals with iron excess than in those with iron deficiency, given both conditions are characterized by low red blood cell counts (4). Moreover, any inflammatory disease can cause an increase in ferritin, as it is also regarded as an acute phase protein. Consequently, long-term ferritin monitoring would be necessary to gather any additional data for a thalassemia or therapy follow-up (5). Iron is among the transition metals required for life. The hemoglobin in red blood cells, which helps carry oxygen, contains the majority of an individual's iron. A significant amount of iron is also

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present in the myoglobin of skeletal muscle cells (6). Because iron is needed as a structural component of several metalloproteins, certain cell types use less iron (7). The primary hormone regulating iron homeostasis at the junction of the erythroid and the controlled reserves of iron is hepcidin, a 25-amino acid peptide generated by hepatocytes (8). Hepcidin is a crucial hormone that modulates iron levels (9). Its synthesis is altered by erythropoiesis, inflammation, iron storage, and hypoxia (10). Hepcidin control over iron is crucial for people with thalassemia, a condition in which iron overload and anemia coexist (9). As the solely recognized cellular iron exporter, hepcidin inhibits enterocytes' ability to absorb iron and macrophages' ability to release iron by degrading ferroprotein (10). Iron overload can occur from excessive iron absorption brought on by insufficient hepcidin synthesis in comparison to body iron storage. Several signaling mechanisms primarily control hepcidin synthesis at the transcriptional level (11). The production of hepcidin is significantly reduced in thalassemia syndromes and other anemia with inefficient erythropoiesis, which are induced by an erythroid signal that is currently unknown (12). Hence, reduced hepcidin expression will lead to reduced protein expression on the membrane of the hepatocyte, ultimately leading to no interaction with the transferrin receptor (TFR1, 2) (13). Forkhead box O1 (FoxO1) is another iron-regulating factor that regulates the pathway(s) directing erythroid maturity and oxidative stress levels in murine erythropoiesis (14). In abnormal erythropoiesis characterized by elevated reactive oxygen species (ROS) levels, as in thalassemia, FoxO1 activation has been suggested as a preventive mechanism (15). Analyzing the regulatory genes for iron metabolism and ferritin, and in thalassemia patients is the study's primary goal.

2. Patients and Methods

2.1. Ethical approval, subjects and sampling

The study was approved by the Scientific and Ethical Committee/Nineveh Health Directorate (Letter No. 48386). Overall 50 participants (age range 8-17years) were randomly selected for this study; out of which 10 healthy control subjects (5 females and 5 males) and forty thalassemia patients (20 females and 20 males). Venous blood samples (6ml) collected from participants and divided into two parts; part one stored at -80oC as whole blood for genetic analysis and part two was separated for serum collection to be stored at -20oC until ready for analysis of iron and ferritin. The hemoglobin levels were directly estimated from whole blood instantly for each sample.

2.2. Biochemical analysis

A total of 3 ml of blood of each research participant were drawn into serum separator vacuum blood collection tubes via vein puncture. So as to measure the serum ferritin level, the serum was extracted from the tubes. The serum was divided into three parts and kept at -20°C until it was required to estimate the iron and ferritin levels in compliance with the guidelines provided by the manufacturer. Analysis of hemoglobin variants was done using HPLC at Al-Hadba'a Hospital (Mosul, Iraq).

2.3. RNA extraction and RT-PCR analysis

Isolating total RNA with an Addbio RNA extraction kit following the manufacturer's instructions was the first step in the PCR process. Then, AddScript Rt Master (Addbio, Korea) reverse transcriptase (RT) was used to convert the extracted RNA into cDNA. The cycle technique consisted of priming at 25Co for 10 minutes, reverse transcription at 50Co for 60 minutes, RT inactivation at 80Co for 5 minutes, and holding at 12Co. The hepcidin and foxO1 genes' cDNA samples were further analyzed in the last stage of RT-PCR (**Table 1**), which was performed using the Step-One Applied Biosystems tool system, USA. Every reaction utilized a final volume of 25 µl, comprising 5 µl of cDNA, 0.5 µmol of sense and antisense specific primers for every primer 2 µl, 5.5 µl of PCR -grade water, and 12.5 µl of Add SYBER Master Addbio, Korea). The template cDNA was denaturized using a 3-minute pre-incubation period at 95 °C. This was followed by 40 cycles of the amplification process, which included denaturation (15 s at 95 °C), annealing (15 s at 60 °C), and extension (30 s at 72 °C). At 72 °C, fluorescence was recorded after every cycle. There was a negative control run for each experiment that used no cDNA template. Plotting the Ct values (cycle threshold) against the log cDNA dilution allowed standard curves to be created using the standard procedures for each target and monitoring gene. This made it possible to carry out relative quantification following PCR. A value of 1 was assigned to the relative mRNA level of control implants in order to express the values. The data was extracted as Ct values, and the fold change was computed using the 2^-(ΔΔCt) approach.

Table 1. Primers designed for the studied genes

Genes	Primers	
Hepcidin	CAC AACAGACGGGACAACTT'3	F
	CGCAGCAGAAAATGCAGATG'3	R
FoxO1	AACTTTCGCTTAGTGGAACGT'3	F
	ACCCTCATACCTTTGGAACAG'3	R
***GAPDH**	ATGACATCAAGAAGGTGGTG'3	F
	CATACCAGGAAAATGAGCTTG'3	R

***GAPDH was used as a house-keeping gene**

2.4. Statistical analysis

Utilizing IBM's version 26 of SPSS software, USA, all data were presented as mean ± SE. Then, a Pearson correlation test was conducted between sex and the studied parameters, with the exception of gene expression, and was applied at $p < 0.05$, which was deemed a significant difference value. Independent Student's t-test was then conducted between female and male thalassaemic subjects as well as between healthy and thalassaemic subjects.

3. Results

Serum iron level in the participants with thalassaemia during the research showed a significant higher elevation in male participants compared to females (p = 0.012). Compared to females, blood samples from male thalassemic patients had higher serum ferritin levels; however, this increase was not statistically significant (P = 0.064). Throughout the course of the study, there were no significant (p>0.05)differences in the concentration of hemoglobin variants (Hb, HbA, and HbF) among male and female thalassemia patients. In addition, there was no difference in HbA2 concentration between males and females' individuals over the study (p=0.341) (**Figure 1**).

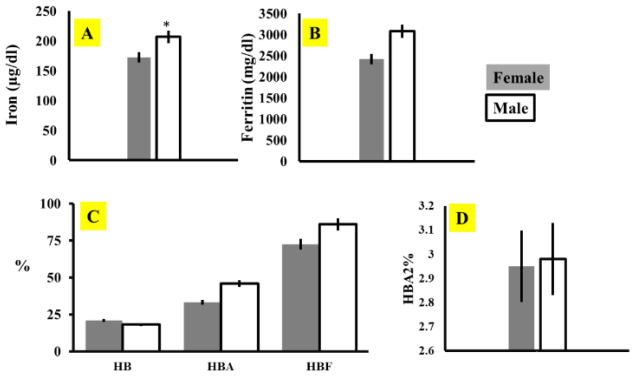

Figure 1. Hemoglobin variants and iron markers in thalassemia patients based on sex. (A) Iron, (B) Ferritin, (C) and (D) Haemoglobin levels. Data expressed as mean±SD, * indicates significant differences at p value less than 0.05 using two sample t-test.

3.1. The relationship between the study's parameters in thalassemia participants:

The results revealed significant direct correlations between iron and sex (r=0.385, p=0.012) and between HbA2 and HbA (r=0.364, P=0.018) in the analyzed data, There was a strong direct correlation between serum ferritin and HbF levels (r=0.651, p=0.0001) (**Table 2**).

Table 2. Correlation between the study's characteristics and sex among thalassemia participants

		Sex	Hb	HbA	HbA2	HbF	Ferritin	Iron
Sex	Pearson Correlation	1	-0.056	0.242	0.013	0.092	0.147	**0.385***
	Sig. (2-tailed)		0.725	0.123	0.937	0.562	0.354	**0.012**
Hb	Pearson Correlation		1	-0.245	-0.160	0.233	0.176	0.011
	Sig. (2-tailed)			0.118	0.310	0.137	0.265	0.945
HbA	Pearson Correlation			1	**0.364***	-0.284	-0.067	0.252
	Sig. (2-tailed)				**0.018**	0.069	0.674	0.108
HbA2	Pearson Correlation				1	-0.151	-0.145	0.031
	Sig. (2-tailed)					0.341	0.359	0.848
HbF	Pearson Correlation					1	**0.651****	-0.006
	Sig. (2-tailed)						**0.0001**	0.971
Ferritin	Pearson Correlation						1	0.039
	Sig. (2-tailed)							0.808
Iron	Pearson Correlation							1

***Correlation is significant at the 0.05 level (2-tailed).**
****Correlation is significant at the 0.01 level (2-tailed).**

3.2. Expression of iron regulating genes (foxO1 and hepcidin) in the study subjects

The calculated fold change of the expression of foxO1 gene in reference to the Ct values of the expressed foxO1 gene revealed four folds increase in thalassemia subjects than healthy one at $p < 0.001$. Moreover, foxO1 showed upregulation in blood samples of thalassemia subjects versus healthy controls.

Furthermore, the derived fold change of the Hepcidin gene from Ct values of the expressed Hepcidin gene in the blood specimens collected from children with thalassemia and

healthy individuals demonstrated an intense (2 folds)and significant increase among healthy controls compared to patients, p=0.024. The thalassemia patients showed a reduction in the expression of that gene compared to the control normal group (**Figure 2**). FoxO1 expression was statistically higher in thalassemia patients compared to healthy controls. Hepcidin expression was statistically lower in thalassemia patients compared to healthy controls

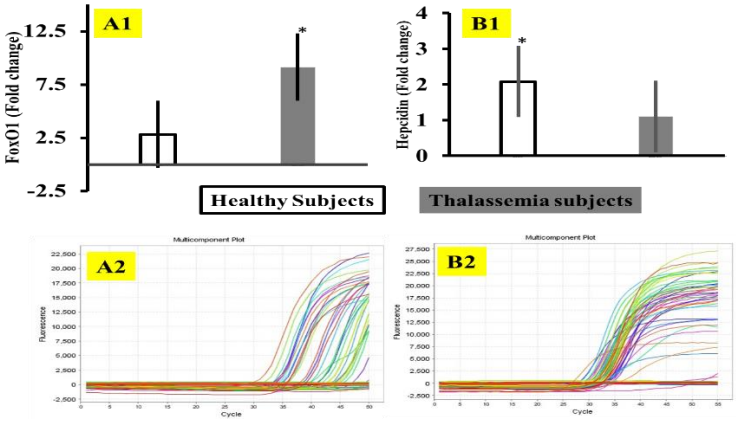

Figure 2. Gene expression profile of FoxO1 and Hepcidin. (A) Fold of changes FoxO1 gene (A1), gene expression curve of FoxO1(A2). (B) Fold of changes Hepcidin gene (B1), gene expression curve of Hepcidin(B2). Data expressed as mean±SD, * indicates significant differences at p value less than 0.05 using two sample t-test.

4. Discussion

Thalassemia stands as one of the most common forms of haemolytic anaemia in the world. Excess iron might have detrimental effects. The main cause of late morbidity and death in thalassaemia patients is transfusional hemosiderosis. Iron-chelation therapy can be used to prevent it since iron overload lowers blood ferritin levels, successfully prevents iron-induced tissue damage, and improves quality of living Conflicting results have been found in the data on iron and ferritin in patients with thalassaemia. The effect of gender on serum ferritin and iron levels were investigated in the first part of the study. The results showed that the concentrations of iron and ferritin in thalassemia males were substantially greater than those in females, at 206.96, 172.21 µg/dl and 3080.5, 2424.79 ng/dl, respectively. A correlation analysis found an interesting link between gender and iron (r = 0.385), and between ferritin and HbF (r = 0.651). These results were consistent with a recent study by Shrestha et al. (2024), who have discovered that ferritin concentration was higher in females than in males due to its correlation with increased transfusion reliance and child age (16). Each participant in the current study has a serum ferritin level that was higher than normal; on average, their level was 2725.645 ng/dl. Moreover, those who required more blood units annually have greater serum iron and ferritin levels. As a result, regardless of gender, children with thalassaemia major have blood levels of iron and ferritin that rise proportionately as they get older. This finding is in agreement with previous studies (17-19), who have reported that approximately 80% of the patients have high mean serum ferritin levels, which causes the body to become iron-overloaded and result in numerous additional severe illnesses and potentially fatal sequelae. Raising awareness among thalassaemia patients about the consequences of iron excess on their bodies is imperative. Serum ferritin levels showed normal iron storage in some investigations, while other studies discovered that patients often have positive iron balance, which put them at high risk for iron overload. Iron therapy would worsen this condition. However, compared to general patients, thalassaemia carriers have a higher prevalence of iron insufficiency (20).

A class of blood disorders known as hemoglobinopathies are caused by abnormalities in the α- or β-globin gene, which results in the creation of an aberrant amount or structure of haemoglobin (Hb), the molecule that carries oxygen.In the current research analysis of hemoglobin variants was done and showed wide differences between their values among males and females thalassaemic

subjects. In the current study, HbA and HbF are higher in thalassaemic females than males with strong direct link between HbF and ferritin, This result is in agreement with Venkatachala et al. (2017), who have presented comparable results and explained the lower HbA levels in iron deficiency by low iron levels inhibiting δ globin production and by β preferentially attaching to α chains rather than δ chains (21). This may be due to deletions that eliminate the regulatory elements in the β gene's promoter region resulted in a subset of β thalassaemia with high HbA levels exceeding 6.5%. A rise in HbF frequently follows these. In healthy adults, a rise in HbF more than 1% indicates a hereditary or acquired disease. The primary modulator of thalassemia's haematological and clinical characteristics is fetal haemoglobin. On the other hand, certain hemoglobinopathy patients have elevated HbF levels (22). This elevation in HbF value as well as HbA might be due to genetic effects of certain regulatory genes and this opinion may be more closer to the finding of Mosca et al. (2009), who or which reported that variants in the BCL11A gene have been linked to elevated HbF in healthy individuals, beta thalassaemia, and sickle cell anaemia (23). Among the acquired causes of increased HbF include diabetes mellitus, pernicious anaemia, aplastic anaemia, and chronic renal failure (24-26). The current study recorded variation in HbA, HbA2 and HbF of studied subjects. This is in agreement with Elsayid et al. (2022), who found that the analysis of haemoglobin patterns, it can be concluded that HbA and HbA2 are the two most important normal haemoglobin types for diagnosis (27). With the exception of individuals with thalassaemia, hemoglobinopathy diagnosis was not shown to be significant in people with haemoglobin F. Generally, certain genes and factors may regulate HbF, such as the BCL11A and HBS1 LMYB genes as noted by previously published studies (28,29). Such genes could be linked to a less severe phenotype and longer lifetime, which would explain some patients' greater HbF levels than others. The current results are in parallel to this opinion in that elevation in HbF might be linked to other regulatory genes.

Iron-regulating genes like foxO1 and hepcidin are other genetic factors that greatly control the cellular and systemic levels of iron and ferritin in thalassaemic patients through a variety of metabolic and signal pathways in the haemopoietic and other tissue cells, such as the liver and kidney. These genes were shown to be independently upregulated and downregulated in both healthy and thalassaemic participants in the current study, respectively. The main factor controlling how well humans absorb iron is hepcidin. By attaching to the iron exporting channel "ferroportin" and causing its internalization and destruction, the peptide prevents cellular iron efflux. Dysregulated iron absorption, iron overload, and tissue misdistribution would be expected outcomes of hepcidin deficiency and changes in its target, ferroportin. This is in agreement with previous studies (30,31), which have found that the human iron absorption is regulated by a combination of factors including tissue oxygenation, body's iron store, and erythropoietic requirement for iron. The majority of hereditary hemochromatosis types are most likely caused by hepcidin deficiency. As a result, hepcidin is becoming a crucial diagnostic metric; yet, there are currently no hepcidin measures available for a range of human illness states (32). The main factor controlling how well humans absorb iron is hepcidin. By attaching to the iron export channel ferroportin and causing its internalization and destruction, the peptide prevents cellular iron efflux. The majority of hereditary hemochromatosis types are most likely caused by its deficiency (32). This is in agreement with previous studies (30,31), who have found that the human iron absorption is regulated by a combination of factors including tissue oxygenation, the body's iron store, and the erythropoietic requirement for iron because thalassaemic subjects exhibited lower levels of hepcidin than healthy ones, this could directly explain our findings. This is in agreement with previous studies (33,34), which have found that hepcidin mRNA expression was discovered to be downregulated in the Hbbth3/1 mice, the murine model of human thalassaemia. The absence of hepcidin in the high-iron environment may expose other organs to iron loading since hepcidin typically functions to retain iron in the liver and spleen, this explains why hepcidin expression in healthy was higher than in thalassaemic subjects in the current study. Conversely, the present study's observation of an indirect relationship between hepcidin and foxO1 regulation to iron and ferritin may account for the elevated foxO1 level in healthy individuals as opposed to thalassaemic ones. This is in agreement with previous studies (33,34), which have found that hepcidin mRNA expression was found to be downregulated in the Hbbth3/1 mice, the murine model of human thalassaemia. The

absence of hepcidin in the high-iron environment may expose other organs to iron loading since hepcidin typically functions to retain iron in the liver and spleen, this explains why hepcidin expression in healthy subjects was higher than in thalassaemic subjects in the current study.

The current study revealed that foxO1 expression was higher in the thalassaemic than healthy participants, and was associated to down regulation of hepcidin in thalassaemic subjects. This is due to foxO1's critical regulation of hepcidin and systemic iron metabolism. This outcome is in line with that of Xu et al. (2024), who concluded that hepatic hepcidin induction and systemic iron homeostasis are controlled by the iron-responsive transcriptional factor in hepatocytes, Forkhead box proteins 1 (foxO1), a well-known regulator of macronutrient metabolism (35). The role of FoxO1 as an iron regulator provides a fresh viewpoint on the complex relationship between iron and glucose metabolism, since the foxOs are the main transcriptional factors of genes regulating glucose homeostasis, cell differentiation and proliferation, and angiogenesis (36). The intricate link between iron and glucose metabolism is supported by the iron regulatory function of FoxO1. Iron appears to directly influence blood glucose levels by starting the synthesis of hepatic hepcidin and glucose through FoxO1-mediated hepatic glucose output. In the current study we found that there was strong link between gender and iron, this result was supported by Latour et al. (2014), who revealed that the hepcidin expression was shown to be reduced in males in comparison to females, and testosterone was revealed to have this effect (37). Therefore, the induction of hepcidin may be attenuated by the interaction between testosterone and hepcidin.

5. Conclusion

Gender was found to be linked to variations in levels of iron, ferritin and expression of some regulatory genes in both thalassemic and health individuals. The content of iron and ferritin in the human body is influenced by hepcidin and foxO1, which are important factors that react to their expression in various body organs. Hepcidin showed an increase in iron regulation in healthy subjects, whereas foxO1 showed an increase in iron regulation in subjects with thalassaemia. This result indicates foxO1's vital control over hepcidin and systemic iron metabolism.

Conflict of interest: The authors have no conflict of interest

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تحليل بعض الجينات التنظيمية فيما يتعلق بالفيريتين واستقلاب الحديد لدى مرضى الثلاسيميا في مدينة الموصل

الخلاصة

المقدمة: يحدث الثلاسيميا ألفا في الغالب بسبب عمليات الحذف في مجمع جينات ألفا جلوبين، مما يؤدي إلى انخفاض أو غياب تخليق سلسلة ألفا جلوبين. تكون سلاسل بيتا جلوبين إما غائبة أو متناقصة في مرض الثلاسيميا بيتا. كان تحليل الجينات التنظيمية (فوكسو و هبسدين) للحديد والفيريتين لدى مرضى الثلاسيميا هو الهدف من هذه الدراسة. **الطرق:** تم اختيار خمسين فردا لهذه الدراسة. عشرة مشاركين (5 إناث و 5 ذكور) كانوا بصحة جيدة عندما تم نقلهم إلى مستشفى الحدباء (مدينة الموصل) في حين أن الأربعين مريضا (20 أنثى و 20 ذكر) مصابون بالثلاسيميا وتتراوح أعمارهم بين 8 إلى 17 سنة. كان لدى المشاركين الذكور مستويات أعلى من الحديد والفيريتين مقارنة بالمشاركين الإناث. علاوة على ذلك، كانت هناك اختلافات ملحوظة بين الذكور والإناث الخاضعين للثلاسيميا. بالإضافة إلى ذلك، ارتبط الفيريتين وهيموجلوبين فاء بشكل مباشر بمستوى الحديد والجنس. وجد تحليل تعبير الهيبسيدين لدى المشاركين الأصحاء وليس المصابين بالثلاسيميا تنظيمًا سفليًا وأعلى؛ أظهر تحليل تعبير صندوق فوكسو نمط أنواع الهيموجلوبين العكسي. **الاستنتاج:** في كل من مرضى الثلاسيميا والأصحاء، ارتبط الجنس بمستويات الحديد والفيريتين في الدم والجينات التي تنظمها. يتزامن الهيبسيدين و فوكسو مع الحديد والفيريتين في جسم الإنسان.

الكلمات المفتاحية: الثلاسيميا، الحديد، الهيموجلوبين، الفيريتين، موروثة فوكس 1، موروثة هبسدين.