

Evaluation of some heart enzymes and Iron levels in β -thalassemia patients in Thi-Qar City, Iraq

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Abstract

Beta thalassemia is one of the most common hereditary diseases in the world caused by a deficiency of globin chains. Heart disease is one of the main complications of this disease as a result of excess iron deposition in the cardiac tissues. Total of 100 patients of 2-18 years diagnosed with β -TM were employed in the current study and admitted to Thi-Qar Center of Hereditary Blood Diseases in Thi-Qar city, Iraq, and 80 healthy participants, matched by age, and geographical area were adopted as control group. The current study included evaluating of serum Troponin I (c.TnI), Creatine kinase-MB isoenzyme (CK-MB), Apelin, aspartate aminotransferase (AST), and Lactate Dehydrogenase enzyme (LDH) of studied groups. The finding revealed a significant increase ($p < 0.01$) of c.TnI, CK-MB, AST, and LDH levels as well as a significant decrease ($p < 0.01$) in apelin level in all patients with β -TM compared to the control group. Pearson's correlation coefficient (r) was also found between the biochemical parameters studied for β -TM patients with ferritin level, were found a significant correlation ($p < 0.01$) between ferritin level with CK-MB, LDH, and AST levels while there was no significant correlation ($P > 0.01$) through apelin and c.TnI levels. The finding showed a clinical predictor to damage cardiac tissues in the near term, which portends the use of more efficient treatment protocols to remove excess iron from β -TM patients.

Keywords: c.TnI, CK-MB, β -thalassemia, Heart disorders, iron overload.

Introduction

A mutation in the Hemoglobin subunit beta (HBB) gene, which is necessary for the production of the oxygen-carrying beta-globin protein of hemoglobin, results in β -thalassemia, which disrupts erythropoiesis¹. It ultimately results in a lack of developed erythrocytes. Additionally, it has been demonstrated that compared to normal erythrocytes, β -thalassemic erythrocytes have a haemolysis percentage that is approximately 115%

higher². This is the cause of the anemia and hypoxia symptoms that thalassaemic individuals experience³. Many thalassaemic individuals need frequent blood transfusions to help lessen the severity of the symptoms¹. However, due to the continual addition and destruction of iron-rich hemoglobin, hemochromatosis can develop as a result of these repeated blood transfusions, which can have adverse effects on the heart, liver, and

hormones level. Iron chelation therapy can assist in resolving these problems ¹. Based on the severity of the symptoms, there are two different forms of β -thalassemia. Thalassemia major, also known as Cooley's anemia ⁴, is a more severe kind that is more likely to require transfusions because of the substantial erythrocyte deficiency. Thalassemia intermedia, the second form, have fewer symptoms for the patients. Additionally, individuals can carry the β -thalassemia gene ¹. However, in a small number of cases, the HBB gene mutation is enough to generate β -thalassemia in an autosomal dominant manner. Both kinds of thalassemia are typically autosomal recessive diseases ⁵. Because of advancements in treatment, β -thalassemia is now regarded as a chronic disease with longer life expectancy for its patients. However, at this time, bone marrow transplants are the sole treatment ¹.

Over the past few decades, chelation therapy, hematopoietic stem cell transplantation, and blood transfusion have all been used to control thalassemia major. Heart disease still accounts for about three-quarters of deaths in these patients despite improvements in the care of thalassemia major ⁶. However, a decade has passed since the widespread adoption of systemic medication, which has further accelerated the age at which heart failure

first manifests itself. The typical age of heart failure onset in the early 1960s was 16 years ⁷. A recent sample of thalassemia patients with a median age of 13 years revealed a prevalence of heart failure of 2.7% ⁸, indicating a delayed control of the cardiac disease.

Over the past few decades, the outcomes for people with heart failure have considerably improved. In 2001 ⁹, the reported 5-year survival rate for these individuals was 48%, compared to the reported 3-month survival rate of fewer than 50% in the 1960s ⁷. Although both men and women have the propensity to collect iron in their hearts, it seems that female patients are more resilient to the toxicity of iron due to a putative decreased sensitivity to persistent oxidative stress ¹⁰. This article will cover the pathophysiology of cardiac conditions in thalassemia patients as well as the prognosis of subsequent cardiac issues. The current study will concentrate on people who have severe β -thalassemia (transfusion-dependent). In order to be employed as a diagnostic and predictive tool for cardiac problem disorders, serum levels of c.TnI, CK-MB, apelin, AST, and LDH were assessed in β -thalassemia patients (β -TM) in Thi-Qar City and compared with the healthy control group.

Materials and Methods

Patients and control

A total 180 subjects aged 2-18 years from Thi-Qar city, Iraq participated in this study, including 100 β -TM patients according to their medical records determined and diagnosed by the "Thi-Qar Center of Hereditary Blood Diseases" and 80 healthy people were recruited as a control group. All of these patients had blood transfusions as part of their treatment. Serum C-reactive protein (CRP) levels in all study patient samples were negative. Patients with diabetes, heart disease, and other chronic diseases were excluded from this study.

The agreement for this study was obtained from all patients and healthy subjects or their parents and was publicly acknowledged.

The Basra University Ethical Committee (CSWC/0921/0054) approved this study, which was

conducted by the ethical guidelines specified in the 1964 Declaration of Helsinki and its later amendments or equivalent ethical standards

Blood specimens

Blood samples were collected from patients before the blood transfusions process from 07:00 am until 08:00 am, after fasting state for 8 hours and in the supine and rest position, where 6 ml of fresh venous blood was taken from thalassemia patients and healthy volunteers, and then placed in a gel-tube and allowed to clot at 25°C and then separated by centrifuge for 10 min at 4000 rpm to get blood serum. The obtained serum collected immediately was allocated into two parts were part one was used to measure some parameters, while part two of the serum was stored in a deep freezer at a temperature of -20 °C for use to measure other parameters.

Biochemical parameters measurement method

In Both studied groups we performed laboratory examinations of serum blood to check serum ferritin and apelin levels were measured by a human ELISA kit (MyBioSource®-USA). Serum CK-MB and c.TnI levels were measured by Robot R1 Automated ECL Analyzer (Canada). Additionally, a direct colorimetric method was used to test the level of another biomarker, such as serum LDH by (spectrum® kit-Egypt), serum iron by (human® kit-German), and serum AST by (biolabo® kit - France). Also, Body Mass Index was calculated using the formula: BMI (kg/m²) = Weight (kg) / [Height(m)]² ¹¹. All kits were

analyzed according to their manufacturer's protocols.

Statistical analysis

The IBM Corporation Software SPSS statistical tool, version 22.0, was used to evaluate the data. The significance of any baseline differences between each group was evaluated using the Student's T-test. Data were shown as mean± standard deviation (SD). The correlation between the measured parameters was evaluated using Pearson's correlation test. For statistical analysis, p<0.05 was regarded as significant, and all p values were two-tailed.

Results and Discussion

Tables 1 and 2 represented the general demographic information and some clinical characteristics, respectively.

Table 1. The general demographic information for each participant in this study (n=180).

The traits		Healthy Control	β-TM
Number (No.)		80	100
Age (mean ± SD)		11.01±4.68	11.93±4.44
BMI (Kg/m ²)		19.66±4.12	18.80±3.48
Gender	Male	34	53
	Female	46	47
Area's demographics	Urban area	53	44
	Rural area	27	56
Chelation treatment (Exjade 500 mg)	Yes	-	82
	No	-	18
Supplement	Folic acid	-	88
Splenectomy	Yes	-	27
	No	-	73

Table 2. Some clinical characteristics of the patients' group (β-TM) (n=100)

Blood transfusion	
2-3 weeks	83 %
4-5 weeks	17 %
Thalassemic brothers/sisters	
0	44 %
1	36 %
2	8 %
3	3 %
4	9 %
Parents Consanguinity	
Non relatives	12 %
1st degree	41 %
2st degree	31 %
3st degree	14 %
4st degree	2 %

The results in Table 3 show that the s.iron and s.Ferritin levels were highly significantly increased ($p < 0.01$) in β -TM patients when compared with the healthy control group (445.95 ± 158.39 mg/dl, and 3168.96 ± 1736.86 ng/ml, vs 85.46 ± 20.62 mg/dl, and 107.77 ± 49.48 ng/ml, respectively) This is due to the increased iron status (iron overload) in β -thalassemia major patients. Also, a significant increase ($p < 0.01$) was observed in the levels of c.TnI, CK-MB, AST, and LDH, while apelin level

significantly decreased ($p < 0.01$) in β -TM patients when compared with the healthy control group.

Table 4 and Fig.1 showed the Pearson correlation coefficient (r) between ferritin level and some heart disorder enzymes (CK-MB, AST, and LDH) in β -TM patients were statistically significant ($p < 0.01$), While it was not statistically significant with c.TnI, and apelin levels ($p = 0.063$, and $p = 0.148$, respectively).

Table 3. Iron status and heart disorder parameters levels between β -TM patients and healthy control group.

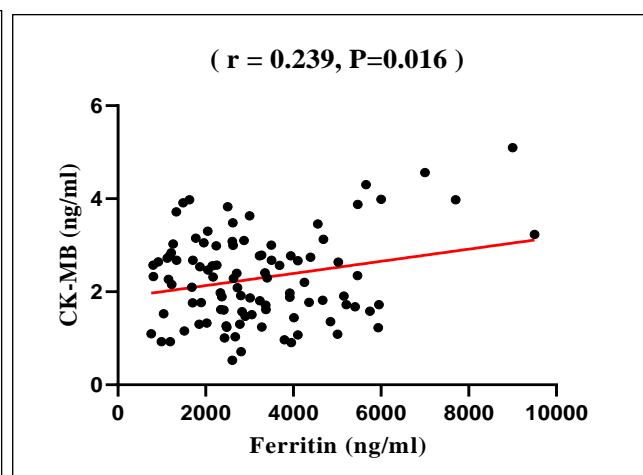
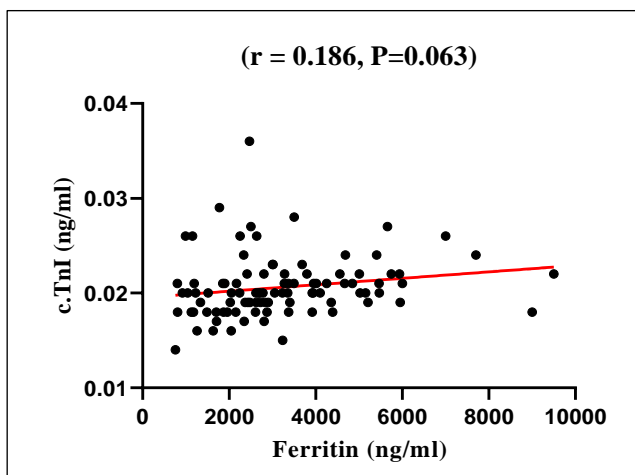
Parameters	Healthy Controls (n=80)	β -TM (n = 100)	P-value (T test)
	Mean \pm SD	Mean \pm SD	
s.Iron(mg/dl)	85.46 \pm 20.62	445.95 \pm 158.39	<0.01
s.Ferritin (ng/ml)	107.77 \pm 49.48	3168.96 \pm 1736.86	<0.01
c.TnI (ng/ml)	0.016 \pm 0.002	0.02 \pm 0.003	<0.01
CK-MB (ng/ml)	1.56 \pm 0.67	2.28 \pm 0.94	<0.01
Apelin (pg/ml)	987.47 \pm 149.56	578.07 \pm 165.21	<0.01
AST (U/L)	22.92 \pm 9.91	61.46 \pm 28.8	<0.01
LDH (U/L)	309.93 \pm 81.05	694.32 \pm 168.37	<0.01

Data represented as Mean \pm S.D P value <0.05 was considered as significant

Table 4. The Pearson correlation coefficient (r) among ferritin level with heart disorder enzymes in β -TM patients.

Heart disorder enzymes parameters	S.Ferritin (ng/ml)	
	R	p-Value
c.TnI (ng/ml)	0.186	0.063
CK-MB (ng/ml)	0.239	0.016*
Apelin (pg/ml)	0.145	0.148
AST (U/L)	0.510	<0.001**
LDH (U/L)	0.258	0.009**

P > 0.05 non-significant correlation. *P < 0.05 significant correlation. **P < 0.01 highly significant relation



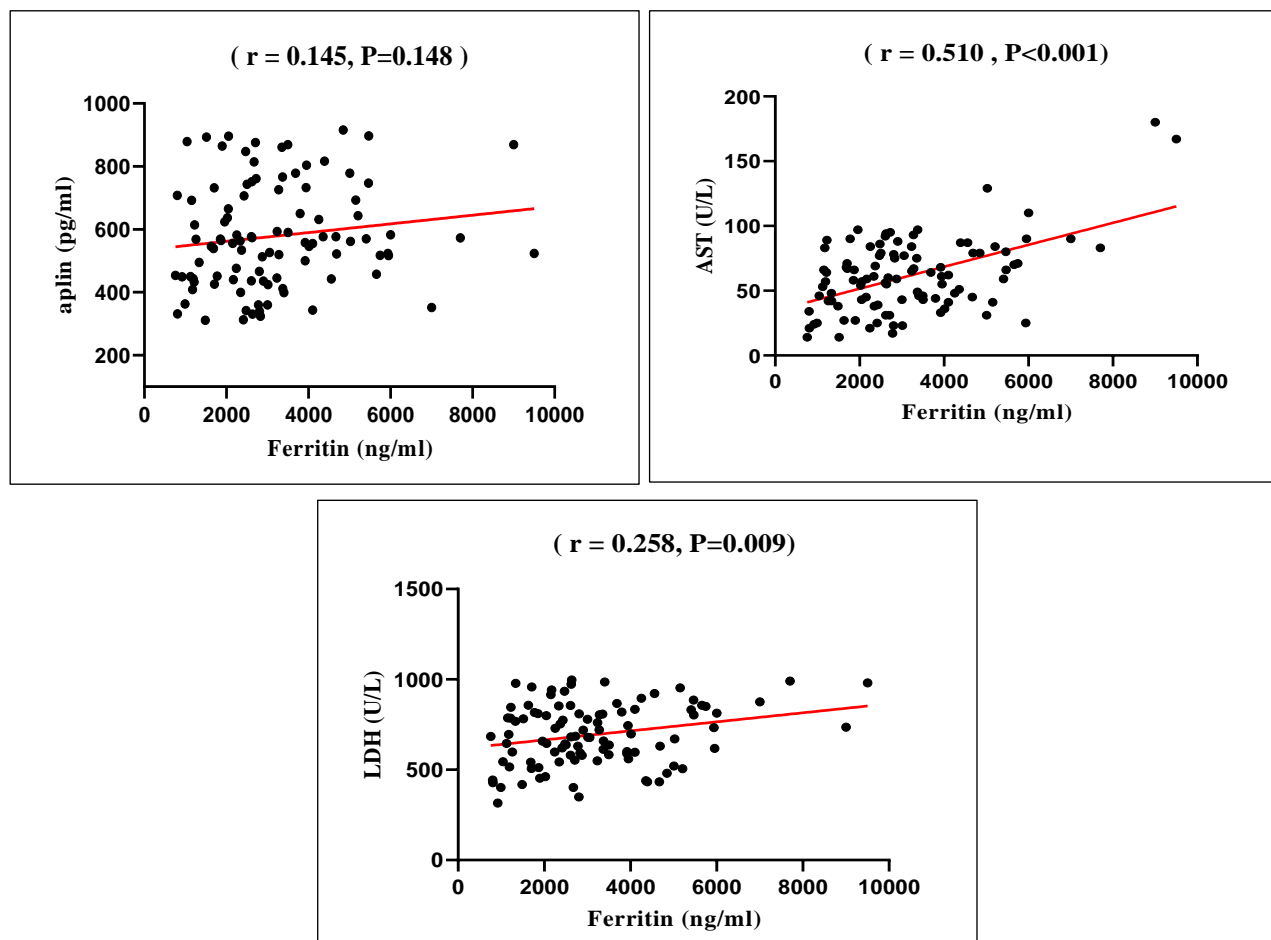


Figure 1. The Pearson correlation coefficient (r) among ferritin level with heart disorder enzymes in β -TM patients.

Discussion

Thalassemia is a hereditary disorder that affects most of the Middle East, particularly Iraq¹². Patients with thalassemia discovered a hereditary deficiency in globin gene production. This failure is caused by gene variation caused by mutation. Because genes are heritable, the faulty hemoglobin gene will be passed down to the children, resulting in defective hemoglobin identical to the parents¹³. Table 3 shows that iron status (iron and ferritin levels) in β -thalassemia major patients is significantly higher ($p < 0.01$) than in the control group (445.95 ± 158.39 mg/dl, and 3168.96 ± 1736.86 ng/ml, vs 85.46 ± 20.62 mg/dl, and 107.77 ± 49.48 ng/ml, respectively). These findings indicate an excess of iron in β -thalassemia major patients as a result of recurrent transfusions and rapid hemolysis. Prolonged transfusion therapy causes iron overload,

which leads to a wide range of problems including cardiac, hepatic, and endocrine system damage¹⁴. The excess iron is retained by the ferritin protein, which is the main protein responsible for storing iron in the body in tissues such as hemosiderin, and thus the accumulation of excess iron in the body leads to the destruction of many tissues and organs due to oxidative stress¹⁵. Globally, β -thalassemia major patients' iron-overload cardiomyopathy is a key contributor to cardiovascular morbidity and mortality^{16,17}. In individuals with β -thalassemia major, myocardial damage is the primary predictor of survival^{18,19}. Myocardial iron overload therapy options are now limited to a select group of iron-chelation techniques, with a number of limitations brought on by the need for high doses and their associated side effects²⁰. The current research

included studying the biochemical parameters of heart disorders for patients with β -thalassemia major and comparing them with the healthy control group to discover the extent to which the heart is affected by iron overload produced as a complication of blood transfusion for β -thalassemia patients. Pearson's coefficient (r) between iron status in the body (s.ferritin level) and all studied variables were also studied to find a correlation relationship.

The cardiac biomarker cardiac troponin I (cTnI) can be used to identify myocardial infarction (MI) Since it can result in iron overload cardiomyopathy, which is brought on by inefficient erythropoiesis, persistent anemia, and hypoxia, myocardial siderosis is known as the primary cause of death in β -thalassemia major patients. As a result, these patients are more vulnerable to ischemia. When cells are damaged and when myocyte contraction force is lost, troponin is released. Because cardiomyocyte metabolism is inhibited by irreversible cardiomyocyte injury, intact cTnI and its metabolic products are released²¹. which was consistent with our current study which showed an increase significantly ($p < 0.01$) in cTnI levels (0.02 ± 0.003) of β -thalassemia major patients compared with the healthy control group (0.016 ± 0.002) but within the normal limits of cardiac troponin I (cTnI) level. The Pearson correlation coefficient was also obtained, which showed that there was no statistically significant correlation ($r = 0.186$) between the level of ferritin and cTnI, as shown in Table 4 and Fig.1. These results are similar to that reported by Deraz et al²².

The CK-MB levels rise in myocardial injury²³. The blood level of CK-MB, which is the combined form of the enzymes PCR kinase isoenzymes CK-M and CK-B, is one indicator of MI²⁴. After a MI, it is first identified in the blood 3 to 9 hours later, peaks in the blood within 10 to 20 hours, and returns to normal within 72 hours²⁵; sensitivity is high if the blood is obtained when the disease is still in its early stages. The main source of CK-MB isoenzymes is the heart, while the skeletal muscle is also a source.

The kind of cardiomyopathies in children impacts the levels of CK-MB. Increased MB

fraction is typically associated with cardiac dysfunction in limited and dilated cardiomyopathies, in contrast to hypertrophic cardiomyopathies in children, with significantly higher values²⁶.

Our current study showed a significant increase ($p < 0.01$) in CK-MB levels (2.28 ± 0.94) of β -thalassemia major patients compared to the healthy control group (1.56 ± 0.67) due to iron overload in the heart muscle where a result of leakage it's into the bloodstream due to free radicals²⁷. These results agree with many previous studies²⁷⁻²⁹.

The statistical data also showed (Table 4, and Fig.1) a weak positive correlation ($r = 0.239$) between the levels of s.ferritin and the level of CK-MB for β -thalassemia patients, which means that increasing the level of s.ferritin leads to an increase in the levels of CK-MB.

Apelin regulates endothelial and smooth muscle cell death and proliferation in a manner similar to and antagonistic to that of vascular endothelial growth factor, contributing to angiogenesis. Ameliorating endothelial nitric oxide synthase (eNOS) production, eNOS-dependent vasodilatation, and angiotensin-II-mediated vasoconstriction in the systemic circulation, apelin also exhibits favorable inotropic and cardioprotective effects³⁰.

In thalassemia, asymptomatic pulmonary hypertension is a major cause of heart failure and death. This condition's precise origin is not known. The two main risk factors, however, have been identified as anemia and iron excess. Persistent hypoxia, long-term splenectomy side effects, coagulation issues, oxidative stress, and chronic hemolysis are additional risk factors³¹.

Lower plasma apelin concentrations and decreased pulmonary endothelial cell expression are found in patients with pulmonary hypertension³². A possible biomarker for pulmonary hypertension has therefore been suggested in the level of apelin³³. The present study aimed to measure apelin serum levels in β -thalassemia major patients and evaluates their relationship to iron overload markers as potential heart risk factors. Therefore, our findings

showed a significant decrease ($p < 0.01$) in the concentration of apelin levels in β -thalassemia major patients when compared with the healthy control group (578.07 ± 165.21 pg/ml, and 987.47 ± 149.56 pg/ml, respectively), and there was no significant correlation ($r = 0.145$, Table 4, Fig. 1) between it and s. ferritin levels when finding the Pearson correlation coefficient.

Although AST was used as a common biomarker for liver disease, was historically considered the first biomarker used in the diagnosis of heart disease (MI) until it was replaced by (LDH, CK, and cardiac troponin) and it's considered more specific to the myocardium than alanine aminotransferase (ALT).

The AST has multiple physiological functions, its increase in blood serum is linked to several factors, the most important of which are cardiovascular diseases like MI due to tissue damage (heart muscle) or apoptosis, as in acute myocardial infarction, which is a common cause of increased AST activity in serum³⁴.

Our current study showed a significant increase ($p < 0.01$) in AST levels of β -thalassemia major patients compared to the healthy control group (61.46 ± 28.8 U/l, and 22.92 ± 9.91 U/l, respectively). This reason is due to the iron overload in β -thalassemia major patients that causes increased oxidative stress to which the heart muscle is exposed. Pearson correlation coefficient (r) was also obtained, which showed a strong positive significant correlation with ferritin levels ($r = 0.51$, Table 4, Fig.1). This means that an increase in the iron depot in β -thalassemia major patients leads to an increase in AST levels. Our current finding agreed with many previous studies^{35,36,37}.

Conclusion

Heart disorders in β -thalassemia patients are considered one of the main causes of death due to iron overload deposition in cardiac tissues associated with transfusion-dependent thalassemia major patients. Our current study presented a comparison of the levels of heart disorders enzymes in β -thalassemia patients with a healthy control group and found a significant increase in enzymes c. TnI, CK-MB, LDH, and AST, while decreasing

Lactate dehydrogenase (LDH) is a tetrameric enzyme that catalyzes pyruvate to lactate intracellularly. It has been used since the sixties of the last century to diagnose heart disease (MI), as it indicates damage to the heart muscle and consists of two subunits (H and M) and thus forms five types of isozymes. Each enzyme is referred to a specific organ, where LDH-1 is in the heart muscle, LDH-3 is in cells Lung tissue, and LDH-5 is in liver tissue³⁸.

Blood levels of LDH and its isoenzyme LDH-1 are elevated after a MI for 5 to 10 hours, reach their highest value in 60 to 144 hours, and then return to normal in 12 days³⁹. However, due to levels being commonly high during acute renal failure and with hemolytic anemia, the LDH-1 isoenzyme cannot be used for particular diagnostic purposes⁴⁰. Nowadays, cardiac-specific Troponin I or Troponin T measures are utilized instead of LDH to diagnose MI.

Our current study showed a significant increase ($p < 0.01$) in LDH levels of β -thalassemia major patients compared to the healthy control group (694.32 ± 168.37 U/l, and 309.93 ± 81.05 , respectively). This reason is due to the tissue damage brought on by free radicals, a lack of oxygen, trauma, or any combination of the three indicated by intracellular LDH leaking. An increased LDH serum is considered a marker of hemolytic-associated thalassemia²⁷.

Pearson correlation coefficient (r) was also obtained, which showed a positive significant correlation with ferritin levels ($r = 0.258$, Table 4, Fig.1). This means that an increase in the iron depot in β -thalassemia major patients leads to an increase in LDH levels.

apelin levels. It also found a significant correlation between CK-MB, AST, and LDH vs ferritin levels (iron stock) in β -thalassemia patients. Thus, our study clinically demonstrated the possibility of heart tissue damage in β -thalassemia patients and the occurrence of future cardiac complications in the short term, which instructs the health organizations in Iraq to improve treatment protocols to remove

excess iron in β -thalassemia patients to avoid cardiac disease complications.

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for

re-publication, which is attached to the manuscript.

- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of Basrah (CSWC/0921/0054, January 4, 2022).

Authors' Contribution Statement

A.J.I. and A.H.M. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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تقييم بعض انزيمات القلب والحديد في مصل مرضى بيتا-تلاسيميا في مدينة ذي قار ، العراق

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الخلاصة

بيتا تلاسيميا هي واحدة من أكثر الأمراض الوراثية شيوعاً في العالم بسبب نقص سلاسل الكلوبين. تعتبر أمراض القلب من المضاعفات الرئيسية لهذا المرض نتيجة ترسب الحديد الزائد في أنسجة القلب. أخذ 100 مريض تتراوح أعمارهم بين 2-18 عامًا تم تشخيص إصابتهم ب- β -TM في الدراسة الحالية التي تم قبولها في مركز ذي قار لأمراض الدم الوراثية في مدينة ذي قار بالعراق ، و80 مشاركاً سليماً ، متطابقين مع العمر والمنطقة الجغرافية تم تبنيها كمجموعة تحكم. لتقييم مصل تروبونين I (c.TnI) و إنزيم الكرياتين كيناز القلبي (CK-MB) وبروتين الألبين و إنزيم اسبارتات امينوترانسفيريز (AST) وإنزيم لانتيت ديهيدروجينيز (LDH) للمجموعات المدروسة كشفت نتائج هذه الدراسة عن زيادة معنوية ($p < 0.01$) في مستويات c.TnI و CK-MB و AST و LDH بالإضافة إلى انخفاض كبير ($p < 0.01$) في مستوى الألبين في جميع المرضى الذين يعانون من β -TM مقارنة لمجموعة التحكم. تم العثور على معامل ارتباط بيرسون (r) أيضاً بين المعلمات البيوكيميائية التي تمت دراستها لمرض β -TM بمستوى الحديد، ولوحظ وجود ارتباط معنوي ($p < 0.01$) بين مستوى الفيريتين مع مستويات CK-MB و LDH و AST. بينما لم يكن هناك ارتباط معنوي ($P > 0.01$) من خلال مستويات β -TM و c.TnI. استنتجت الدراسة الحالية وجود مؤشر سريري لتلف أنسجة القلب على المدى القريب ، مما يندرج باستخدام بروتوكولات علاج أكثر كفاءة لإزالة الحديد الزائد من مرضى β -TM.

الكلمات المفتاحية: c.TnI , CK-MB، بيتا تلاسيميا ، اضطرابات القلب، زيادة الحديد.