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Evaluation of oxidative status, potassium, magnesium, and lipid profile in serum of patients with β-thalassemia major, Thi-Qar, Iraq.

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ORIGINAL STUDY

Evaluation of Oxidative Status, Potassium, Magnesium, and Lipid Profile in Serum of Patients with β-thalassemia Major, Thi-Qar, Iraq

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Abstract

Beta thalassemia major (β_TM) is one of the more prevalent hereditary diseases in the globe due to a deficiency of globin chains. It is associated with lipid abnormalities, electrolytes, and oxidative stress that can lead to potentially fatal complications. The current study included 100 patients diagnosed with β_TM in an age group of 2−18 years compared to 80 healthy subjects. The current study included evaluating Complete blood count (CBC), iron status, lipid profile, potassium, and magnesium. Also, Oxidative status represented by Superoxide dismutase (SOD), Catalase (CAT), and Nitric oxide (NO) were investigated. The finding of this study included a significant increase of triglycerdes (Tg), very low-density lipoprotin (VLDL), and Potassium levels of the patients with β_TM compared to the healthy control group, while a significant decrease in total cholsterol (TC), high-density lipoprotin (HDL), low-density, lipoprotin (LDL), SOD, CAT, NO, and magnesium levels. Moreover, Pearson's correlation coefficient (r) was also found between the oxidative status parameters, Potassium, and magnesium studied for β-thalassemia patients vs ferritin levels that were found a negative correlation with SOD, CAT, NO, and magnesium levels whereas positive correlation with Potassium level. The finding of the current study showed a clinical predictor of dyslipidemia, state of oxidative stress, and high risk each of Hyperkalemia and hypomagnesemia, which portends the use of more efficient treatment protocols to remove excess iron from β_TM patients.

Keywords: Beta thalassemia, Oxidative stress, Potassium, Magnesium, Lipid profile

1. Introduction

Beta Thalassemia(β_TM) is one of the more prevalent hereditary disorders defined by improper production of the β-globin chain of hemoglobin, which is brought on by the deficient or absent production of the β-globin chain [1]. The alpha/beta-globin ratio rises as a result of hemoglobin expression. The excess free chains accumulate and precipitate in erythroblasts, causing damage of plasma membrane and overproduction of reactants of oxygen species (ROS), which impairs erythropoiesis. More than 350 mutations in the beta thalassemia gene have recently been discovered [2]. The variance in the clinical conditions or progression of the disease may be mostly caused by genetic variations. According to previous conventions, the degree of thalassemia patients severity has been divided into beta thalassemia Major (β_TM) also known as Cooley's anemia, beta thalassemia Intermediate, and beta thalassemia Minor categories based on the frequency of blood transfusions needed to survival [3]. Clinical signs of β-thalassemia include imbalanced globin-chain buildup, inefficient production of erythroid, severe anemia, excessive gastrointestinal iron absorption (iron overload), and resulting subsequent multi complications [1]. β-thalassemia patients requires therapy treatment protocols according to disease severity and clinical manifestations. Hematopoietic cell transplantation is now the sole curative treatment,

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but it is only available to just a few percent of individuals [3]. Chronic Anemia, which is the primary cause of death in *β_TM* patients during their first ten years of life, can be treated by blood transfusion therapy along with iron chelation drugs to greatly extend survival [4]. Despite receiving the necessary chelation therapy, patients with β-thalassemia suffered difficulties like iron overload in major organs like the liver, heart, and kidney [5]. In addition to overloading transferrin's ability to bind iron, too much iron also serves as a catalyst for the creation of ROS [4]. Patients with β-thalassemia major experience oxidative stress due to an overproduction of ROS, which damages tissues by causing lipid peroxidation and protein oxidation [5].

2. Materials and methods

2.1. Patients

180 subjects aged 2–18 years from Thi-Qar City, Iraq participated in this study, including 100 β-thalassemia major (*β_TM*) patients corresponding 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. Patients with diabetes, heart disorders, hypertension, and other long-term disorders were excluded from this study.

2.2. Specimens collection

Blood specimens were obtained from β-thalassemia patients before the blood transfusion processes and also healthy control group from 07:00 am until 08:00 am, after fasting state for 10 h about (10 ml) of forearm vein blood was drawn. blood was subdivided into two tubes (2 and 8 ml); the first tube (2 ml) containing EDTA was used for CBC analysis while the second tube (8 ml) contains gel (without anticoagulant) and allowed to clot at 25 °C then that separated by centrifuge for 10 min at 4000 rpm to get blood serum. The obtained serum collected instantly was used in the detection of biochemical parameters in this study, and the rest serum was saved at −20 °C until use.

2.3. Biochemical parameters measurement method

In Both studied groups we performed laboratory examinations of whole blood to check CBC was measured by an XP-300 Haematology auto-analyzer(Sysmex®-Germany), also serum ferritin was determined by a Mini-VIDAS (BioMérieux®-France). serum SOD, CAT, and NO were measured by a human ELISA kit (MyBioSource®-USA). lipid profile were measured by BS-230 Automated Analyzer (Mindray®-China). Additionally, a direct colorimetric method was used to test the level of other parameters such as serum iron by (human® kit-German), serum Potassium by (spectrum® kit-Egypt), and serum Magnesium by (human® kit-German), moreover, Body Mass Index was calculated using the formula: BMI (kg/m2) = Weight (kg)/[Height(m)]^2.

2.4. Statistical analysis

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

3. Results & discussion

Thalassemia is a prevalent hereditary disorder that affects most of the Middle East, particularly Iraq [2]. 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 parents [5].

The results descriptive data of the present study in Table 1 show that there are non-significant variances in regards to age in patients with *β_TM* compared with healthy control group (11.93 ± 4.44, and 11.01 ± 4.68 years, respectively). This is due to the selection of the ages of the control group close to

Table 1. The descriptive data of the present study.

The traits		Patients with β_TM	Healthy Control	p-value
Number (N)		100	80	
Age (year) Mean ± SD		11.93 ± 4.44	11.01 ± 4.68	0.183
Gender	Male N (%)	53 (53%)	40 (50%)	0.178
	Female N (%)	47 (47%)	40 (50%)	0.453
BMI (kg/m^2) Mean ± SD		16.03 ± 1.55	19.22 ± 2.76	<0.01

BMI: body mass index; SD: Standard devation; P > 0.05: non-significant variance; $P < 0.05$ significant variance; $P < 0.01$: high significant variance.

the ages of the patients being studied so that there was no discrepancy between the ages of the studied subjects. Therefore, non-significant differences were in the age of the studied groups. Also regarding gender and when a comparison has been made between the randomly selected studied groups, non-significant differences were found in the two groups as follows patients with *β_TM* [male (53%) and female (47%)], and control [male (50%) and female (50%)].

Regarding the body mass index (BMI), there was a highly significant decrease in patients with *β_TM* when compared with the healthy control group (16.03 ± 1.55, and 19.22 ± 2.76, respectively). Growth failure is a commonly documented problem in kids and teens with *β_TM*. This can result from many factors, including chronic hemolytic anemia attributed to the disease, increased iron overload, and endocrinopathies associated with iron overload [6]. Although many patients with *β_TM* receive regular blood transfusions to reduce the symptoms of *β_TM*, growth failure persists. A recent study found that growth hormone (GH) replacement therapy might represent a viable treatment option for patients with, *β_TM* who experience growth failure [1]. Distribution has been of patients with *β_TM* and healthy control group according to BMI for-age percentile as shown in Fig. 1. The results showed that 64% of patients with *β_TM* were underweight (<5th) and 36% were within normal weight (5th - 85th), while all participants in the healthy control group were within normal weight. The failure to thrive results from the negative effects of chronic severe anemia and increased iron deposition attributed to frequent blood transfusions. In addition to growth failure, chronic anemia causes several deleterious effects, including cognitive impairment, delayed puberty, and weakened immune system [7].

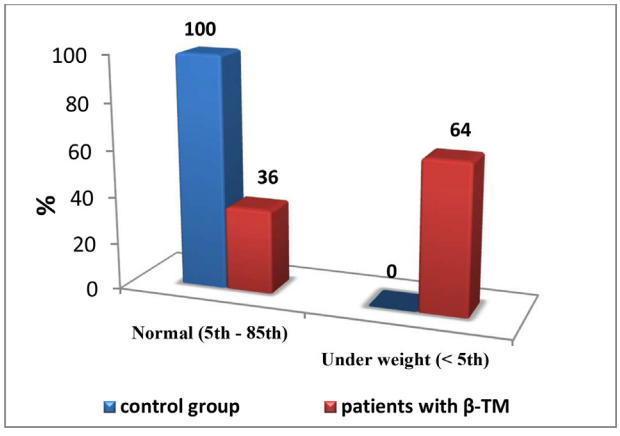

Fig. 1. Distribution of patients with β_TM and healthy group according to BMI for-age percentile.

The results in Table 2 show the Iron status parameters, which are iron, and ferritin, in patients, with *β_TM* and healthy control group. where shown a highly significant, increase in iron and ferritin levels were found in patients, with *β_TM* (445.95 ± 158.39 mg/dl, and 3168.96 ± 1736.86 ng/ml, respectively), compared to the healthy control, group (85.46 ± 20.62 mg/dl, and 107.77 ± 49.48 ng/ml, respectively).These results indicate patients with *β_TM* suffer from high iron concentration (iron overload) due to chronic hemolytic anemia, repeated blood transfusions, and difficulty getting rid of iron from the human body [8]. The degree of iron accumulation in different organs varies within and across individuals due to varying routes and rates of iron loading [6]. For individuals with thalassemia, major, the most common cause of morbidity and death is iron overload [5]. So iron level is expected to be elevated in *β_TM* patients in the, current study. After 10 to 12 blood transfusions, β-thalassemia patients are susceptible to iron overload because the body lacks a mechanism to eliminate extra iron [2]. The overall amount of cellular Labile iron pool (LIP) in the body rises as a result, of chronic iron overload. In patients with, severe thalassemia, free iron that is not chelated might trigger the Fenton reaction, which can increase the creation of free radicals [9].

The results in Table 3 show the complete blood count (CBC) parameters of the study groups. Chronic anemic manifestations were observed in the patients with *β_TM* as compared to the healthy controls. Where highly significantly decreased erythrocytes (RBC) and hematocrit (HCT) levels (2.81 ± 0.54 × 10^{12}/L, and 21.95 ± 3.87%, respectively) in patients, with *β_TM* compared, to healthy control group (4.75 ± 0.35 × 10^{12}/L, and 42.32 ± 2.79%, respectively). Moreover, the hemoglobin level in patients, with *β_TM* significantly dropped, to about 46% of the level, recorded in healthy control group (7.63 ± 1.25, and 13.5 ± 0.94 g/dL, respectively).

Table 2. Parameters of iron status in patients with β_TM and healthy group.

Parameters	Healthy Control n = 80	Patients with β_TM n = 100	p-value
	Mean ± SD	Mean ± SD	
Iron (mg/dl)	85.46 ± 20.62	445.95 ± 158.39	p < 0.01
ferritin (ng/ml)	107.77 ± 49.48	3168.96 ± 1736.86	p < 0.01

SD: Standard devation; $P < 0.01$: high significant variance.

Table 3. Complete Blood Count (CBC) in patients with β_TM and healthy control group.

Parameters	Healthy Control n = 80	Patients with β_TM n = 100	p-value
	Mean ± SD	Mean ± SD	
WBC × 10^9/L	7.09 ± 1.56	19 ± 7.88	p < 0.01
RBC × 10^{12}/L	4.75 ± 0.35	2.81 ± 0.54	p < 0.01
Hb (g/dL)	13.5 ± 0.94	7.63 ± 1.25	p < 0.01
HCT (%)	42.32 ± 2.79	21.95 ± 3.87	p < 0.01
MCV (fl)	89.15 ± 2.77	78.35 ± 5.54	p < 0.01
MCH (pg)	28.42 ± 1.02	27.37 ± 2.53	p < 0.01
PLT × 10^9/L	243.22 ± 55.59	364.32 ± 123.66	p < 0.01

WBCs: white blood cells; RBCs: red blood cells; Hb: heamoglobin; HCT: heamotocrit; MCV: mean, corpscular volume; MCH: mean, corpscular heamoglobin; PLT: platelets count; SD: Standard devation; $P < 0.01$: high significant variance.

Generally, Patients with β-thalassemia have, problems synthesis with the beta globin, chains of, hemoglobin. So they will have fewer, healthy red blood cells, and less hemoglobin, than normal in, their blood. Low hemoglobin and Mean corpuscular volume (MCV) are the first clinical indicator for diagnosing thalassemia after excluding iron deficiency as a cause of anemia [4]. Because excessive erythrocytes (RBC) destruction and inefficient erythropoiesis may result in a decline in RBC count, hemoglobin concentration, and hematocrit (HCT), these findings are expected in thalassaemic patients [10].

Microcytosis and hypochromic are decrease significantly more noticeable in the patients, with *β_TM* than in healthy controls where decreased levels of MCV and MCH values (78.35 ± 5.54 fl, and 27.37 ± 2.53 pg, respectively) in patients, with *β_TM* compared, to healthy control group (89.15 ± 2.77 fl, and 28.42 ± 1.02 pg, respectively). These results could be attributed to genetic abnormalities in genes essential for hemoglobin protein chain synthesis resulting in a disturbance in globin chain biosynthesis and a loss of hemoglobin manufacturing balance [10]. However, the number, shape, and size of red, blood cells as they form in the bone, marrow may be affected. As a result, the red blood cells are extremely small and do not occupy the same amount of space as typical red blood cells. However, red blood cells entering the circulatory system may be phagocytosed by splenic kupffer cells which phagocytose abnormal and aging RBCs [11].

In addition, the results show a significantly increased secondary thrombocytosis (platelets count) was recorded in patients with *β_TM* (364.32 ± 123.66 × 10^9/L) compared to healthy control group (243.22 ± 55.59 × 10^9/L). This result could be attributed to could be associated to the proliferation and development of marrow mononuclear cells to produce colony-forming unit megakaryocytes [12].

Moreover, a highly significant increase in leukocytes was also reported in patients with *β_TM* (19 ± 7.88 × 10^9/L) compared to healthy controls (7.09 ± 1.56 × 10^9/L). These results can be attributed to several factors: Firstly, General illness conditions and immune system hyperactivation in patients who receive blood from a variety of donors regularly as demonstrated by the spread of fever soon after transfusion. Secondly,The kidney's release of "erythropoietin hormone" which urges the bone marrow to increase red and white blood cell production is boosted by the "high break percentage" of red blood cells within and outside bone marrow. Third, Thalassemia causes an increase in monocytes which break down the damaged red blood cells [13].

The results in Table 4 show the Lipid profile in patients with *β_TM* and the healthy control group. where shown a significantly increased in Tg, and VLDL levels (172.14 ± 43.16, and 34.43 ± 8.63 mg/dl, respectively) in patients, with *β_TM* compared, to the healthy control group (106.1 ± 21.23, and 21.78 ± 4.85 mg/dl, 3.19 ± 0.58, respectively). In addition, there was, a significant decrease in TC, LDL, and HDL levels in,patients with *β_TM* (110.58 ± 19.92, 54.75 ± 20.79, and 22.15 ± 5.29 mg/dl, respectively) compared to the healthy control group (155.63 ± 19.21, 85.55 ± 18.55, and 49.61 ± 6.33 mg/dl, respectively). Increased hemolysis and enhanced oxidative stress brought on by iron overload both result in excessive use of the minerals needed for antioxidant enzyme activity as co-factors [12]. The transfusion-dependent thalassemia (TDT) has also been associated with lipid abnormalities levels due to oxidative stress, which can promote early atherosclerosis and raise the risk of cardiovascular disease (CVD) and stroke, which adds to illnesses and even early mortality. One of the important factors that contribute to dyslipidemia in thalassemia is lipid peroxidation [14]. According to previous literature, patients with *β_TM* are at increased risk for acquiring early atherosclerosis, because of chronic hemolytic anemia, iron overload, and dyslipidemia [15].

Table 4. Lipid profile in patients with β_TM and healthy control group.

Parameters	Healthy Control n = 80	Patients with β_TM n = 100	p-value
	Mean ± SD	Mean ± SD	
TC (mg/dl)	155.63 ± 19.21	110.58 ± 19.92	p < 0.01
Tg (mg/dl)	106.1 ± 21.23	172.14 ± 43.16	p < 0.01
LDL (mg/dl)	85.55 ± 18.55	54.75 ± 20.79	p < 0.01
HDL (mg/dl)	49.61 ± 6.33	22.15 ± 5.29	p < 0.01
VLDL (mg/dl)	21.78 ± 4.85	34.43 ± 8.63	p < 0.01

TC: total cholsterol; Tg: triglycrides; LDL: low-density lipoprotin; HDL: high-density lipoprotin; VLDL: very low-density lipoprotin; SD: Standard devation; $P < 0.01$: high significant variance.

Overall, adult patients with *β_TM* have been observed to have a higher incidence of early atherogenesis, thromboembolic events, and endothelial dysfunctions, which are likely caused by dyslipidemia and its effects [16]. The lipid abnormality raises the risk of pancreatitis due to raised serum triglycerides (TG) levels, as well as the risk of cardiovascular and cerebrovascular diseases due to atherogenesis [14].

Our current study showed a highly,significant,decrease in superoxide dismutase levels (SOD) of approximately 41.77% in patients with *β_TM* compared to the healthy control group as shown in Table 5. Pearson's correlation coefficient (r) was also obtained, which showed a negative significant correlation ($r = -0.356$, $P < 0.001$) between ferritin and superoxide dismutase (SOD) levels of patients with *β_TM* as shown in Fig. 2. The low levels of superoxide dismutase in our study of patients, with β-thalassemia,can be, attributed to several reasons, the most possible of which is its inhibition by heme iron that results from hemoglobin degradation [17]. where the increased production of free radicals generated inside the cells (due to excess iron that resulting from frequency transfusions and hemoglobin degradation) and hypoxia leads to a disorder of the pro-oxidation-Antioxidants balance (PAB) system [18], therefore act iron (Fe) on convert oxygen into reactive, oxygen, radicals, superoxide anion, and, hydroxyl radical groups through, the Fenton, and Haber–Weiss reactions [15]. This explanation is supported by its significant negative correlation with high ferritin levels that indicate iron overload in these patients and it has been confirmed by previous literature [19].

Regarding catalase (CAT), our current study showed a highly significant, decrease in its levels of about 32.8% in patients, with *β_TM* compared, to the healthy control, group as shown in Table 5. Pearson's correlation coefficient (r) was also obtained, which showed a negative, significant correlation, ($r = -0.571$, $P < 0.001$) between ferritin and catalase levels of patients with *β_TM* as shown in Fig. 2. The low levels of catalase in our current study may be due to direct damage to hydroxyl radicals that are formed through the reaction of free iron with hydrogen peroxide. Thus, these free radicals depolymerize polysaccharides, disrupt functional proteins, and break DNA strands [20]. This explanation is supported by its significant negative correlation with high ferritin levels that indicate iron overload in these patients. Therefore, patients, with *β_TM* are more, susceptible to the negative effects of oxidative stress [6].

Table 5. Oxidative status parameters, in patients with β_TM and healthy control group.

Parameters	Healthy Control n = 80	Patients with β_TM n = 100	p-value
	Mean ± SD	Mean ± SD	
SOD (ng/ml)	9.24 ± 1.94	5.38 ± 2.23	p < 0.01
CAT (pg/ml)	44.45 ± 6.96	29.87 ± 6.94	p < 0.01
NO (μmol/l)	15.75 ± 1.55	9.76 ± 4.68	p < 0.01

SOD: suproxide, dismutase; CAT: Catalase; NO: Nitric oxide; SD: Standard devation; $P < 0.01$: high significant variance.

Regarding Nitric oxide (NO), our current study showed a highly, significant, decrease in its levels of about 38.03% in patients, with *β_TM* compared, to the healthy control, group as shown in Table 5. Pearson's correlation coefficient (r) was also obtained, which showed a negative significant, correlation, ($r = -0.213$, $P = 0.033$) between ferritin and Nitric oxide levels in patients, with, *β_TM* as shown in Fig. 2. The Low levels of Nitric oxide are associated with the pathophysiology of β-thalassemia, which is characterized by hemolytic anemia leads to increased hemoglobin degradation and the release of abundant amounts of cytosolic arginase, which converts L-arginine (the main substrate for the synthesis of nitric oxide) into ornithine, and thus a decrease in the bioavailability of nitric oxide [21]. In addition, more Nitric oxide is consumed by interacting with free radicals resulting from oxidative stress associated, with, iron overload in β-thalassemia disease [18].

Our current study showed, a significant, increase in serum potassium levels of patients with *β_TM* (4.52 ± 0.63 mmol/l) compared to the healthy control group (3.89 ± 0.57 mmol/l) as shown in Table 6. Pearson correlation coefficient (r) was also obtained, which showed a positive significant, correlation ($r = 0.363$, $P < 0.001$) between ferritin and potassium levels of patients with *β_TM* as, shown in Fig. 3. Patients with *β_TM* suffer from the risk of hyperkalemia for several reasons, the most important of which are related to the nature of the thalassemia associated with the increase in the selective permeability of the cell membrane for potassium that occurs in deformed RBC cells and thus leakage of potassium to the extracellular [22]. In addition, Weakness of renal function as a result of excess iron deposition and thus its inability to excrete potassium at the normal rate [23]. Also, oxidative stress as a result of iron deposition plays an important role in cellular potassium leakage by increasing K–Cl cotransport activity [24].

Regarding magnesium, our current study showed a significant decrease in its levels, in patients, with *β_TM* (1.88 ± 0.21 mg/dl) compared, to the healthy control, group (2.26 ± 0.18 mg/dl) as shown in Table 6. Pearson's correlation coefficient (r) was also obtained,

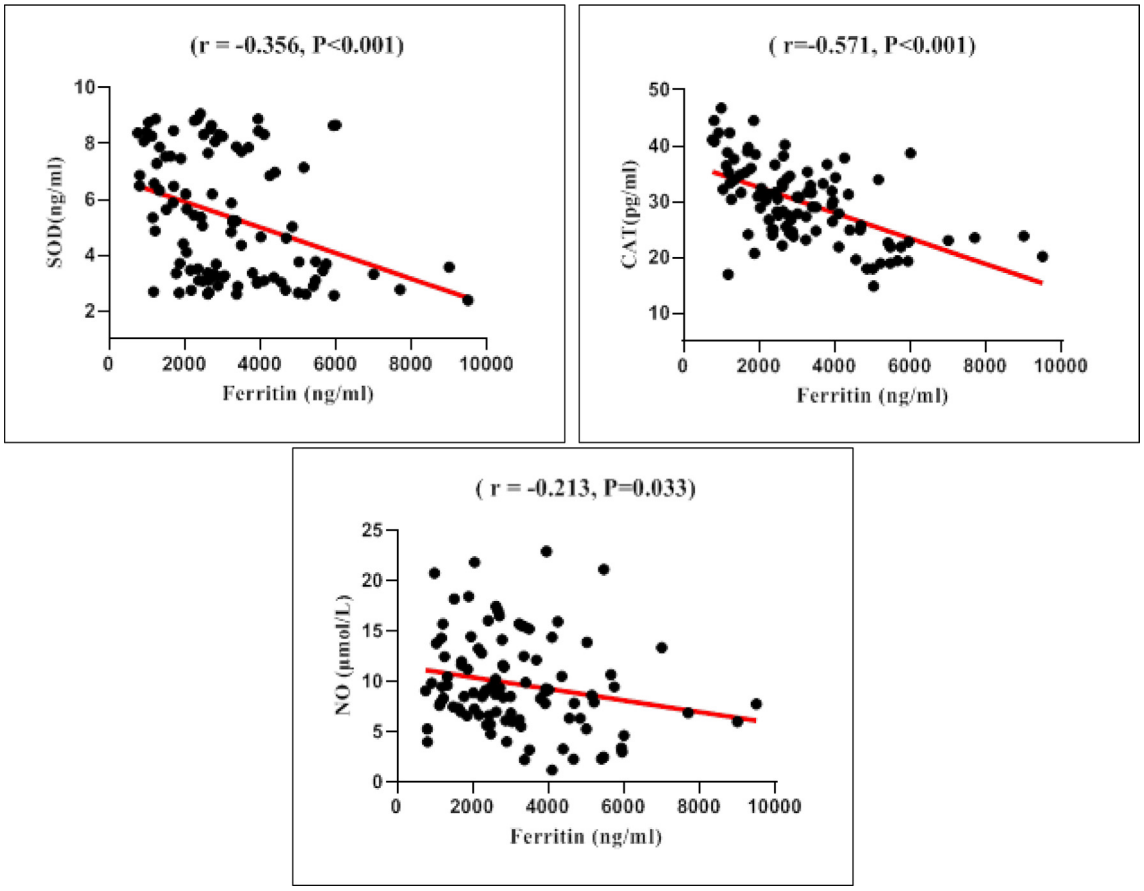

Fig. 2. The Pearson correlation coefficient (r) among ferritin level with Oxidative status parameters in patients with β_TM.

which showed a negative significant correlation ($r = -0.367$, $P < 0.001$) between ferritin and magnesium levels of patients, with *β_TM* as, shown in Fig. 4. The Low levels of magnesium in patients, with *β_TM* may be the result of oxidative stress, hemolysis, psychological problems, nutritional deficiencies, and metabolic and endocrine disorders [25]. Overall, magnesium deficiency is associated with reduced secretion of Parathyroid hormone (PTH), which is frequent in patients, with β-thalassemia due to excess, iron, deposition in the parathyroid tissues [23]. Also, previous literature revealed that magnesium deficiency is affected by homozygous β-thalassemia, so magnesium supplementation is recommended taken to stabilize, red blood, cells through its specific, interactions, with the K−Cl cotransport, and its effects, on the plasma membrane, survival, and morphology of erythrocytes [24].

Table 6. Levels of serum potassium and magnesium in patients with β_TM and healthy control group.

Parameters	Healthy Control n = 80	Patients with β_TM n = 100	p-value
	Mean ± SD	Mean ± SD	
K (mmol/l)	3.89 ± 0.57	4.52 ± 0.63	p < 0.01
Mg (mg/dl)	2.26 ± 0.18	1.88 ± 0.21	p < 0.01

K: serum potassium; Mg: serum magnesium; SD: Standard devation; $P < 0.01$: high significant variance.

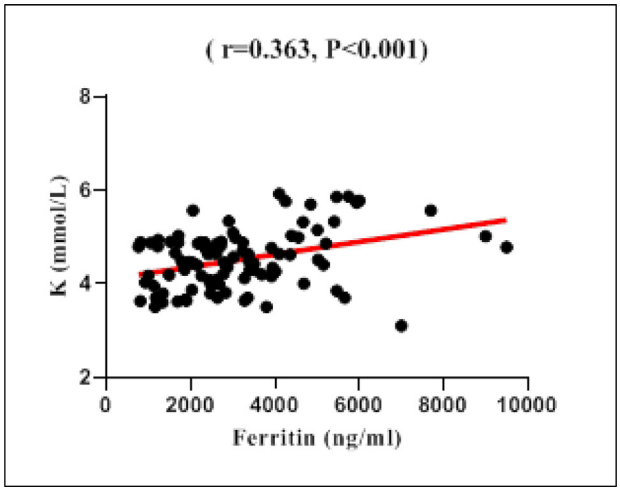

Fig. 3. The Pearson correlation coefficient (r) among ferritin levels with potassium, levels in patients with β_TM.

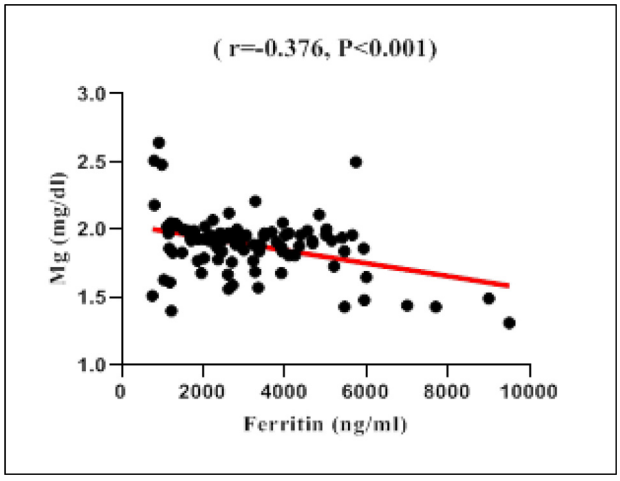

Fig. 4. The Pearson correlation coefficient (r) among ferritin levels with magnesium levels in patients with β_TM.

4. Conclusion

The results, of this, research revealed that β-thalassemia patients in Thi-Qar City, Iraq suffer from iron, overload damage, oxidative, stress, and dyslipidemia, which indicates early development of cardiovascular diseases, atherosclerosis, and other fatal complications. in addition to disturbances in potassium and magnesium levels, which warns of an increase in risk factors of hyperkalemia and hypomagnesemia. Moreover, given that stem cell transplantation is a limited and unavailable option in Iraq for the definitive treatment of β-thalassemia, our study demonstrates the importance of enhancing clinical assessments and continuous follow-up of thalassemia patients with chelation therapy, which can be highly recommended to develop or modify management protocols and thus improve their clinical condition.

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