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Role of Quercetin Supplementation on Iron Parameters in Blood Transfusion-Dependent Thalassemia Patients

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Abstract

Background: Thalassemia is a group of inherited blood disorders that affect the production of hemoglobin, a protein in red blood cells that carries oxygen throughout the body. Iron overload is a condition in which the body absorbs and stores too much iron. In addition to repeated blood transfusions, increased gastrointestinal tract (GIT) iron absorption plays an important role in iron overload with thalassemia. Quercetin, a common flavonoid present in fruits and vegetables, exhibits diverse biological effects. ***Objective***: To assess the effect of quercetin on iron overload parameters in blood transfusion-dependent thalassemia patients (TDT). ***Methods***: A randomized, double-blind, placebo-placebo group-led study was conducted on 110 TDT patients, more than 12 years of age, who were supplemented with either quercetin or a placebo capsule daily (500 mg) for 3 months. A blood sample was obtained for laboratory parameters at baseline and at the end of 3 months. ***Results***: At the baseline time of the study, the demographic features and iron overload parameters of patients and the placebo group were not statistically different, while after three months of supplementation, there was a significant decrease in levels of serum iron, UIBC, serum ferritin and ferritin saturation rate, and a significant increase in TIBC in the patients compared with the placebo group. ***Conclusions***: The study shows the significant role of quercetin on iron overload parameters in blood transfusion-dependent thalassemia patients.

Keywords: Iron overload, Quercetin, Thalassemia.

دور مكملات الكويرسيتين على معايير الحديد في مرضى الثلاسيميا المعتمدين على نقل الدم

الخلاصة

الخلفية: الثلاسيميا هي مجموعة من اضطرابات الدم الموروثة التي تؤثر على إنتاج الهيموجلوبين، وهو بروتين في خلايا الدم الحمراء يحمل الأكسجين في جميع أنحاء الجسم. الحمل الزائد للحديد هو حالة يمتص فيها الجسم ويخزن الكثير من الحديد. بالإضافة إلى عمليات نقل الدم المتكررة ، تلعب زيادة امتصاص الحديد في الجهاز الهضمي دورا مهما في زيادة الحديد مع الثلاسيميا. يظهر الكويرسيتين، وهو فلافونويد شائع موجود في الفواكه والخضروات، تأثيرات بيولوجية متنوعة. **الهدف**: تقييم تأثير الكويرسيتين على معلمات الحمل الزائد للحديد في مرضى الثلاسيميا المعتمدين على نقل الدم. **الطريقة**: أجريت دراسة عشوائية مزدوجة التعمية بدلالة مجموعة الدواء الوهمي على 110 مريضا ب TDT، أكثر من 12 عاما، والذين تم علاجهم إما بالكويرسيتين أو كبسولة الدواء الوهمي يوميا (500 مجم) لمدة 3 أشهر. تم الحصول على عينة دم للمعلمات المختبرية عند خط الأساس وفي نهاية 3 أشهر. **النتائج**: في بداية للدراسة، لم تكن السمات الديموغرافية ومعلمات الحمل الزائد للحديد للمرضى ومجموعة الدواء الوهمي مختلفة إحصائيا، بينما بعد ثلاثة أشهر من الستخدام الكويرسيتين، كان هناك انخفاض كبير في مستويات الحديد في الدم ، UIBC ، فيريتين المصل ومعدل تشبع الفيريتين، وزيادة كبيرة في TIBC في المرضى مقارنة مع مجموعة الدواء الوهمي. **الاستنتاجات**: تظهر الدراسة الدور الهام للكويرسيتين في معلمات الحمل الزائد للحديد في مرضى الثلاسيميا المعتمدين على نقل الدم.

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INTRODUCTION

Thalassemia is a hereditary blood disorder prevalent in Mediterranean, Middle Eastern, and Southeast Asian people [1]. Hemoglobin gene mutations cause this autosomal recessive disease. Thalassemia carriers with one mutant gene may be asymptomatic. When both parents are carriers, each child has a 25% probability of getting thalassemia, 50% of becoming a carrier, and 25% of receiving two normal gene copies [2,3]. Transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) are crucial to treatment and patient care in thalassemia research. TDT involves severe beta or alpha thalassemia that requires lifelong transfusion therapy and medical care. However, NTDT includes milder varieties such as beta thalassemia intermedia, hemoglobin E/B, and others that do not require blood transfusions. NTDT patients may not need transfusions, but they still need medical supervision, including hemoglobin monitoring and disease-related consequences. The difference between TDT and NTDT allows doctors to customize thalassemia therapy and management regimens for each patient, improving care and results [4,5]. Iron, with an atomic number of 26, is a critical metallic chemical element for human health. Iron is abundant in nature and vital to the organism. Iron can quickly switch between ferrous (Fe^{2+}) and ferric (Fe^{3+}) oxidation states through oxidation-reduction processes. Iron metabolism and biochemical processes are complex [6]. This syndrome causes iron overload due to the complex relationship between blood transfusions and GIT iron absorption. Targeted iron burden management strategies require understanding this phenomenon's mechanisms. There are several reasons why thalassemia patients absorb more iron. Thalassemia increases erythropoietin (EPO) production, which produces new red blood cells. This raises iron levels, increasing GIT iron absorption. Second, boosting intestinal cell transferrin receptor expression helps the body absorb iron from the diet. The transport protein transferrin allows this. This increased receptor expression boosts GIT iron absorption. Last, thalassemia patients have more iron overload because they produce less hepcidin, a hormone that controls iron metabolism by limiting GI iron absorption. By understanding the intricate mechanisms of GIT iron absorption in thalassemia [7], iron toxicity from iron overload can cause cellular damage and organ malfunction, making it difficult to treat. Iron toxicity in human tissues is caused by a complex interaction of processes, revealing its complexity. The Fenton reaction, which happens in excess iron with H_2O_2 or reactive oxygen species, causes iron poisoning. Due to iron overload, tissues can undergo the Fenton reaction. Iron ions convert hydrogen peroxide into highly reactive hydroxyl radicals. These radicals can damage lipids, proteins, and DNA through numerous methods. Lipid peroxidation, which degrades cell membrane lipids, can produce harmful lipid metabolites and damage membranes. Protein misfolding and aggregation into insoluble clusters can affect cellular function, causing organ failure. Excess iron induces apoptotic cell death, demonstrating its negative impact on cell viability. By understanding the complex pathways of iron toxicity and how it impacts cellular function, we can understand how these things work and find solutions to reduce the health risks of iron excess [8,9]. Quercetin, derived from the Latin word "quercetum," meaning oak forest or Quercus (oak), is a major dietary flavonoid that has scientists interested. Quercetin, a yellow flavonoid, is a flavanol. It dissolves completely in lipids and alcohol. Hot water limits its solubility, whereas cold water eliminates it, illustrating this bioactive compound's diverse characteristics. Quercetin is found in many foods; however, it accounts for 75% of human flavanol intake. Since the body does not synthesize quercetin, dietary sources are needed to integrate it into physiological systems. We want to study quercetin's unique properties, dietary significance, health advantages, and medicinal uses. Collective study in this sector may reveal quercetin's many health benefits and enable creative approaches to use its bioactive qualities to improve global health [10]. In cell-free buffer solutions and the intracellular environment, quercetin has been shown to affect Fe (II)-induced hydroxyl radical (OH•) release. These investigations have shown that quercetin decreases luminescence due to the Fe (II)-dependent production of OH•, suggesting that it may modulate labile iron processes in cells. The fluorescent probe Phen Green SK (PGSK) confirmed that iron inside cells forms a chelation complex with quercetin that prevents producing OH• radicals. Quercetin, a bioactive molecule found in many fruits and vegetables, can chelate intracellular iron and reduce oxidative stress, making it a prospective therapeutic candidate. Oral quercetin is a promising candidate for research and therapeutic use due to its safety and absence of known adverse effects. Its capacity to permeate cell membranes via glucose transport proteins (GLUTs) makes it an effective intracellular iron chelator, especially in MDCK cells that exhibit the high-affinity glucose transporter GLUT1 [11].

METHODS

Study design and setting

This research employed a randomized placebo-group-led trial (RCT) study design. The study involved blood samples collected from both patients and placebo groups. The patient samples were divided into two groups: the quercetin group, comprising patients who received treatment during the study period, and the placebo group, consisting of patients who received a placebo treatment during the study period. Patients diagnosed with thalassemia routinely visited the

hematology clinic at the Thalassemia Hematology Center in Al-Kut Maternity and Pediatrics Hospital. They underwent transfusions and chelation therapy (Figure 1).

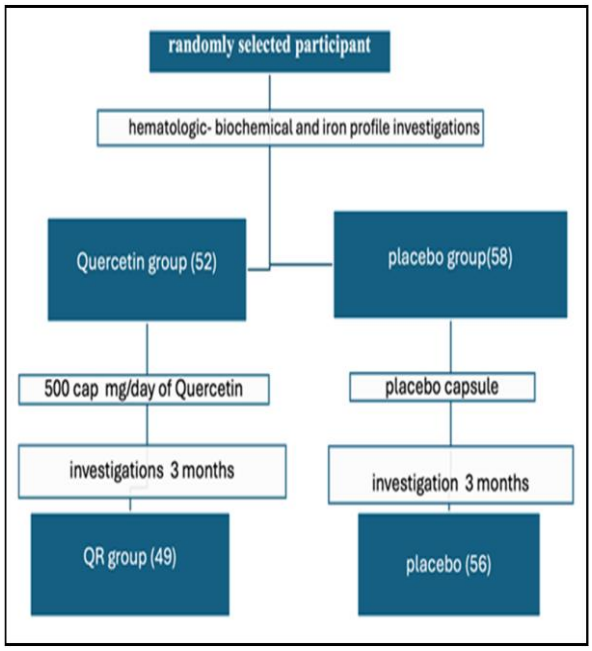

Figure 1: Flow chart of the study.

Outcome measurements

The enrolled patients were monitored for hemoglobin (Hb) levels and iron status. The diagnosis of blood transfusion-dependent thalassemia relied on clinical presentation, hematological indices, and hemoglobin electrophoresis. Patient selection for the study was conducted randomly and sorted into groups blindly. The study was conducted from May 2023 to the end of December 2023. Verbal and written consent was obtained from the patients or their guardians.

Inclusion criteria

Patients aged over 12 years with blood transfusion-dependent thalassemia were included in the study. Patients had to be registered at the Inherited Blood Disorders Center, agree to receive medication during the study period, and be present during the study period.

Exclusion criteria

Patients aged over 12 years with blood transfusion-dependent thalassemia were excluded if they refused to participate in the study. Patients with comorbidities such as heart failure, diabetes mellitus, viral hepatitis, and alloimmunization were excluded. Patients who had undergone a splenectomy were also excluded from the study.

Ethical consideration

The study protocol received approval from the Ethics Committee of the Medical College, University of Baghdad (Pharamacomuvb 23.3).

Intervention and outcome measurements

The diagram below illustrates the distribution of patients who were administered either quercetin or a placebo in a randomized, blinded manner. At the commencement of the study, there were fifty-two patients. However, after three months, three patients discontinued treatment: one due to travel outside Iraq and two due to poor compliance. Among the patients who were administered the placebo, there were 58 individuals at the start of the study. After three months, this number decreased to 56 patients. Each subject participating in the study, including those receiving treatment and those receiving a placebo, had 5 milliliters of venous blood collected via vein puncture. This blood was then divided nearly equally, with 2 milliliters allocated to Ethylenediamine Tetraacetic Acid (EDTA) tubes and 3 milliliters to serum tubes. The samples were collected in labeled EDTA and plain plastic tubes. After collection, the 3 milliliters of blood in the serum tubes were allowed to clot at room temperature (25 °C) for 1 hour. Subsequently, centrifugation was performed at 4000 revolutions per minute (rpm) for 5 minutes to separate the serum. The serum was then transferred using a micropipette and divided into five equal fractions across five test tubes. These fractions were used to analyze the biochemical parameters using commercially available kits.

Statistical analysis

Statistical analysis was conducted using SPSS version 20 statistical software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was utilized to assess the normal distribution of variables. Quantitative variables were expressed as mean ± standard deviation, and qualitative variables were presented as frequency (number and percentage). Intra-group changes were evaluated using the paired-samples t-test, while inter-group changes were analyzed using the independent t-test. Significance was defined as a p-value < 0.05 for all analyses.

RESULTS

Table 1 presents the demographic data of patients treated with QC and placebo. The sample selection was randomized, indicating no statistical difference between the two groups in terms of sex distribution. The male-to-female ratio was 1.3:1 in the QC group and 1.2:1 in the placebo group. The mean age of patients was 22.7 years in the QC group and 21.9 years in the placebo group (p=

0.1). In the QC group, 28 patients were treated with deferoxamine and 24 with deferasirox as iron chelators.

Table 1: Baseline characteristics of the participants

Item	QC	Placebo group	Total	*p* value
Male	30(57.7)	32(55.2)	62(56.4)	0.4
Female	22(42.3)	26(44.8)	48(43.6)	
deferoxamine	28(53.8)	------	----	
deferasirox	24(46.2)	-----	---	
≤ 22 years	30(57.7)	40(69)	70(63.6)	0.1
> 22 years	22(42.3)	18(31)	40(36.4)	
Age (year)	22.7±4.5	21.9±5.1	22.3±4.6	0.1

Values were expressed as frequencies, percentages, and mean±SD.

Tables 2 and 3 display hematological and biochemical parameters at the beginning of the study, showing no statistical differences between the groups. As blood samples were drawn before the blood transfusion, the hemoglobin (Hb) level for both groups was below 10 g/dL. Patients with a fever or splenectomy were excluded from the study.

Table 2: Hematological parameter of the QC and placebo groups

Item	QC (n=52)	Placebo (n=58)	*p* value
Hb (g/dl)	8.4±1.2	8.6 ±0.9	0.4
PCV (%)	26.0±4.5	26.7±4.2	0.4
RBC (10^6/µl)	3.8±0.3	3.6±0.6	0.6
MCV (f/l)	77.1±6.1	75.1±5.2	0.06
MCHC (g/dl)	31.2±1.9	30.7±1.9	0.1
MCH (pg)	24.8±2.1	24.4±2.2	0.3
WBC ($\times10^9$/µl)	8183.1±3.9	6581.6±2.2	0.1
Platelet ($\times10^{12}$/µl)	313.7±18.9	314.7±17.6	0.9

Values were expressed as mean±SD. Hb: hemoglobin, PCV: packed cell volum, RBC: red blood cells, MCV: mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, MCH: mean corpuscular hemoglobin, WBC: white blood cells.

Table 3: Biochemical parameter QC and placebo group

Item	QC	Placebo	*p* value
TSB (mg/dl)	2.3±1.0	2.2±0.6	0.6
Alkaline phosphate (U/L)	191.5±5.5	176.3±4.7	0.1
ALT (U/L)	28.3±2.9	32.4±2.4	0.4
AST U/L	28.7±2.6	32.7±2.1	0.3
Blood urea (mg/dl)	24.0±1.0	24.9±7.6	0.6
S.Cr (mg/dl)	0.8±0.4	0.7±0.1	0.1
Serum iron (µg/dL)	230.1±3.8	225.8±3.3	0.5
TIBC (µ/dL)	365.7±7.6	380.8±5.7	0.2
UIBC (µg/dL)	112.5±4.5	126.5±2.3	0.06
Serum ferritin (ng/mL)	2982.9±1.5	3112.7±4.7	0.5
Ferritin saturation (%)	0.64±0.07	0.61±0.07	0.1

Values were expressed as mean±SD. TSB: total serum bilirubin, SGOT: serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, S.Cr: serum creatinine, TIBC: Total iron binding capcity, UIBC: unsaturated iron-binding capacity.

The blood indices did not differ statistically between the groups. Patients with liver or renal disease were also excluded. Renal and liver function tests for both groups did not show statistical differences. At baseline, the mean serum iron level was 230.1±3.8 mcg/dL for the QC group and 225.8±3.3 mcg/dL for the placebo group (p= 0.5). The total iron-binding capacity (TIBC) for the QC group and placebo group was 365.7±7.6 and 380.8±5.7 mcg/dL, respectively (p= 0.2). Unsaturated iron-binding capacity (UIBC) was statistically insignificant between the QC and placebo groups (p= 0.06). The mean serum ferritin level was 2982.9±1.5 ng/mL for the QC group and 3112.7±4.7 ng/mL for the placebo group (p= 0.5). The difference in ferritin saturation percentage between the QC and placebo groups was statistically insignificant (p= 0.9), as shown in Tables 2 and 3. Table 4 presents the iron parameters for both the QC and placebo groups at the end of the study. The serum iron levels were 211.8±3.6 mcg/dL for the QC group and 232.9±4.7 mcg/dL for the placebo group, showing a statistically significant difference with a p-value of 0.01. The total iron-binding capacity (TIBC) underwent changes at the end of the study, decreasing in the QC group and increasing in the placebo group, with a p= 0.001. Similarly, there was an increase in unsaturated iron-binding capacity (UIBC) for the QC group and a decrease for the placebo group, with values of 105.1±4.3 and 142.1±2.6, respectively, and a p= 0.001. The changes in serum ferritin levels and ferritin saturation percentage were statistically significant for both groups, with p-values of 0.001 and 0.008, respectively.

Table 4: Iron parameter changes after 3 months of treatment of QC and placebo group

Item	QC (n=49)	Placebo (n=56)	*p*-value
Serum iron (µg/dL)	211.8±3.6	232.9±4.7	0.01
TIBC (µg/dL)	385.8±6.7	336.9±4.0	0.001
UIBC (µg/dL)	105.1±4.3	142.1±2.6	0.001
Serum ferritin (ng/mL)	2412±12.5	3168.4±46.2	0.001
Ferritin saturation (%)	0.57±0.06	0.63±0.1	0.008

Values were expressed as mean±SD.

Table 5 depicts the changes in iron parameters within the same groups (QC and placebo). In the QC group, there was a decrease in the levels of serum iron, unsaturated iron-binding capacity (UIBC), serum ferritin, and ferritin saturation percentage at the end of the three-month treatment with quercetin, all showing statistical significance with p-values of 0.001, 0.004, 0.001, and 0.01, respectively. Conversely, there was an increase in the level of total iron-binding capacity (TIBC) with a significant p-value of 0.001. In contrast, for the placebo group, at the end of the study period, there was an increase in all studied iron parameters except for TIBC, which decreased significantly with significant p-values. Table 6 presents the association between types of iron chelators and changes in iron parameters for the QC group. There was no statistically significant difference in serum iron levels between patients treated with

deferoxamine and those treated with deferasirox, both at baseline and after 3 months of supplementation with quercetin, with *p*-values of 0.7 and 0.8, respectively.

Table 5: Biochemical changes after 3 months of treatment with QC and placebo

Item	Base line values	After 3 months	*p* value
QC group (n=49)			
Serum iron (µg/dL)	226.91±37.1	211.8±36.2	0.001
TIBC (µg/dL)	361.5±77.1	385.8±67.3	0.001
UIBC (µg/dL)	113.7±46.4	105.1±43.9	0.004
Serum ferritin (ng/mL)	2914.3±148.6	2412±125.4	0001
Ferritin saturation (%)	0.64±0.07	0.57±0.06	0.01
Placebo group (n=56)			
Serum iron (µg/dL)	225.1±34.1	232.9±47.8	0.1
TIBC (µg/dL)	379.1±55.6	336.9±40.5	0.001
UIBC (µg/dL)	126.6±24.1	142.1±26.6	0.001
Serum ferritin (ng/mL)	3115.9±47.2	3168.4±46.8	0.001
Ferritin saturation (%)	0.62±0.07	0.63±0.1	0.04

Values were expressed as mean±SD.

Despite statistical changes in iron parameters over the course of the study for patients treated with either deferoxamine or deferasirox, these changes were not significant based on the type of iron chelator at the same time points of the study.

Table 6: Association between iron chelator types of the QC group and time of the study

Variable	Desferrioxamine (n=28)	Deferasirox (n=24)	*p* value
Serum iron (µg/dL)			
Baseline	228±36	231±41.1	0.7
After 3 months	212.6±35	210.8±36.9	0.8
p value	0.001	0.001	
TIBC (µg/dL)			
Baseline	362.3±74.6	369.5±80.5	0.7
After 3 months	387.0±58.9	384.5±77.0	0.9
p value	0.01	0.01	
UIBC (µg/dL)			
Baseline	114.2±40.4	110.5±51.9	0.7
After 3 months	103.5±38.5	106.9±50.1	0.6
p value	0.002	0.001	
Serum ferritin (ng/mL)			
Baseline	2559.0±999.6	3477.4±1916.9	0.03
After 3 months	2096.3±768.6	2769.0±1579.7	0.06
p value	0.001	0.004	
Ferritin saturation (%)			
Baseline	0.64±0.07	0.63±0.07	0.8
After3 months	0.58±0.07	0.56±0.06	0.2
p value	0.001	0.002	

Values were expressed as mean±SD.

DISCUSSION

Iron overload happens in people with thalassemia because they absorb more iron, need regular blood transfusions, don't make enough red blood cells, have low hepcidin levels, and don't get enough iron chelation therapy [12,13]. The use of quercetin as a supplement in patients with thalassemia is a recent subject; few articles are available about that. Quercetin is one of the most abundant flavonoids in the human diet and is known for its antioxidant and anti-inflammatory properties [14,15]. The current study shows that quercetin has a strong effect on iron levels in people who are iron-deficient. It lowers serum iron, serum ferritin, and other iron levels in patients who took quercetin supplements compared to those who did not take quercetin supplements. This finding aligns with the 2019 Hezaveh study, which involved 84 patients and demonstrated quercetin's ability to decrease iron overload parameters [16]. Researchers conducted other studies on animals to examine the impact of quercetin on iron levels. Numerous studies have discussed the various mechanisms through which quercetin lowers the iron levels in the human body. Quercetin contains multiple hydroxyl groups that allow it to form complexes with iron ions through chelation. Quercetin molecules bind to iron ions in this process, forming stable complexes that the body can excrete. By chelating iron, quercetin reduces the pool of free iron available for oxidative reactions and other processes [17–19]. Another way is by lowering the amount of free iron. This is because Fenton reactions, in which iron reacts with hydrogen peroxide to make reactive oxygen species, can cause oxidative stress and damage. Quercetin's chelation of iron reduces the concentration of free iron ions, thereby diminishing the potential for oxidative damage [20,21]. Some studies suggest that quercetin may also inhibit the absorption of dietary iron in the intestine. By chelating or forming complexes with iron in the digestive tract, quercetin may stop enterocytes from taking iron in, which means less iron gets into the bloodstream [22,23]. Quercetin may modulate the expression and activity of proteins involved in iron storage (e.g., ferritin) and transport (e.g., transferrin). We do not fully understand the exact mechanism by which quercetin modulates the expression and activity of iron storage proteins, and it may vary depending on the specific protein and cellular context. Several possible ways that iron metabolism might work have been suggested based on how gene expression is controlled by transcription factors or other controlling parts in the cell. Some examples are that it might change the activity of transcription factors such as Nrf2 or IRPs [24], which can then change the expression of ferritin, which is the main protein in cells that stores iron. It may also alter signaling pathways involved in cellular processes, such as those that deal with iron metabolism. By interacting with signaling molecules or receptors, quercetin may indirectly affect the expression

and activity of proteins involved in iron storage. For example, research has shown that quercetin starts the AMP-activated protein kinase (AMPK) pathway, which changes iron metabolism through signaling cascades further down the line [25,26]. Quercetin also changes hepcidin, a key regulator of iron homeostasis in the body. It controls how much iron is absorbed from the intestine, how much iron is released from macrophages, and how much iron is recycled from old red blood cells. Some evidence suggests that quercetin may influence hepcidin expression, potentially affecting overall iron balance and distribution [27,28]. Quercetin affects hepcidin in many ways, such as modulating the BMP/SMAD signaling pathway by interacting with key components involved in its activation or inhibition. Some research shows that quercetin can start SMAD signaling by increasing BMP expression, which might cause the production of more hepcidin [29]. It's possible that quercetin can stop IL-6 signaling or other inflammatory pathways that happen later on, which would lower the expression of hepcidin. This mechanism could be particularly relevant in conditions associated with chronic inflammation, such as thalassemia [30]. According to the above mechanism and the results of the current study, quercetin has a potential effect on iron overload in patients with thalassemia. It lowers serum iron and ferritin levels, which is a significant issue for those patients.

Study limitations

An important limitation of this study is the availability of iron-chelation treatments. During the study period, there was a shortage of deferoxamine, with many patients obtaining it on their own.

Conclusion

We strongly support the implementation of quercetin as a substantial dietary supplement to mitigate iron levels in thalassemia patients, especially in areas where medication is scarce and for indefinite periods of time. Furthermore, we propose that additional research endeavors incorporate more extensive patient cohorts and protracted observation durations.

Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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