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Discrepancies in Copper and Zinc Levels Among Iraqi Children with Thalassemia

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ABSTRACT

Background and Objective: Thalassemia is a chronic genetic disorder characterized by impaired hemoglobin synthesis, resulting in anemia, bone marrow expansion, and systemic iron overload. While iron metabolism in thalassemia has been widely studied, limited attention has been given to other essential trace metals. This study aimed to evaluate the impact of thalassemia on serum Cu and Zn levels in pediatric patients in Iraq, addressing a knowledge gap regarding micronutrient imbalances associated with the disease. **Materials and Methods:** This cross-sectional study was conducted on a sample of 120 children, including 60 diagnosed with thalassemia and 60 age- and sex-matched healthy controls. Serum concentrations of copper and zinc were measured using atomic absorption spectrophotometry. Statistical analysis was performed using appropriate parametric and non-parametric tests to determine the significance of differences between groups, with a $p<0.05$ considered statistically significant. **Results:** Thalassemic patients exhibited a statistically significant elevation in serum copper levels ($p<0.01$) and a marked reduction in serum zinc levels ($p<0.01$) compared to healthy controls. These alterations are likely linked to the hemolytic nature of the disease and the recurrent blood transfusions, which may disrupt normal trace metal metabolism. No significant associations were observed between metal levels and age or sex within the thalassemic group. **Conclusion:** This study highlights notable imbalances in copper and zinc levels among pediatric thalassemia patients in Iraq, underlining the necessity for regular trace metal monitoring and targeted nutritional interventions. Recognizing and managing these micronutrient disturbances may enhance clinical outcomes and quality of life. Future research should further explore the underlying mechanisms and therapeutic implications of these findings.

KEYWORDS

Pediatric thalassemia, trace, copper levels, zinc levels, hemoglobin disorders, nutritional deficiencies

INTRODUCTION

Thalassemia is a genetic hemoglobin disorder arising from mutations in the α or β globin genes, resulting in decreased or absent globin chain production, hemolysis, and ineffective erythropoiesis[1]. Clinical presentations range from asymptomatic carriers to severe anemia and hydrops fetalis, severe cases necessitate lifelong blood transfusions, leading to iron overload and consequent organ damage[2]. The Hb F and A2 levels are influenced by thalassemia types, age, and sex; in children aged 6-23 months, Hb F

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decreases and Hb A2 increases, suggesting age-dependent globin gene expression[3,4]. The β-thalassemia major (TM), sometimes referred to as Cooley's or Mediterranean anemia; β-thalassemia intermedia (TI); and β-thalassemia minor (trait or carrier) are the three primary forms of β-thalassemia, a genetic anemia caused by decreased or missing β-globin production. People with β-thalassemia minor are frequently heterozygous with β0 or β+ mutations, whereas patients with TM and TI are homozygous or compound heterozygous. There are also uncommon dominant variations[4,5]. From 6 to 24 months of age, TM is a severe form of anemia that requires frequent red blood cell transfusions. TM is usually discovered at this point, starting the transfusion procedure[6], if it was not discovered during pregnancy Untreated or insufficiently Stunted growth, jaundice, hyperpigmentation, muscle weakness, knock-knees, hepatosplenomegaly, leg ulcers, extramedullary hematopoiesis, and bone marrow expansion are some of the symptoms that transfusion recipients may exhibit[7-9]. The purpose of this study is to investigate and compare the serum concentrations of copper and zinc in Iraqi pediatric thalassemia patients and healthy controls, to identify potential trace metal imbalances and their clinical significance.

MATERIALS AND METHODS

Study population: This study included 70 Iraqi children diagnosed with thalassemia, of whom 60 successfully completed the biochemical analysis. The patients had a mean age of 8.5±3.2 years and an average BMI of 16.4±4.2. All participants were evaluated at Marjan Teaching Hospital in Babylon, Iraq, during September and October, 2024. Thalassemia diagnosis was confirmed through clinical symptoms, laboratory investigations, and hemoglobin electrophoresis.

A control group of 30 age-matched healthy children was included for comparison. The control group had a mean BMI of 17.22±2.9 and an average fasting serum glucose level of 90.4±8.8 mg/dL.

Anthropometric and biochemical measurements: The BMI-for-age was used as a standard measure to evaluate nutritional status in children, recognizing its relevance due to age and sex-specific variations. Fasting serum glucose levels were recorded for both groups, with thalassemic children showing an average of 104.5±4.2 8 mg/dL.

In thalassemia patients, BMI tends to decrease with age due to several disease-related factors such as growth retardation, frequent transfusions, iron overload, and potential nutritional deficiencies. Identifying BMI deviations early is crucial for minimizing associated health risks.

Blood sample collection and processing: Five milliliters of venous blood were collected from each participant using sterile plastic syringes and disposable needles. Blood samples were distributed into two gel tubes and two anticoagulant tubes. After allowing coagulation at room temperature for 15 min, samples were centrifuged at 3000 g for 5 min. The resulting serum was carefully separated and stored in sterile tubes for biochemical analysis.

Statistical analysis: The Chi-square (χ^2) test was used to assess associations between categorical variables in contingency tables. The Student's t-test was employed to compare continuous variables between the thalassemia and control groups. Spearman's rank-order correlation and Pearson's product-moment correlation were used to examine relationships between variables. A two-tailed $p<0.01$ was considered statistically significant. All statistical analyses were conducted using IBM SPSS version 26 on a Windows platform.

Ethical consideration: This study was conducted in compliance with the ethical principles. Ethical approval was obtained from the "Ethics Committee of the College of Pharmacy, University of Babylon", and written informed consent was obtained from the parents or legal guardians of all participants. Participants' data were kept confidential and used solely for research purposes. All procedures were designed to ensure minimal risk and full respect for the rights and well-being of the participants involved.

RESULTS AND DISCUSSION

The data suggested that there is no significant difference in the age of the children's patients and body mass index with thalassemia disease infection, as shown in p-value sequentially (0.1, 0.4), and this value is greater than 0.05 ($p \geq 0.05$), as shown in Table 1.

In children with thalassemia, a genetic hematologic disorder, the relationship between age and Body Mass Index (BMI) is being investigated in detail. Research has shown that younger patients with thalassemia major (30.4% of patients) had a higher BMI than older patients (70.4% of patients)[10]. This implies that, in comparison to their healthy peers, although BMI is a useful measure of overall health, it is not comprehensive, particularly when it comes to children whose growth and developmental stages are very important. Other factors, such as dietary practices, degree of exercise, and the severity of thalassemia, may also have an effect on these outcomes. Larger sample sizes and more comprehensive research are therefore required for conclusive results and comprehensive care approaches[11]. More research is needed to fully comprehend how age and BMI relate to children with thalassemia and to develop workable strategies for improving their overall health and nutritional status. For individualized guidance, speaking with a healthcare professional is recommended[12].

Building on previous discussions, it is evident that children's body mass and nutritional status are significantly impacted by the inherited disorder thalassemia. Our findings suggest that this condition significantly affects blood glucose levels; a statistically significant change in fasting serum glucose (FSG) is indicated by a p-value of 0.001 ($p<0.01$). Additionally, the study shows a strong correlation between pediatric thalassemia and changes in lipid profiles. With a p-value of 0.001, there were significant differences ($p<0.01$) in triglycerides (TG), total cholesterol (TC), High-Density Lipoprotein (HDL), Very Low-Density Lipoprotein (VLDL), and Low-Density Lipoprotein (LDL). These results demonstrate how thalassemia significantly affects children's metabolic profiles. Blood glucose levels fluctuate due to the considerable influence of thalassemia, a genetic blood condition[13]. In patients with thalassemia major, who require frequent blood transfusions, this is especially important since iron excess can have an impact on endocrine systems, including insulin secretion[14]. The intricacy of these relationships is shown by recent research showing diverse effects on insulin and glucose levels across various forms of thalassemia and other anemias[15]. According to research, insulin resistance is present in 27.5% of thalassemia patients, and a significant percentage of these individuals have been diagnosed with diabetes or prediabetes[16]. Serum ferritin levels and the length of blood transfusions are two of the many variables linked to this resistance[17]. Children with transfusion-dependent thalassemia may experience dyslipidemia as a result of the disorder's disruption of lipid metabolism[18]. This illness is characterized by increased. There are serious cardiovascular risks associated with triglycerides, decreased HDL, and an elevated total cholesterol to HDL ratio[19]. Thus, routine lipid profile monitoring is crucial for the early identification and treatment of any possible anomalies in thalassemia patients[20].

The most common metal in the brain, iron, is essential for many biological processes. Through transferrin-mediated endocytosis, it enters the brain. Iron balance is maintained by ferritin, a 24-subunit iron storage protein, whose presence in exosomes suggests a role in controlling systemic iron homeostasis. A p-value of 0.001 ($p<0.01$) in the study showed that patients with thalassemia had substantial changes in these parameters shown in Table 2.

Transferrin, which is mostly produced in the liver, testes, and central nervous system, is necessary to deliver iron to erythrocytes. It binds ferric iron and prevents water from entering the two coordination sites when an anion, typically carbonate, is present. Current results demonstrate substantial differences with a p-value of 0.001 ($p<0.01$), suggesting that thalassemia has a strong impact on some iron-related parameters. Because thalassemia, a genetic hematologic disorder, commonly results in iron overload in young patients due to repeated transfusions, effective iron management measures are required[21].

Table 1: Comparison of biochemical and anthropometric parameters between patients (n = 60) and control (n = 30) groups

Parameter	Patients group (n = 60) Mean±SD	Control group (n = 30) Mean±SD	p-value
Age year	8.5±3.2	10.2±2.4	0.1
BMI	16.4±4.2	17.22±2.9	0.4
FSG (mg/dL)	104.5±4.2	90.4±8.8	0.001**
TG (mg/dL)	123.8±20.4	90.7±12.6	0.001**
TC (mg/dL)	104.746±18.269	145.5±22.4	0.001**
HDL-C (mg/dL)	18.4±3.1	25.2±2.3	0.001**
VLDL-C (mg/dL)	24.6±3.3	18.8±2.7	0.001**
LDL-C (mg/dL)	53.4±13.2	91.774±20.1	0.001**

Data represented as Mean±SD, NS: Non-significant differences at ($p \geq 0.05$), *Significant differences at ($p < 0.05$), **Significant differences at ($p < 0.01$), FSG: Fasting serum glucose, TG: Triglycerides, TC: Total cholesterol, HDL-C: High-Density Lipoprotein Cholesterol, VLDL-C: Very-Low-Density Lipoprotein Cholesterol and LDL-C: Low-Density Lipoprotein Cholesterol

Table 2: Serum levels of ferritin, Copper (Cu), and Zinc (Zn) in patients (n = 60) and control (n = 30) groups

Parameter	Patients group (n = 60) Mean±SD	Control group (n = 30) Mean±SD	p-value
Ferritin (ng/mL)	3114.2±788.3	98.14±19.12	0.001**
Cu (µg/dL)	75.1±8.631	102.634±2.132	0.001**
Zn (µg/dL)	61.365±12.320	75.110±14.226	0.001**

Data represented as Mean±SD, NS: Non-significant differences at ($p \geq 0.05$), *Significant differences at ($p < 0.05$) and **Significant differences at ($p < 0.01$)

Ferritin, an iron storage protein, is a crucial measure of iron status; growth retardation is associated with hyperserotonemia in children with thalassemia[22]. Iron chelation therapy is used to treat iron overload, however, potential adverse effects and administration challenges may make adherence challenging. More study is needed to develop more effective and patient-friendly iron control strategies for kids with thalassemia[23,24].

With a mean serum ferritin concentration of 1,560.9 µg/L and 45.71% of patients having serum ferritin concentrations >2,500 µg/L, hyperserotonemia has been substantially associated with growth retardation in juvenile thalassemia patients. These results demonstrate how iron dysregulation may affect a child's growth and general development if they have thalassemia[25,26]. Iron overload in thalassemia is indicated by transferrin saturation (TfS) values more than 75%. TfS levels may rise to 80 and 100% or even greater in certain situations. Growth abnormalities may result from this iron excess and high ferritin levels. According to one study, 77% of children with thalassemia were underweight, and 65.71% of them were low in stature[27,28].

The findings show that the serum Copper (Cu) levels of thalassemia patients and the healthy control group differ significantly. Patients with thalassemia had a mean Cu level of 75.1 µg/dL with an 8.6 standard deviation, while the control group had a higher mean Cu level of 102.6 µg/dL with a 42.1 standard deviation. Given the statistical significance of this discrepancy, a thorough investigation of the possible underlying mechanisms is necessary.

An important trace metal, copper is crucial for several physiological activities, such as iron metabolism, enzyme activity, and immune system maintenance[29]. Numerous elements pertaining to the pathophysiology of the condition and its treatment may be responsible for the decreased Cu levels seen in thalassemia patients[30].

Possible explanations for reduced copper levels in thalassemia patients

Iron overload and chelation therapy: Patients with thalassemia frequently have frequent blood transfusions, which can result in iron overload. Iron chelation therapy is used to lessen this. Although it works well to lower iron levels, chelation therapy may unintentionally bind to other trace metals, such as copper, decreasing their bioavailability[31].

Nutritional deficiencies: Because of chronic disease and the body's heightened nutrient requirements, thalassemia is frequently linked to nutritional deficiencies. The reduced serum copper levels seen in these patients may be caused by inadequate food intake or copper malabsorption[32].

The metabolism of copper depends heavily on the liver. Iron overload is a common cause of liver problems in thalassemia patients[33], which can affect the liver's capacity to maintain copper homeostasis and result in lower serum copper levels[34].

Inflammation and oxidative stress: These conditions are prevalent in thalassemia and can affect trace element metabolism. Copper metabolism may be changed by oxidative damage and inflammatory cytokines, which could lead to decreased serum levels[35,36].

The study results show a significant difference in serum Zinc (Zn) levels between pediatric thalassemia patients and healthy controls. Thalassemia patients had a mean zinc level of 61.3 µg/dL with a standard deviation (SD) of 12.3, whereas the control group had a higher mean zinc level of 75.1 µg/dL with an SD of 14.2. This finding underscores the impact of thalassemia on zinc metabolism and warrants further discussion.

Potential reasons for reduced zinc levels in thalassemia patients

Chronic hemolysis and increased demand: Chronic hemolysis is a hallmark of thalassemia[37], which raises the body's need for vital nutrients like zinc. Depleted zinc levels could result from this increased demand, particularly in young patients who are still growing and developing[38].

Frequent blood transfusions: Zinc metabolism may be impacted by routine blood transfusions, a standard treatment for thalassemia. Blood transfusions supply vital red blood cells, but they can also cause trace element imbalances, which may result in less zinc available[39].

Dietary intake and absorption: Zinc consumption in children with thalassemia may be impacted by dietary restrictions or a lack of appetite brought on by their condition. Furthermore, gastrointestinal function and zinc absorption efficiency may be impacted by the chronic character of the condition[40].

Oxidative stress and inflammation: Zinc metabolism may be hampered by the increased oxidative stress and persistent inflammation that thalassemia patients frequently experience. The therapy of thalassemia is made more difficult by the fact that zinc is essential for antioxidant defense and that its deficiency might worsen oxidative damage[41].

The reported drop in zinc levels in children with thalassemia has significant clinical implications. Zinc is essential for several biological processes, such as immune response, enzyme activity, and cellular growth and repair[42]. For young children, zinc deficiency can lead to major problems such as delayed wound healing, poor development, and a compromised immune system.

CONCLUSION

This study reveals significant disturbances in copper and zinc levels among pediatric thalassemia patients in Iraq, characterized by elevated copper and reduced zinc concentrations. These imbalances, potentially resulting from chronic hemolysis and repeated transfusions, highlight the importance of routine trace metal assessment. Integrating micronutrient monitoring and tailored supplementation into clinical care may support better management of thalassemia and improve patient outcomes. Further research is warranted to investigate the mechanisms behind these alterations and to evaluate the effectiveness of corrective interventions.

SIGNIFICANCE STATEMENT

Thalassemia is a lifelong inherited condition that disrupts hemoglobin production, leading to anemia, enlarged bone marrow, and excessive iron accumulation in the body. This study explores the impact of thalassemia on the concentrations of essential trace metals, specifically Copper (Cu) and Zinc (Zn), in addition to another parameter in pediatric patients in Iraq.

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