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CALCIUM-PHOSPHORUS AND IRON METABOLISM IN CHILDREN WITH MAJOR BETA-THALASSEMIA

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Abstract

β-thalassemia is a widely prevalent inherited blood disorder that results in disrupted iron metabolism due to iron accumulation, while also influencing calcium metabolism and exacerbating clinical outcomes. The research included analyses from 30 children aged 6-11 years who had regularly received blood transfusions from 2019 to 2023, with a control group of 15 healthy children of similar age. Alongside the general blood analysis parameters, the study measured the levels of iron, ferritin, calcium, phosphorus, vitamin D, ferroportin, hepcidin, and fibroblast growth factor-23 (FGF-23) in the blood serum, comparing these with the control group. The study revealed that, in patients with major beta-thalassemia, the accumulation of iron and ferritin in the blood serum was associated with a decrease in hepcidin ($p<0.001$), while a deficiency in vitamin D ($p<0.001$) led to an increase in FGF-23 levels ($p<0.05$). The correlation analysis between the studied markers showed that an increase in FGF-23 levels in the blood serum not only affects calcium-phosphorus metabolism but also iron metabolism. The findings obtained may be significant for the diagnosis and treatment planning of major β-thalassemia in the future.

Keywords: *β-thalassemia major; vitamin D; hepcidin; ferroportin; FGF-23*

1. Introduction

Thalassemia is a widespread genetic blood disorder that is especially prevalent in areas with high malaria transmission, including the Mediterranean, the Middle East, and parts of Asia. This inherited condition arises from mutations in the genes responsible for producing hemoglobin, leading to an imbalance in the synthesis of the globin chains [1, 2]. As a result, this imbalance hampers the proper formation of red blood cells, causing ineffective erythropoiesis and chronic anemia. Individuals with thalassemia often need regular blood transfusions to maintain sufficient levels of hemoglobin in their bloodstream. Beyond the primary issue of iron

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overload, which is characteristic of the disorder, there is also significant disruption in the metabolism of calcium and phosphorus. These disturbances in mineral homeostasis further complicate the pathophysiology of thalassemia, contributing to various complications such as bone disease and organ dysfunction. Therefore, thalassemia requires complex management strategies to address both the blood-related issues and the mineral metabolism disturbances that arise as part of the condition's multifaceted nature [3, 4, 5].

The imbalance in calcium-phosphorus metabolism contributes to the skeletal complications seen in thalassemia patients, such as osteopenia, osteoporosis, and deformities, especially in the craniofacial bones. Over time, patients with thalassemia exhibit characteristic bone changes, particularly in the facial bones of the skull, as a result of metabolic disturbances. As per the World Health Organization (WHO), thalassemia affects around 300,000 individuals globally, with over 250 million carriers of the disease. Among these, homozygous β-thalassemia presents more severe clinical manifestations compared to other forms of the disease [1, 6, 7].

In thalassemia, iron accumulation occurs due to repeated blood transfusions, leading to a substantial body iron overload, which can cause damage to vital organs such as the heart, liver, and endocrine glands. While iron overload is the primary concern, calcium-phosphorus disturbances significantly exacerbate skeletal issues in these patients. The relationship between iron metabolism and bone metabolism remains an area of active research, particularly in the context of new biomarkers that could provide insight into these complex processes [8, 9].

Iron metabolism in thalassemia is regulated by hepcidin, a key hormone that controls iron homeostasis by inhibiting iron absorption in the gut and promoting iron sequestration in macrophages. Hepcidin levels are often elevated in iron overload conditions but can also be influenced by inflammatory processes, which are common in chronic diseases such as thalassemia. Ferroportin, another critical protein in iron export, also plays a significant role in regulating systemic iron levels, and its dysfunction can contribute to the dysregulation of iron homeostasis in thalassemia patients [10, 11,12].

Recent research has also highlighted the role of Fibroblast Growth Factor 23 (FGF-23) in bone metabolism. FGF-23 regulates phosphate metabolism by inhibiting phosphate reabsorption in the kidneys, which may have implications for bone health, particularly in the context of chronic diseases like thalassemia. Elevated FGF-23 levels have been observed in patients with bone metabolism disturbances, including those with thalassemia [13, 14].

Calcium plays a crucial role in bone metabolism, as it is a key component of bone structure and function. Disruptions in calcium homeostasis can lead to bone demineralization and an increased risk of fractures, which is often observed in patients with chronic diseases like thalassemia [15].

This study aims to explore the relationship between markers of iron metabolism, specifically hepcidin and ferroportin, and bone metabolism markers, such as FGF-23, in children with major β-thalassemia. By examining these relationships, we seek to gain a better understanding of the metabolic disturbances in thalassemia and to improve the diagnostic tools available for monitoring bone health and the effectiveness of treatments in these patients. This research is essential for advancing our understanding of the complex metabolic disruptions in thalassemia and developing better management strategies for these patients.

2. Materials and Methods

The study cohort consisted of 30 children aged 6-11 years (primary group) who received treatment at the Thalassemia Center of the Republic of Azerbaijan from 2021 to 2023. The control group included 15 healthy children of corresponding age.

The indicators of calcium-phosphorus metabolism, alongside iron metabolism, were assessed in the children included in the study. Furthermore, the levels of hepcidin, ferroportin, and FGF-23 proteins in blood serum were determined.

Blood samples were analyzed at the Scientific Research Laboratory of the Department of Biological Chemistry at Azerbaijan Medical University. The general blood analysis parameters were determined using the impedance method. The levels of iron, calcium, and phosphorus minerals in blood serum were measured by the colorimetric method using reagent kits from the “Human” company (Germany). The levels of ferritin, hepcidin,

ferroportin, and FGF-23 proteins in blood serum were determined by the "ELISA" method, and measurements were performed using the “Star Fax” immunoferment analyzer.

Statistical analysis of the data was carried out using the SPSS-16 program with standard methods of descriptive statistics. During the statistical processing of the obtained results, the Fisher and Wilcoxon-Mann-Whitney criteria were also used.

3. Results and Discussion

Among the children in the main group (n=30) included in the study, 3 (10%) received transfusions once a month, 21 (70%) received transfusions twice a month, and 6 (20%) received transfusions 3-4 times a month at the Thalassemia Center of the Republic of Azerbaijan. All children were regularly prescribed calcium or vitamin D supplements by a hematologist.

Of the 24 children with splenomegaly (80%), 18 (75%) also exhibited hepatomegaly. Before each transfusion, a complete blood count, and the levels of iron, ferritin, calcium, and phosphorus in the blood serum were investigated for all children included in the study. In all children of the main group, the hemoglobin levels were found to be below normal, while the serum iron and ferritin levels were higher than the internationally accepted normative values.

Hypocalcemia and hypophosphatemia were observed in 12 children (40%) and 1 child (3.3%), respectively, in the main group. Vitamin D levels were found to be below normal in the entire patient group. Specifically, mild deficiency was observed in 12 children, moderate deficiency in 8 children, and severe deficiency in 10 children. According to internationally accepted standards, a vitamin D level of 20-30 ng/ml is considered mild deficiency, 10-20 ng/ml is moderate deficiency, and below 10 ng/ml is considered severe deficiency. The vitamin D level in the main group was 16.7 ± 1.42 ng/ml, ranging from 5.1 to 28.5 ng/ml. This was 2.2 times lower ($p<0.001$) compared to the healthy control group (Table 1).

Table1. Iron and Calcium Metabolism Parameters in Children Aged 0-5 Receiving Transfusions with Severe β-Thalassemia (M±m) (min.-max.)

Parameters	Main group (n=30)	Control group (n=25)
Hemoglobin, g/dL	9,3 ± 0,1 (8,2-10,4) *	13,9 ± 0,05 (13,6-14,3)
Ferritin, ng/ml	1233 ± 25.6 (931.2-1655.1) *	96.2 ± 15.3 (76.2-114.6)
Fe+ , µg/L	26.8 ±1.6 (18.7-36.2) *	10.2 ± 0.5 (9.2-12.6)
25OH-D Vitamin, ng/ml	16.7 ± 1.42 (5.1-28.5) *	37.4 ± 1.2 (32.4-49.5)
Ca 2+, mg/dL	8.4±0.2 (7.3-9.0) *	9.2 ± 0.3 (8.5-9.8)
P+, mg/dL	4.2 ± 0.6 (3.5-5.0)	4.6 ± 0.3 (4.3-5.0)
Hepsidin, ng/ml	6.2 ± 0.3 (3.1-12.2) *	18.1 ± 0.5 (12.5-25.6)
Ferroportin, pg/ml	0.22 ± 0.05 (0.16-0.23)	0.17 ± 0.03 (0.11-0.17)
FGF-23, pg/ml	128.2 ± 2.4 (96.7-161.1) *	56.1 ± 1.8 (40.3-66.5)

Note: * – Statistical significance of the difference compared to the control group ($p<0.05$)

The level of FGF-23 protein in the serum of the main group was found to be 2.3 times higher ($p<0.001$) compared to the control group. No statistically significant difference ($p=0.621$) was observed in the levels of ferroportin, a representative of membrane proteins, when compared to the control group.

In patients with severe β-thalassemia, increased serum iron and ferritin levels are accompanied by a decrease in hepcidin. It is hypothesized that this reduction in hepcidin is related to a decreased absorption of iron from the duodenal villi through a feedback mechanism. This can be considered as a disruption in the regulation of iron metabolism. The lack of a statistically significant difference in ferroportin levels further confirms that the decrease in hepcidin, without membrane damage to cells, facilitates its compensatory mechanisms.

Some studies have found a correlation between vitamin D deficiency and elevated levels of FGF-23, suggesting that it is directly associated with disturbances in calcium-phosphate metabolism. High levels of FGF-

23 could be used as a valuable laboratory marker by hematologists to assess bone metabolism in patients [12, 13].

4. Conclusion

Thus, the findings of this study may lead to several practical recommendations. The determination of hepcidin and ferroportin levels, alongside iron metabolism indicators in children with severe β-thalassemia, could contribute to a deeper understanding of the molecular mechanisms behind the accumulation of excessive iron in the body and may assist in future advancements in treatment. The measurement of FGF-23 in children with severe β-thalassemia could also be useful in the early detection of disturbances in calcium-phosphate metabolism and in implementing timely measures to address these issues, thereby improving the clinical outcomes of patients.

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