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**G.E. Hamidova<sup>1,2</sup>, G.I. Azizova<sup>1</sup>, I.J. Shahverdiyeva<sup>1</sup>, G.A. Jafarova<sup>1</sup>**

## Calcium and iron metabolism in children with major beta-thalassemia

<sup>1</sup>Azerbaijan Medical University, Baku  
<sup>2</sup>International Prime Hospital, Baku, Azerbaijan

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Beta-thalassemia major ( $\beta$ -TM) is an inherited blood disorder characterized by ineffective erythropoiesis and chronic anemia, which often necessitates blood transfusions. Beyond iron overload, disturbances in calcium and phosphorus metabolism contribute significantly to skeletal complications in these patients.

**Aim.** This study investigates the relationship between iron and bone metabolism markers in children with  $\beta$ -TM to optimize the correction of iron overload and related complications.

**Material and methods.** A cohort of 30 children aged 6–11 years with  $\beta$ -TM, receiving regular blood transfusions, was compared to 25 age-matched healthy controls (control group). Blood samples were analyzed for markers of calcium and phosphorus metabolism, including serum calcium, phosphorus, vitamin D, and fibroblast growth factor 23 (FGF-23) levels, along with iron metabolism markers such as ferritin, hepcidin, and ferroportin.

**Results.** Significant findings include elevated serum ferritin and iron levels in  $\beta$ -TM patients, along with a decrease in hepcidin ( $p < 0.001$ ). Vitamin D deficiency ( $p < 0.001$ ) was observed, correlating with increased FGF-23 levels ( $p < 0.05$ ). These findings suggest a reciprocal relationship between calcium and phosphorus, and iron metabolism in  $\beta$ -TM.

**Conclusion.** The results highlight the critical interplay between iron and bone metabolism in  $\beta$ -TM. FGF-23 could serve as a key marker for bone metabolism disturbances, and the regulation of hepcidin and ferroportin may offer insights into managing iron overload and related complications. The research was carried out in accordance with the principles of the Declaration of Helsinki. The informed consent of the patients was obtained for conducting the studies.

The authors declare no conflict of interest.

**Keywords:**  $\beta$ -thalassemia major, vitamin D, hepcidin, ferroportin, fibroblast growth factor 23 (FGF-23).

### Кальцієвий та залізний обмін у дітей із великою бета-таласемією

**G.E. Hamidova<sup>1,2</sup>, G.I. Azizova<sup>1</sup>, I.J. Shahverdiyeva<sup>1</sup>, G.A. Jafarova<sup>1</sup>**<sup>1</sup>Азербайджанський медичний університет, м. Баку<sup>2</sup>International Prime Hospital, м. Баку, Азербайджан

Велика бета-таласемія ( $\beta$ -TM) – це спадкове захворювання крові, що характеризується неефективним еритропоезом і хронічною анемією, яка часто потребує регулярних гемотрансфузій. Окрім перевантаження залізом, порушення кальцієво-фосфорного обміну суттєво сприяють розвитку скелетних ускладнень у цих пацієнтів.

**Мета** – вивчення взаємозв'язку між показниками обміну заліза та маркерами кісткового метаболізму в дітей із  $\beta$ -TM для оптимізації корекції перевантаження залізом і пов'язаних ускладнень.

**Матеріали та методи.** У дослідженні охоплено 30 дітей віком 6–11 років із  $\beta$ -TM, які отримували регулярні гемотрансфузії, та 25 практично здорових дітей відповідного віку (контрольна група). У зразках крові визначали показники кальцієво-фосфорного обміну, зокрема рівень кальцію, фосфору, вітаміну D та фактора росту фібробластів 23 (FGF-23), а також маркери обміну заліза (феритин, гепсидин і феропортин).

**Результати.** У пацієнтів із  $\beta$ -TM виявлено достовірне підвищення рівня феритину та сироваткового заліза, а також зниження рівня гепсидину. Встановлено дефіцит вітаміну D, що корелював із підвищеним рівнем FGF-23 ( $p < 0,05$ ). Отримані дані свідчать про взаємозв'язок між кальцієво-фосфорним та залізним обміном при  $\beta$ -TM.

**Висновки.** Результати підкреслюють важливу взаємодію між обміном заліза та кістковим метаболізмом при  $\beta$ -TM. FGF-23 може розглядатися як ключовий маркер порушень кісткового обміну, а регуляція гепсидину та феропортину відкриває перспективи для оптимізації корекції перевантаження залізом і пов'язаних ускладнень.

Дослідження виконано відповідно до принципів Гельсінської декларації. На проведення досліджень отримано інформовану згоду батьків пацієнтів.

Автори заявляють про відсутність конфлікту інтересів.

**Ключові слова:**  $\beta$ -таласемія мажор, вітамін D, гепсидин, феропортин, фактора росту фібробластів 23 (FGF-23).

Thalassemia is a prevalent inherited blood disorder, particularly common in regions with high malaria incidence, such as the Mediterranean, the Middle East, and parts of Asia. The condition results from mutations in the genes responsible for

hemoglobin production, leading to an imbalance in globin chain synthesis and ineffective erythropoiesis. This results in chronic anemia, which requires frequent blood transfusions to maintain adequate hemoglobin levels. In addition to iron over-

load, which is a hallmark of thalassemia, disturbances in calcium and phosphorus metabolism play a critical role in the pathophysiology of the disease. The early diagnosis of hereditary metabolic diseases in children plays a critical role in preventing severe outcomes and improving quality of life [4,5].

The imbalance in calcium and phosphorus metabolism contributes to the skeletal complications seen in patients with thalassemia, 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 beta-thalassemia ( $\beta$ -TM) presents more severe clinical manifestations compared to other forms of the disease [1,12].

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 and 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 [2,3].

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 patients with thalassemia [7].

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 [6].

This study *aims* to explore the relationship between markers of iron metabolism, specifically hep-

cidin and ferroportin, and bone metabolism markers, such as FGF-23, in children with major  $\beta$ -TM. 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.

### Material and methods of the study

The cohort study consisted of 30 children aged 6–11 years (Main group) who received treatment at the Thalassemia Center of the Republic of Azerbaijan from 2021 to 2023. The Control group included 25 healthy children of the corresponding age.

The indicators of calcium and 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. Continuous variables are presented as mean  $\pm$  standard deviation ( $M \pm SD$ ). Statistical significance was set at  $p < 0.05$ .

The research was carried out in accordance with the principles of the Declaration of Helsinki. The informed consent of the patients was obtained for conducting the studies.

### Results of the study and discussion

Among the children in the Main group ( $n=30$ ) included in the study, 3 (10%) received transfu-

sions 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 (80%) children with splenomegaly, 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 (40.0%) children and 1 (3.3%) child, 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 (40.0%) children, moderate deficiency in 8 (26.7%) children, and severe deficiency in 10 (33.3%) 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  $16.7 \pm 1.42$  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 (see Table).

The study found that children with  $\beta$ -TM had significantly higher serum ferritin ( $1233 \pm 25.6$  ng/ml) and iron levels ( $26.8 \pm 1.6$   $\mu$ g/L) compared to controls ( $96.2 \pm 15.3$  ng/ml and  $10.2 \pm 0.5$   $\mu$ g/L, respectively). Hepsidin levels were significantly lower in the study group ( $6.2 \pm 0.3$  ng/ml vs.  $18.1 \pm 0.5$  ng/ml,  $p < 0.001$ ), supporting the hypothesis of reduced iron regulation. FGF-23 levels were also significantly higher in  $\beta$ -TM patients ( $128.2 \pm 2.4$  pg/ml vs.  $56.1 \pm 1.8$  pg/ml,  $p < 0.001$ ), suggesting a disturbance in phosphate metabolism.

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  $\beta$ -TM, 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 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 [9,10].

Table

**Iron and calcium metabolism parameters in children aged 0–5 receiving transfusions with severe  $\beta$ -thalassemia,  $M \pm m$  (min.–max.)**

Parameters	Main group (n=30)	Control group (n=25)	p - value
Hemoglobin (g/dL)	$9.3 \pm 0.1$ (8.2–10.4)	$13.9 \pm 0.05$ (13.6–14.3)	<0.001
Ferritin (ng/ml)	$1233.0 \pm 25.6$ (931.2–1655.1)	$96.2 \pm 15.3$ (76.2–114.6)	<0.001
Fe <sup>+</sup> ( $\mu$ g/L)	$26.8 \pm 1.6$ (18.7–36.2)	$10.2 \pm 0.5$ (9.2–12.6)	<0.001
25OH-D Vitamin (ng/ml)	$16.7 \pm 1.42$ (5.1–28.5)	$37.4 \pm 1.2$ (32.4–49.5)	<0.001
Ca <sup>2+</sup> (mg/dL)	$8.4 \pm 0.2$ (7.3–9.0)	$9.2 \pm 0.3$ (8.5–9.8)	<0.01
P <sup>+</sup> (mg/dL)	$4.2 \pm 0.6$ (3.5–5.0)	$4.6 \pm 0.3$ (4.3–5.0)	0.135
Hepsidin (ng/ml)	$6.2 \pm 0.3$ (3.1–12.2)	$18.1 \pm 0.5$ (12.5–25.6)	<0.001
Ferroportin (pg/ml)	$0.22 \pm 0.05$ (0.16–0.23)	$0.17 \pm 0.03$ (0.11–0.17)	0.621
FGF-23 (pg/ml)	$128.2 \pm 2.4$ (96.7–161.1)	$56.1 \pm 1.8$ (40.3–66.5)	<0.001

Note: p – statistical significance of the difference compared to the Control group.

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 and phosphate metabolism. High levels of FGF-23 could be used as a valuable laboratory marker by hematologists to assess bone metabolism in patients [7,11].

Neonatal screening programs play an essential role in the early diagnosis of hereditary metabolic diseases, such as  $\beta$ -TM, enabling timely intervention to prevent severe health complications. As highlighted in T.V. Holota's review on neonatal screening, integrated programs provide a modern approach to the early detection of such conditions, which can lead to more effective treatment strategies and improved outcomes for patients, particularly in managing the disruptions in iron and bone metabolism observed in patients with major  $\beta$ -TM [4].

## Conclusions

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 major  $\beta$ -TM, 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.

This study provides significant insights into the relationship between iron and bone metabolism in children with major  $\beta$ -TM. The results suggest that iron overload and calcium and phosphorus disturbances, particularly through the modulation of FGF-23 and hepcidin, play pivotal roles in the pathophysiology of the disease. Monitoring these biomarkers can aid in the early detection of bone health issues and improve therapeutic strategies.

*The authors declare no conflict of interest.*

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### Відомості про авторів:

**Hamidova Gulnara Eldar** – аспірантка каф. біохімії Азербайджанського медичного університету. E-mail: gulnara.hamidova@primehospital.az. <https://orcid.org/0009-0003-0742-0091>.

**Azizova Gulnara Ibrahim** – д.мед.н., проф., зав. каф. біохімії Азербайджанського медичного університету. E-mail: gezizova@amu.edu.az. <https://orcid.org/0009-0007-9334-2315>.

**Shahverdiyeva Ilaha Jamshid** – ст.н.с. каф. біохімії Азербайджанського медичного університету. E-mail: i.shahverdiyeva@amu.edu.az. <https://orcid.org/0000-0003-3368-1124>.

**Jafarova Gulnara Alisha** – ст.н.с. каф. біохімії Азербайджанського медичного університету. E-mail: xeyalcafarov4@gmail.com. <https://orcid.org/0000-0001-8318-7920>.

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