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Association of ghost Na^+/K^+-ATPase activity and 2,3-bisphosphoglycerate levels with deferoxamine use in β-thalassemia

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β-thalassemia is set of genetic illnesses defined by abnormalities in the synthesis of the beta chains of hemoglobin. A broad spectrum of phenotypes is observed, they are presented inside red blood cells. 2,3-bisphosphoglycerate (2,3-bpg) is a key component that controls the hemoglobin's oxygen binding. The study examined the effect of the drug deferoxamine on the levels of 2,3-bisphosphoglycerate, Na^+/K^+ ATPase in patients with thalassemia type beta. The study was a case-control study. A total of 130 individuals were involved: a total of 70 patients with β-thalassemia, 60 healthy controls. The initial group was carefully selected based on the patients' clinical symptoms. The 2,3-bisphosphoglycerate level was determined by using the enzyme-linked immunesorbent assay (ELISA), while Na^+/K^+ ATPase was measured by ghost. Patients exhibited elevated 2,3-bisphosphoglycerate levels in comparison to the control group, accompanied by elevated Na^+/K^+ ATPase levels in patients compared to the controls. Elevated levels of 2,3-bisphosphoglycerate dehydrogenase in β-thalassemia patients are due to increased hemolysis, as it is formed within the red blood cell as a result of glycolysis. The level of sodium potassium ATPase, present in the red blood cell membrane, also rises during red blood cell breakdown.

Keywords: β-thalassemia; Na^+/K^+-ATPase; 2,3-bisphosphoglycerate.

Introduction

β-thalassemia is a genetic disorder that results from mutations or deletions in the beta-globin gene (Ansharullah et al., 2025). The globin gene, located on chromosome 11, is responsible for the synthesis of hemoglobin. In the absence of this gene, or in cases where it is not fully expressed, the body experiences a deficiency in hemoglobin, which can lead to a variety of health complications. Beta chains are a subject of interest in this field (Galanello et al., 2011).

There are several forms of beta thalassemia, including beta-thalassemia minor, this particular form of beta-thalassemia arises from a mutation in one of the beta globin genes. However, it seldom results in substantial interference with the capacity of the hemoglobin protein to carry out its customary operations (Shafique et al., 2021). Individuals who are carriers of the thalassemia minor gene are predominantly clinically asymptomatic. However, they may occasionally manifest moderate anemia (Muncie et al., 2009).

In β-thalassemia intermediate patients suffering from this syndrome possess two defective genes yet still manage to produce a certain amount of β-globin. The disease is characterized by severe anemia, fatigue, weakness, shortness of breath, bone deformities, moderate jaundice, and an enlarged spleen due to a lack of beta polypeptide in the hemoglobin (Muncie et al., 2009; Shafique et al., 2021).

β-thalassemia major, which is also called Cooley anemia, is a condition where both genes are not working well together. It might be missing entirely. HbF (fetal hemoglobin) is present at birth and symptoms usually start to appear when the child is six months old (Cappellini, 2012).

Untreated patients usually show the following signs of illness: anemia that requires transfusions, an enlarged spleen, bone abnormallities, slow growth, a unique face (Cappellini, 2012). 2,3-bisphosphoglycerate (2,3-BPG) is a key component that controls the hemoglobin's oxygen binding. It works by lowering hemoglobin's oxygen affinity and moving the oxygen dissociation curve to the right (StatPearls, 2023). Later research showed that 2,3-DPG is a major controller of Hb's affinity to oxygen (Bunn, 2022). A result of the anaerobic Embden-Meyerhof pathway, the glycolytic intermediate 2,3-DPG has been discovered to be present at the highest amounts of all organic phosphates in human erythrocytes (Haidas et al., 1975). Na^+/K^+-ATPase (EC 7.2.2.13) it is a membranous enzyme has a key role in controlling nerve cell excitability by electrochemical gradients maintaining via the active transport of sodium and potassium ions across the cell membrane (Al-Rikabi et al., 2021).

This enzyme uses the energy released from the hydrolysis of ATP to ADP + P_i to pump three sodium ions out of the cell and two potassium ions into the cell simultaneously, generating sodium-potassium ion gradients across membrane of the cell membrane (Zhou et al., 2008).

Patients are required to regularly administer DFO (marketed as Desferal) to eliminate excess iron resulting from hemolysis of blood cells. The human body lacks a natural mechanism for eliminating excess iron, leading to its accumulation in essential organs, especially the heart and liver. This phenomenon produces numerous harmful toxic effects (Taher et al., 2017; Pivovarov et al., 2019).

Materials and methods

The scientific committee of the Maternity and Children's Hospital and Centre for Thalassemia in Babylon province obtained ethical approval. The aims of this investigation were communicated to all study participants to acquire verbal acceptance from the attending patients. The research was approved by the scientific committee of the Chemistry Department of Babylon College of Science. The local ethics committee reviewed and approved the research protocol, subject data, and consent on 26/11/2024 under document number 1977.

Blood samples were obtained from patients with beta thalassemia who were registered at the Thalassemia Center at the Maternity and Children's Hospital in Babylon, Iraq, to conduct this case-control study. The ages of the patients who participated in the study ranged from 1–25 years. A total of 130 cases were categorized into two groups: 70 patients with beta thalassemia aged 25 ± 1 years, 60 healthy controls aged 25 ± 2 years. All clinical data were documented, including the duration of treatment, the number of doses, and repeated blood transfusions. Patients with a history of heart and kidney disease and patients who had had their spleen removed were excluded and divided according to the duration of treatment.

Samples were collected according to established protocols. 2 mL of blood was extracted and transferred to an EDTA tube to ensure ho-

mogeneity and shaken well. The blood sample was stored at –20 °C. The EDTA was then transferred to the laboratory for immediate centrifugation at 3,000 × g. Following this procedure, plasma was separated into separate Eppendorf tubes, according to standard laboratory protocols. Meanwhile, the lower cell layer was immediately processed to prepare red blood cell membrane ghosts for measuring sodium potassium ATPase activity, while plasma was used to determine 2,3-bisphosphoglycerate levels. The 2,3-bisphosphoglycerate was measured by Enzyme Linked Immunosorbent Assay (ELISA) Sunlong kit, China, while Na^+/K^+-ATPase was measured by spectrophotometer Biolabo (France).

The mean and standard deviation (SD) presentations of the data using T-test and linear regression analysis, which helped to find noteworthy variations between the groups and the normalcy of continuous variables was evaluated. The results were compared using the Tukey test with Bonferroni correction. P-values were considered highly significant if less than 0.001 and significant if less than 0.05.

Results

As shown in Table 1, the levels of 2,3 bisphosphoglycerate were significantly elevated ($P < 0.01$) in the patients' group. Also as shown in Table 2, the levels of 2,3 bisphosphoglycerate were significantly elevated in the patients' group ($P < 0.01$) when compared with the control group according sex distribution.

Table 1
2,3-bisphosphoglycerate (ng/mL) in patients and controls

Groups	N	Mean ± SD
Controls	60	17.6 ± 6.3
Patients	70	59.5 ± 25.0**

Note: ** – $P < 0.01$.

Table 2 shows clear and significant differences in 2,3-bisphosphoglycerate levels between males and females when comparing patients and the control group. Healthy males recorded a mean level of 17.7 ± 5.4 ng/mL, while male patients showed a significantly higher level of 49.2 ± 15.6 ng/mL ($P < 0.01$). The results also showed an even greater difference in females, with the mean biomarker level in the control group being 16.9 ± 6.4 ng/mL, compared to a significantly higher level of 67.1 ± 27.1 ng/mL in female patients ($P < 0.01$). These differences confirm that the increase in 2,3-BPG levels is associated with disease status in both sexes, although the increase was more pronounced in females than in males.

Table 2
2,3-bisphosphoglycerate (ng/mL) in patients and controls according sex (mean ± SD)

Sex	Control	N (control)	Patients	N (patients)
Male	17.7 ± 5.4[a]	30	49.2 ± 15.6[b]	35
Female	16.9 ± 6.4[a]	30	67.1 ± 27.1[b]	35

Note: different letters indicate values which reliably differed one from another within one line of the table according to the results of comparison using the Tukey test with Bonferroni correction.

Table 3 shows significant differences in 2,3-bisphosphoglycerate levels between different age groups when comparing patients to healthy individuals. The 1–10 year age group showed a mean level of 45.9 ± 13.6 ng/mL in the patients compared to 18.2 ± 5.5 ng/mL in the control group. The 11–20 year age group recorded the highest mean biomarker among patients at 64.2 ± 26.3 ng/mL compared to 16.4 ± 6.4 ng/mL in healthy individuals, while 2,3-BPG levels in patients in the 21–25 year age group reached 59.4 ± 20.7 ng/mL compared to 17.6 ± 6.0 ng/mL in the control group. These results show a significant increase ($P < 0.01$) in the levels of this biomarker across all age groups in patients compared to the healthy control group, confirming the association between age and disease status in determining 2,3-BPG levels.

The ROC curve results show the excellent diagnostic value with sensitivity and specificity (98.5%, 95.4%) respectively and area under curve is 98.5% with cut off value 20.2 ng/mL, as shown in Table 4.

Table 3
2,3-bisphosphoglycerate (ng/mL) in patients and controls grouped by age (mean ± SD)

Age groups, years	N (controls)	Controls	N (patients)	Patients
1–10	22	18.2 ± 5.5[a]	22	45.9 ± 13.6[b]
11–20	27	16.4 ± 6.4[a]	31	64.2 ± 26.3[b]
21–25	11	17.6 ± 6.0[a]	17	59.4 ± 20.7[b]

Note: see Table 2.

Table 4
The ROC curve parameters of 2,3-bisphosphoglycerate

Area	SE	Sensitivity	Specificity	P-value	Asymptotic 95% confidence interval	
					lower bound	upper bound
98.5%	0.025	98.5%	95.4%	<0.01	0.874	0.970

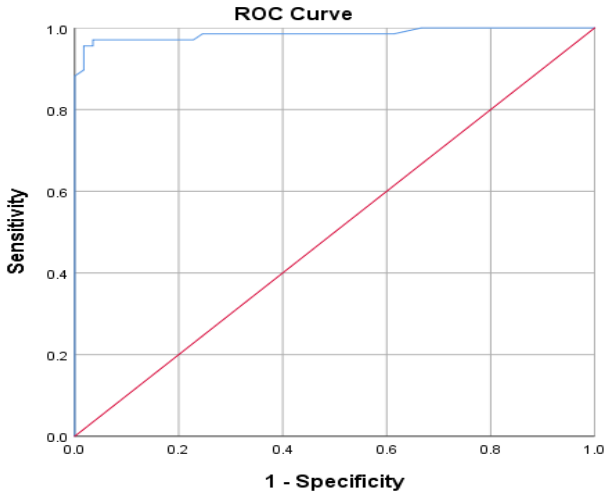

Fig. 1. The ROC of 2,3 bisphosphoglycerate

Table 5 shows a significant increase in Na^+/K^+-ATPase enzyme levels in the patient group compared to the control group, with a mean concentration of 569.4 ± 168.0 µg/g in patients versus 327.4 ± 66.1 µg/g in healthy individuals, indicating high statistical significance ($P < 0.01$). This marked increase in enzyme activity suggests the presence of a physiological disorder or changes associated with the disease, making this indicator important for assessing the condition and accurately describing the differences between the two groups.

Table 5
Na^+/K^+-ATPase (µg/g) in patients and controls (mean ± SD)

Groups	N	Mean ± SD
Controls	60	327 ± 66
Patients	70	569 ± 168**

Note: ** – $P < 0.01$.

Table 6 shows significant differences in Na^+/K^+-ATPase enzyme levels between males and females when comparing patients and the control group. The average enzyme concentration in healthy males was 330.8 ± 70.4 µg/g, while in male patients it was significantly higher, reaching 582 ± 157 µg/g ($P < 0.01$). Females in the control group showed an average of 320 ± 54 µg/g, while females with the disease recorded a significantly higher level of 550 ± 179 µg/g ($P < 0.01$). These results indicate that enzyme activity is clearly elevated in patients of both sexes, with only slight variations between males and females, reflecting a strong correlation between physiological differences and disease state in determining Na^+/K^+-ATPase levels.

Table 7 shows clear and significant differences in Na^+/K^+-ATPase enzyme levels between patients and the control group across different age groups. The 1–10 year age group recorded the highest enzyme level in the patient group, with an average of 607.0 ± 174.6 µg/g, compared to 331.2 ± 68.8 µg/g in healthy individuals. The 11–20 year age group recorded an average of 561.1 ± 177.3 µg/g in patients, compared to 323.6 ± 55.6 µg/g in the control group. Finally, the enzyme

levels in the 21–25 year age group reached 497.0 ± 136.0 µg/g in patients, compared to 320.7 ± 63.4 µg/g in healthy individuals. These results confirm a significant increase ($P < 0.01$) in enzyme activity across all age groups of patients, clearly indicating the effect of age and disease status on Na^+/K^+-ATPase levels.

Table 6
Na^+/K^+-ATPase (µg/g) in patients and controls according sex (mean ± SD)

Sex	Control	N (control)	Patients	N (patients)
Male	331 ± 70[a]	30	582 ± 157[b]	35
Female	320 ± 54[a]	30	550 ± 179[b]	35

Note: see Table 2.

Table 7
Na^+/K^+-ATPase (µg/g) in patients and controls according age (mean ± SD)

Age groups, years	N (controls)	Controls	N (patients)	Patients
1–10	22	331 ± 69[a]	22	607 ± 175[b]
11–20	27	324 ± 56[a]	31	561 ± 177[b]
21–25	11	321 ± 63[a]	17	497 ± 136[ab]

Note: see Table 2.

As shown in Table 8, the ROC curve results show the excellent diagnostic value with sensitivity and specificity (92.6%, 64.9%) respectively and area under curve 92.2% with cut off value 340 (µg/g).

Table 8
The ROC curve parameters of Na^+/K^+-ATPase

Area	SE	Sensitivity, %	Specificity, %	P-value	Asymptotic 95% confidence interval	
					lower bound	upper bound
92.2	0.025	92.6	64.9	<0.01	0.874	0.970

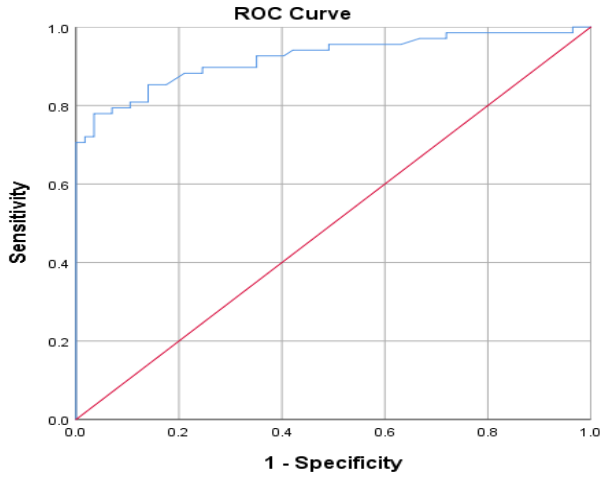

Fig. 2. The ROC of Na^+/K^+-ATPase

Discussion

In the present study, patients' 2,3BFG levels were higher than those of the controls because of lower tissue oxygen supply and increased hemolysis, which caused more 2,3-BPG production to improve oxygen release from hemoglobin. Oxygen availability to tissues is improved by this shift rightward in the dissociation curve (Geering, 2008). Along with this, there was a surplus of unpaired alpha-globin chains in β thalassemia precipitate, producing oxidative damage and membrane instability. This pressure could indirectly increase 2,3-BPG synthesis to offset compromised oxygen delivery (Patel et al., 2023). Hemolysis is the destruction of RBCs, leading to the release of intracellular contents – including 2,3-BPG – into plasma/serum.

These findings are consistent with Sadiq et al. (2024), who proposed that the increased 2,3-DPG levels in β thalassemia heterozygotes lead to lower oxygen affinity, with P50 (the partial pressure at which hemoglobin is 50% saturated with oxygen) shifted to the right by around 2 mmHg above the normal mean. Despite reduced hemoglobin levels, this physiological adaptation guarantees sufficient tissue oxygenation (Sadiq et al., 2024).

In human red blood cells, 2,3-bisphosphoglycerate (2,3-BPG) is a crucial modulator of hemoglobin's affinity for binding oxygen. This anionic molecule, present at quantities about 5 mmol/L, stabilizes deoxygenated hemoglobin (T-state) by occupying its central cavity and establishing salt bridges with β-chain residues (lysine and histidine). This interaction diminishes hemoglobin's oxygen affinity by around 30%, promoting oxygen release to tissues (Webb et al., 2022).

The core cavity of deoxygenated hemoglobin (the T-state) is bound by 2,3-bisphosphoglycerate (2,3-BPG), which controls the release of oxygen from hemoglobin. This interaction stabilizes the T-state conformation, characterized by a diminished affinity for oxygen. Consequently, hemoglobin is predisposed to discharge oxygen into tissues. The presence of 2,3-BPG changes the oxygen dissociation curve to the right, indicating that at any certain partial pressure of oxygen, hemoglobin will release a greater amount of oxygen than it would in the absence of 2,3-BPG. This technique is especially crucial in circumstances like hypoxia or anemia, when tissues need increased oxygen supply. The control is essential for effective oxygen delivery, particularly in scenarios when oxygen demand is heightened or supply is diminished (Jorge et al., 2016; Patel et al., 2023). Studies and biochemical understanding indicate that when red cells lyse, the 2,3-BPG they contain may be released into the surrounding plasma or serum. The ROC curve results show excellent diagnostic value with sensitivity and specificity (98.5%, 95.4%) respectively and area under curve 98.5% with cut off value 20.2 ng/mL. While 2,3-BPG levels represent erythrocyte adaptation to anemia in beta thalassemia, they do not provide a definite diagnosis. Their significance is in understanding disease pathogenesis and directing care, rather than as a solitary diagnostic marker, and no other research has confirmed this yet (Omar et al., 2017).

In this study, the activity of Na/K ATPase in patients could be attributed to a compensatory mechanism for adaptation to low oxygen levels and its physiological function within the cell. This was in line with Omar et al. (2017). The study revealed that the activity in healthy individuals exhibited much lower values compared to patients with iron deficiency, with the difference being highly significant. This suggests that the activity of Na^+/K^+-ATPase may be utilized for the evaluation of individuals with hematological diseases or disorders (Zhang et al., 2022). More precisely, studies have shown that Na^+/K^+-ATPase activity is diminished in milder forms of thalassemia (thalassemia-like cells), but it is elevated in severe alpha-thalassemia and β-thalassemia cells. This contradictory rise in Na^+/K^+-ATPase activity in extreme cases may signify a compensatory reaction to heightened cellular stress. In thalassemia, oxidative damage caused by free globin chains drastically alters the enzyme's function, which has been linked to the development of membrane defects (Hirsch etv al., 2017).

In this study, the ROC curve results show the excellent diagnostic value with sensitivity and specificity (92.6%, 64.9%) respectively and area under curve 92.2% with cut off value 340 (µg/g), while Omar et al. (2017) suggest that measuring Na^+/K^+-ATPase activity can serve as an additional biomarker for differentiating thalassemia from other blood disorders, with reported sensitivity and specificity values as high as 94% and 93%, respectively, at certain cut-off values (Omar et al., 2017).

In β-thalassemia patients, 2,3-bisphosphoglycerate in red blood cells is mostly due to glycolytic pathway activity and hemoglobin regulation of oxygen supply. Bisphosphoglycerate mutase converts 1,3-bisphosphoglycerate to 2,3-BPG in the Rapoport-Luebering pathway during glycolysis in RBCs. A balance between energy production and oxygen delivery is shown by bypassing an ATP-generating phase (Lyu et al., 2024). Hypoxia results from persistent anemia and inadequate erythropoiesis in beta-thalassemia. RBCs boost 2,3-BPG production to adapt. The increased 2,3-BPG binds exclusively to hemoglobin's deoxygenated beta subunits, maintaining the deoxy state and lowering oxygen affinity. This action helps tissues release oxygen, counteracting hypoxia despite beta-thalassemia's decreased or faulty he-

moglobin (Sun et al., 2017).The enhanced glycolysis in β thalassemia increases 2,3-BPG levels due to metabolic changes and surface enzyme activity in RBCs undergoing rapid destruction and production. β-Thalassemia patients compensate by increasing oxygen release capability despite anemia (Fibach et al., 2017).

Conclusion

In conclusion, levels of 2,3-bisphosphoglycerate represent the adaptation of red blood cells to anemia in beta thalassemia, but they do not provide a specific diagnosis. Their importance lies in understanding the causes of the disease and guiding care, not as a single diagnostic sign. No other research has confirmed this to date. High sodium potassium ATPase activity in patients results from a compensation. mechanism to adapt to the low oxygen and physiological cycle in the cell. Measuring sodium potassium ATPase activity serves as an additional biomarker to differentiate thalassemia from other blood disorders.

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