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Evaluation the Role of Melatonin and Cortisol in Thalassemia Patients with Sickle Cell Anemia

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A B S T R A C T

The study included the estimation of some biochemical variables in thalassemia patients with sickle cell anemia of both sexes, comparing them with a group of healthy control. The study included (43) cases collected from Al-Hadba Hospital in Mosul city and was divided into two groups: the first group consisted of 20 patients, and the second group included 23 healthy cases. Levels of melatonin and cortisol were analyzed, in addition to other blood indicators such as hemoglobin (Hb), white blood cell count (WBC), and platelets (PLT). The results showed that thalassemia patients with sickle cell anemia suffered from a significant decrease in hemoglobin levels compared to healthy individuals, along with varying increases in white blood cell and platelet counts. Moreover, melatonin concentration decreased, and cortisol increased significantly compared to the control group, with clear differences in some biomarkers between the two studied age categories. Higher levels of both melatonin and cortisol were recorded in females compared to males.

1 Introduction

Thalassemia considered a complex hemoglobin disorder, resulting from the simultaneous inheritance of the HbS mutation responsible for sickle cell anemia, and beta-thalassemia mutations that lead to a disruption in the production of the beta chain of hemoglobin. This disorder is classified into two main types: the HbS/β^o-thalassemia type, which is characterized by a complete absence of beta chain (β^o) production and presents clinical symptoms similar to homozygous sickle cell anemia (HbSS), and the HbS/β^+-thalassemia type, which is characterized by partial production of the beta chain (β^+) (Ware et al., 2017). Clinically, patients experience chronic anemia, vaso-occlusive crises, in addition to complications such as splenomegaly, recurrent infections, and growth delays. The severity of symptoms varies depending on the type of accompanying thalassemia mutation and the number of red blood cells carrying fetal hemoglobin (HbF). In terms of treatment, the care strategy resembles that used in sickle cell anemia, including the use of hydroxyurea to increase HbF levels, pain management, and prevention from infection. Patients are also evaluated for cases of iron overload due to repeated blood transfusions. The effectiveness of gene therapy in improving hematological indicators in some complex cases, which opens up future therapeutic prospects for this complicated group of patients (Brousse et al., 2021). Melatonin is an indole hormone derived from the essential amino acid tryptophan, and is primarily

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produced in the pineal gland. The synthesis process begins with the conversion of tryptophan into serotonin, which is then converted into melatonin in the pineal gland through a series of enzymatic reactions that are primarily dependent on light (Claustrat et al., 2005). Melatonin plays an important role in preventing cellular damage resulting from chronic oxidative stress, which is a key component in chronic blood diseases such as sickle cell anemia, thalassemia, and sickle cell-thalassemia, where large amounts of free radicals are released due to the chronic breakdown of red blood cells and recurrent inflammatory reactions (Hardeland, 2021). The use of melatonin supplements as an adjunct treatment for diseases associated with oxidative stress, including sickle cell anemia and thalassemia, is being explored, due to its high safety and effectiveness in restoring oxidative balance within the body (Ahmed et al., 2020). In addition, cortisol is a steroid hormone that belongs to the glucocorticoids group and is secreted from the zona fasciculata in the adrenal cortex. This hormone is derived from cholesterol (Nelson & Cox, 2017). In the context of chronic diseases like sickle cell disease thalassemia, elevated or irregular levels of cortisol have been observed, especially during pain episodes or inflammatory crises. This persistent increase may lead to increased cell damage, sleep disturbances, and worsening pain perception, and it is also believed to contribute to the weakening of chronic immune response. Additionally, the dysregulation of the HPA axis in these cases is usually accompanied by a decrease in melatonin secretion, exacerbating oxidative stress and inflammation (El-Far et al., 2023). Monitoring cortisol levels in patients with sickle cell anemia and thalassemia may provide important information about the internal inflammatory condition and the degree of physiological stress the body is experiencing (Mohamed et al., 2023). In hereditary blood disorders such as decreased hemoglobin (Hb) levels reflect disease severity due to chronic hemolysis or ineffective erythropoiesis (Cappellini et al., 2020; Ware et al., 2017). It has been shown that an increase in white blood cells (WBC) often indicates the presence of chronic inflammation, even in the absence of infection. White blood cells also contribute to the onset of vascular obstruction by interacting with sickle-shaped red blood cells and endothelial cells, leading to microvascular occlusion. (Darbari et al., 2013; Taher et al., 2018). Platelets (PLT), although essential for blood clotting, may increase in response to chronic congestion or bone marrow stimulation. In patients, an increase in platelet count is associated with an increased risk of clots and strokes, especially in children (Ataga et al., 2007; Musallam et al., 2012).

2. Previous studies

Many studies dealt with this disease as I already mentioned in the introduction.

3. MATERIALS AND METHODS

3.1 *Sample Collection:* Blood samples were collected from 43 participants (20 SCA/Thalassemia, 23 healthy controls) at Al-Hadba General Hospital, Mosul, between November 2024 and March 2025. Approvals and consents were obtained, and analyses were performed at Al-Ahliya External laboratories.

3.2 Patient Group:

This group consisted of 20 blood samples from individuals diagnosed with hereditary blood disorders (SCA/Thalassemia), aged between 2 and 48 years.

3.3 Control Group:

This group consisted of 23 blood samples from healthy individuals aged between 2 and 50 years, with no history of blood disorders.

3.4 Preparation of Serum:

Preparation of Serum Samples Venous blood (5 mL) was collected from the arm using a sterile 5 mL syringe. Blood was transferred into clean, dry gel-separator tubes (yellow-capped). Tubes were left at room temperature for 10–15 minutes to clot, then centrifuged at 3000 × g for 10 minutes. The serum was separated using a micropipette and transferred to clean, dry tubes for biochemical analysis.

3.4 Determination of Selected Biochemical Parameters in Serum:

Determination of Melatonin Concentration in Serum

Use Instruction General Melatonin ELISA Kit BT LAB Cat. NOE1013Hu (BT LAB, n.d.), Determination of Cortisol in Serum Use Instruction General Cortisol ELISA Kit BT LAB Cat .NO EA0010Ge (Bain et al., 2017). Hemoglobin was measured using the microhematocrit method by collecting blood in capillary tubes filled with heparin and then centrifuging at 12,000 × g for 5 minutes. Afterwards, the volume of packed cells was measured using a standard table, and the concentration of hemoglobin was then inferred accordingly (Dacie & Lewis, 1995). White Blood Cell Count (WBC) WBC count was determined using a hemocytometer. Blood was diluted and loaded into the counting chamber. Cells in four large squares were counted, and total WBC count was calculated using the formula:

WBC count = n × 50, where n is the number of squares counted (Dacie & Lewis, 1995). Platelet Count Platelet count was determined by mixing blood with ammonium oxalate solution, loading into a counting chamber, and allowing the platelets to settle. Using a microscope (40×), platelets in five small squares of the central large square were counted (Sood, 1996).

3.5 Statistical analysis:

Statistical analysis of the results was carried out to determine the differences between the patients and control groups at the probability of ($P \leq 0.05$) using the statistical program SPSS version 18 (Hinton, 2004).

4. Results and discussion

4.1 Levels of variables in the serum of thalassemia patients with sickle cell anemia compared to a healthy group:

4.1.1. Melatonin

Melatonin levels were significantly higher in patients with SCA/thalassemia (0.89 ± 0.10 ng/ml) compared to the control group (0.45 ± 0.60 ng/ml), likely reflecting a compensatory antioxidant response to chronic oxidative stress resulting from anemia, indicating an increased defensive mechanism against the disease (Yilmaz et al., 2023).

4.1.2. Cortisol:

Cortisol levels were increased in patients with sickle cell anemia/thalassemia (0.88 ± 0.11 ng/ml) compared to the control group (0.50 ± 0.063 ng/ml), indicating that patients with these conditions experience chronic physiological and psychological stress, leading to elevated cortisol levels due to the chronic nature of the psychological and physiological stress associated with the disease (Hassan et al., 2022; Ibrahim et al., 2023).

4.1.3. Hemoglobin:

The average Hb was significantly low in patients (7.86 ± 0.63 g/dL) compared to controls (12.70 ± 0.27 g/dL). This decrease was attributed to the combined effect of sickle cell anemia and thalassemia on the blood's ability to carry oxygen due to the increased destruction of red blood cells and dysfunction in hemoglobin production, as confirmed by the study (Oliveira et al., 2020).

4.1.4. White Blood Cells:

The results of this study indicated that the average white blood cell count in the serum of healthy individuals was (7.27 ± 0.43 *103/mL). Meanwhile, in the sickle cell thalassemia group, it was (15.78 ± 2.24 *103/mL), with a high statistical significance. The increase in the white blood cell count indicates a significant difference due to a chronic inflammatory response resulting from repeated tissue damage caused by structural changes in red blood cells, as confirmed by this study (Ibrahim et al., 2022).

4.1.5. Platelets:

The results did not show a significant difference between the patients (266.82 ± 33.99*103/ml) and the healthy individuals (293.00 ± 12.76*103/ml), even though their average was slightly lower in patients with the condition. Recent studies indicate that the number of platelets may vary among patients depending on the degree of spleen damage and the activity of the bone marrow (Kumar et al., 2021).

Table 1. Levels of variables in the serum of thalassemia patients with sickle cell anemia compared to the healthy group

Biochemical parameter	Group	Mean±Std.Error
Melatonin(ng/mL)	Control	0.45 ± 0.06
	Sickle cell/Thalassemia	0.89 ± 0.102*
Cortisol (ng/mL)	Control	0.50 ± 0.063
	Sickle cell/Thalassemia	0.88 ± 0.11*
Hb(g/dl)	Control	12.70 ± 0.27
	Sickle cell/Thalassemia	7.86 ± 0.063*
WBC(×10³/ml)	Control	7.27 ± 0.43
	Sickle cell/Thalassemia	15.78 ± 2.24*
PLAT(×10³/ml)	Control	293.00 ± 12.76
	Sickle cell/Thalassemia	266.82 ± 33.99

*Indication of a significant meaningful difference

4.2 Analysis of age-related outcomes of thalassemia sickle cell anemia:

4.2.1. Melatonin

Melatonin levels declined during adolescence (13–18: 0.53 ± 0.41 ng/mL) compared to children 0.69 ± 0.41), then rose again in adults 0.68 ± 0.45). This age-related pattern aligns with developmental changes and is influenced by sleep, stress, and chronic illness (Zhao et al., 2022; Elias & Bdaiwi, 2023).

4.2.2. Cortisol:

The age group under 12 years recorded a higher average of cortisol (0.95 ± 0.47) compared to the 13–30 years group (0.66 ± 0.18). The decrease may be due to therapeutic effects or insufficiency in the adrenal-pituitary-hypothalamic axis among the young patient group (Lupien et al., 2009).

4.2.3. Hemoglobin:

Hb levels were highest in children (8.01 ± 1.24 g/dL) and declined with age, reaching 7.28 ± 0.45 g/dL in adults. This decline is linked to disease progression and transfusion-related complications (Voskaridou et al., 2020).

4.2.4. White Blood Cells

White blood cell levels were highest in children (12.16 ± 6.38×10³/mL) and decreased with age. This indicates early immune hyperactivity that may stabilize with treatment. This increase in children reflects the inflammatory response associated with recurrent episodes in sickle cell anemia and thalassemia, which is consistent with findings that indicated leukocytosis as an indicator of chronic inflammation in children suffering from these conditions (Aygun et al., 2014).

4.2.5. Platelets:

The average platelet count decreased from (274.08 ± 154.97) in children under 12 years to (243.25 ± 87.84) in youth, indicating a relative improvement in the inflammatory condition or a long-term therapeutic effect. A study supports this result, showing that elevated PLAT is common among younger individuals due to splenic hyperactivity or recurrent inflammation (Ataga et al., 2012).

Table 2. Analysis of age-related outcomes of thalassemia sickle cell disease

Age group	Biochemical parameter	Mean±Std. Error
Less than 12	Melatonin(ng/mL)	0.93 ± 0.47
13-30 year		0.78 ± 0.25*
Less than 12	Cortisol (ng/mL)	0.95 ± 0.47*
13-30 year		0.66 ± 0.18
Less than 12	Hb(g/dl)	7.84 ± 2.83
13-30 year		7.95 ± 1.90*
Less than 12	WBC(×10³/ml)	17.92 ± 9.56*
13-30 year		8.83 ± 2.33
Less than 12	PLAT(×10³/ml)	274.08 ± 154.97*
13-30 year		243.25 ± 87.84

*Indication of a significant meaningful difference

4.3 Analysis of sex results for thalassemia patients with sickle cell anemia:

4.3.1. Melatonin:

Melatonin levels were higher in females (0.93 ± 0.14 ng/mL) compared to males (0.80 ± 0.09 ng/mL). This result is consistent with studies, as melatonin levels increase in females under normal conditions due to the effect of estrogen, and females may have a greater ability to regulate oxidative stress (Zhao et al., 2021).

4.3.2. Cortisol

Cortisol was also higher in females (0.93 ± 0.15 ng/mL) vs. males (0.77 ± 0.08 ng/mL), possibly reflecting stronger adrenal responses to chronic stress in females with thalassemia sickle cell (Serjeant, 2021).

4.3.3. Hemoglobin

Females showed higher Hb levels (8.06 ± 0.81 g/dL) than males (7.40 ± 0.96 g/dL), potentially due to better treatment adherence or transfusion response (Al-Khatti et al., 2021; Alhaboo & Bdaiwi, 2021).

4.3.4. White blood cell:

The white blood cell count was higher in males (17.04 ± 4.66×10³/mL) compared to females (15.25 ± 2.64×10³/mL), which may be due to recent inflammation or vascular blockage, and the elevated white blood cell (WBC) count in males could be attributed to a recent injury or uncontrolled pain episode (Francis & Haywood, 2019; Bdaiwi et al., 2023).

4.3.5. Platelet:

No significant sex-based difference in PLT was observed (males: 284.00 ± 65.42×10³/mL; females: 259.67 ± 41.43×10³/mL), aligning with findings in chronic hematologic conditions (Ataga et al., 2020; Saleh & Bdaiwi, 2023).

Table 3. Analysis of sex results for patients with sickle cell anemia + thalassemia

Biochemical parameter	Sex	Mean ±Std.Error
Melatonin(ng/mL)	Male	0.80 ± 0.09
	Female	0.93 ± 0.14*
Cortisol (ng/mL)	Male	0.77 ± 0.082
	Female	0.93 ± 0.145*
Hb(g/dl)	Male	7.40 ± 0.958
	Female	8.06 ± 0.81*
WBC(×10³/ml)	Male	17.04 ± 4.66*
	Female	15.25 ± 2.64
PLAT(×10³/ml)	Male	284.00 ± 65.42
	Female	259.67 ± 41.43

*Indication of a significant meaningful difference

4.4 Blood typing analysis for sickle cell anemia/thalassemia patients:

4.4.1. Melatonin:

Blood type B^+ exhibited the highest melatonin level (1.098 ± 0.082 ng/mL). While genetic and individual

variations affect melatonin production, a direct link to blood type remains unclear (Bubenik, 2002).

4.4.2. Cortisol:

Cortisol peaked in blood type B^+ (1.126 ± 0.924 ng/mL), suggesting heightened stress response or adrenal dysfunction in some patients (Angeli et al., 2019).

4.4.3. Hemoglobin (Hb):

The highest hemoglobin averages were in AB^+ (9.00 g/dL) and A^- (8.90 g/dL), while B^+ showed the lowest (5.10 ± 0.28 g/dL). This aligns with findings that blood types A and AB tend to have higher RBC production rates (Sharma et al., 2020).

4.4.4. White Blood Cell:

WBC counts were highest in AB^+ (32.00×10^3/mL) and A^- (31.70×10^3/mL), consistent with a reported association between blood type and immune activity (Ahmed et al., 2019).

4.4.5. Platelet:

Platelets were highest in AB^+ (490.00×10^3/mL) and lowest in B^+ ($118.00 \pm 4.24\times10^3$/mL), possibly indicating an increased bleeding risk in B^+ individuals with chronic anemia (Celik et al., 2019; Bdaiwi et al., 2023).

Table 4. Blood typing analysis for thalassemia patients with sickle cell anemia

Blood group	Melatonin (ng/mL)	Cortisol (ng/mL)	Hb (g/dl)	WBC $\times10^3$ /ml	PLAT $\times10^3$/ml
O+	0.890 ± 0.470	0.912 ± 0.361	8.12 ± 2.71	13.08 ± 7.81	256.15 ± 120.13
A-	0.790 ± -	0.272 ± -	8.90 ± -	31.70 ± -	480.00 ± -
AB+	0.608 ± -	0.584 ± -	9.00 ± -*	32.00 ± -*	490.00 ± -*
B+	1.098 ± 0.082*	1.126 ± 0.924*	5.10 ± 0.28	17.25 ± 4.31	118.00 ± 4.24

*Indication of a significant meaningful difference

4.5 Discussion of correlation coefficients of melatonin and cortisol results with biomarkers in serum of sickle cell anemia/thalassemia patients.

A statistically significant negative correlation was observed between melatonin levels and platelet count ($r = -0.537$, $p = 0.026$) in thalassemia patients with sickle cell anemia, indicating that higher melatonin concentrations are associated with lower platelet counts. This suggests melatonin's potential immunomodulatory role in regulating inflammation and oxidative stress, which may influence platelet production or consumption in these hereditary blood disorders Al-Gahtani et al., 2018). No significant correlations were found between melatonin and other biomarkers (hemoglobin, WBC), nor between cortisol and any studied biomarkers. These cortisol findings align with evidence that cortisol level changes in sickle cell patients mostly reflect HPA axis disruption due to chronic stress, rather than direct effects on routine hematological parameters (Taksande et al., 2015; Al-Taee & Al-Helaly, 2024).

Table 5 Correlation coefficients of melatonin and cortisol results with biomarkers in serum of thalassemia patients with sickle cell anemia

	Melatonin ng/mL	ng/mL Cortisol	Hb g/dl	WBC ml/10^3×	PLAT ml/10^3×
Melatonin	1	.171 p=.513	-.035 p=.895	-.067 p=.798	-.537* p=.026
Cortisol	.171 p=.513	1	.039 p=.882	-.122 p=.641	-.256 p=.321
Hb	-.035 p=.895	.039 p=.882	1	-.046 p=.860	.028 p=.914
WBC	-.067 p=.798	-.122 p=.641	-.046 p=.860	1	.375 p=.138
PLAT	-.537* p=.026	-.256 p=.321	.028 p=.914	.375 p=.138	1

5. Conclusions and recommendations

5.1 conclusions

1-The study revealed a significant decrease in melatonin levels in Thalassemia Patients with Sickle Cell Anemia, indicating chronic oxidative stress and dysfunction.

These results highlight the importance of melatonin's protective role in counteracting the oxidative damage associated with the disease and suggest its potential use as a therapeutic aid to improve patients' quality of life.

2- The study showed clear differences between males and females in some biomarkers. It was observed that the average melatonin concentration was higher in females compared to males, which may indicate a difference in hormonal activity or adaptation to oxidative stress.

5.2 Recommendations

Making more studies about this diseases and its relation with other oxidative stress markers.

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Conflict of interests

The author declares no conflicts of interest.

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