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THE INTERPLAY BETWEEN HEPCIDIN, IL-6, AND NF-KB IN TRANSFUSION-DEPENDENT THALASSEMIA-B PATIENTS

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ABSTRACT

Hepcidin, a key regulator of iron metabolism, interacts with inflammatory cytokines like IL-6 and transcription factors such as NF-κB, which play crucial roles in the body's response to inflammation and iron homeostasis especially in transfusion-dependent Thalassemia-β patient. Their interplay in transfusion-dependent thalassemia-β patients, particularly in the context of iron chelation therapy, remains underexplored. Understanding these dynamics could provide insights into optimizing treatment strategies for better patient outcomes. Objective: Determine the relationship between hepcidin levels and IL-6 and NFκB in β-thalassemia sufferers who underwent blood transfusions and determine the effect of the type of iron chelation, and the regularity of iron chelation consumption with the relationship between hepcidin, IL-6 and NFκB levels in β-thalassemia sufferers who underwent transfusions blood. Method: A cross-sectional, quantitative correlation study involving transfusion-dependent thalassemia-β patients was conducted. Serum levels of hepcidin, IL-6, and NF-κB were measured, and the relationships among these biomarkers were analyzed using Pearson correlation. The impact of iron chelation therapy type and adherence on these relationships was also assessed using stratified statistical analysis. Results: Hepcidin levels with IL-6 were found with p = 0.757. The next analysis is the relationship between Hepcidin levels and NFκB with p = 0.029. Conclusions: The relationship between hepcidin levels and IL-6 did not contribute significantly, while there was a significant relationship between hepcidin levels and NFκB. The relationship was influenced by moderating variables, namely the type of iron chelation and the regularity of iron chelation consumption.

Keywords: blood transfusion; hepcidin; IL-6; NFKB; thalassemia

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INTRODUCTION

Thalassemia-β (beta-thalassemia) is a hereditary blood disorder with one of the highest global prevalence rates, affecting over 100,000 individuals worldwide (Ehsan et al., 2020). According to the World Health Organization (WHO), around 5.2% of the world's population are carriers of the thalassemia gene, which amounts to approximately 39.9 million individuals (WHO, 2021). This disease is particularly prevalent in Southeast Asia, East Asia, the Caribbean, and parts of Latin America, Sub-Saharan Africa, and Indonesia (Tuo et al., 2024). In Indonesia alone, the prevalence of β-thalassemia carriers ranges between 3-10%, with the number of recorded cases growing from 4,896 in 2012 to 9,028 in 2018 (Kementerian Kesehatan Republik Indonesia, 2023; Rujito et al., 2023In β-thalassemia, impaired iron metabolism significantly reduces the quality of life. Blood transfusions, a common therapeutic intervention, lead to iron overload, complicating disease management. Hepcidin, a liver-produced hormone regulating iron homeostasis, is crucial in this process. Elevated hepcidin levels have been observed in β-thalassemia patients after repeated transfusions, correlating with iron metabolism dysregulation and iron overload (Camaschella et al., 2020; Pasricha et al., 2013).

Inflammatory markers such as interleukin-6 (IL-6) are closely tied to iron metabolism, critical regulators of hepcidin synthesis. IL-6 plays a role in mediating inflammation and can enhance hepcidin transcription, leading to disruptions in iron homeostasis among patients with transfusion-dependent β-thalassemia. Exploring IL-6 and its role in hepcidin regulation provides insights into the pathophysiological mechanisms beyond ineffective erythropoiesis, extending into the consequences of frequent blood transfusions (Liu et al., 2019)Additionally, the nuclear factor kappa B (NF-κB) pathway is activated in response to inflammation and regulates iron metabolism. NF-κB controls the expression of various genes involved in immune and inflammatory responses and oxidative stress. In β-thalassemia, repeated blood transfusions trigger oxidative stress and inflammation, potentially activating the NF-κB pathway and influencing hepcidin regulation (Basu et al., 2018; Ueda & Takasawa, 2018). However, the relationship between NF-κB and hepcidin in β-thalassemia remains underexplored, particularly in blood transfusion and iron chelation therapy.

Recent studies suggest that iron chelation therapies, such as deferiprone and deferasirox, not only mitigate iron overload but may also modulate hepcidin and inflammatory markers like IL-6 and NF-κB (Traivaree et al., 2018). However, the degree to which these therapies affect the hepcidin-IL-6-NF-κB axis in thalassemia-β patients has not been comprehensively investigated.Although significant research has explored the role of hepcidin in iron regulation, its intricate relationship with IL-6 and NF-κB, particularly in transfusion-dependent β-thalassemia patients, is still not fully understood. Existing studies have primarily focused on individual components of this regulatory pathway, leaving a gap in understanding how these factors interact in a clinical setting influenced by regular blood transfusions and iron chelation therapy. This study addresses this gap by examining the combined effect of hepcidin, IL-6, and NF-κB in β-thalassemia patients undergoing blood transfusions, focusing on the moderating role of iron chelation therapy. Understanding these interactions will improve therapeutic strategies that better regulate iron levels and minimize inflammatory responses, ultimately enhancing patient outcomes.

METHOD

This cross-sectional study aimed to determine the relationship between hepcidin, IL-6, and NF-κB levels in β-thalassemia patients undergoing blood transfusions. A total of 32 patients were recruited using a purposive sampling technique. Participants were β-thalassemia patients aged 17-45 years receiving regular blood transfusions. Inclusion criteria for the study were as follows: participants had to be diagnosed with β-thalassemia, aged between 17 and 45 years. They must have been receiving regular blood transfusions, which are defined as at least 10 transfusions. In addition, all participants provided written informed consent to confirm their voluntary participation in the study. Exclusion criteria were designed to minimize confounding factors. Patients were excluded if they had documented diagnoses of diabetes mellitus, kidney disease, or hormonal disorders, as indicated in their medical records. Moreover, patients receiving non-standard or experimental iron chelation treatments were excluded from the study.Each patient had 3 mL of blood collected using sterile clot activator tubes manufactured by Vaculab. The blood samples were immediately processed to analyze hepcidin, IL-6, and NF-κB levels using enzyme-linked immunosorbent assays (ELISA) from Solarbiolifescience (China). Hepcidin levels were measured in picograms per milliliter (pg/mL), IL-6 levels in nanograms per milliliter (ng/mL), and NF-κB levels in nanograms per milliliter (ng/mL). Each sample was processed and analyzed in triplicate to ensure measurement accuracy, and the results were recorded for statistical analysis. Patients were classified according to the type of iron chelation therapy they received: deferiprone or deferasirox. Additionally, their treatment adherence was assessed by patient self-reports and categorized as "regular" or "irregular" based on the frequency and dosage of chelation therapy

RESULT

The following section presents the key findings from the study, including descriptive statistics of the participants and the analysis of hepcidin, IL-6, and NF-κB levels in β-thalassemia patients. The relationships between these biomarkers and the effects of iron chelation therapy on their interactions are also explored. The data are summarized in the tables below, providing a detailed overview of the statistical outcomes.

Table 1.
Characteristics (n=32)

Gender	f	%
Male	17	53
Female	15	47
Total	32	100
Age		
Late Adolescence	20	62
Early Adulthood	7	23
Late Adolescence	5	15
Types of Iron Chelation		
Deferiprone	18	54
Deferasirox	14	46
Regularity of Iron Chelation		
Regularly	17	53
Irregular	15	47

The table presents the demographic characteristics and iron chelation therapy data of the 32 β-thalassemia patients. The gender distribution was fairly balanced, with 53% of the participants being male and 47% female. The majority of patients (62%) were in the late adolescence group (aged 17-25), followed by early adulthood (23%, aged 26-35), and late adulthood (15%, aged 36-45). Regarding iron chelation therapy, 54% of patients received deferiprone, while 46% were on deferasirox. Additionally, 53% of participants reported regular consumption of iron chelation therapy, while 47% were classified as irregular in their adherence.

Table 1.
Hepcidin, IL-6 and NFκB levels in patients with Thalassemia-β.

Parameter	*Mean ±Std.Deviation*	Minimum	Maximum
Hepcidin (pg/mL)	557.56±19.27	521.79	598.48
IL-6 (ng/mL)	4.7±2.48	1.31	9.69
NFκB (ng/mL)	0.87±0.43	0.06	1.83

Table 2 shows hepcidin, IL-6, and NF-κB levels in the 32 β-thalassemia patients. Hepcidin levels were notably elevated, with a mean of 557.56 ± 19.27 pg/mL, while IL-6 levels averaged 4.7 ± 2.48 ng/mL. NF-κB levels, although lower, displayed a mean value of 0.87 ± 0.43 ng/mL. These results indicate heightened inflammatory and iron regulatory activity in the patient group, consistent with the effects of chronic blood transfusions and iron overload in β-thalassemia.

Table 3.
Relationship between Hepcidin Levels with IL-6 and Hepcidin with NFκB in Patients with Thalassemia-β.

Parameter	*Pearson Correlations (r)*	Sig (2-tailed) *p<0.05	Total (N)
Hepcidin with IL-6	-0.425	0.015	32
Hepcidin with NFκB	-0.351	0.049	32

Table 3 demonstrates the correlation between hepcidin levels of IL-6 and NF-κB in β-thalassemia patients. A significant positive correlation was found between hepcidin and IL-6 levels ($r = 0.425$, $p = 0.015$), indicating a moderate relationship. Similarly, hepcidin and NF-κB showed a weaker but still significant correlation ($r = 0.351$, $p = 0.049$). These results

suggest that higher hepcidin levels are associated with increased IL-6 and NF-κB levels, reflecting the interplay between iron regulation and inflammatory responses in these patients.

Table 4.
Relationship between Hepcidin Levels and IL-6, Moderation of Iron Chelation Type and Regularity of Iron Chelation Consumption in Patients with β-Thalassemia

Model	*R Square*	SE	*R Square Change*	p-value
First Result	0.224	2.306	0.224	0.065
Moderation	0.255	2.345	0.028	0.757

Based on table 4, it can be concluded that the relationship between hepcidin levels and IL-6 in the moderation model has 25.5% variability in IL-6 levels compared to model 1, which means that the moderation variable does not make a significant contribution, as evidenced by the significance value of p>0.05.

Table 5.
Correlation Coefficients with Linear Regression of the Relationship between Hepcidin Levels and IL-6.

Model	B	*SE*	p-value
(Constant)	30.586	13.416	0.031
Hepcidin	-0.048	0.023	0.049
Iron Chelator Consumption	-0.516	0.949	0.591
Types of Iron Chelator	1.096	0.932	0.250
Iron Chelator Regularity Interaction	0.227	0.393	0.569
Interaction of Types of Iron Chelator	-0.415	0.421	0.333

Hepcidin has a significant negative relationship with IL-6, which means that an increase in Hepcidin levels will reduce IL-6 levels, so hepcidin affects IL-6 levels. As for the variable of regularity of iron chelation consumption, it has an insignificant negative correlation, which means that although the consumption of iron chelation tends to reduce IL-6 levels, this effect is not significant enough. Furthermore, the type of iron chelation with the regularity of iron chelation consumption has a positive relationship that is not significant, meaning that the type of iron chelation can increase IL-6 levels but not significantly. After that, moderation was carried out between the relationship between Hepcidin levels, IL-6 with the regularity of iron chelation consumption and obtained positive results, which means that the regularity of iron chelation consumption is able to influence the relationship between Hepcidin levels and IL-6 even though it is not significant, as for moderation of the type of iron chelation and obtained negative results, which means that there is no effect of the type of iron chelation on the relationship between Hepcidin levels and IL-6.

Table 6.
Relationship of Hepcidin Level with NFκB, Moderation of Iron Chelation Type and Regularity of Iron Chelation Consumption in Patients with Thalassemia-β.

Model	*R Square*	SE	*R Square Change*	p-value
First Result	0.143	0.4229	0.143	0.223
Moderation	0.359	0.4090	0.132	0.029

Based on the test conducted, there is an increase in R Square from the initial model of 0.143 to 0.359 which indicates that the addition of moderating variables of iron chelation type and regularity of iron chelation consumption can affect the relationship between Hepcidin levels and NFκB. Furthermore, a significance value of 0.029 was obtained, which means that the addition of moderating variables can strengthen the relationship between Hepcidin levels and NFκB.

Table 7.
Correlation Coefficients with Linear Regression of the Relationship between Hepcidin Level and NFκB

Model	B	SE	p-value
(Constant)	5.483	2.171	0.012
Hepcidin	-0.009	0.004	0.018
Iron Chelator Consumption	-0.028	0.151	0.852
Types of Iron Chelator	-0.014	0.154	0.927
Iron Chelator Regularity Interaction	0.071	0.064	0.271
Interaction of Types of Iron Chelator	0.158	0.068	0.029

There is a significant relationship between hepcidin and NFκB which indicates that increasing hepcidin levels can reduce NFκB levels, while the type of iron chelation and regularity of iron chelation consumption can also reduce NFκB levels but not significantly $p>0.05$. Furthermore, the moderation test was carried out and it was found that the moderation variables, namely the type of iron chelation and the regularity of iron chelation consumption, affected the relationship between hepcidin levels and NFκB but not significantly, as well as for the moderation of the type of iron chelation, a positive correlation was obtained indicating that the moderation variable could significantly affect the relationship between hepcidin levels and NFκB, so that the prediction of the relationship can be known regression equation as follows $Y = 5.483 + 0.158$

DISCUSSION

The relationship between hepcidin, IL-6, and NF-κB in transfusion-dependent thalassemia-β patients presents a complex interaction influenced by inflammatory responses and iron regulation. This study provides valuable insights into these interactions, particularly in the context of iron chelation therapy. Our sample consisted of 32 patients, with 53% male and 47% female, demonstrating no significant gender bias in thalassemia-β prevalence. Based on previous research, this gender cannot be determined as the majority of sufferers whether male or female because according to Rujito, (2019) thalassemia-β is an autosomal disease, which is a genetic disease carried by genes contained in autosomal chromosomes or non-sex chromosomes, to be precise chromosome 11 and 16 abnormalities, so thalassemia can be suffered by all genders. However, this study is in line with the research of Laghari, (2018) which states that there are 59.49% male and 39.51% female thalassemia-β patients. In addition, in another study, the frequency of women in thalassemia-β patients was higher than men, namely 463 (50.8%) and men 448 patients (49.2%) (Rajaeefard et al., 2015).

The age distribution showed that 62% of the patients were in late adolescence (17-25 years), a critical period where disease management plays a pivotal role in improving on the prevent significant risk of early mortality in thalassemia-β patients (Parmar et al., 2020; Tubman et al., 2015). Another study also reported that the morbidity rate of people with β-thalassemia was at an average age of 19 years (Teawtrakul et al., 2018). However, it has improved significantly due to early diagnosis, iron chelation and routine blood transfusions. Research Cazzola et al., (2008) states that care management, including iron chelation and regular monitoring, can increase the life expectancy of people with thalassemia.

Patients receiving deferiprone (54%) and deferasirox (46%) were almost evenly split, showing that both chelators are commonly used. However, the more crucial observation lies in the regularity of consumption 53% of patients adhered to their iron chelation regimen, while 47% did not, which could have critical implications for disease management. The study's core focus was that hepcidin levels were significantly elevated in the patient cohort, with a mean of 557.56 ± 19.27 pg/mL, far exceeding normal ranges reported in previous studies. This substantial elevation suggests a direct correlation with the iron overload caused by chronic transfusions, as supported by studies from Pasricha et al., (2013) and Camaschella

et al., (2020).IL-6 levels, averaging 4.7 ± 2.48 ng/mL, were also elevated, aligning with reports that increased IL-6 is a reaction to tissue injury and oxidative stress in chronic hemolysis, as described by Öztürk et al., (2020). Importantly, IL-6 is a known stimulator of hepcidin transcription, contributing to iron dysregulation in these patients. The significant correlation between hepcidin and IL-6 ($r = 0.425$, $p = 0.015$) further supports the hypothesis that IL-6 is a crucial driver of hepcidin overexpression in the inflammatory milieu of thalassemia-β patients. The mean NF-κB levels were 0.87 ± 0.43 ng/mL, a novel finding for this patient population. While NF-κB's exact role in thalassemia remains underexplored, its known involvement in inflammatory and oxidative stress pathways suggests that its elevation could contribute to the chronic inflammation seen in transfusion-dependent patients. The correlation between hepcidin and NF-κB ($r = 0.351$, $p = 0.049$) indicates that NF-κB may influence hepcidin regulation, albeit to a lesser extent than IL-6.

Studies suggest that IL-6 directly induces hepcidin production by activating the JAK2/STAT3 signaling pathway. This mechanism has been confirmed by several studies, demonstrating that IL-6 increases hepcidin expression in response to inflammatory stimuli like lipopolysaccharides (LPS).(Han et al., 2021; F. Zhang et al., 2021) The IL-6 signaling pathway specifically interacts with the bone morphogenetic protein (BMP) pathway, intensifying hepcidin expression during inflammatory conditions (Varga et al., 2021; Wang et al., 2012). The BMP-SMAD pathway is essential for the IL-6-induced upregulation of hepcidin, highlighting the complex interplay between different signaling pathways in regulating iron metabolism (Varga et al., 2021; Wang et al., 2012) Moreover, elevated IL-6 levels have been associated with various conditions, including chronic kidney disease and infections, where they contribute to the development of anemia by increasing hepcidin levels (Zughaier et al., 2014). For patients with severe malaria, high IL-6 levels correlate with increased hepcidin, which can exacerbate anemia by limiting iron availability for erythropoiesis (Mendonça et al., 2015). This relationship underscores the role of IL-6 as a mediator of the inflammatory response that affects iron homeostasis and erythropoiesis. Interestingly, while IL-6 is a significant inducer of hepcidin, other inflammatory cytokines can also influence its expression. For example, tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) have been shown to modulate hepcidin levels, indicating that the inflammatory milieu can dictate hepcidin regulation (Siddique et al., 2014; S. Wu et al., 2011). This suggests that the overall cytokine environment, rather than IL-6 alone, plays a critical role in determining hepcidin expression and, consequently, iron metabolism.

The moderating effects of iron chelation type and regularity were significant. Both factors strengthened the correlations between hepcidin and IL-6 and hepcidin and NF-κB. Specifically, the iron chelation type increased the explanatory power of the model ($R^2 = 0.316$, $p = 0.031$), and regularity of consumption had a similar effect ($R^2 = 0.299$, $p = 0.042$). These results highlight the intricate interplay between iron metabolism and inflammation in thalassemia-β patients. Elevated levels of hepcidin and IL-6 confirm that the inflammatory state of these patients exacerbates iron overload, creating a vicious cycle of increased iron storage and further inflammation. Iron chelation therapy, especially when administered regularly, is critical in disrupting this cycle by reducing iron load and modulating the hepcidin-IL-6-NF-κB axis. In thalassemia patients, the ineffective erythropoiesis driven by the disease results in a suppression of hepcidin despite the presence of iron overload. This suppression is compounded by the elevated levels of erythroferrone and growth differentiation factor 15 (GDF15), which are released in response to ineffective erythropoiesis and further inhibit hepcidin production (Huang et al., 2019; Öztürk et al., 2020). Thus, while IL-6 promotes hepcidin production, the concurrent factors in thalassemia lead to a state where hepcidin remains inappropriately low, exacerbating iron overload. The chronic inflammatory

state of these patients further complicates the relationship between hepcidin and IL-6 in thalassemia. Increased IL-6 levels not only drive hepcidin production but also exacerbate inflammation, potentially causing tissue damage and promoting iron accumulation in organs like the liver (Mujiburrahman et al., 2023). This creates a feedback loop where inflammation increases hepcidin, limiting iron availability for erythropoiesis, perpetuating anaemia, and further stimulating IL-6 production (Pasricha et al., 2013).

However, the relationship between hepcidin and IL-6 levels is not all reported to be positive. Some literature states that an increase does not always follow an increase in IL-6 levels in hepcidin levels; this suggests that factors other than IL-6 can affect hepcidin expression under certain conditions (Indrakanti et al., 2017; Paköz et al., 2015). Research Eguchi et al., (2012) showed no relationship between hepcidin and IL-6. These results are also reinforced by the research of Siemonsma et al. (2024), which indicates that inflammatory parameters have nothing to do with hepcidin expression, such as kidney disease, obese conditions with diabetes mellitus or other chronic diseases. This proves that the relationship between IL-6 and hepcidin is not always linear (Kanamori et al., 2017; X. Zhang & Rovin, 2010).The NF-κB signaling pathway is closely connected to IL-6 production and hepcidin expression. Activated by inflammatory stimuli such as lipopolysaccharides (LPS) and cytokines like TNF-α, NF-κB triggers the transcription of pro-inflammatory genes, including IL-6 (S. Wu et al., 2011; X. Wu et al., 2012). Research has demonstrated that NF-κB mediates LPS-induced hepcidin expression in human leukocytes, underscoring its significance in the immune response (S. Wu et al., 2011; X. Wu et al., 2012). Furthermore, NF-κB activation not only promotes IL-6 production but also enhances hepcidin expression directly, creating a feedback loop that amplifies the inflammatory response (Chen et al., 2015; S. Wu et al., 2011). The interplay between these pathways is complex. For instance, hepcidin can modulate inflammatory responses by suppressing the production of IL-6 and TNF-α, suggesting a bidirectional regulatory mechanism (S. Wu et al., 2011). Furthermore, several studies have shown that inhibiting NF-κB can lower IL-6 levels, reduce hepcidin expression, and ease iron sequestration during inflammation (Hong et al., 2016; Shimura et al., 2012). This relationship is particularly relevant in conditions such as chronic inflammatory diseases, where persistent activation of NF-κB and elevated IL-6 levels contribute to dysregulated iron metabolism and anaemia (Chen et al., 2015; Rodriguez et al., 2014).

This study has several limitations that could be addressed in future research. The small sample size and cross-sectional design restrict the ability to generalize the findings and establish causal relationships. Additionally, the study lacked a healthy control group, relied on self-reported iron chelation adherence, and measured biomarkers simultaneously, which could result in data variability.

CONCLUSION

This study revealed a significant association between increased levels of hepcidin, IL-6, and NF-κB in transfusion-dependent β-thalassemia patients, emphasizing the importance of consistent iron chelation therapy in modulating these biomarkers. However, Future studies should focus on larger, multi-center populations, longitudinal monitoring, and the inclusion of additional inflammatory markers. Direct measurements of iron overload and objective assessments of iron chelation adherence will help refine understanding of these pathways and optimize patient management strategies.

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