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Research Article

Effect of Chelation Therapy Adherence on Hepcidin, Ferritin, and Fertility Hormones in Adult Females with Beta Thalassemia Major

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Abstract

BACKGROUND: Chelation therapy plays a crucial role in the management of beta-thalassemia major, a genetic disorder characterized by defective hemoglobin production, leading to chronic anemia and iron overload due to frequent blood transfusions. Over time, excess iron accumulates in vital organs, causing significant damage, which is why chelation therapy, aimed at removing excess iron, is a standard treatment approach. However, this therapy's impact extends beyond iron regulation, influencing various physiological processes, including the regulation of hepcidin, ferritin, and fertility hormones. Hepcidin is a key regulator of iron homeostasis, while ferritin serves as an iron storage protein that reflects the body's iron levels. Understanding the complex interplay between chelation therapy and these biomarkers is critical for improving the management of beta-thalassemia major and mitigating potential long-term complications

OBJECTIVES: This study aims to evaluate the impact of chelation therapy on iron regulation and fertility hormones in females with beta thalassemia major.

Materials and Methods: A case –control study was conducted over a period of 12 months from January to June 2024 involving 180 women (90 healthy control and 90 patients) aged 16-40 years. Patients were randomly selected according to the specific inclusion and exclusion criteria. The Serum level of hepcidin hormone, ferritin, and fertility hormones were measured by Enzyme Linked Immunosorbent Assay. SPSS Program was used to code, enter, and process the gathered data.

RESULTS: Serum hepcidin levels in patients with good compliance did not differ significantly from those with poor compliance while Ferritin levels were significantly lower in good compliance patients (769.16±176.36) vs. poor compliance (868.62±140.81), $p=0.005$. LH and prolactin showed non-significant increases in good compliance (1.40±0.77, 2.55±1.11) vs. poor compliance (1.39±0.86, 2.28±1.08). FSH and estradiol levels were significantly higher in good compliance patients (2.51±1.20, 11.65±0.95) compared to poor compliance (1.87±0.95, 11.20±1.04), $p<0.05$.

CONCLUSINOS: Patients with better compliance to iron chelation had higher hepcidin, lower ferritin, and improved FSH and E2 levels, emphasizing the importance of adherence to therapy.

Keywords: Hepcidin, Fertility Hormone, Ferritin , Thalassemia , Chelation Therapy.

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1. Introduction

Beta thalassemia major is a severe inherited blood disorder characterized by defective hemoglobin synthesis, leading to chronic anemia and dependence on regular blood transfusions [1]. While blood transfusions are essential for survival, they result in excessive iron accumulation, which can disrupt various physiological functions, including hormonal regulation [2].

Iron chelation therapy is an essential treatment for individuals with beta thalassemia major[3]. beta thalassemia Patients often require frequent blood transfusions to manage their anemia, but these transfusions result in an accumulation of iron in the body [4]. The body has no natural mechanism to eliminate excess iron, which can gradually build up in vital organs such as the liver, heart, and endocrine glands, leading to severe complications like organ failure [5] .

The purpose of iron chelation therapy is to reduce this iron overload by binding to excess iron in the body and facilitating its removal [6] . There are several chelating agents available, including deferoxamine, deferasirox, and deferiprone, these agents work by forming complexes with iron, which are then excreted through urine or feces [7]. Chelation therapy is typically a lifelong treatment for patients with beta thalassemia major to prevent iron-induced damage and to maintain the proper functioning of essential organs[8] .

While the primary goal of iron chelation therapy is to manage iron levels, research has shown that it may also influence other biological processes, such as the regulation of hepcidin and ferritin, proteins involved in iron metabolism. Moreover, the long-term use of chelation therapy can have various effects on endocrine function, fertility, and overall health [9].

Iron metabolism stands as a pivotal component in the pathophysiology of thalassemia, particularly characterized by the dysregulation of hepcidin and ferritin dynamics[10] . Hepcidin, a peptide hormone produced in the liver, is essential for maintaining systemic iron homeostasis through its regulatory influence on ferroportin, the primary iron exporter within cells [11] . In individuals afflicted with thalassemia, hepcidin concentrations are markedly diminished relative to healthy counterparts, whereas ferritin levels frequently surge, resulting in a paradoxical state that intensifies iron overload conditions [12].

Ferritin, a marker of iron storage, reflects the extent of iron overload in these individuals [13] . In females with beta thalassemia major, iron overload can negatively impact fertility by altering the levels of reproductive hormones, potentially leading to delayed puberty, menstrual irregularities, and infertility [14]. Chelation therapy plays a crucial role in managing iron overload by facilitating iron excretion, but its effects on hepcidin, ferritin, and fertility hormones remain a subject of ongoing investigation [15] .

2. Materials and Methods

A case-control study was conducted from January 2024 to June 2024 . one hundred eighty women were enrolled in this study including 90 healthy woman and 90 patient women. The study participants age range was between 16 and 40 years, Participants were randomly selected using a computer-generated randomization list to reduce selection bias. To minimize information bias, data collectors and laboratory personnel were blinded to the patients' clinical status and genetic results. The patients were selected randomly, sampled from the attendee of the thalassemia care centers in Ibn AL Baladi hospital in Baghdad city.

Controls were selected from the same geographic area to ensure homogeneity.

Patient data were gathered through a comprehensive pre-prepared questionnaire which included information on age, weight, height, marital status, number of children, menstrual history, and medical history, along with a review of their medical records .

Patients were divided into two groups based on their compliance with chelation therapy.

Compliance was assessed using a combination of medical records, serum ferritin trends, and patient self-report during clinical interviews.

Good compliance was defined as adherence to the prescribed chelation regimen (e.g., Deferoxamine, Deferasirox, or Deferiprone) for ≥5 days/week and ≥75% of the time during the past year.

Poor compliance was defined as irregular use, <3 days/week, or <50% adherence over the same period.

Venous blood samples were aseptically collected from all patients before transfusion. Three milliliters of the anticoagulated sample were used for biochemical analysis, including the measurement of hepcidin, ferritin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and prolactin levels.

Inclusion criteria:

1-Women patients aged 16-40 years diagnosed with Beta thalassemia Major confirmed by hemoglobin electrophoresis .
2- healthy females as control group.

Exclusion criteria:
1- Women with recent infection or inflammation excluded by CRP

2- Patients with other blood disorder or coexisting chronic disease affecting hormone levels.
3- Women with a history of Previous ovarian surgery or those who are Pregnant.

Ethical consideration
This study received approval from the Institutional Review Board of the College of Medicine at Al-Nahrain University (Approval Number 85). All participants provided written informed consent before taking part in the research. Data confidentiality was maintained in accordance with the principles outlined in the revised Declaration of Helsinki on bioethics [17].

Statistical analysis
Data analysis was conducted using the Statistical Package for the Social Sciences version 26. Data were presented as mean ± standard deviation (SD). A P-value greater than 0.05 was considered statistically non-significant, while a P-value below 0.01 was interpreted as highly significant. To assess potential correlations, Pearson's correlation test was applied.

3.Results and Discussion

Demographic data
This study included 180women (90 healthy woman and 90 patient women), there was no significant difference between both groups concerning age (24.67±7.16 vs. 26.01±6.90) while the Thalassemia patients women group had a significantly lower BMI compared With controls (P = ≤ 0.001) An Independent Samples t-test was used to compare the means between groups. As shown in Table 1.

Table 1: Demographic characteristics in patients and control

parameter	Control Mean±S.D.	Patients Mean±S.D	P value
Age(years)	26.01±6.90	24.67±7.16	0.2
BMI(Kg/m2)	24.93±4.77	21.44±2.62	<0.001

comparison of serum hepcidin and Serum ferritin between patients and control group.
The Serum Ferritin and serum hepcidin were detected in patients and controls. The difference was significant (P= 0.001) in patients when compared with healthy controls, with a mean ±SD as shown in table (2).

Table 2: The serum level of Hepcidin and Ferritin of the studied groups.

Parameter	study group	Concentration (Mean±S.D.)	Range	p value
Serum Hepcidin (ng/mL)	Control90	20.21±2.94	13.21-25.11	<0.001
	Patients 90	5.18±1.30	3.23-7.93	
Serum ferritin (ng/mL)	Control90	48.81±30.45	15-159	
	Patients 90	801.21±171.44	482-999	<0.001

A statistical experiment was conducted to examine the relationship between two categorical variables by applying the Chi-square test to determine if there is a significant association between them.
The mean±SD of serum hepcidin in controls was 20.21±2.94 ng/ml (ranged13.21-25.11 ng/ml) and 5.18±1.30 ng/ml in patients (ranged3.23-7.93 pg/ml), The serum hepcidin level in patients group was statistically significantly lower than in control group (P = 0.001) as show in table [1].
As shown in (table 2) the mean±SD of serum ferritin in female patients group was 801.21±171.44 ng/ml (ranged 3.23-7.93ng/ml) and 48±30.45 ng/ml (ranged 15-159 ng/ml) in control.
According to research the serum ferritin level in patients group were statistically significantly higher than in control group (P = <0.001) and all patients have higher serum ferritin level than the normal range.
Correlations of Hepcidin with ferritin, LH ,FSH, Estradiol ,prolactin.
Pearson's correlation was used to explore the possible correlations of Hepcidin with other variables in thalassemia female patients. Hepcidin demonstrated a significant positive correlation with each of LH , FSH , Estradiol and prolactin ,while Hepcidin demonstrated significant negative correlation with ferritin (r= -0.932 p= 0.001) as shown in(table 3).

Table3: Pearson's correlation of hepcidin with other numerical variables(Ferritin ,LH, FSH, Estradiol and Prolactin) in patients with Beta thalassemia Major.

Parameter		Ferritin (ng/mL)	LH (miu/ml)	FSH (miu/ml)	Estradiol(pg/ml)	Prolactin (ng/mL)
Hepcidin (ng/mL)	Pearson Correlation (r)	-0.932	0.242	0.430	0.575	0.616
	P value	<0.001	0.022	0.001	0.001	0.001

Pearson correlation of Ferritin with other hormones in patients.
ferritin demonstrated a highly significant negative correlation with each of FSH (r=- 0.441, p=0.001) , Estradiol (r=- 0.539, p=0.001) and prolactin (r= -0.528 p=0.001) while ferritin demonstrated insignificant negative correlation with LH (r= -0.203 p= 0.06) as shown in
(table 4).

Table4: correlation of Ferritin with other hormones

Parameter		LH (miu/ml)	FSH (miu/ml)	Estradiol (pg/ml)	Prolactin (ng/mL)
Ferritin (ng/mL)	Pearson Correlation (r)	-0.203	-0.441	-0.539	-0.528
	P value	0.06	0.001	0.001	0.001

Mean difference of Hepcidin and ferritin levels in Patients according to use of iron chelation therapy.

As presented in Table 5 and illustrated in Figure 3, the mean ± SD of serum hepcidin levels in patients with good compliance to iron chelation therapy was higher compared to those with poor compliance; however, this difference was not statistically significant (P = 0.3).

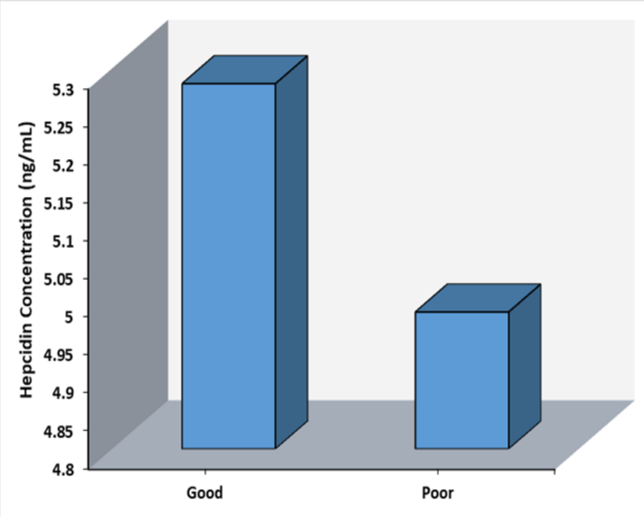

Figure 3:level of hepcidin in patient according to chelation therapy

As shown in Table 5, A statistical experiment was conducted to examine the relationship between two categorical variables by applying the Chi-square test to determine if there is a significant association between them.

the mean ± SD of serum ferritin levels in patients with good compliance to iron chelation therapy was significantly lower compared to those with poor compliance.

Table 5. The levels of Hepcidin and ferritin in Patients according to chelation

Parameters	chelation type	NO. (%)	Concentration (Mean±S.D.)	P value
Hepcidin(ng/mL)	Good compliance	61 (67.7%)	5.28±1.30	0.3
	Poor compliance	29 (32.2%)	4.98±1.31	
Ferritin(ng/mL)	Good compliance	61 (67.7%)	769.16±176.36	0.005
	Poor compliance	29 (32.2%)	868.62±140.81	

Mean difference of Hormones levels in Patients according to use of iron chelation therapy.

as shown the (table 6) The results presented non-significant (P>0.05) increase in Level of Serum LH and prolactin in patient with good compliance of iron chelation therapy compared to patients with poor compliance of chelation therapy and ,while there was significant (p<0.05) increase in Level of Serum FSH and Estradiol in patients with good compliance of chelation therapy Compared to patients with poor compliance of chelation therapy .

Table 6: The levels of hormones in Patients according to chelation

Groups	Chelation type	Number (%)	Concentration (Mean±S.D.)	P value
LH (miu/ml)	Good compliance	61 (67.7%)	1.40±0.77	0.9
	Poor compliance	29 (32.2%)	1.39±0.86	
FSH (miu/ml)	Good compliance	61 (67.7%)	2.51±1.20	0.01
	Poor compliance	29 (32.2%)	1.87±0.95	
Estradiol (pg/mL)	Good compliance	61 (67.7%)	11.65±0.95	0.05
	Poor compliance	29 (32.2%)	11.20±1.04	
Prolactin (ng/mL)	Good compliance	61 (67.7%)	2.55±1.11	0.28
	Poor compliance	29 (32.2%)	2.28±1.08	

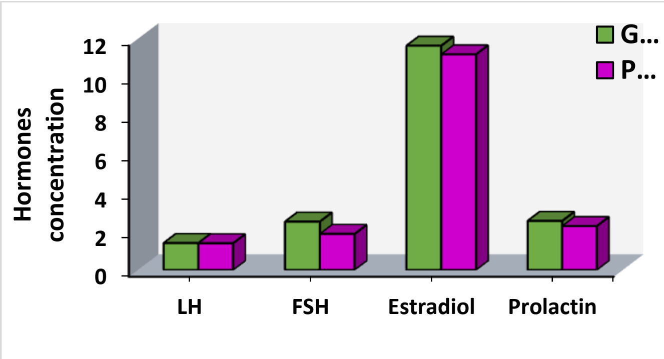

Figure 5:Hormones levels in Patients according to use of iron chelation therapy

Iron metabolism is essential for physiological balance, and its dysregulation in thalassemia is reflected by altered serum hepcidin and ferritin levels. In this study, patients showed significantly decreased hepcidin and elevated ferritin levels compared to healthy controls (Table 2). These findings are consistent with previous studies by Porter et al. [18], Pasricha et al. [19], and Tanno et al.

[20], which demonstrated low hepcidin despite iron overload and significantly higher ferritin levels in thalassemia patients.

The regulation of hepcidin production is a complex interplay of physiological factors, intricately influenced by iron reserves, erythropoietin activity, and the presence of inflammatory mediators[21] . Serum ferritin is a widely used marker of iron stores and overload. In thalassemia patients, its elevation is attributed to increased intestinal iron absorption due to low hepcidin levels and frequent blood transfusions, which introduce excess iron that cannot be excreted, leading to tissue accumulation and elevated ferritin levels [22]. The current study demonstrated a significant negative correlation between serum hepcidin and ferritin ($r = -0.932$, $p = 0.001$; Table 3). These results are not consistent with Salwan et al. [23] who reported no significant correlation, but agree with Badawy et al. , who found an inverse relationship between the two markers[24].

The current study found a significant positive correlation between serum hepcidin and LH, FSH, estradiol, and prolactin levels ($p = 0.001$; Table 3). Low hepcidin exacerbates iron toxicity, leading to pituitary damage and dysregulation of the hypothalamic-pituitary-gonadal axis. Similar positive correlations between hepcidin and gonadotropins have been reported by Sokkar et al. and Lai et al. , who noted the complex interplay of iron overload, inflammation, and endocrine dysfunction in thalassemia[25,26].

For instance, Soliman et al. reported that low hepcidin levels in thalassemia patients correlated with endocrine failure due to excessive iron accumulation in pituitary and gonadal tissues. Their study demonstrated that as serum ferritin (a surrogate marker for iron overload) increased, LH, FSH, and estradiol levels decreased, indicating iron-induced endocrine dysfunction [27] .

The current study also showed a negative non-significant correlation between ferritin and LH while ferritin demonstrated a highly significant negative correlation with each of FSH , Estradiol and prolactin as shown in (table 4).these results agree with study by Jabir reported that although ferritin levels were markedly elevated in thalassemia patients due to frequent transfusions, no significant relationship with LH [28].

In thalassemia patients, iron accumulation in the pituitary and gonadal tissues disrupts hormone levels. Increased serum ferritin correlates with decreased FSH, estradiol, and prolactin, reflecting iron-induced endocrine dysfunction [29]. The negative correlation with estradiol suggests a protective role through enhanced hepcidin activity or antioxidant effects reducing oxidative stress [30]. Ambrogio et al. reported an inverse relationship between prolactin and iron burden markers, highlighting hepcidin's role in pituitary dysfunction [31]. Iron deposition leads to hypogonadotropic hypogonadism by damaging pituitary gonadotrophs, causing reduced LH and FSH levels and subsequent estradiol deficiency in thalassemia major patients [32]. Beta thalassemia major patients require lifelong transfusions, causing iron overload that impairs growth, sexual development, and organ function, necessitating continuous iron chelation therapy [33].

Regarding the effect of chelation therapy on the level of hepcidin in thalassemia patients .The current results showed that the serum Hepcidin level patient with good compliance of iron chelation therapy was not statistically significantly differ from those with poor compliance of iron chelation therapy p=0.3 as show in(table 5), this result indicate that iron chelation therapy treatment dose not significantly impact serum hepcidin regulation in patient with beta thalassemia major, treatment with iron chelation therapy if not effective in some patients due to considering factors like treatment adherence and individual variability in response to treatment, and this lead to iron overload [33].

Regarding the effect of iron chelation therapy on the level of ferritin in thalassemia patients .The current results showed that beta thalassemia major patients with good compliance of iron chelation therapy exhibit statistically significantly lower serum ferritin level compared to patients with poor compliance of iron chelation therapy as show in (table 5), This study demonstrates that iron chelation therapy significantly reduces serum ferritin levels in beta thalassemia major patients, indicating effective management of iron overload. Patients adhering to chelation agents such as deferasirox or deferoxamine showed decreased ferritin, reflecting improved iron mobilization and reduced oxidative stress. These findings are consistent with previous studies reporting significant ferritin reduction following treatment [34].

Regarding the effect of iron chelation therapy on the of levels of fertility hormones (LH,FSH,E2 and prolactin) in patients with beta thalassemia major . The result showed non-significant ($P>0.05$) increase in Level of Serum LH and prolactin in patient with good compliance of iron chelation therapy as compared to patients with poor compliance of chelation therapy ,while there was significant ($p<0.05$) increase in Level of Serum FSH and Estradiol in patients with good compliance of chelation therapy as Compared to patients with poor compliance of chelation therapy as show in (table 6) . Our findings indicate that good compliance with iron chelation therapy is associated with significant increases in serum FSH and estradiol levels, reflecting improved pituitary and ovarian function in beta thalassemia patients. No significant changes were observed in LH and prolactin levels, likely due to complex hormonal regulation and individual variability. These results align with Desanctis et al. [35], who reported improvements in FSH and estradiol following chelation, and Ali et al. [36], who found no significant effect on LH and prolactin. This suggests that hormonal responses to iron chelation may be influenced by factors beyond treatment adherence.

4. CONCLUSION

Hepcidin levels were significantly lower, while serum ferritin levels were markedly higher in a beta-thalassemia patient compared to controls, hepcidin Levels Were positively correlated with LH, FSH, E2 and prolactin Whereas ferritin showed a Negative Correlation with FSH , E2 and Prolactin, This indicates that iron overload may Contribute to Endocrine dysfunction in thalassemia patients.

Patients with good compliance to iron chelation therapy had slightly higher hepcidin levels and significantly lower ferritin levels compared to those with poor compliance, a significant increase in FSH and E2 hormones was observed in patients with better adherence to chelation therapy, highlighting the importance of treatment adherence in managing beta-thalassemia complications.

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