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Key components of iron metabolism relationship in patients with hypothyroidism and iron deficiency (IDA)

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Abstract
Hypothyroid happens when thyroid gland is underactive. This can exist at any age, but the risk raises as you become older and it is most generally promoted via genetics. thyroid gland is hypoactive, making less thyroid hormone. These hormones regulate the body's energy balance and metabolism. Iron is very important in maintaining many body functions, including the production of hemoglobin, the molecule in your blood that carries oxygen. Iron is also necessary to maintain healthy cells, skin, hair, and nails. Iron deficiency is very common, especially among women and in people who have a diet that is low in iron. There are several reports suggesting interrelation between iron deficiency anemia with thyroid dysfunction. This study was instituted to examine the influence of thyroid hormones in hypothyroidism states on the levels of TIBC, Hepcidin and Ferritin; in comparison with control group. Also, to study the correlation of serum TIBC and Ferritin with thyroid hormones in hypothyroidism. The present study included 196 Iraqis female patients for hypothyroidism with age ranged between (20-50) years and 100 healthy controls with same age ranged. Serum samples were collected from Tikrit Teaching Hospital, from January 2024 to March 2024. This study is conducted to investigate the relationship between hypothyroidism and iron deficiency anemia in female Iraqi women as well as knowing the relationship between hepcidin, ferritin, and TBIC and the effect of their concentrations on both diseases. Thyroid hormones (TSH, T_4 and T_3) were determined by using the ELFA technique. The level of Hb was determined by a digital Hb Reader instrument. Detection of Total iron binding capacity (TIBC), Ferritin and Hepcidin levels in the serum were determined by an enzyme linked immunosorbent assay (ELISA) kits. The results showed a significant decrease in the levels of Hemoglobin, Ferritin, TIBC, and Hepcidin in patients with hypothyroidism and iron deficiency anemia for patients group compared to healthy subjects. This study proved that there is a relationship between hypothyroidism and iron deficiency anemia, through the results that showed a significant positive correlation between levels of T_3, T_4 and the levels of both Ferritin and TIBC.

Keywords: Hypothyroidism, Iron Deficiency (IDA), Total Iron Binding Capacity (TIBC), Ferritin and Hepcidin

Introduction
The thyroid gland is a butterfly-fashioned gland this is roughly 2 inches in length and weighs much less than 1 ounce. Situated inside the front location of the neck, under the larynx, or voice container, this structure consists of lobes, one positioned bilaterally adjacent to the windpipe. The thyroid gland constitutes an element of the endocrine gadget [16]. The endocrine system's glands are answerable for the synthesis and garage of hormones, which are then secreted into the bloodstream. Subsequently, the hormones traverse the whole thing of the organism and govern the cell tactics within the frame. The production of two thyroid hormones, specifically triiodothyronine (T_3) and thyroxine (T_4), is accomplished through the thyroid gland [1]. T_3 is derived from T_4 and is the hormone with greater hobby, exerting an instantaneous effect at the tissues. Thyroid hormones exert have an effect on various physiological techniques, together with metabolism, mind development, breathing, cardiac and neurological system functioning, body temperature law, muscular energy, skin hydration, menstrual cycles, body weight, and levels of cholesterol [2]. The metabolism of thyroid hormone is controlled by using thyroid-stimulating hormone (TSH), which is synthesized by way of the pituitary gland positioned inside the brain. In cases of low thyroid hormone levels

in the bloodstream, the pituitary gland secretes an extended amount of TSH [64]. Elevated levels of thyroid hormone cause a lower inside the technology of thyroid-stimulating hormone (TSH) by the pituitary gland. Hypothyroidism is a clinical situation characterized through inadequate manufacturing of thyroid hormone by means of the thyroid gland, resulting in an inadequate supply to satisfy the body's requirements [4]. The thyroid hormone governs metabolism and exerts impact on almost all organs within the frame. [3] Inadequate tiers of thyroid hormone bring about a deceleration of several physical systems. Hypothyroidism may be attributed to different factors, along with: Hashimoto's disease (HD), Thyroiditis, which refers to the inflammation of the thyroid gland, Congenital hypothyroidism, which is the condition of having a low thyroid gland from birth [61], Thyroidectomy, Thyroid radiation therapy and Certain medications [18]

What is iron-deficiency anemia?

Iron deficiency Anemia is a hematological condition that impacts the erythrocytes in your blood. It is the predominant kind of anemia. Iron deficiency occurs when the body lacks sufficient iron to produce hemoglobin, a component of red blood cells responsible for transporting oxygen throughout the body [63]. Consequently, a deficit in iron can lead to symptoms such as dyspnea or fatigue. These symptoms gradually manifest over a period of time. Upon diagnosis of iron insufficiency, iron supplements may be prescribed [65].

Iron insufficiency is a prevalent condition, especially affecting children, young women, and older individuals [64]. While serum iron measurement, total iron binding capacity (TIBC), and transferrin saturation are frequently employed to assess iron shortage, they are not suitable for diagnosing the underlying cause of the condition. However, they can be valuable in confirming and monitoring acute iron poisoning in children [7]. Iron toxicity is commonly characterized by a serum iron level that above the total iron body count (TIBC) [10]. While SI concentration and TIBC measures have been employed as supplementary tools, the most dependable approach for diagnosing iron shortage is the cytochemical staining of bone marrow aspirate, which allows for the identification of hemosiderin's presence or absence [50]. The total iron balance of the blood (TIBC) fluctuates in disorders of iron metabolism. It is often elevated in cases of iron-deficiency anemia and reduced in chronic inflammatory disorders, malignancies, and hemochromatosis (iron overload). In these cases, there is a high concentration of serum iron and transferrin, but the TIBC remains normal or low [6].

How does iron-deficiency anemia affect my body?

The symptoms of iron-deficiency anemia gradually develop over time [19]. At first, you may experience a deficiency in iron and feel unaffected, or you may have symptoms that are so subtle that they go unnoticed. If left untreated, iron-deficiency anemia can result in symptoms such as fatigue and debility. One may see the presence of pallid complexion and frigid extremities [10]. Dizziness or lightheadedness may also manifest as symptoms of iron-deficiency anemia [52]. At times, it may induce angina, tachycardia, and dyspnea. A shortage in iron can lead to atypical cravings for non-nutritive substances, such as ice, dirt, or paper [9].

How does iron-deficiency anemia develop?

Typically, the human body acquires a consistent influx of iron through dietary intake. The body reserves surplus iron to ensure its availability for the production of hemoglobin [51]. Iron-deficiency anemia occurs when the body depletes its iron reserves at a rate that exceeds their capacity for replenishment, or when the influx of iron into the body has decelerated [8]. This phenomenon unfolds in three distinct phases:

First stage: Iron reserves have been exhausted. During this phase, the availability of iron for the production of new hemoglobin and red blood cells is diminishing, but it has not yet impacted your red blood cells [23].

Second stage: Insufficient iron stocks disrupt the regular process of erythropoiesis. The process of iron-deficient erythropoiesis, also known as latent iron deficiency, is observed [49]. Erythropoiesis refers to the biological process of generating fresh red blood cells. During this phase, the bone marrow produces red blood cells insufficiently due to a lack of hemoglobin [56].

Third stage: Iron-deficiency anemia occurs due to insufficient iron levels, which hinders the production of hemoglobin for red blood cells. [44] During this phase, the concentration of hemoglobin will decrease below the established normal level. At this point, you may start to observe symptoms of iron-deficiency anemia [43].

Total iron-binding capacity (TIBC): The overall iron-binding capacity (TIBC) take a look at is a crucial diagnostic tool for figuring out iron deficient anemia and other iron metabolism problems [40]. The concept of iron binding capacity refers back to the capacity of transferrin to form complexes with iron. This examine examines awesome types of iron binding potential, particularly TIBC and unsaturated iron-binding ability (UIBC) [33]. Depletion of iron reserves results in an elevation in transferrin degrees inside the bloodstream. The iron saturation of transferrin in serum is constrained to approximately one-0.33, ensuing in a further binding capacity of 67% for transferrin. This refers back to the potential of unsaturated iron to bind [39]. The overall of serum iron and UIBC is denoted as TIBC. The calculation of percent transferrin saturation includes the division of serum iron through TIBC, followed by way of the multiplication of the quotient through 100 [50].

Ferritin: Ferritin, a prominent protein liable for iron storage, plays a crucial position in maintaining iron balance in the frame and is implicated in various physiological and pathological mechanisms. Ferritin enables the accessibility of iron for vital cellular functions, even as safeguarding lipids, DNA, and proteins towards the potentially deleterious influences of iron [17]. Ferritin is in the main employed inside the area of clinical medicine as a biomarker for assessing the general iron degrees within the body. Serum ferritin performs a critical function in diagnosing and handling instances of iron insufficiency and overload [53]. It is evident that ferritin levels below the reference variety are normally indicative of iron deficiency inside the body [34]. According to a current examine, ferritin has been identified as a greater sensitive, particular, and reliable indicator for early detection of iron deficiency [54]. On the contrary,

individuals showing ferritin degrees beyond the mounted reference variety may additionally probably represent numerous clinical issues, such as iron overload, infections, inflammations, collagen illnesses, hepatic sicknesses, neoplastic ailment, and continual renal failure [59].

Hepcidin: Hepcidin, an iron-regulatory hormone, performs an essential position inside the law of plasma iron concentrations and the overall iron content material of the body. The secretion of hepcidin via hepatocytes serves the reason of regulating the interest of ferroprotein, a cellular iron exporter chargeable for transporting iron from intestinal iron absorption and iron storage to the plasma [36]. Iron loading and inflammation cause an upward thrust in hepcidin attention in plasma, at the same time as erythropoietic stimulation and being pregnant decrease it [12]. A loss of hepcidin ends in immoderate accumulation of iron in hemochromatosis and anemia due to inadequate production of crimson blood cells [13]. Exceedance of hepcidin results in the development of iron-restrictive anemia, which encompasses anemia of irritation [37]. Enhancing the remedy of iron troubles can be accomplished by the development of hepcidin diagnostics and the advent of therapeutic agonists and antagonists [60].

Materials and Methods

This study was conducted in Tikrit Teaching Hospital in Salah AL-Deen Government from January 2024 to March 2024, using a cross-sectional design. The current investigation comprised 196 female patients from Iraq diagnosed with hypothyroidism, aged between 20 and 50 years, and 100 healthy controls within the same age range (Table1). The ELFA technique was employed to detect the levels of thyroid hormones (TSH, T_4, and T_3). The Hb level was measured using a digital Hb Reader device. An enzyme linked immunosorbent assay (ELISA) kit was used to detect the levels of Total Iron Binding Capacity (TIBC), Ferritin, and Hepcidin in the serum.

Table 1: Demographic Samples distribution

Groups	No. of Individuals	Age
Control (C)	100	(20-50)
Patients Group (G)	196	(20-50)

The statistical analysis: The statistical analysis was conducted utilizing the statistical software Minitab. Group comparisons were performed using one-way analysis of variance (ANOVA), while the arithmetic means for parameters were assessed using the Duncan multiple ranges test to determine significant differences, particularly between groups. Regression plots were used to determine the Pearson correlation coefficient (R) between parameters. The statistical significance level was established at a significance level of P≅0.01 and P 0.05.

Results

The primary transporter of oxygen is hemoglobin. The levels of hemoglobin decrease in cases with common anemia. The present investigation has demonstrated a relationship between low hemoglobin levels and subclinical hypothyroidism. The mean standard deviation (SD) of hemoglobin levels in the patient's group was 10.481 ± 0.791 g/dl, whereas in the control group, the mean SD of hemoglobin levels was 12.250 ± 0.500 g/dl. The data shown in Table 2 and Figure 1

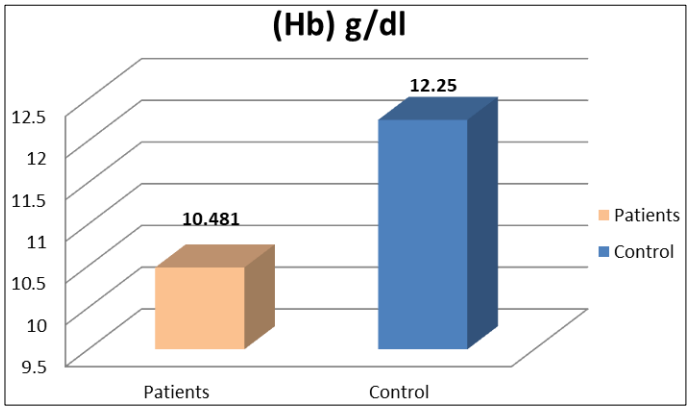

Fig 1: Levels of hemoglobin in patients and control groups.

As previously stated, the primary role of hemoglobin is to transport oxygen. Hemoglobin is a protein that contains iron and is transported by red blood cells. Consequently, a shortage in iron might result in a deficiency of hemoglobin in the bloodstream. This study presents the hemoglobin levels of individuals belonging to two distinct age groups. Furthermore, there is a statistically significant difference observed when comparing the experimental group to the control group ($p \geq 0.01$). The hemoglobin ratios obtained from this research have the potential to indicate the progression of anemia. Prudent analysis is necessary when relying solely on hemoglobin to diagnose anemia and choose appropriate therapies, such as evaluating factors linked to the occurrence of anemia following intellectual disability. This finding is consistent with the findings of Addo *et al*. (2023) [2] and Mansour *et al*. (2021) [40].

The findings indicate that the mean ± standard deviation (SD) of TIBC levels in the patient group was 151.38 ± 43.86 µg/dl, whereas in the control group it was 226.50 ± 11.12 µg/dl, as presented in Table 2 and Figure 2. The patients' groups exhibit significantly reduced levels of total iron binding capacity (TIBC) compared to the control group ($p \geq 0.01$). The present findings align with the outcomes reported in the studies conducted by Yu, FITRIANI *et al*. (2020) [20], and Al-Alimi *et al*. (2018) [6]. The present findings are inconsistent with the findings reported by Al Azad *et al*. (2021) [5] and Laller *et al*. (2021) [36].

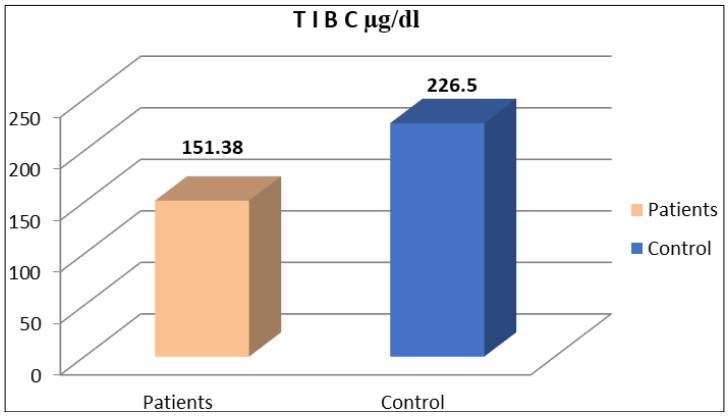

Fig 2: Levels of TIBC in patients and control groups.

The findings indicate that the mean standard deviation (SD) of hepcidin hormone in the patient's group was 24.49 ± 3.74 µg/dl, but in the control group, the mean SD of hepcidin hormone was 31.10 ± 7.30 µg/dl. Based on the data presented in Table 2 and Figure 3.

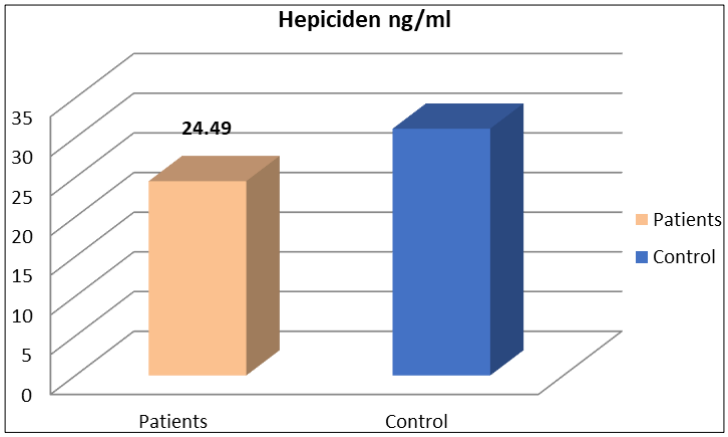

Fig 3: Levels of Hepcidin hormone in patient and control groups.

Prior research has examined the correlation between hepcidin levels and the occurrence of hypothyroidism, wherein various patient features, autoimmune, and maybe dietary condition have been considered. The current findings are consistent with the research conducted by Uysal, Krygier *et al.* (2022) [35], and Stojkovic Lalosevic *et al.* (2020). The findings of this study indicate that there is no statistically significant difference in serum hepcidin levels between the general patient population and the control group ($p \geq 0.05$). In contrast to the findings of Panichsillaphakit Hernick *et al.* (2019) [27], and Galetti *et al.* (2021) [21], the present investigation is incongruous.

The findings indicate that the mean (± standard deviation) of ferritin levels in the sick group was 24.95 ± 13.97 ng/ml, while in the control group, the mean (± SD) of ferritin levels was 54.75 ± 8.18 ng/ml. The data shown in Table 2 and Figure 4.

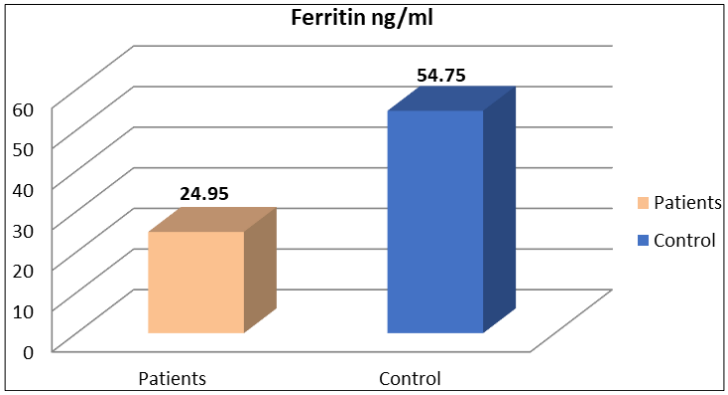

Fig 4: Levels of ferritin in patients and control groups.

The ferritin levels in the patient groups were found to be significantly lower compared to the control group ($p < 0.01$). The present findings align with the research conducted by Mansour *et al.* (2021) [40], Sezgin, and Lone *et al.* (2021). Nevertheless, the present findings contradict the findings of Oh *et al.* (2018) [49] and Gell (2018) [23], who verified that the correlation between Serum ferritin and

BMD is not influenced by hemoglobin levels. It is worth noting that hemoglobin, despite containing iron, has been demonstrated to have a detrimental effect on BMD in women.

Table 2: Arithmetic average for Hb, TIBC, Hepcidin and ferritin concentrations in the studied groups.

Group	Mean ± SD			
	Hb g/dl	TIBC µg/dl	hepcidin ng/ml	ferritin ng/ml
Control	12.250 ± 0.500	226.50 ± 11.12	31.10 ± 7.30	54.75 ± 8.18
Patients	10.481 ± 0.791	151.38 ± 43.86	24.49 ± 3.74	24.95 ± 13.97

The findings from Pearson's correlation analysis, as presented in Tables (3) and Figures (5,6,7,8), indicate a negative correlation between TSH and the variables Hb, ferritin, and TIBC. This correlation is visually represented by the correlation coefficients depicted in the regression graphs presented in Figures (5,6,7). Conversely, a positive correlation between TSH and the hepcidin hormone is illustrated in the regression graphs presented in Figure (8).

Table 3: Correlation coefficient (R) between thyroid hormones with parameters in hypothyroid and IDA patients

Parameters	Statistical variables	T_3	T_4	TSH	Ferritin	Hb	TIBC
T_4	R	0.453	---	---	---	---	---
	P	0.000 **	---	---	---	---	---
TSH	R	0.227	0.210	---	---	---	---
	P	0.051*	0.071*	---	---	---	---
Ferritin	R	0.266	0.325	-0.166	---	---	---
	P	0.021*	0.004**	0.154 *ns*	---	---	---
Hb	R	0.038	0.111	-0.203	0.244	---	---
	P	0.744*ns*	0.342*ns*	0.080*	0.035*	---	---
TIBC	R	0.240	0.329	-0.213	0.371	0.275	---
	P	0.038*	0.004**	0.066*	0.001**	0.017*	---

R: Correlation coefficient**; P:** p-value**; *** P<0.05**; **** P<0.01**; ns:** Not significant.

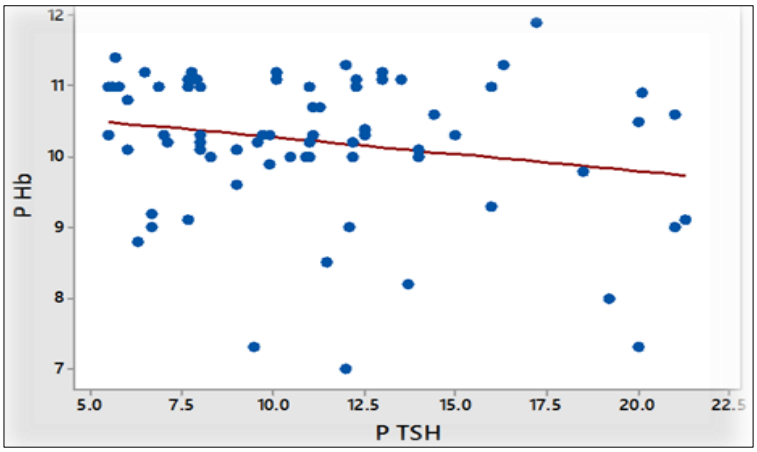

Fig 5: Correlation between TSH with Hemoglobin (Hb) in patients.

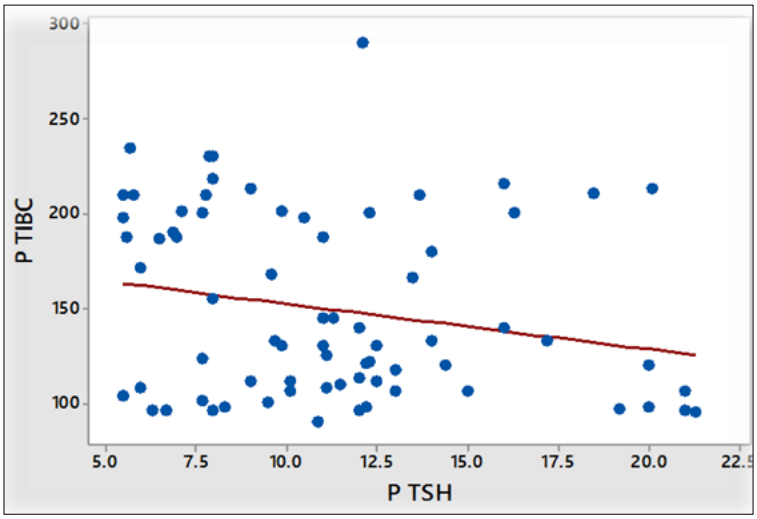

Fig 6: Correlation between TSH with Total iron binding capacity (TIBC) in patients.

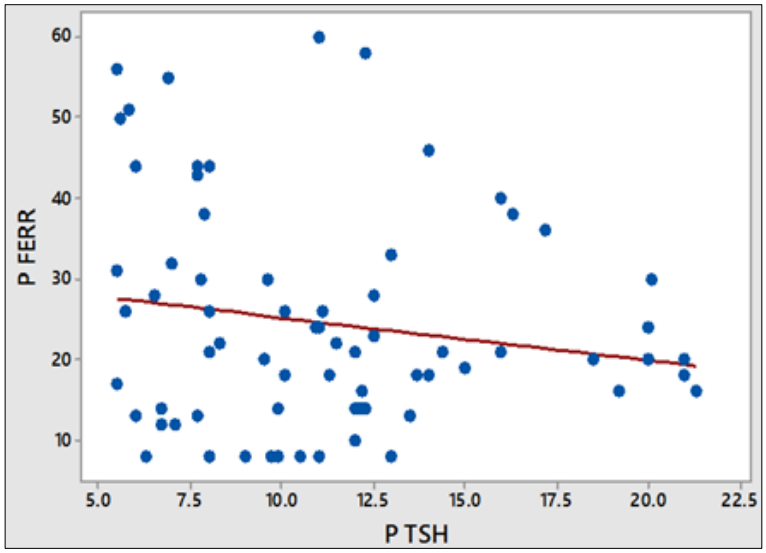

Fig 7: Correlation between TSH with Ferritin in patients.

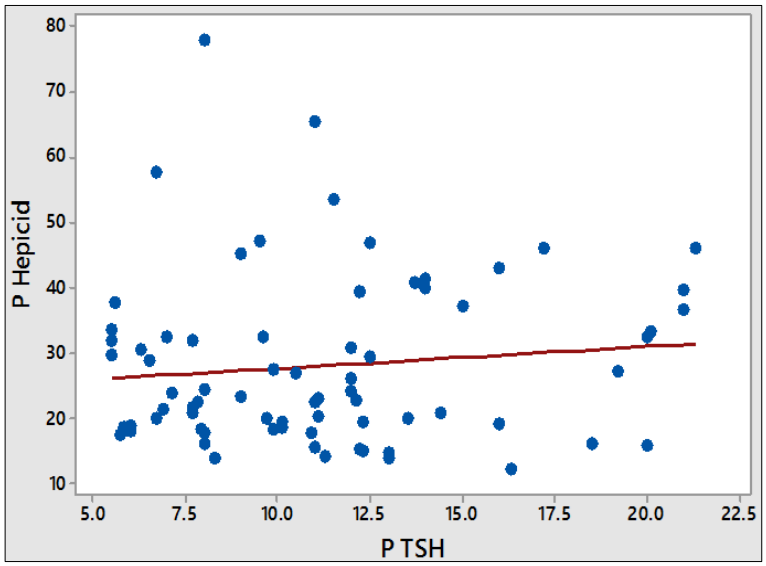

Fig 8: Correlation between TSH with Hepcidin hormone in patients.

Discussion

There exists a significant correlation between the occurrence of anemia and the existence of clinical-subclinical hypothyroidism in patients. Patients with anemia had a 2.7-fold higher prevalence of clinical-subclinical hypothyroidism compared to those without anemia [15]. The link between hypothyroidism and anemia has been hypothesized to be caused by the absence or insufficiency of thyroid hormones, which hinder the stimulation of erythropoiesis [26]. Normochromic normocytic anemia refers to the condition characterized by an inadequacy or deficit of erythropoietin. Hypothyroidism leads to a decrease in the formation of red blood cells and the development of anemia due to the lower availability of thyroid hormones, which restricts bone marrow activity [20]. Based on a study published in the Endocrine Journal in 2012, it was found that a significant proportion of individuals with overt (symptomatic) hypothyroidism, specifically 43 percent, exhibit anemia, in contrast to the general population where the prevalence is 29 percent [28]. Persistent weariness is a prominent characteristic of anemia. It is noteworthy that a study released in 2017 also indicates a potential association between iron deficiency and the onset of hypothyroidism. The significance of iron lies in its pivotal role in the synthesis of erythrocytes and thyroid stimulating hormone (TSH) [66]. Indeed, the deficiency of iron can give rise to a distinct type of anemia referred to as iron deficiency anemia. The interplay among iron, erythrocytes, and thyroid-stimulating hormone (TSH) can potentially contribute to the development of hypothyroidism by disrupting the regular functioning of the thyroid gland [67].

TIBC is renowned for its capacity to transport iron, and the level of serum transferrin rises during iron deficiency. TIBC, serving as a surrogate for transferrin, exhibits a lower susceptibility to rapid fluctuations in concentration compared to plasma iron concentration. Plasma iron concentration is prone to significant diurnal fluctuations and is influenced by dietary intake. Consequently, TIBC possesses inherent stability as an indication of iron status [23].

The co-occurrence of anemia and thyroid illness is a prevalent clinical issue frequently seen by medical practitioners. In many cases, iron-deficient anemia may serve as the primary manifestation of hypothyroidism, often referred to as the hematological mask of hypothyroidism [35]. Therefore, it is imperative to assess thyroid dysfunction in

individuals with recurrent anemia who exhibit resistance to iron therapy. In contrast, it has been observed that the favorable impact of iodine supplementation on thyroid function might be nullified by iron insufficiency [21]. The combination of L-thyroxine and iron salt is found to be more effective than either medication alone in treating subclinical thyroid dysfunction with iron deficient anemia [29].

Hepcidin, a key regulator of systemic iron homeostasis, exerts a significant influence on the formation of erythrocytes. Increased levels of hepcidin impede the absorption of iron in the intestines and the recycling of iron by macrophages, resulting in iron-restricted erythropoiesis and the development of anemia [30]. Reduced levels of hepcidin promote the availability of iron in the bone marrow for the synthesis of hemoglobin and the generation of red blood cells [31]. Increased production of red blood cells, such as after bleeding or therapy with erythropoietin, inhibits the activity of hepcidin by causing a sudden decrease in the amount of transferrin and the release of the erythroblast hormone and hepcidin inhibitor erythroferrone [33]. The process of erythropoiesis is inhibited in a quantitative manner, which limits the consumption of iron. This leads to a rise in transferrin saturation and stimulates the transcription of hepcidin [44]. The occurrence of anemia in three specific situations, namely iron resistant iron deficiency anemia (IRIDA), acute inflammatory disorders, and chronic inflammatory disorders, is linked to the deregulation of hepcidin production [59]. Concurrent occurrences of anemia and TPO-positive hypothyroidism are common, and it is important to evaluate hypothyroidism in cases when the cause of anemia is uncertain [48]. The mechanisms are ambiguous and potentially influenced by multiple factors. The most common forms of anemia observed in individuals with hypothyroidism are normocytic, normochromic, and hypo proliferative, although it can also manifest as microcytic or macrocytic [49]. Insufficient synthesis of thyroid hormone leads to a decrease in the potentiation of erythropoietin on bone marrow erythroid colonies, which serves as a purposed mechanism. Another potential mechanism that could be considered is anemia of chronic illness [46]. The persistent inflammatory condition triggers the production of interleukin-6, which enhances the activity of hepcidin, leading to a decrease in both the absorption of iron in the intestines and the release of iron from macrophages. A previous study has provided evidence of a reduction in hepcidin levels in individuals with TPO-positive hypothyroidism subsequent to the restoration of euthyroid [11]. Anemia might serve as an initial indication of hypothyroidism. Therefore, it is crucial to always take into account hypothyroidism in patients with anemia, particularly in cases when the cause is uncertain [42].

The circulating ferritin within the peripheral blood has been proposed to originate from the iron reserves seen in reticulo-endothelial cells [13]. Ferritin serves as a reservoir of iron that can be utilized as wanted for the manufacturing of hemoglobin or different compounds containing iron. This phenomenon holds sizeable importance in states characterized by a terrible iron stability, since it leads to the mobilization and eventual entire depletion of saved iron. Ferritin, an acute segment protein, well-known shows an enormous correlation with infection and is multiplied regardless of the presence of iron reserves [40]. Prior research conducted on medical institution populations has predominantly in comparison ferritin stages to bone marrow iron stages so as to stumble on iron insufficiency. However, that research is probably to be prompted by using a excessive occurrence of inflammation. The degrees of ferritin in pre-menopausal women are comparatively lower than the ones in post-menopausal ladies because of the loss of iron through menstrual blood, which is regarded as one of the mechanisms contributing to iron depletion in girls [25]. Iron deficiency and autoimmune thyroid disease are critical elements within the improvement of anemia in hypothyroidism. Anemia in hypothyroidism mainly arises from reduced erythropoietin production by the kidneys, as well as a deficit in iron, folic acid, and diet B12, due to damage to the gastrointestinal tract organs [14]. The unique system by using which iron supplementation influences the thyroid gland remains uncertain. Iron deficiency anemia has the potential to intervene with thyroid metabolism because of decreased oxygen transportation. Additionally, the regulation of thyroid metabolism with the aid of the important apprehensive device may be altered, doubtlessly main to a disruption in the binding of nuclear triiodothyronine [22]. Consequently, the levels of thyroxine and triiodothyronine inside the blood fall, main to a lower in the conversion of 1 hormone into every other. This decrease within the metabolism of triiodothyronine can also result in a growth in the quantity of thyroid-stimulating hormone circulating in the pituitary gland [23].

Conclusion

The present investigation demonstrates a correlation among hypothyroidism and iron deficiency anemia in premenopausal ladies, with each circumstance together influencing the physiological functioning of the frame. This has a look at demonstrated that hypothyroid patients enjoy a greater impact on the level of TSH as compared to the ranges of T_3 and T_4. Patients with hypothyroidism and IDA see a drop inside the levels of Hb, Ferritin, TIBC, and hepcidin hormone. Hypothyroidism and IDA are related through superb institutions, wherein decrease stages of T_3 and T_4 are related to lower levels of Hb, Ferritin, and TIBC.

Conflict of Interest

Not available

Financial Support

Not available

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