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Assessments of serum ferritin and iron status among hypothyroidism patients with and without levothyroxine treatment

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Abstract

Background: Hypothyroidism is a common disorder in which the thyroid gland does not synthesize and secrete enough thyroid hormone into the circulation. Hypothyroidism is diagnosed with a low concentration of plasma thyroxin (T4) and triiodothyronine (T3) with an elevation in the concentration of thyroid-stimulating hormone (TSH). Hypothyroidism symptoms include tiredness, weight gain, loss of concentration, and be unable to tolerate cold temperatures. The main treatment for hypothyroidism is hormone replacement therapy with levothyroxine.

Material and methods: This cross-sectional study was conducted between March 2022 and April 2023. Sixty males and females were enrolled in the study, ages 25 to 50. All samples were collected from the private medical laboratory and general hospitals in Baghdad city. These patients were classified into 2 groups; Group 1 included 30 patients newly diagnosed with hypothyroidism without thyroid hormone therapy and Group 2 included 30 hypothyroid patients treated with levothyroxine.

Results: According to the results there were no significant differences in mean patient's age ($p=0.317$) and gender distribution ($p=0.584$) between the three studied groups. There were also significantly lower T3 and T4 levels and significantly higher TSH levels among untreated hypothyroid patients ($p< 0.001$). Serum iron levels and serum transferrin saturation were significantly higher among levothyroxine-treated patients ($p< 0.001$); although total iron binding capacity (TIBC) and serum ferritin levels were significantly higher among untreated patients (Group 1) ($p < 0.001$ and $p=0.006$ respectively).

Keywords: Hypothyroidism; Levothyroxine; Iron; TIBC; Ferritin; Transferrin Saturation

1. Introduction

Hypothyroidism also has several causes. They include Hashimoto's disease, the most common cause, is an autoimmune disorder where the immune system attacks the thyroid gland [1]. Other less common causes include; sub-acute thyroiditis, congenital hypothyroidism, surgical removal of part or all of the thyroid gland, radiation therapy to the thyroid gland, certain medications, in rare cases, pituitary disease and iodine deficiency [2].

There is a relationship between the thyroid gland and iron, as iron is involved in the synthesis of thyroid hormones, and its deficiency means an imbalance in the functions of the thyroid gland [3]. Studies also suggest that there is an

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association between hypothyroidism and iron levels, which are controlled by the hormone hepcidin, which is an inflammatory response, and elevated IL-6 and CRP [4].

Patients with Hashimoto's disease have also been shown the treatment used to treat hypothyroidism which is levothyroxine, as it is a replacement for the thyroid hormone that is deficient. The treatment showed a decrease in inflammatory indicators in the body, as levothyroxine treatment is considered an anti-inflammatory in the thyroid gland and thus reduces inflammatory markers as a decrease in the level of acute phase protein ferritin and its release of iron in the body [5].

2. Materials and Methods

This cross-sectional study was carried out between March 2022 and April 2023. Sixty males and females their ages ranging from 25 to 50 were participated in the study. The samples were collected under the supervision of endocrinologists. The subjects were divided into 2 groups: Group 1 consisted of 30 newly diagnosed hypothyroidism patients without therapy (9 men and 21 women) and group 2 consists of 30 individuals with hypothyroidism who had received treatment with levothyroxine for no more than a year (11 men and 19 women). The exclusion criteria including; iron supplements, thalassemia, renal and liver disorders, diabetes mellitus, and hypertension.

Aspirated from each patient after that, clear serum was collected and kept frozen at -20 C until it was used for the measurement of thyroid function tests and iron study. Thyroid function tests and serum ferritin were measured by electro chemiluminescence immunoassay “ECLIA” (Cobas e411). Serum iron, TIBC and transferrin saturation were measured by chemistry auto-analyzer.

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 23.0. The descriptive statistics including frequency, mean and standard deviation were measured to describe the data. The groups were compared by applying independent sample t-test and chi square. The degree of association between continuous variables was calculated by Pearson’s correlation coefficient (r) and the results were considered statistically significant when p value was equal to or less than 0.05.

3. Results

The results were expressed in mean ± standard deviation while gender distributions were expressed in frequency and percentage. According to the results there were no significant differences between the studied groups concerning mean patient’s age (p=0.317) and gender distribution (p=0.584), on the other hand there were significantly lower T3 levels (0.47 ± 0.28 vs.1.35 ± 0.35; p< 0.001) and T4 levels (3.16 ± 1.64 vs. 8.06 ± 1.63; p< 0.001); on the contrary there was significantly higher TSH levels (19.72 ± 3.52 vs. 1.87 ± 0.93; p< 0.001) among untreated hypothyroid patients (Group 1) as demonstrated in table 1.

Table 1 Comparison of demographic features and thyroid status between the studied groups

Parameter (Mean ± SD)		**(Group1) Hypothyroidism without treatment**	**(Group 2) Hypothyroidism with treatment**	**p value**
Age (years)		39.40 ± 8.50	38.30 ± 8.07	0.317 Ŧ NS
Gender	Male	9 (30 %)	11 (36.7 %)	0.584 x2 NS
	Female	21 (70 %)	19 (63.3 %)	
T3 (ng/ml)		0.47 ± 0.28	1.35 ± 0.35	< 0.001 Ŧ S
T4 (µg/dl)		3.16 ± 1.64	8.06 ± 1.63	< 0.001 Ŧ S
TSH(µIU/ml)		19.72 ± 3.52	1.87 ± 0.93	< 0.001 Ŧ S

SD: Standard deviation; NS: Not significant (p > 0.05); S: Significant (p≤0.05); Ŧ: Independent sample t test; x^2: Chi square; T3: Triiodothyronine; T4: Thyroxin; TSH: Thyroid stimulating hormone

Serum iron levels (27.52 ± 3.37 vs. 56.42 ± 5.31), serum transferrin saturation (7.51 ± 1.17 vs. 20.99 ± 3.28) were significantly higher among group 2 patients (p< 0.001), on the contrary total iron binding capacity (TIBC) (419.9 ± 75.86

vs. 349.5 ± 79.02) and serum ferritin levels (175.4 ± 34.39 vs. 73.59 ± 12.94) were significantly higher among untreated patients (Group 1) ($p < 0.001$ and $p=0.006$ respectively) as presented in table 2 and figure 1.

Table 2 Comparison of serum ferritin and iron status between the studied groups

Iron status	(Group1) Hypothyroidism	(Group 2)	p value
Serum iron (µg/dl)	27.52 ± 3.37	56.42 ± 5.31	< 0.001 Ŧ S
Serum TIBC (µg/dl)	419.9 ± 75.86	349.5 ± 79.02	< 0.001 Ŧ S
Transferrin saturation %	7.51 ± 1.17	20.99 ± 3.28	< 0.001 Ŧ S
Serum ferritin (ng/ml)	175.4 ± 34.39	73.59 ± 12.94	0.006 Ŧ S

S: Significant (p ≤ 0.05); TIBC: Total iron binding capacity; Ŧ: Independent sample t test

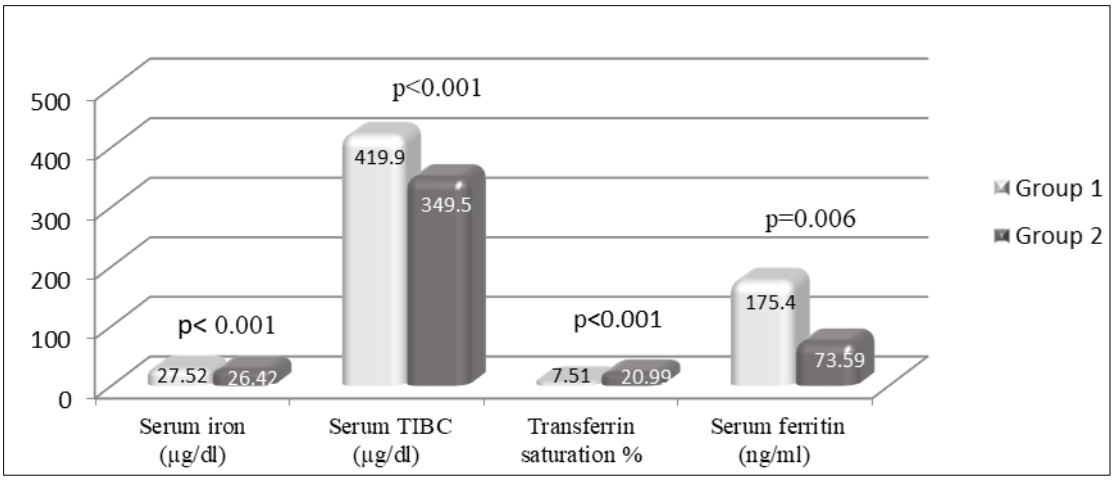

Figure 1 Comparison of serum ferritin and iron status between the studied groups

The correlations between thyroids function tests with iron status in untreated hypothyroid patients were presented in table 3, according to the results there were; significant positive correlation between T4 and iron levels (r= 0.640 & p <0.001), significant negative correlation between T4 and TIBC (r= -0.559 & p=0.001) and significant positive correlation between T4 level and transferrin saturation % (r= 0.628 & p <0.001). On the other hand, there were no significant correlations between thyroid function tests and iron status among patient received levothyroxine therapy (Table 4).

Table 3 Correlation between thyroid function tests with serum iron status among untreated hypothyroid patients

Iron status	Statistics	T3	T4	TSH
Iron	r	-0.110	0.640*	0.142
	p	0.564	< 0.001	0.453
TIBC	r	0.083	-0.559*	-0.005
	p	0.664	0.001	0.980
Transferrin saturation %	r	-0.113	0.628*	0.136
	p	0.553	< 0.001	0.474
Ferritin	r	0.114	0.004	-0.062
	p	0.548	0.983	0.746

TIBC: Total iron binding capacity; r: Pearson's correlation coefficient; T3: Triiodothyronine; T4: Thyroxin; TSH: Thyroid stimulating hormone; *: Significant correlation

Table 4 Correlation between thyroid function tests with serum iron status among hypothyroid patients treated with levothyroxine

Iron status	Statistics	T3	T4	TSH
Iron	r	-0.054	0.167	-0.293
	p	0.776	0.376	0.116
TIBC	r	0.226	0.004	0.055
	p	0.230	0.983	0.775
Transferrin saturation %	r	0.248	0.183	-0.097
	p	0.186	0.332	0.612
Ferritin	r	0.104	-0.186	-0.215
	p	0.585	0.325	0.254

TIBC: Total iron binding capacity; r: Pearson's correlation coefficient; T3: Triiodothyronine; T4: Thyroxin; TSH: Thyroid stimulating hormone

4. Discussion

There were no statistical differences concerning patient's age and gender, however the results of the present study show that the rate of hypothyroidism is often higher in females than in males [6]. According to a study conducted on a group of people in Europe, they were diagnosed with hypothyroidism revealed the prevalence of hypothyroidism tends to be higher in female patients [7] and hypothyroidism is the second most common endocrine disorder in women [8].

The results revealed that patients in group1 had hypothyroidism, and this was shown by a significant increase in the TSH hormone and a relative significant decrease in the T3 and T4 hormones it also coincides with the results of other studies [9]. As for the group 2 patients who suffered from hypothyroidism and were treated with levothyroxine for 3-6 months, the TSH hormone significant decreased and the stability of T4 and T3 hormones were obtained, and this proves the effectiveness of the drug levothyroxine in treating Hypothyroidism [10, 11].

Thyroid hormones play an important role in regulating the body's metabolic activities, including the elements and minerals in the body. One of the most important minerals in the human body is iron because it is important in hemoglobin in the blood. There is a relationship between the thyroid gland and the iron homeostasis and iron deficiency will affects the synthesis of thyroid hormones [12].

The results in group 1, people with untreated hypothyroidism, were a decrease in the level of iron and also a significant increase in TIBC, and transferrin saturation was less than 20%, and this indicates that there is a relationship between hypothyroidism and low iron, where there is a role for the decrease in thyroid hormones [13, 14]. Thyroid hormones and inflammation play a role in changing iron levels in the body through the physiological effect of hormone and its control of the body's metabolism rate or through inflammation and its indirect effect, and this was cleared in the present study [15, 16]. As for group 2 patients, who were treated with levothyroxine, the results showed that the iron state began to return to its normal levels and this was agreed with other studies [17, 18]. In the present study there was a significant increase in the level of ferritin among untreated hypothyroidism patients (Group1) and no significant increase among group 2 patients [19], Both TIBC and transferrin saturation depend on the levels of iron in the body, as when an iron deficiency occurs, there will be more places over transferrin protein (To which iron molecules bind), so the percentage of TIBC is higher than normal, and the percentage of transferrin saturation In cases of iron deficiency, it is less than normal. This is what our research indicates in the results were agrees with other sources [20].

Hashimato's disease is hypothyroidism due to autoimmune disease, Primary autoimmune hypothyroidism is an inflammatory disease characterized by elevated cytokine levels that decrease with levothyroxine therapy [21]. Also, if in people with thyroiditis in Hashimato's disease, there is a significant increase in the levels of CRP, which is the protein that rises in cases of inflammation in the body is in response to the rise of IL6 [22, 23]. and As for the hepcidin hormone, it is a response to the rise of IL-6, where the rise of the cytokine IL-6 leads to a positive response in the hepcidin hormone, as the rise of this hormone leads to a reduction in the proportion of iron in the body, and therefore, since it responds to IL-6, this means that there is a positive response from this hormone to inflammation in the body [24].

There were also significant higher ferritin levels of ferritin among people with untreated hypothyroidism, compared to subjects treated with levothyroxine (Group2). In inflammatory conditions, the rise in ferritin may not be real, as it is

considered acute phase proteins, so it does not give a true indication of the correct amount of iron stores in the body and in cases of hashimato's disease, an inflammation due to autoimmunity may lead to elevated ferritin values as acute phase proteins [25].

Also, there is a response of ferritin to interleukin-6. In the case of inflammation, this response can lead to an increase in ferritin [26]. Hepcidin, a hormone that regulates iron, is a promising diagnostic for distinguishing between iron shortage and inflammatory anemia. The amount of smaller, non-biologically active isoforms of hepcidin also increases under inflammatory circumstances, when the concentration of hepcidin increases as a result of inflammation this leads to a reduction in the level of iron in the body, this means may indicates that there is a relationship between the inflammation resulting from autoimmunity and thyroiditis and the level of iron in the body [27, 28].

Hashimoto's disease had an increase in the inflammatory indicators as IL6, and after treatment with levothyroxine, a significant decrease was observed in the rate of inflammation in the thyroid gland, and a decrease in the inflammatory indicators as IL6, according to what this study states [29].

5. Conclusion

There were significantly lower T3 and T4 levels and significantly higher TSH levels among untreated hypothyroid patients ($p< 0.001$). Serum iron levels and serum transferrin saturation were significantly higher among levothyroxine-treated patients ($p< 0.001$); although total iron binding capacity (TIBC) and serum ferritin levels were significantly higher among untreated patients ($p < 0.001$ and $p=0.006$ respectively).

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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