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Bone and thyroid nexus in thyroid disease patients

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Abstract
Background: Hypothyroidism is the second most prevalent endocrine disease in women, characterized by insufficient production of thyroid hormone by the thyroid gland.
Objectives: The present study aims to assess the serum level of osteocalcin, T_3, T_4, TSH, and thyroid peroxidase in women with hypothyroidism and to investigate the effect of medical therapy on osteocalcin, T_3, T_4, TSH, and thyroid peroxidase levels in subjects with hypothyroidism.
Methods: This study has investigated 180 women (70 women before treatment, 70 after treatment and 40 controls), who's ages range between (15-54) years. Patients were referred to two primary hospitals, Azadi Hospital in Kirkuk City and Kirkuk General Hospital, between September 2023 and December 2023. The participants in this research are categorized into three groups: Before therapy, a group of 70 women with hypothyroidism was diagnosed by medical professionals. The second group consisted of 70 women who had hypothyroidism and had undergone therapy compared to the control group. Serum levels of osteocalcin and thyroid peroxide (TPO), TSH, T_3, and T_4 were measured.
Results: According to the presented data show a decrease in the mean of the serum level of osteocalcin, T_3, and T_4 in hypothyroidism women before and after treatment compared with the control group (13.4±4.9 versus 19.8±5.1 and 21.5±5.0), (2.49±0.65 versus 6.17±1.40 and 5.65±2.04 ng/ml), (6.85±1.72 versus 14.83±4.21 and 14.86±3.11 ng/ml) respectively. The result was significant ($P < 0.01$) while increasing the mean of TSH and TPO in hypothyroidism before and after treatment compared with the control group (32.78±8.83 versus 4.26±1.77 and 4.48±1.68 ng/ml).
Conclusion: It was concluded that the osteocalcin, T_3, and T_4 decreased in women with hypothyroidism before treatment in comparison with women after treatment and healthy women, while Furthermore increase the mean of TSH and TPO in hypothyroidism before and after treatment compared with the control group.

Keywords: Hypothyroidism, osteocalcin, TSH and TPO, T_3, T_4

Introduction
The thyroid gland is situated in front of the larynx on both sides and in front of the trachea, resembling the form of a butterfly. It generates thyroxine, a hormone that controls the body's metabolic activity. The thyroid gland produces two hormones: thyroxin (T_4) and triiodothyronine (T_3) [1]. Thyroid illness progresses through many stages, from initial to severe manifestations. Patients with thyroid diseases are classified based on the function parameters as either "hypothyroidism," characterized by low T_4 levels, or "hyperthyroidism," characterized by increased T_4 or T_3 levels and reduced TSH [2]. Hypothyroidism affects 0.3% to 0.4% of the population in the United States, with a higher frequency in older individuals and more often affecting females [3].
Hypothyroidism, a prevalent endocrine disorder, occurs due to a lack of thyroid hormone or reduced activity at the tissue level. This condition results in insufficient thyroid hormone production, slowing metabolism, deepening of the voice, weight gain, and water retention, and can hinder growth and mental development in children. Both disorders also affect hair and skin development, gastrointestinal function, and menstrual flow [4]. Thyroid hormone is produced from thyroglobulin by a process called biosynthesis, which is facilitated by an integral membrane protein called thyroid peroxidase (TPO). TPO is a significant autoantigen in autoimmune thyroid disorders [5]. Osteocalcin (Oc), also known as bone-Gla protein (BGP), is the predominant noncollagenous protein found in fully developed human bone, making up about 1 to 2% of the total protein content. Produced by osteoblasts, it is integrated into the bone matrix [6].

Osteocalcin is a significant indicator of bone activity, used in disease diagnosis and assessing the impact of medications on bone metabolism. Patients with hypothyroidism showed a quick rise in blood osteocalcin levels after starting L-T_4 medication, indicating a direct impact of thyroid hormone on osteoblasts [7].

Materials and Methods

Subjects: This research examined 180 individuals with hypothyroidism, consisting of 70 patients and 40 controls. Among them, 70 patients were newly diagnosed with hypothyroidism and received therapy for 3 months. The follow-up study included individuals aged between 15 and 54 years. Patients were sent to two primary institutions, Azadi Hospital in Kirkuk City and Kirkuk General Hospital, between September 2023 and December 2023 was used to gather clinical history data including age, sex, weight, and height, family history of thyroid illness, chronic conditions, and treatment details. Patients with diabetes and chronic diseases who are using oral contraceptives, antiandrogenic medications, glucocorticoids, antihypertensive meds, antidiabetic pharmaceuticals, and antiobesity drugs, and who smoke or have hypertension are excluded.

Sample Collection: Approximately 5 ml of venous blood was drawn from each participant using a sterile disposable syringe. The blood was then transferred into gel tubes and left to clot at room temperature for 20 minutes. After centrifugation at 3000 rpm for 15 minutes, the samples were separated into three Eppendorf tubes, each containing 500 µl of serum. The tubes were then maintained at -20 °C until they were utilized for the test, which comprised parameters such as TSH, T_3, T_4, thyroid peroxidase, and osteocalcin.

Estimation of osteocalcin and thyroid peroxide (TPO): This ELISA kit utilizes the Sandwich-ELISA technique from SunLong, China. The Microelisa stripplate in this kit is pre-coated with antibodies that target osteocalcin and TPO. Standards or samples are added to the designated wells of the Microelisa stripplate and mixed with the corresponding antibody. An antibody specific for osteocalcin and TPO is conjugated with Horseradish Peroxidase (HRP) and applied to each well of the Microelisa stripplate for incubation. Unattached components are removed. The TMB substrate solution is introduced into each well. Wells containing osteocalcin, TPO, HRP conjugated osteocalcin, and TPO antibody will become blue and then yellow once the stop solution is added. The optical density is determined using spectrophotometry at a wavelength of 450 nm. The optical density value is directly related to the levels of osteocalcin and TPO.

Estimation of serum levels of TSH, T_3, and T_4: The test utilizes the one-step sandwich enzyme immunoassay technology from Biomérieux company, which is followed by a final fluorescence detection phase known as Enzyme-Linked fluorescence test (ELFA).

Ethical considerations: The ethical protocols were followed in the conduct of the study. The goal of the study was explained to the participants orally. The research team carefully selected patients to be included in the study and obtained ethical approval before starting sample collection. The participants were effectively informed of the purpose and methodology of the survey by the researcher, who also gave them standard instructions and guidance to make completing the questionnaire easier. After being carefully reviewed, the study concept, patient data, and consent form were approved on October 9, 2023, by the local Ethics Committee 221/7/3.

Statistical analysis: The data was analyzed using the Minitab application using the ANOVA test. However, the mean was found to be statistically significant according to the Duncan multiple range test at a significance level of 0.05.

Results

The total number of subjects that participated was 180 subjects (70 patients with hypothyroidism after treatment, 70 patients with hypothyroidism before treatment and 40 controls healthy subjects). This study showed that increase in hypothyroidism in women between 28-41 years and its percentage was 46.4%, while the least age group was 15-27 years and its percentage was found to be 23.6%, see Table (1).

Table 1: Relation the number of hypothyroidism women with Age.

Age group(years)	n(%)	%
15-27	33	23.6%
28-41	65	46.4%
42-54	42	30%
Total	140	100%
p-value	P-Value = 0.015	

Table (2) explains the number of hypothyroidism women with BMI, were 30(21.4%) women with normal weight (18.5 – 24.9), 54 (38.6%) overweight (25 – 29.9), and 56 (40%) with obese (≥ 30).

Table 2: Relation the number of hypothyroidism women with BMI.

BMI (Kg/m^2)		Studied group
		Hypothyroidism women
Normal weight	n	30
(18.5 – 24.9)	%	21.4%
Overweight	n	54
(25 – 29.9)	%	38.6%
Obese (≥ 30)	n	56
	%	40%
Total	n	140

**Chi-Square = 14.802 P-Value = 0.002

As shown in Figure (1), the presented data show the mean Mean±SD of the serum level of osteocalcin in hypothyroidism women before and after treatment compared with the control group (9.8±4.7 versus 14.35±12.63 and 15.20±14.73) respectively. The result was significant (P <0.01).

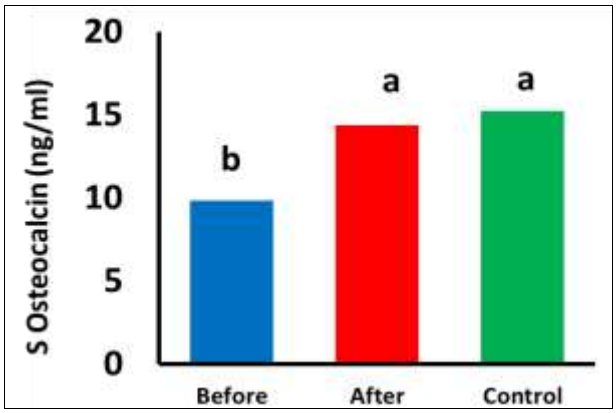

Fig 1: Comparison between hypothyroidism patients and healthy individuals regarding the mean± SD of Serum osteocalcin before and after treatment

As shown in Figure (2), the mean of the serum level of Thyroid Hormones in hypothyroidism before and after treatment compared with the control group, The results of the study showed an increase in the levels of the TSH hormone in women with hypothyroidism before taking treatment compared with the results of the hormone levels after taking treatment and comparing with the control groups (32.78±8.83versus 4.26±1.77 and 4.48±1.68 ng/ml) respectively. The result was significant (P <0.01).

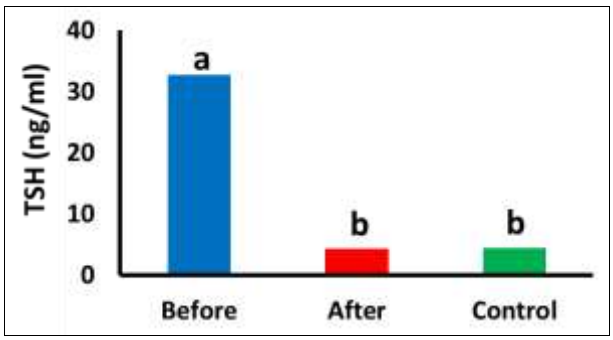

Fig 2: Serum Level of TSH in Women with hypothyroidism before and after treatment.

As shown in Figure (3), the mean of the serum T_3 levels decreased in women with hypothyroidism before taking treatment compared with the results of the hormone levels after taking treatment and comparing with the control groups (2.49±0.65 versus 6.17±1.40 and 5.65±2.04 ng/ml) respectively. The result was significant (P <0.01).

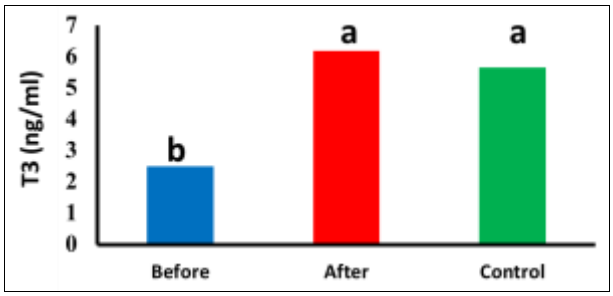

Fig 3: Serum Level of T_3 in Women with hypothyroidism before and after treatment.

As shown in Figure (4), the mean of the serum level T_4 of Thyroid Hormones in hypothyroidism before and after treatment compared with the control group (6.85±1.72 versus 14.83±4.21 and 14.86±3.11 ng/ml) respectively. The result was significant (p<0.01).

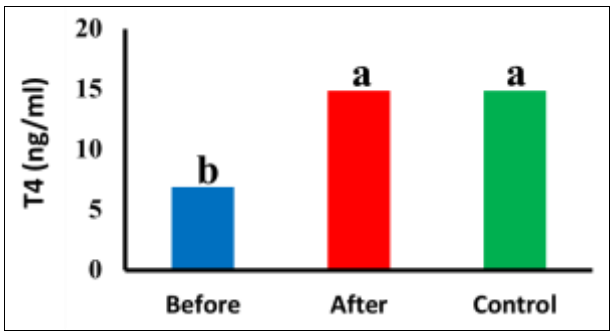

Fig 4: Serum Level of T_4 in Women with hypothyroidism before and after treatment

As shown in Figure (5), the presented data show the Mean±SD of the serum level of Human TPO in hypothyroidism women before and after treatment compared with the control group (3498.2±503.75 versus 2756±1810.9 and 2629.47±289.5) respectively. The result was significant (P <0.01).

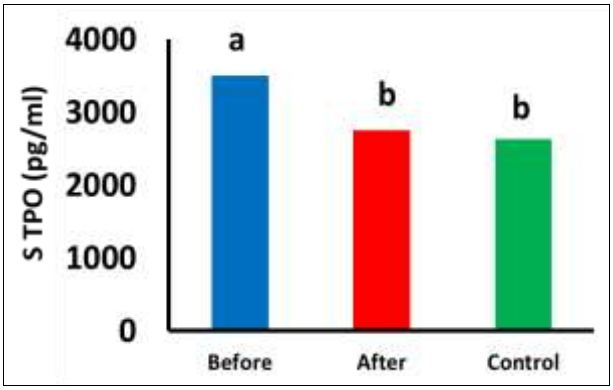

Fig 5: Serum Level of Human TPO (Thyroid Peroxidase) in Women with hypothyroidism before and after treatment

Discussions

According to this study, there is a higher incidence of hypothyroidism in the age range of 28–41, 42–54, and 15–27. According to SALIH *et al*.'s study conducted in Kirkuk [8], there is a higher incidence of hypothyroidism in (30-39). Another Diyala study by MOHAMMUD HABASH *et al*. [9] reveals a significant frequency of thyroid illness in people between the ages of 31 and 40. Thyroid disease was shown to be highly prevalent in adults (ages 32 to 51), practically constant in old age (≥52 years), young age (≤30 years), and finally in children (<12) [10]. Thyroid disorders were more common in patients between the ages of 41 and 60, according to two studies from Malaysia and India [11, 12]. Table (2) shows the correlation between obesity and hypothyroidism. The research conducted by HASSAN and ABBAS (2022) revealed a negative correlation between T_3 and T_4, but a favorable link with TSH levels and body weight and BMI [13]. Verma *et al*. (2008) found in another study that 44% of patients with hypothyroidism were obese [14]. Obesity and hypothyroidism often coexist in differing degrees of severity. Because of increased mucin deposition in the skin and other organs as well as salt and water retention, overt hypothyroidism causes an increase in body weight [15].

This result shows a decreased level of osteocalcin in hypothyroidism patients compared with control at (p<0.01), while no differences between osteocalcin levels after treatment with levothyroxine and the control group. An abrupt rise in blood OC levels was found after the commencement of supplementary L-T_4 therapy in individuals with hypothyroidism. This indicates a direct impact of thyroid hormone on osteoblasts in hypothyroid patients. This result agrees with Kojima *et al*., (1992) [16] who showed a decrease in osteocalcin in hypothyroid patients which suggested Osteoblastic activity is increased in persons with hyperthyroidism and decreased in those with hypothyroidism [16], also this study agrees with [17], that show a decrease of osteocalcin level in hypothyroidism patients.

Osteocalcin, a protein produced by osteoblasts, serves as a valuable indicator of bone remodelling and likely indicates the metabolic function of osteoblastic bone cells [18]. Hyperthyroidism leads to an increase in bone turnover, whereas hypothyroidism causes a reduction in bone turnover [19]. Moreover, there is a notable and favourable association between the concentration of serum osteocalcin (OC) and the levels of

serum triiodothyronine (T_3), thyroxine (T_4), free triiodothyronine (FT_3), or free thyroxine (FT_4) in blood samples collected from untreated individuals with hypothyroidism. This connection might be attributed to the direct influence of thyroid hormones on bone metabolism, as shown by previous research [19]. Consistent with a prior study [20], the blood levels of osteocalcin (OC) in six individuals with hypothyroidism showed a concurrent rise with the increase in serum thyroxine (T_4) levels, occurring within 1-2 months following therapy. This research contradicts the findings that indicate no substantial difference in osteocalcin levels before and after LT_4 therapy [21]. Another research demonstrates that there is no notable disparity in osteocalcin levels between individuals with hypothyroidism and those without the condition [22].

This study shows increased TSH in hypothyroidism women while decreasing T_3 and T_4. This result agrees with Rustam and Hassan. (2021); Zahra *et al*., (2020), that show an increase in TSH, while a decrease in T_4 hypothyroidism patients [23, 24]. The research conducted by Mohamed showed a substantial rise in TSH levels (p=0.046) and a significant drop in T_3 (p=0.040) and T_4 (0.029) levels in patients compared to the Control group [25].

Thyroid hormones are essential for controlling the body's metabolism by activating metabolic processes in tissues, which in turn increases the basal metabolic rate and body heat generation. The thyroid gland significantly influences several bodily functions such as growth, reproduction, and metabolic control. Thyroid hormone-induced thermogenesis is triggered by a heightened demand for ATP due to increased cellular activity and reduced efficiency in ATP production individuals with hypothyroidism exhibit delayed and reduced metabolic activity, generally resulting in an elevated BMI, while individuals with hyperthyroidism have the opposite effect [26]. Previous studies have connected hypothyroidism with elevated oxidative stress, which may harm thyroid follicular cells responsible for producing T_3 and T_4, leading to reduced levels of these hormones in the bloodstream and a rise in TSH [27].

Hypothyroidism in women may be caused by elevated estrogen levels, which can interfere with the hormones T_3 and T_4 by competing for binding sites on receptor proteins. Additionally, disruptions in the thyroid gland in females can be linked to the sex hormones progesterone and estrogen, potentially leading to nervous tension during the menstrual cycle or pregnancy [28]. Estrogen controls the transport proteins that bind to thyroxin (TBG) by reducing their clearance from the circulation and increasing their creation. Estrogen also activates the immune system to produce more anti-thyroid antibodies [29].

In this prospective investigation, we identified a significant result ($p< 0.0001$) in women with or without thyroid autoantibodies. Our findings indicate that thyroid autoimmune disease should be considered while investigating female hypothyroidism conditions. In 2015, Negro *et al*. found that there was a slightly greater percentage of women with TPOAb among those with hypothyroidism, while raised TSH levels were a major predictor against the condition [30].

Conclusion

In hypothyroidism, Human TPO and TSH levels were considerably elevated compared to the control group, but osteocalcin, T_3, and T_4 levels decreased. There was a strong positive association seen among Thyroid hormones TSH, T_3, and T_4 in female patients with Hypothyroidism.

Conflict of Interest

Not available

Financial Support

Not available

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