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Comparison the levels of bone turnover parameters between premenopausal and postmenopausal women after thyroidectomy

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ABSTRACT: **Background**: Both pre-menopausal and postmenopausal women after post-thyroidectomy patients are at increased risk of osteoporosis; however, the endocrine pathways leading to bone loss differ—estrogen deficiency versus altered thyroid hormone and TSH homeostasis. While the bone effects of menopause have been extensively characterized, there is limited research directly comparing biochemical bone turnover profiles between these two groups.

Aim of the Study: To compare the levels of selected bone turnover parameters between pre-menopausal and postmenopausal women after thyroidectomy.

Materials and Methods: A total of 150 samples were collected and divided equally into three groups, 50 samples permenopausal after thyroidectomy, 50 samples postmenopausal after thyroidectomy, and 50 control.

Result: The study found significantly elevated levels of triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), β-C-terminal telopeptide (β-CTX), and N-MID osteocalcin in the serum of both premenopausal and postmenopausal women than in the control group. The different superscript letters represent significant differences between the groups ($p < 0.05$).

Conclusion: Thyroid hormone levels (T3, T4 and TSH) are significantly changed in menopausal status compared with the control group. Inaddition Increased levels of β-CTX and N-MID in the serum suggests increased bone resorption due to estrogen depletion in menopause.

INTRODUCTION

Bone is a metabolically active tissue that is continuously remodelled by osteoclasts that resorb mineralized bone and osteoblasts that deposit new matrix. This remodelling is necessary for skeletal strength maintenance, microdamage repair and mineral homeostasis regulation (Khosla & Hofbauer, 2017). Systemic hormones such as sex steroids, especially oestrogen, and thyroid hormones (triiodothyronine [T3] and thyroxine [T4]), are tightly regulating the process (Manolagas et al., 2013). Disruption in the balance of these hormones may shift the coupling between bone formation and resorption predisposing individuals to bone fragility and osteoporosis (Eastell et al., 2016). Women with serum estradiol levels < 9 pg/mL have significantly higher levels of bone turnover markers such as osteocalcin and C-terminal telopeptide (CTX) compared to women with higher levels (Slemenda et al., 1996). Some studies reported a threshold effect, with greater bone resorption than bone formation at estradiol

≤ 10 pg/mL (Greendale et al., 2012). Oestrogen deficiency mechanistically causes upregulation of osteoclastogenic cytokines such as interleukin-1 (IL-1), tumour necrosis factor-alpha (TNF-α) and receptor activator of nuclear factor kappa-B ligand (RANKL), and downregulation of osteoprotegerin (OPG), which enhances osteoclastic activity and accelerates bone loss (Khosla et al., 2012).

➢ Long term TSH suppression therapy with levothyroxine is often necessary after total or near total thyroidectomy especially in patients treated for differentiated thyroid carcinoma. Chronic TSH suppression has been linked to reductions in BMD, particularly in postmenopausal women (Heijckmann et al., 2005; Flynn et al., 2010). Meta-analyses of TSH suppression have reported measurable decreases in BMD at the lumbar spine and femoral neck, sites rich in trabecular bone and highly metabolically active (Faber et al., 2002; Zhang et al., 2016). Nevertheless, no significant differences in serum calcium, phosphorus or parathyroid hormone (PTH) levels have been observed in patients after thyroidectomy compared with matched controls in previous studies suggesting that skeletal effects may be more subtle and site-specific (Marcocci et al., 1990). The remodelling cycle can be broken down into discrete phases: activation, resorption, reversal, formation, and mineralization(Delaisse, J. M. (2014) Osteoclasts, originating from the monocyte-macrophage lineage, degrade mineralized bone via enzymatic and acidic processes, thereby releasing calcium and phosphorus into the circulation(Sun, Y., Li, J., et al.,2021). Osteoblasts are mesenchymal derived cells which synthesise and mineralise bone matrix and secrete proteins such as collagen type I and osteocalcin. Osteocytes are mature osteoblasts that have differentiated and act as mechanosensors and regulators of osteoclast and osteoblast activity(Zappalà, A., et al., 2023). The bone resorption markers are degradation products of type I collagen and enzymes released by osteoclasts during bone matrix degradation. C-Terminal Telopeptide of Type I Collagen (CTX), a widely used serum and urine marker reflecting collagen degradation. CTX levels rise in conditions of high bone resorption, such as postmenopausal osteoporosis and hyperthyroidism (Szule *et al*., 2016).

N-Terminal Telopeptide of Type I Collagen (NTX): A different collagen breakdown marker, measurable in urine or serum that reflects osteoclastic activity. Postmenopausal women and patients after thyroidectomy are both at increased risk for osteoporosis but the endocrine pathways leading to bone loss are different, oestrogen deficiency vs. altered thyroid hormone and TSH homeostasis. While the bone effects of menopause are well characterised, there is little research directly comparing biochemical bone turnover profiles in these two groups. A head-to-head comparison might reveal common or differential patterns that could inform risk stratification and targeted prevention strategies. To compare the level of selected bone turnover parameters in patients after thyroidectomy and in postmenopausal women.

MATERIALS AND METHODS

3.1 Study Design

This study was a cross-sectional analytical study to evaluate thyroid related biomarkers among patients attending private clinics, Tikrit Teaching Hospital and Al-Tawfiq Private Hospital. Laboratory analyses were performed in an effort to compare hormonal variations in three different groups. The analytical design of the study enabled identification of variations in thyroid-related biomarkers in the studied groups in real clinical conditions. The study was cross-sectional in design, providing a snapshot of hormonal status at the time of sample collection, and is suitable for the assessment of prevalence patterns and group based comparisons.

This design also made it possible to collect data efficiently in a short time frame while maintaining rigour in the science. Standardised laboratory procedures and uniform sample handling protocols, employed at all participating centres, minimised any potential for confounding variables.

3.3 Study Population

A total of 150 participants were recruited consecutively according to pre-defined inclusion and exclusion criteria to ensure sample homogeneity and minimise selection bias. We included both male and female patients. Participants were recruited from private medical clinics, Tikrit Teaching Hospital and Al-Tawfiq Private Hospital in Iraq. A total of 150 samples were collected and equally divided into three groups- 50 premenopausal after thyroidectomy, 50 postmenopausal after thyroidectomy and 50 control. The study was carried out in private medical clinics , Tikrit Teaching Hospital and Al-Tawfiq Private Hospital , Iraq. They comprise specialised units and certified laboratories in these health care facilities. All biochemical analyses were done in accredited hospital laboratories with standardised quality-control procedures.

3.5 Data Collection

Blood samples were collected from all participants under strict aseptic conditions by qualified laboratory personnel. Approximately 5 mL of venous blood was drawn from each subject using sterile disposable syringes and transferred into plain vacutainer tubes. The collected samples were allowed to clot at room temperature for 20–30 minutes and subsequently centrifuged at 3000 rpm for 10 minutes to separate the serum.

The obtained serum samples were carefully aliquoted into labeled Eppendorf tubes and stored at −20 °C until further biochemical analysis. Repeated freeze–thaw cycles were avoided to preserve sample integrity.

Serum samples were analyzed for thyroid-related hormonal parameters, including:

Thyroid Stimulating Hormone (TSH), Triiodothyronine (T3), and Thyroxine (T4). The quantitative measurement of serum TSH, T3, and T4 levels was performed using an automated chemiluminescence immunoassay (CLIA) system (Cobas e 411 analyzer, Roche Diagnostics, Mannheim, Germany). All assays were carried out in accordance with the manufacturer's instructions.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 22; IBM Corp., Armonk, NY, USA). Prior to inferential statistical testing, the normality of continuous variables, including serum levels of thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), osteocalcin, and beta-C-terminal telopeptide of type I collagen (B-CTX), was assessed using the Shapiro–Wilk test.

Quantitative data were summarized using descriptive statistics and expressed as mean ± standard deviation (SD), along with 95% confidence intervals where appropriate. Comparisons of biochemical parameters among the three study groups (pre-intervention, post-intervention, and control groups) were conducted using one-way analysis of variance (ANOVA). The assumption of homogeneity of variances was evaluated using Levene's test.

When statistically significant differences were identified by ANOVA, post-hoc multiple comparison analyses were performed using Tukey's honestly significant difference (HSD) test to determine group-specific differences. All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

RESULT

The study found significantly elevated levels of triiodothyronine (T3) in the serum of both premenopausal and postmenopausal women (3.515±0.547, 3.247±0.67) than in the control group, as shown in Table (1) and Figure 1. The different superscript letters represent significant differences between the groups ($p < 0.05$).

Table 1 Descriptive Statistics for T3 Levels (Mean ± SD) with 95% Confidence Intervals

Group	N	Mean	SD	CI 95%
Pre.T3	30	3.515 a	0.547	(3.2859, 3.7442)
Post.T3	30	3.247 a	0.670	(3.018, 3.476)
Con.T3	30	2.135 b	0.669	(1.906, 2.364)

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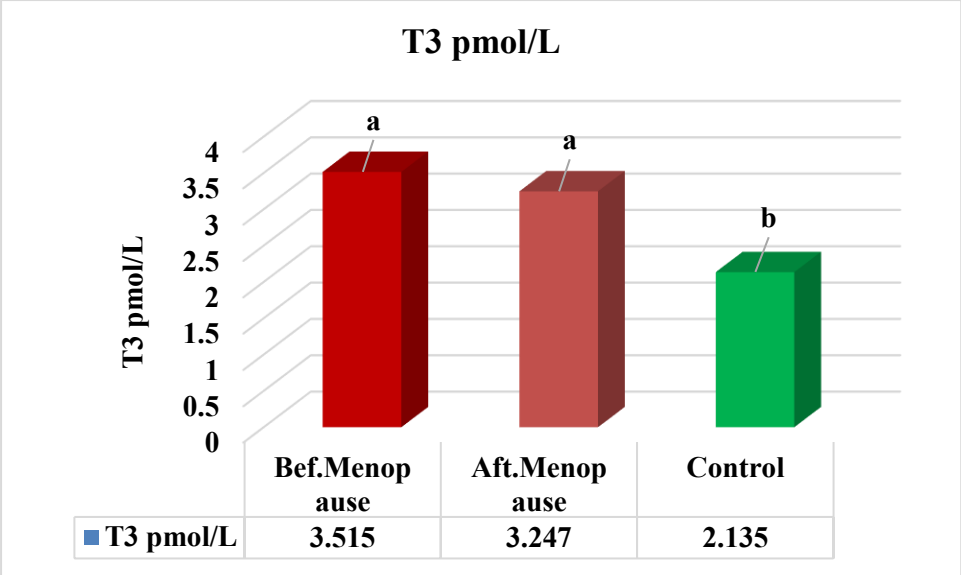

Figure 1. Serum triiodothyronine (T3) levels in premenopausal, postmenopausal, and control groups.

Values are expressed as mean ± SD. Different superscript letters indicate statistically significant differences among groups ($p < 0.05$).

Levels of serum thyroxine (T4) were significantly increased in premenopausal and postmenopausal women (5.003±1.779, 5.133±1.427) compared to the control group, as illustrated in Table (2) and Figure 2.

Table 2 Descriptive Statistics for T4 Levels (Mean ± SD) with 95% Confidence Intervals.

Factor	N	Mean	St. Dev	95% CI
Pre.T4	30	5.003 a	1.779	(4.382, 5.624)
Post.T4	30	5.133 a	1.427	(4.512, 5.754)
Con.T4	30	4.389 b	1.893	(3.768, 5.010)

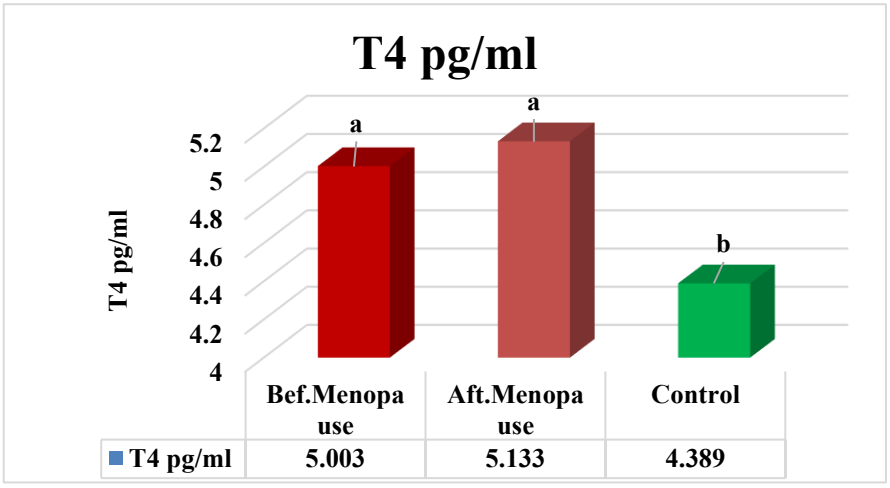

Figure 2. Serum thyroxine (T4) levels in premenopausal, postmenopausal, and control groups.

Data are shown as mean ± SD. Values with different superscript letters are significantly different ($p < 0.05$).

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In the case of thyroid-stimulating hormone (TSH), we found significantly higher levels in premenopausal and postmenopausal women (656.9±51.5, 599.5±37.2) **pg/mL** than in the control group, with the highest values in premenopausal women, as shown in Table 3 and Figure 3.

Table 3 Descriptive Statistics for TSH Levels (pg/mL)

Factor	N	Mean	St. Dev	95% CI
Pre.TSH	30	656.9 a	51.5	(597.6, 716.2)
Post.TSH	30	599.5 b	37.2	(540.2, 658.8)
Con.TSH	30	467.0 c	29.3	(407.7, 526.3)

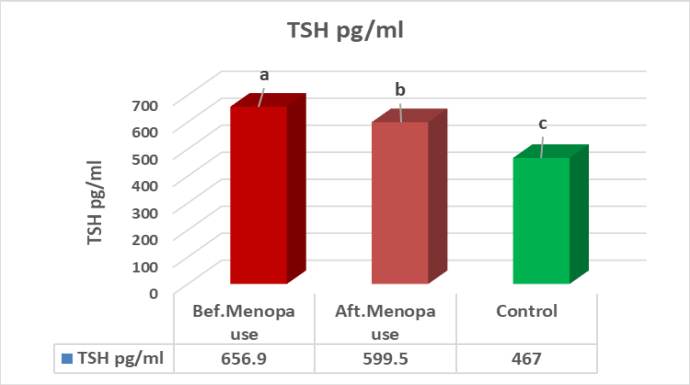

Figure 3. TSH levels in premenopausal, postmenopausal, and control groups.

The present study found increased serum β-C-terminal telopeptide (β-CTX) in premenopausal and postmenopausal women (432.4±45.2, 416.4±34.0) versus controls, as illustrated in Table (4) and Figure 4.

Table 4 Descriptive Statistics for β-CTx Levels

Factor	N	Mean	St. Dev	95% CI
Pre. ßCTx	30	432.4 a	45.2	(385.2, 479.6)
Post. ßCTx	30	416.4 a	34.0	(369.2, 463.7)
Con. ßCTx	30	332.1 b	37.9	(284.9, 379.4)

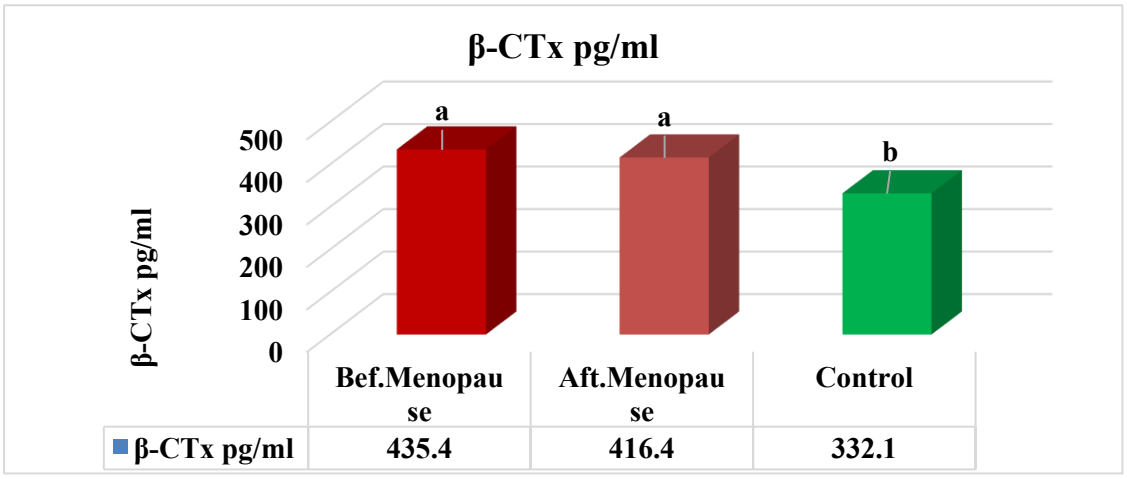

Figure 4. Serum β-C-terminal telopeptide (β-CTX) levels in premenopausal, postmenopausal, and control groups.

The present study demonstrated a significant increase in serum N-MID osteocalcin levels in premenopausal and postmenopausal women (2.2575±0.4793, 1.9080±0.8800) compared to the control group, as illustrated in as illustrated in Table (4) and Figure 5.

Table 5 Descriptive Statistics for N-MID Osteocalcin Level

Factor	N	Mean	St. Dev	95% CI
Pre.N-MID	30	2.2575 a	0.4793	(2.0266, 2.4884)
Osteocalcin	30	1.9080 a	0.8800	(1.678, 2.139)
Con.N-MID	30	1.0267 b	0.4583	(0.7958, 1.2575)

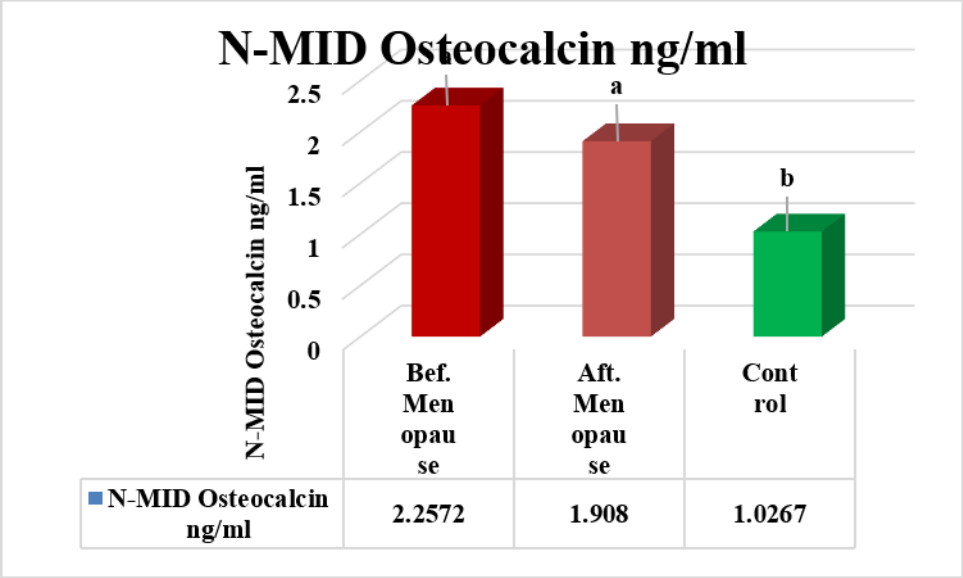

Figure 5. Serum N-MID osteocalcin levels in premenopausal, postmenopausal, and control groups.

Values are expressed as mean ± SD. Different superscript letters indicatestatistically significant differences among groups ($p < 0.05$).

DISCUSSION

Hormonal changes during menopause, including decreased estrogen levels, which are involved in the metabolism of thyroid hormones and conversion of thyroxine (T4) to the more active triiodothyronine (T3), may contribute to this increase in T3 levels. Metabolic changes associated with the aging process may also play a role. Our results are in line with those of other studies that observed a rise in T3 levels in menopausal women (Abdullah et al., 2020; Rasmussen et al., 2019). But the current findings are in contrast to those of Kim et al. (2018), who reported no changes in T3 levels, which may be related to differences in sample size, ethnicity and methods used.

In addition, levels of serum thyroxine (T4) were significantly increased in premenopausal and postmenopausal women compared to the control group. This may be due to the estrogen-induced changes in thyroid hormone binding proteins, such as thyroxine-binding globulin, which affect hormone levels in circulation. Further, menopausal may affect the responsiveness of the thyroid gland and hormone secretion. The results are consistent with reports of significant variations in T4 levels in postmenopausal women by Ahmed et al. (2021) and Rinaldi et al. (2022). However, Lee et al. (2017) reported no considerable change in T4 levels, which may be due to different dietary iodine intake or environmental effects.

In the case of thyroid-stimulating hormone (TSH), we found significantly higher levels in premenopausal and postmenopausal women than in the control group, with the highest values in premenopausal women, as shown in Figure 5-3.

This may be due to altered function of the hypothalamic-pituitary-thyroid axis during the menopause. The loss of estrogen may decrease the negative feedback loop, resulting in increased TSH levels. These results are consistent with those of Santoro et al. (2020) who found age- and menopause-associated increases in TSH levels. In contrast, Biondi et al. (2016) failed to detect a relationship between menopause and TSH levels, which may have been a result of more stringent exclusion criteria or health status of the participants.

With respect to bone turnover, we found increased serum β-C-terminal telopeptide (β-CTX) in premenopausal and postmenopausal women versus controls, as shown in Figure 5-4. Higher β-CTX levels reflect bone resorption, which is known to be increased as a result of estrogen loss during menopause. In addition, fluctuations in thyroid hormone levels may further increase bone turnover via increased osteoclastic activity. Higher β-CTX levels reflect bone resorption, which is known to be increased as a result of estrogen loss during menopause. In addition, fluctuations in thyroid hormone levels may further increase bone turnover via increased osteoclastic activity. This is in agreement with Eastell et al. (2018) and Seibel (2020), who found increased bone resorption markers with menopause. But, Chen et al. (2017) found no differences in β-CTX levels, which could be due to differences in vitamin D, calcium intake or other lifestyle factors. In summary, the results of the current study indicate that menopausal status is associated with changes in thyroid hormones and bone turnover markers. The changes in hormone levels may predispose menopausal women to greater metabolic and skeletal risks and warrant routine monitoring of thyroid function and bone health during this important life transition.

The observed differences among groups indicate enhanced bone turnover activity associated with menopausal status. N-MID osteocalcin is a well-established marker of bone formation, and its elevation reflects increased osteoblastic activity occurring in response to hormonal changes during the menopausal transition.

The increase in N-MID osteocalcin may be attributed primarily to estrogen deficiency, which disrupts the balance between bone formation and bone resorption. Although estrogen withdrawal predominantly accelerates bone resorption, it also induces a compensatory increase in bone formation markers as part of the high-turnover bone remodeling process characteristic of menopause. Furthermore, alterations in thyroid hormones observed in the current study may contribute to enhanced osteoblastic activity, as thyroid hormones are known to influence bone metabolism and osteocalcin synthesis.

These findings are consistent with previous studies reporting elevated osteocalcin levels in postmenopausal women. Eastell *et al.* (2018) and Seibel (2020) reported that increased serum osteocalcin reflects accelerated bone turnover following menopause. Similarly, Garnero *et al.* (2019) demonstrated a significant rise in N-MID osteocalcin levels in postmenopausal women, supporting its utility as a sensitive biomarker for bone formation.

In contrast, other studies have reported no significant changes in osteocalcin levels across menopausal status. Chen *et al.* (2017) suggested that the absence of significant differences may be related to variations in calcium and vitamin D intake, physical activity, or differences in assay sensitivity. These discrepancies highlight the multifactorial nature of bone metabolism and the influence of lifestyle and endocrine factors on bone turnover markers.

In summary, the elevated levels of N-MID osteocalcin observed in this study suggest increased bone remodeling activity in premenopausal and postmenopausal women. When interpreted alongside elevated β-CTX levels, these findings indicate a state of high bone turnover, which may predispose menopausal women to an increased risk of bone loss and osteoporosis. Therefore, monitoring N-MID osteocalcin in combination with resorption markers may provide valuable insight into bone health during the menopausal period.

5. CONCLUSION

Thyroid hormone levels (T3, T4 and TSH) are significantly changed in menopausal status compared with the control group. These changes in thyroid hormones reflect dysfunction of the hypothalamic-pituitary-thyroid axis during menopause. Inaddition Increased levels of β-CTX and N-MID in the serum suggests increased bone resorption due to estrogen depletion in menopause.

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