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Original Article

Relationship between Menopause and Complications of Hyperthyroidism in Female Patients in Iraq

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Abstract

Hyperthyroidism is a health problem characterized by an overactive thyroid gland, resulting in extra triiodothyronine (T3) and thyroxine (T4) production, as well as a decrease in thyroid-stimulating hormone (TSH). The oxidative stress indicators in hyperthyroid patients and the relationship with impaired metabolism of lipid are still controversial, especially in menopausal women suffering from a lack of ovulation hormones. In this study, blood samples were withdrawn from 120 subjects, including healthy premenopausal (n=30) and postmenopausal women (n=30) as control groups (G1 and G2), as well as 30 hyperthyroid women in each group of premenopausal and postmenopausal patient groups (G3 and G4). The levels of T3, T4, and TSH, blood pressure, and lipid profiles, such as triglyceride, total cholesterol (TC), high-density lipoprotein, and low-density lipoprotein, superoxide dismutase (SOD) activity, malondialdehyde (MDA), and advanced oxidation protein products (AOPP) in the two healthy control groups and patient groups with hyperthyroidism were measured. In addition, serum progesterone levels were measured by the Bio-Merieux kit France, according to the manufacturer's instructions. The results revealed a significant decrease in SOD activity in the postmenopausal group, as compared to that in premenopausal women and control groups. Hyperthyroidism groups demonstrated a significant increase in MDA and AOPP levels, compared to control groups. Patient groups reported a decreased level of progesterone, in comparison with control groups. Moreover, there was a significant increase in T3 and T4 in patient groups (G3 and G4), compared to that in control groups (G1 and G2). There was a significant increase in systolic and diastolic blood pressure in menopausal hyperthyroidism (G4), compared to that in other groups. The TC decreased significantly in G3 and G4, compared to that in both control groups ($P<0.05$); nonetheless, there was no significant difference between patient groups (G3 and G4), as well as between control groups (G1 and G2). The study suggested that hyperthyroidism causes an increase in oxidative stress, which negatively affects the antioxidant system and drops levels of progesterone in both premenopausal and postmenopausal female patients. Therefore, low levels of progesterone are linked with hyperthyroidism, leading to aggravating symptoms of the disease.

Keywords: Hyperthyroidism, Oxidative stress, Postmenopausal hyperthyroidism, Premenopausal hyperthyroidism, Progesterone

1. Introduction

Thyroid dysfunction is the most prevalent endocrine disorder worldwide, ranking second after diabetes. Women are more affected by this disease than men, and the percentage of this disorder increases with age (1). According to research, thyroid disease is more common in women than men due to unknown reasons (2). Thyroid hormones have a major role to play in the regulation of metabolism and respiratory rate (3, 4). Hyperthyroidism is characterized by increased secretion of triiodothyronine (T3) and thyroxine (T4), which promote energy metabolism, glucose oxidation

(5), and the oxidative catabolism of fats and proteins, which are linked with oxidative stress injury (3, 4). It indicated that hyperthyroidism-stimulated impairment of the respiratory chain results in the enhancement of reactive oxygen species (ROS) construction and maybe prompt alterations in the antioxidant defensive system (3).

Numerous factors, such as the menstrual cycle, gestation, and menopausal status, affect thyroid gland function (6). Multiple studies have demonstrated that menopause has a major role in oxidative stress and inflammatory activation (7). They added that female hormones, such as estrogens and progesterone, can adjust immune system role; moreover, progesterone deficiency can disrupt the effectiveness of the thyroid gland and subsequently thyroid hormone production (8). In light of the aforementioned issues, the present study aimed to evaluate the levels of thyroid hormones in premenopausal and postmenopausal hyperthyroid women and assess the effect of menopause on oxidative markers in these women.

2. Materials and Methods

2.1. Sampling and Study Design

The study was performed on 120 subjects, including healthy premenopausal (n=30) and postmenopausal women (n=30) as control groups (G1 and G2), as well as 30 hyperthyroid women in each group of premenopausal and postmenopausal patient groups (G3 and G4). Both patient groups were primarily diagnosed with primary hyperthyroidism and had not received treatment, the identification of hyperthyroidism was according to "Guidelines for the diagnosis and treatment of thyroid diseases (2016 version)" (9) without any other disorder. The mean age scores of the G1 and G2 control groups were reported as 36.12±2.91 and 58±3.28, respectively. On the other hand, the mean age scores of the G3 and G4 patient groups were obtained at 32.42±3.6 and 55.63±4.63 years, respectively.

The characteristics of each group and the data of clinical parameters, such as age, and body mass index (BMI), were recorded. Blood pressure (Systolic blood pressure and diastolic blood pressure) readings were taken for each subject after 10 min rest by the electronic sphygmomanometer (HBP-9020; Omron, Dalian, China).

2.2. Biochemical and Hormone Assays

Five ml of venous blood sample was withdrawn from all participants and collected in sterile gel tubes for 30 min, allowing it to clot. Blood was centrifuged at 4000 rpm at room temperature for 15-20 min to isolate the serum which was divided into several parts in Eppendorf tubes and kept frozen at (-20°C) till used for biochemical analysis. Lipid profiles, such as total cholesterol (TC), triglyceride (TG) high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were measured by an automated analyzer (Abbott, USA) in Al-Diwaniyah Teaching Hospital.

Serum levels of T3, T4, and Thyroid-stimulating hormone (TSH) were measured by the Bio – Merieux kit, France, as instructed by the manufacturer, using VIDAS automated analyzer, the assessment protocol combines the enzyme immunoassay method with a final fluorescent detection (ELFA). Progesterone level was measured by the Bio-Merieux kit, France. The progesterone levels of premenopausal control and hyperthyroid patients were measured before the start of menstruation. The test principle combines an enzyme immunoassay sandwich method, accompanied by the ELFA. Serum superoxide dismutase (SOD) activity was determined by Misra and Fridovich (10) method. Serum Malondialdehyde Concentration was assessed by Guidet and Shah (11) method, and serum advanced oxidation protein products (AOPP) concentration was determined by Witko-Sarsat, Friedlander (12) method.

2.3. Statistical Analysis

Data were expressed as mean and standard deviation (mean±SD). The SPSS software (version 22) was used for statistical analysis. One-way ANOVA and multiple range tests (Post Hoc Tests) were used to compare the difference between the

groups. A p-value less than 0.05 was considered statistically significant.

3. Results

The characteristics and clinical information of healthy cases and patients are displayed in table 1. In terms of BMI in four groups, it was demonstrated that there were no significant differences between control groups G1 and G2, as well as between patients groups G3 and G4. Nonetheless, there was a significant decrease in BMI in G3 and G4, compared to that in both G1 and G2 groups (*P<0.05*). Based on the results, G1, G2, and G3 did not differ significantly in systolic and diastolic blood pressure; however, there was a significant increase in blood pressure in menopausal hyperthyroidism (G4), compared to that in other groups (*P<0.05*).

Two patient groups (G3 and G4) demonstrated a significant decrease in TG level, as compared to control groups (G1 and G2) (*P<0.05*). There was an increased TG level in G2, compared to that in G1 (*P<0.05*), although G2 was also a control group. There were significant differences among all groups (*P<0.05*). Moreover, TC decreased significantly in G1, compared to that in G2 (*P<0.05*). The TC decreased significantly in G3 and G4, compared to that in both control groups(*P<0.05*); nonetheless, there was no significant difference between patients groups G3 and G4, as well as between control groups G1, and G2.

There was no significant difference between control groups in HDL-C level, HDL-C significantly decreased in the two patient groups G3 and G4, in comparison with that in G1 and G2 (*P<0.05*). The level of LDL-C increased significantly in patient groups, compared to that in both control groups G1 and G2 (*P<0.05*). There were significant differences among all study groups in LDL-C levels (*P<0.05*).

As illustrated in table 2, there was a significant increase in T3 and T4 in G3 and G4, compared to that in G1 and G2 (*P<0.05*), while there was no significant difference between control groups, as well as between patient groups. There was no significant difference in TSH level between G3 and G4 patient groups; however, it significantly decreased, compared to control groups (*P<0.05*). Moreover, it significantly decreased in G2, compared to that in G1, although both groups were healthy due to the normal physiological state of menopause in G2 (*P<0.05*). Progesterone hormone measurements demonstrated that there was no significant difference between postmenopausal control G2 and hyperthyroid women in groups G3 and G4; however, there was a significant increase in progesterone level in G1, compared to that in other groups (*P<0.05*).

As displayed in table 3, a significant decrease in SOD activity was observed in G2, G3, and G4, compared to that in G1 (*P<0.005*); however, there was no significant difference between G2, G3, and G4 groups. The malondialdehyde (MDA) and AOPP levels as a marker of lipid peroxidation and protein oxidation were significantly increased in G3 and G4, compared to those in control groups G1 and G2 (P<0.05), pointing to a significant difference between groups (*P<0.05*).

Table 1. Characteristics analysis of hyperthyroidism disorders for Premenopausal and Postmenopausal women (G3 and G4), compared to control groups (G1 and G2)

Parameter± SD	Premenopausal Control (G1)	Postmenopausal Control (G2)	Premenopausal Hyperthyroid (G3)	Postmenopausal Hyperthyroid (G4)
Age	36.12±2.91	58±3.28	32.42±3.6	55.63±4.63
BMI (Kg/m^2)	26.5±3.5	26.78±1.82	21±0.86	23±3.67
Systolic blood pressure (mmHg)	122.9±3.04	124.99±3.13	132±5.10	143±9.63
Diastolic blood pressure (mmHg)	80.2±1.2	80.6±1.1	88±0.67	100±0.012
TG (mg/dl)	148.5±9.61	151±10.36	116±17.22	110±16.78
TC (mg/dl)	166.16±13.75	170.34±9.91	135±13.71	136±13.52
HDL-C (mg/dl)	43.4±6.90	42.32±5.46	32.1±5.57	31.1±4.83
LDL-C(mg/dl)	87±15.23	90±12.07	105±19.91	114±14.04

MBI: Body mass index, TG: triglyceride, TC: *total cholesterol,* HDL-C: high-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol

Table 2. Analysis of the level of thyroid, and progesterone hormone levels in study groups

Parameter± SD	Premenopausal Control (G1)	Postmenopausal Control (G2)	Premenopausal Hyperthyroid (G3)	Postmenopausal Hyperthyroid (G4)
T3 nmol/l	1.99±0.8	1.80±0.74	5.20±0.95	5.98±1.62
T4 nmol/l	99.30±7.88	101.7±7.29	181.02±5.89	176.24±8.59
TSH nmol/l	2.45±0.36	1.22±0.14	0. 115±0.04	0.117±0.06
Progesterone ng/ml	10.9±4.02	1.41± 0.22	4.11±0.37	0.9±0.038

Table 3. Analysis of *superoxide dismutase*, *malondialdehyde*, and advanced oxidation protein products levels in study groups

Parameter± SD	Premenopausal Control (G1)	Postmenopausal Control (G2)	Premenopausal Hyperthyroid (G3)	Postmenopausal Hyperthyroid (G4)
SOD activity (U/ml)	4.609±0.286	3.95±0.158	3.99±0.467	3.461±0.322
MDA (µmol/L)	1.28±0.08	1.7±0.111	2.5033±0.139	3.809524±0.486
AOPP	33.414±5.806	39.17±4.2840	60.947±4.843	70.602±7.127

SOD: *Superoxide Dismutase, MDA: Malondialdehyde, AOPP:* advanced oxidation protein products

The SOD activity was positively correlated with progesterone level in both patient groups G3 and G4 ((r =0.5823; r= 0.8667; *P<0.05;* Figure 1); however, MDA levels were negatively correlated with progesterone (r=-0.598; r=-0.818; *P<0.05*; Figure 2). The T3 level was positively correlated but not significantly with progesterone level in both control groups G1 and G2 (r=0.0677; r=0.2097); nonetheless, there was a negative correlation between these factors in patients groups G3 and G4 (r=-0.2955; r=-0.587); moreover, there was a significant correlation between these factors in G4 (*P<0.05*; Figure 3).

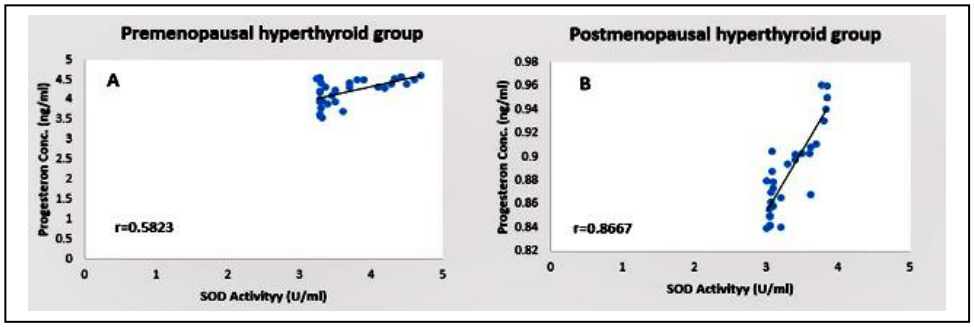

Figure 1. Correlation between serum SOD activity and progesterone level in: A- Premenopausal hyperthyroid women patients (G3), B- Postmenopausal hyperthyroid women patients (G4)

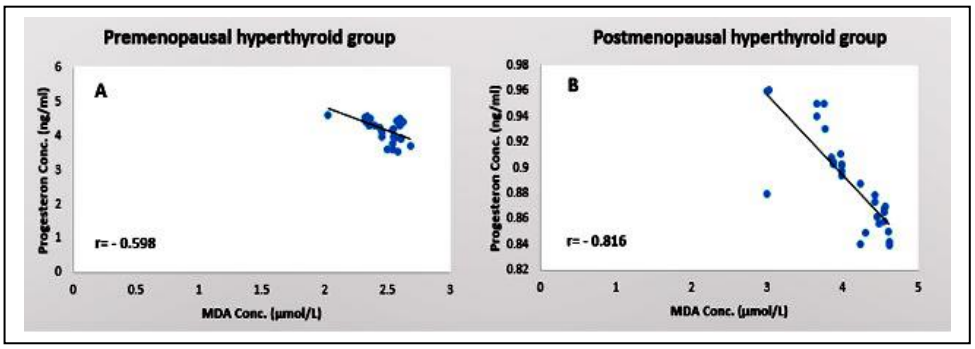

Figure 2. Correlation between serum MDA and progesterone levels in: A- Premenopausal hyperthyroid women patients (G3), B- Postmenopausal hyperthyroid women patients (G4)

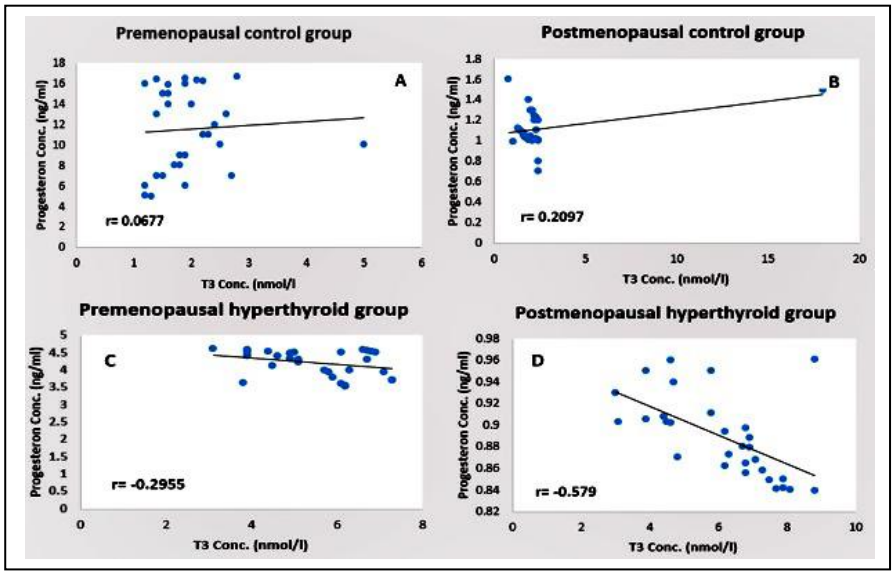

Figure 3. Correlation between serum T3 and progesterone levels in: A- Premenopausal Control (G1), B- Postmenopausal control (G2), C-Premenopausal hyperthyroid women patients (G3), D- Postmenopausal hyperthyroid women patients (G4)

4. Discussion

Hyperthyroidism is triggered by extreme secretion of T3 and T4 thyroid hormones due to an overactive thyroid gland, leading to metabolic syndrome. In the present study, the diagnosis of hyperthyroidism was primarily determined by examining the level of thyroid hormone, which is characterized by an increase in serum T3 and T4, as well as a decrease in TSH. The examination of various parameters in this study demonstrated a decrease in body weight of patient groups, compared to healthy groups, indicating that increased levels of T3 and T4 thyroid hormone improved the degradation of a great number of lipids than synthesis, thereby reducing lipid storage levels of diverse plasma lipid due to an increase in metabolic rate (1).

The assessment of blood pressure as another factor indicated that G1, G2, and G3 did not significantly differ in this regard; nonetheless, there was a significant increase in blood pressure in postmenopausal hyperthyroid patients, as compared to that in other groups. The interaction of high T3 and T4 levels with low progesterone levels may play a role in hypertension. In their study, Uygur, Yoldemir (13) pointed to the relationship between menopause and hyperthyroidism which both are related to the development and increased risk of cardiovascular disease, including hypertension.

Hyperthyroidism causes an increase in blood pressure and correlated hormones in a renin-angiotensin-aldosterone system (14). The extra amount of T3 leads to metabolic and hemodynamic alterations, triggering an increased cardiac output and hypertension (15). The T3 and T4 also motivate the secretion of erythropoietin and increase cardiac muscle contraction, causing expanded pulse pressure (16). On the other hand, progesterone is considered a vasoactive hormone, has a role as an inhibitor of agonist-induced vasoconstriction, blocks the uptake of Ca^{+2} through calcium channels in muscle cells, and leads to lower blood pressure (17). Progesterone affects the increase in plasma volume and overall expansion of extracellular fluid (18). These two factors are crucial for blood pressure and fluid regulation (19); accordingly, blood pressure was the highest in G4 since T3 and progesterone can affect each other and trigger symptoms.

In this study, decreased levels of TG, TC, and HDL-C were reported in the two patient groups (G3 and G4), compared to those in the control groups since an increased excretion of cholesterol increases the

turnover of LDL-C and results in a decrease of TC (20). The increased catabolism of LDL particles related to the expression of its receptor gene (21), apart from LDL oxidation, is affected by thyroxin levels. Increased thyroid hormone levels can affect HDL-C metabolism via stimulating cholesteryl ester transferase activity, which converts cholesteryl esters and TG in HDL-C to VLDL-C in reverse (22) and increases HL-mediated HDL catabolism (21). These results are consistent with the findings of the current study, which demonstrated that lipid metabolism in patients with hyperthyroidism undergoes significant changes. These factors lead to the acceleration of oxidative metabolism, thereby increasing superoxide radical production and lipid peroxidation (23).

Elevated lipid peroxidation was firmly associated with an increase in thyroid hormone levels. The end-product of lipid peroxidation is MDA, an increased level of which in hyperthyroidism is due to changes and acceleration of the respiratory chain, which is clearly related to any modification in the thyroid function (24). Moreover, hyperthyroid patients reported a higher arachidonic acid level which is rapidly oxidized and contributes to the formation of lipid peroxidation (25). Previous studies have pointed to increased plasma protein carbonyl and lipid oxidation in postmenopausal women (26), while some researchers revealed that the products of lipid peroxidation were decreased (27).

The AOPP products as a result of protein oxidation were increased in patient groups, especially in G4, compared to those in control groups G1 and G2, and there were significant differences between all study groups. An elevated metabolic status in hyperthyroidism, accompanied by oxygen consumption, leads to increased construction of ROS (28). It can oxidize diverse cellular constituents comprising DNA, lipids, and proteins, resulting in changes in tissue functions. Increased protein oxidation has been proved in diverse tissues in experimental hyperthyroidism. An increase in protein oxidation indicator was demonstrated in the plasma of hyperthyroid patients (29).

The level of oxidative stress has a direct effect on the antioxidant system, and the present study demonstrated the decreased activity of SOD in premenopausal and postmenopausal control and hyperthyroid women, as compared to that in the control group G1. Increasing the destructive effect of lipid peroxidation led to a decrease in antioxidant enzymes in experimental hyperthyroidism (30); therefore, a decrease in SOD activity in menopause may be due to age (31). The results of studies on the activity of antioxidant enzymes in hyperthyroid patients are actually different.

Some studies pointed out that there were no significant differences between the hyperthyroid and control groups (32). On the other hand, several studies have revealed diminished antioxidant enzymes in the hyperthyroidism group due to increased levels of free radicals related to the damaging result of lipid peroxidation (33, 34). However, some studies have reported conflicting results which are suggestive of increased activity of antioxidant enzymes in hyperthyroidism. It seems that antioxidant response in hyperthyroidism may be linked to a compensatory reaction related to enhanced peroxidation as protection against the effects of oxidative stress by increasing the activity of SOD as a defense mechanism (35, 36).

As illustrated by the results, progesterone levels significantly decreased in G2, G3, and G4 groups, compared to those in the G1 control group. There is a dearth of information on progesterone levels in hyperthyroidism. Studies pointed out that hyperthyroidism is an obstacle to pregnancy due to diminished fertility, which is directly related to changes in ovulation hormones (37, 38). In the present study, low levels of progesterone may be associated with decreased antioxidant enzymes and increased oxidative stress. Some studies have illustrated that progesterone exhibits antioxidant properties (39) that may be affected by increased oxidative stress stimulated in hyperthyroidism.

Menopause is usually associated with low progesterone levels and is a risk factor for the stimulation of oxidative stress (40). The current study indicated decreased progesterone levels in the premenopausal and postmenopausal hyperthyroid female patients due to an elevation in oxidative stress that is stimulated by high levels of T3 and T4 hormones, as well as insufficient effectiveness of antioxidant enzymes. There was probably a reciprocal relationship between these variables and decreased level of progesterone. Some studies indicated that progesterone may affect and regulate the expression of SOD (41, 42); therefore, progestin therapy in postmenopausal women enhanced blood SOD activity and increased total antioxidant capacity, as compared to postmenopausal women without hormone therapy (41, 43).

Based on the study results, there was a positive correlation between progesterone and SOD activity in both patient groups and a revers negative correlation with MDA levels. Therefore, the levels of ovulatory hormones may be directly related to the level of oxidative stress. On the other hand, T3 had a negative correlation with progesterone in the patient groups, while there was a positive insignificant correlation between these factors in the control group, signifying that metabolic defect resulting from rapid cellular respiration has a direct effect on the homeostasis of the body. An increase in thyroid hormones had an adverse effect on the level of progesterone in patient groups. Although there was a direct relationship between T3 and progesterone levels in the healthy group, it was found that there was a correlation between the decreased level of progesterone and increased oxidative stress.

As evidenced by the results of this study, it can be concluded that high levels of thyroid hormones led to an increased risk of oxidative stress, particularly in menopausal women. Progesterone decreases even in non-elderly female patients whose menstruation has not yet stopped. This hormone may play a role in antioxidant defense and is affected by high levels of thyroid hormone-stimulated oxidative stress; therefore, hyperthyroidism may lead to a reduced probability of fertilization in patients. Further studies should be conducted to shed more light on the relationship of reproductive hormones with thyroid hormone levels and biologic pathways interrelating reactive oxygen species to determine the pathogenesis of hyperthyroidism-induced complications.

Authors' Contribution

Study concept and design: N. K. J.
Acquisition of data: Z. N. A.
Analysis and interpretation of data: A. J. T. A.
Drafting of the manuscript: R. A. H. A.
Critical revision of the manuscript for important intellectual content: N. K. J.
Statistical analysis: N. K. J.
Administrative, technical, and material support: N. K. J.

Ethics

This study comprised blood samples and experiment protocols permitted by the Ethics Committee of Al-Diwaniyah Teaching Hospital, University of Al-Qadisiyah. In addition, informed consent was acquired from each subject before sample collection.

Conflict of Interest

The authors declare that they have no conflict of interest.

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