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RESEARCH PAPER

THE INFLUENCE OF CARBIMAZOLE ON SERUM LEPTIN HORMONE AND INSULIN RESISTANCE IN PATIENTS WITH HYPERTHYROIDISM

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A B S T R A C T:

Carbimazole is one of the common antithyroid drugs for the treatment of hyperthyroidism. It interferes with the synthesis of thyroid hormones and results in the reducing of thyroid hormones level. Apart from determining the effects of carbimazole on serum TSH, T3, T4, insulin, HOMA-IR, HOMA-IS and leptin, the drug effects on corrected QT (QTc) interval duration in hyperthyroidism patients were examined concomitantly Female patients were recruited after obtaining informed consent. Venous blood samples were collected from control healthy subjects and hyperthyroid patients. Treatment with carbimazole results in the improvement of thyroid status and achievement of euthyroidism with a significant decrease in insulin level, and improvement in insulin resistance. The therapy also led to a significant increase in leptin levels. Nonetheless, the non-significant effect on QTc interval duration was observed. In conclusion, this treatment could be beneficial for hyperthyroidism who are at risks of insulin resistance syndrome.

KEY WORDS: Hyperthyroidism; carbimazole; insulin; insulin resistance; leptin; QTc interval.
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1. INTRODUCTION :

Excess in production of thyroid hormones by thyroid gland or overactive thyroid gland is called hyperthyroidism or thyrotoxicosis (Golden et al., 2009, Ross et al., 2016).

The production and release of thyroid hormones are regulated by a sensitive negative feedback loop involving the hypothalamus, pituitary gland, and thyroid gland. The hypothalamus releases thyroid-releasing hormone (TRH), which stimulates the pituitary to release Thyroid stimulating and triiodothyronine (T3). The increased production of thyroid hormone normally causes inhibition of TRH and TSH release by the hypothalamus and pituitary respectively. Disruption of this delicate system leads to additional production and release of thyroid hormone and subsequent hyperthyroidism (Devereaux and Tewelde, 2014).

Hyperthyroidism predictable prevalence range is between 0.2% to 1.3%. The most common cause being Graves disease (GD) with an incidence of 20 to 50 cases per 100,000 persons which accounts for up to 70% of cases, followed by toxic multinodular goiter (TMNG) and toxic adenoma (TA) and less common cause include thyroiditis, increase in iodine intake, drugs(amiodarone). Women more affected by GD which mainly aged between 20 to 50 years. Male to female ratio of GD is (1: 4) it may occur at any age in both

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genders (Kravets, 2016). In Ranya town and Erbil city/Iraq the same prevalence of hyperthyroidism are observed (Al–Bustany, 2011, Wsso and Rasul, 2017).

Patients with thyrotoxicosis usually present with weight loss, heat intolerance, palpitations, tremor, increased sweating, diarrhea, fatigue, infertility and menstrual cycle abnormality which are the typical symptoms of hyperthyroidism (Cooper, 2003, Reid and Wheeler, 2005)

Treatment strategy and therapy choices for hyperthyroidism differ according to the cause. It includes antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, and surgery. β blockers are used for controlling symptoms associated with thyrotoxicosis (Cooper, 2005, De Leo et al., 2016, Kravets, 2016). Carbimazole, a prodrug which is converted to the active form methimazole, is used for the treatment of hyperthyroidism by Interferes with the synthesis of thyroid hormones and as a result reduces the level of thyroid hormones (Mohan et al., 2015, Uduak et al., 2014).

In hyperthyroidism, decreased, normal, or even increased levels of plasma insulin have been reported. Thyrotoxicosis which has been associated with insulin resistance, the mechanism of insulin resistance induced by thyrotoxicosis has not been completely elucidated (Brenta, 2011, Chu et al., 2011). Association have been founded between Insulin and leptin. Leptin is a 167-amino-acid peptide , it is a potent anorexic hormone that is mainly expressed in white adipose tissue (WAT), but is also found in a variety of tissues including placenta, mammary gland, ovary, skeletal muscle, stomach, pituitary gland, and lymphoid tissue (Margetic et al., 2002). In compare between the euthyroid population with female hyperthyroid patients, decrease (Baig et al., 2003), and increase (Ozata et al., 1998) of leptin level have been reported.

Thyroid hormones have a significant impact on cardiac function and structure. Excess thyroid hormone affects cardiovascular hemodynamics (Osuna et al., 2017).The most common electrocardiogram (ECG) abnormality is sinus tachycardia (Ertek and Cicero, 2013).The second most common finding is arterial fibrillation (AF) with incidence increasing with age (Satpathy et al., 2013). Prolonged QT intervals have been reported in hyperthyroidism (Colzani et al., 2001, Kulairi et al., 2017, Lee et al., 2015).

Due to few studies regarding the association of hyperthyroidism and carbimazole treatment with leptin, insulin resistance and QTc interval duration. The present study was done to evaluate the alteration in thyroid hormones, insulin, leptin, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and for insulin sensitivity (HOMA-IS) with QTC interval duration from ECG study pre- and post-treatment with carbimazole in hyperthyroid female patients and compared to healthy control group in Erbil city.

2. MATERIALS AND METHODS

2.1 Patients and design of the study

A prospective randomized clinical trial study was carried out at Rizgary teaching hospital department of internal medicine consultant and Hawler teaching hospital department of hormonal consultant in Erbil, Kurdistan Region from November 2017 to December 2018. The study design was approved by Regional Ethical Committee in the College of Pharmacy at Hawler Medical University. A verbal and consent form were obtained from each patient before the enrollment into the study. The patients were recruited from both hospitals, which attended the hospitals for management and follow-up of their disease Condition. A history is taken from patients using a previously prepared questionnaire. Each patient examined thoroughly by the consultant and then allocated to be enrolled in the study. Only female patients aged above 18 years who are recently diagnosed thyrotoxicosis and candidate to receive only carbimazole were included. Females with diabetes, liver and kidney disorders, cardiac failure and underlying infections were excluded. None of them was alcoholic or receiving medications known to affect the study parameters. The patients were followed up for a period of 12 weeks, blood samples and ECG were taken two times from the patients during this period; first at the start of the study, second after three months of follow up.

The subjects that were included in the study divided into two groups: Group 1 in which the total number of patients that were included is (35 females) newly diagnosed with thyrotoxicosis. Group 2 which is healthy control group includes (26 female).

2.2 Hormonal assay and QTc interval

A 10 to 12-hour overnight fasting 7-10ml of venous blood were obtained via venous puncture using a 10ml syringe from patients and collected into a test tube containing separator gel and Ethylene diamine tetra acetic acid (EDTA) tube. The serum separated within 20 minutes (coagulation time) after blood draw by centrifugation at 3000 rpm for 10 minutes. The samples were conserved at -80°C in medical research Centre/Hawler medical University. Serum Insulin, TSH, T3 andT4 were estimated using fully automated biochemical analyzer (Cobas-e 411 analyzer, Germany), leptin level estimated using enzyme-linked immunosorbent assay (ELISA) while fasting serum glucose was determined using Accent 200 analyzer. And QTc interval duration taken from ECG study in each patient which is measured in milliseconds(ms).

2.3 Statistical Analysis

Data analysis was performed using Graphpad Prism (version6) (California corporation, USA). The unpaired t-test performed for comparing the difference between control and patients group, using Mann-Whitney test regarding non-parametric data. Paired t-test performed for comparison within the patients group, using Wilcoxon matched paired t-test regarding non-parametric data. The results were considered statistically significant at P value ≤ 0.05. Parameters level accuracy for the diagnosis of hyperthyroidism was presented in terms of sensitivity and specificity. Receiver Operating Characteristic (ROC) curve is a graphical display of sensitivity on y-axis and (1-specificity) on the x-axis for varying cut-off points of test values. Spearman's Correlation coefficient (r) was also used to correlate the measured parameters (T_3, T_4, TSH, leptin, HOMA-IR and QTc).

3. RESULTS

The study group consisted of 46 patients with hyperthyroidism as (group 1), 35 females of them completed the study as seven patients excluded and four patients didn't attend follow up, with mean age of (42 ± 0.8117) years and mean body mass index of (25.98 ± 0.576) on monotherapy (carbimazole 5 mg); maximum starting dose of Carbimazole 45 mg and minimum dose 15 mg. The study also includes 26 healthy females as (group 2), with a mean age of (42.35 ± 1.296) years and mean body mass index of (25.57 ±0.7532). Almost all patients have gain weight after carbimazole therapy with an average of 3.5 kg. None of the participants were smoker, having any other diseases or taking other medications.

3.1 Baseline measurements and effect of carbimazole treatment on serum thyroid hormones (T3, T4 and TSH) level in hyperthyroidism patients and healthy control group.

The mean serum levels of T_3 and T_4, in hyperthyroidism subject's pre-treatment, was significantly higher compared to the control group (4.842 ± 0.3023 vs 1.681± 0.04436 nmol/l, $p<0.0001$) and (200.2 ±7.619 vs 105.1± 4.206 nmol/l, $p<0.0001$) respectively. While the serum level of TSH in hyperthyroid subject's pre-treatment treatment was significantly lower compared to the control group (0.01632 ± 0.0059 vs 2.317 ± 0.2027 uIU/ml, $p<0.0001$). After 3 months of treatment with carbimazole (median dose of 30 mg/day), all patients achieved an euthyroid state with a significant decrease in T_3 (1.867 ± 0.1014 nmol/l, $p<0.0001$), T_4 (92.46 ± 3.940 nmol/l, $p<0.0001$) and increase in TSH levels (2.176 ± 0.2848 uIU/ml, $p<0.0001$) (Figure 1).

3.2 Baseline measurements and the effect of carbimazole treatment on serum leptin level in hyperthyroidism patients and a healthy control group.

Serum leptin level in female patients with hyperthyroidism pre-treatment with carbimazole compared to the control group was non-significant (18.5 ± 2.28 ng/ml and 11.4 ±1.58 ng/ml respectively, $p>0.05$). Whereas after three months of therapy with carbimazole serum leptin level in hyperthyroid patients significantly increased compared to pre-treatment with carbimazole (24.6 ± 2.93 ng/ml and 18.5 ± 2.28 ng/ml respectively, $p<0.0001$) (Figure 2). Very-weak non-significant

positive correlation observed between T3 and T4 with leptin. Furthermore, a weak significant negative correlation seen between serum TSH with leptin (Figure 5). Moreover, the ROC curve of leptin and QTc doesn't verify a difference (sensitivity) between hyperthyroid patients and the healthy individuals (Figure 6).

3.3 Baseline measurements and the effect of carbimazole treatment on QTc interval duration in hyperthyroidism patients and a healthy control group.

Treatment with carbimazole shows non-significant effect on QTc interval in patients with hyperthyroidism pre-and post-treatment (425.11 ± 36.182 ms vs 422.894 ± 38.178 ms, $p > 0.05$) also non-significant difference in pre-treatment value compared to control group (411.2 ± 18.524 ms, $p > 0.05$) (Figure 3). Spearman's correlation shows a very weak non-significant positive correlation between serum T3 and T4 with QTc while a very weak significant negative correlation between serum TSH with QTc observed (Figure 5). Additionally, the ROC curve of QTc interval duration doesn't show discrimination between hyperthyroid patients and healthy individuals (Figure 6).

3.4 Baseline measurements and the effect of carbimazole treatment on serum insulin level and insulin resistance in hyperthyroidism patients and a healthy control group.

Serum insulin level and HOMA-IR value in control group was significantly lower than in hyperthyroid patients (10.2 ± 0.741 vs 23.1 ± 2.75 µU/ml, $p<0.0001$) and (2.58 ± 0.194 vs 6.02 ± 0.764, $p<0.0001$) respectively. While HOMA-IS in control group was significantly higher than in hyperthyroid patients (0.456 ± 0.0411 vs 0.253 ± 0.0276, $p<0.0001$).

Carbimazole significantly lowers insulin level and improves HOMA-IS in patients group (23.1 ± 2.75 vs 15 ± 1.87 µU/ml , $p<0.0001$) and (0.253 ± 0.0276 vs 0.396 ± 0.0436, $p<0.0001$) respectively after three months of treatment. Besides there was a significant decrease in HOMA-IR after treatment (6.02 ± 0.764 vs 3.86 ± 0.502, $p<0.0001$) (Figure 4). There was a significant positive correlation observed between serum T3 and T4 with HOMA-IR, whereas there was a significant negative correlation between serum TSH with HOMA-IR (Figure 5). Furthermore, the ROC curve of HOMA-IR, HOMA-IS verifies a difference (sensitivity) between hyperthyroid patients and healthy individuals (Figure 6).

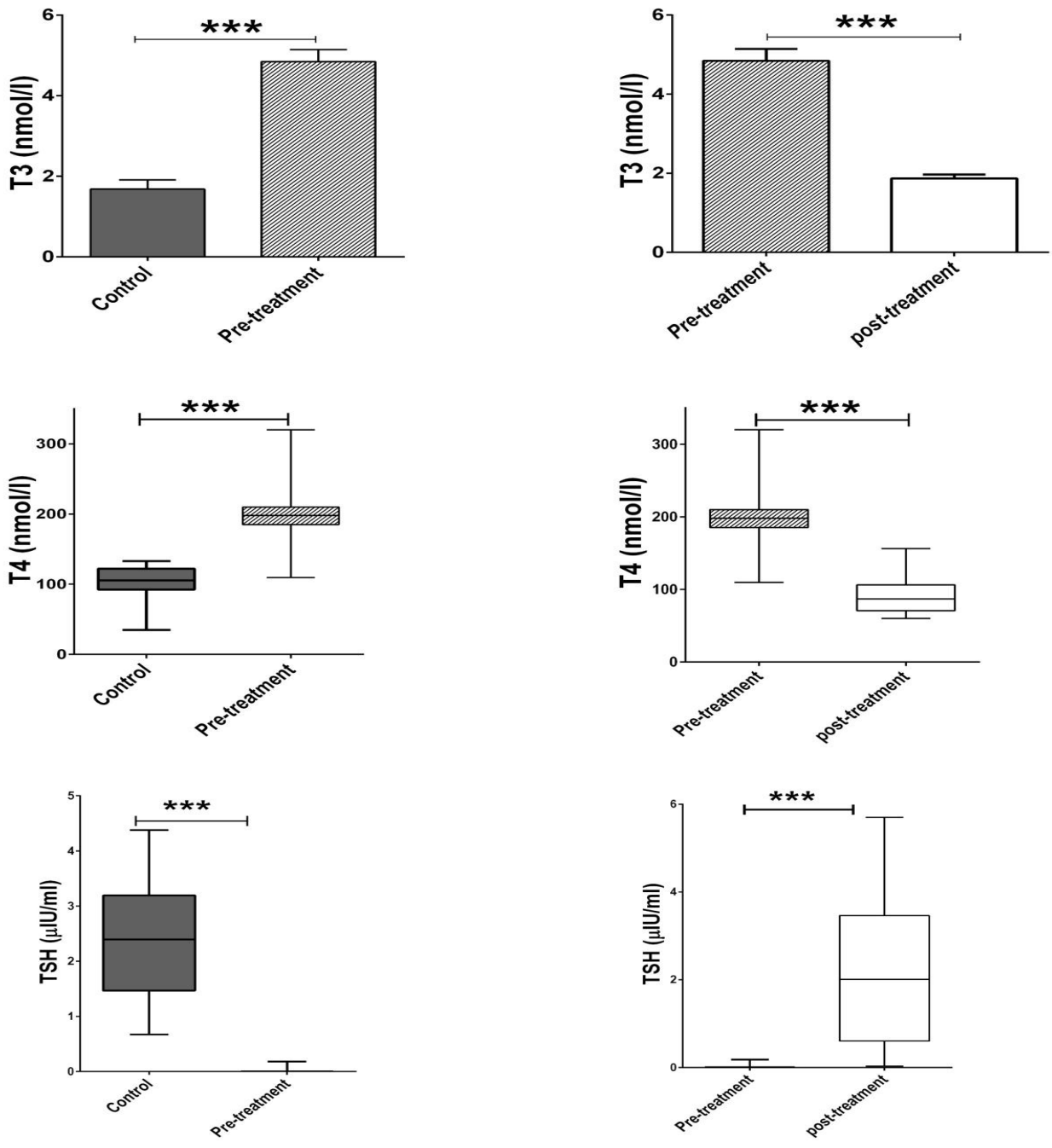

Figure 1. Effects of Carbimazole therapy on serum level of T3, T4 and TSH in female patients with hyperthyroidism and control subjects.

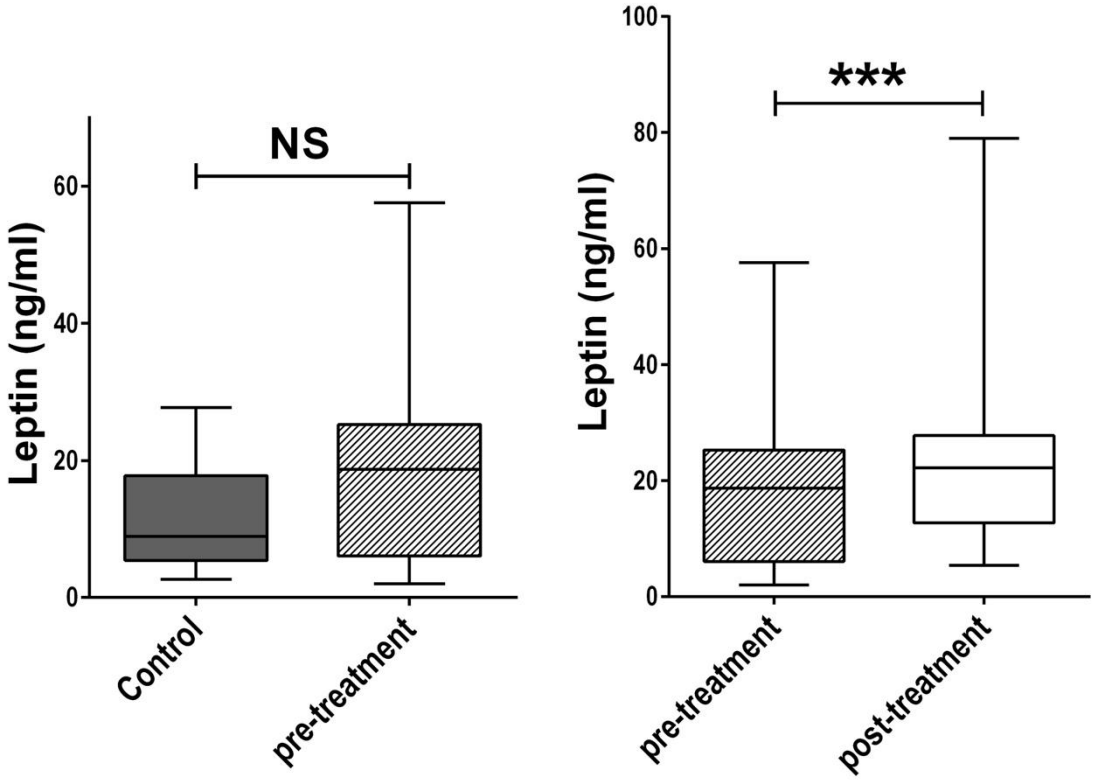

Figure 2. Effects of Carbimazole therapy on serum level of leptin in female patients with hyperthyroidism and control subjects.

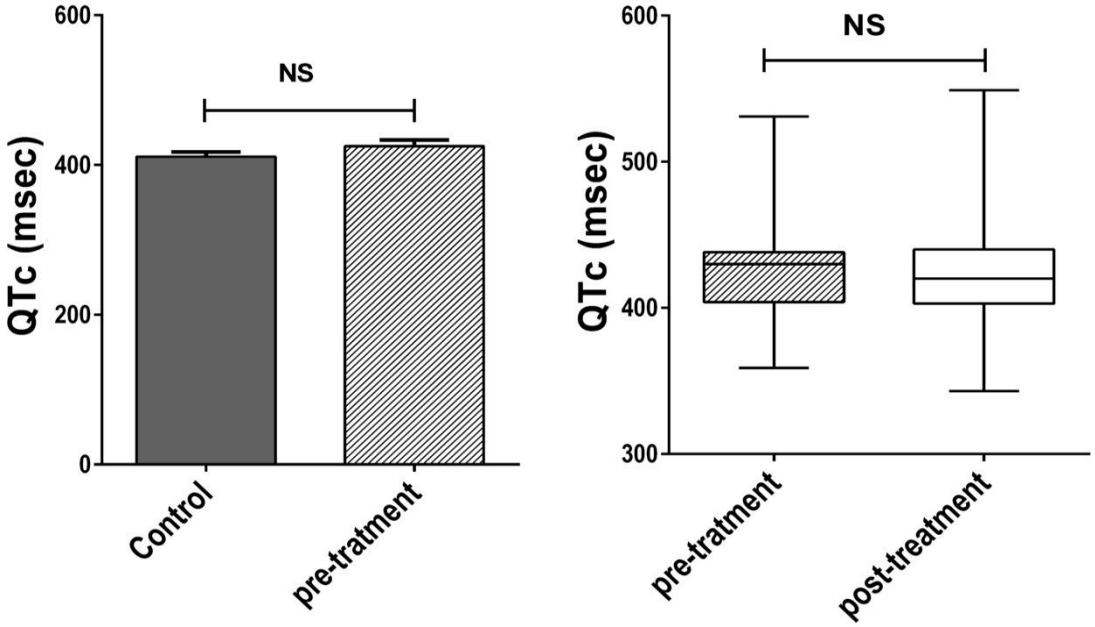

Figure 3. Effects of Carbimazole therapy on QTc interval in female patients with hyperthyroidism and control subjects.

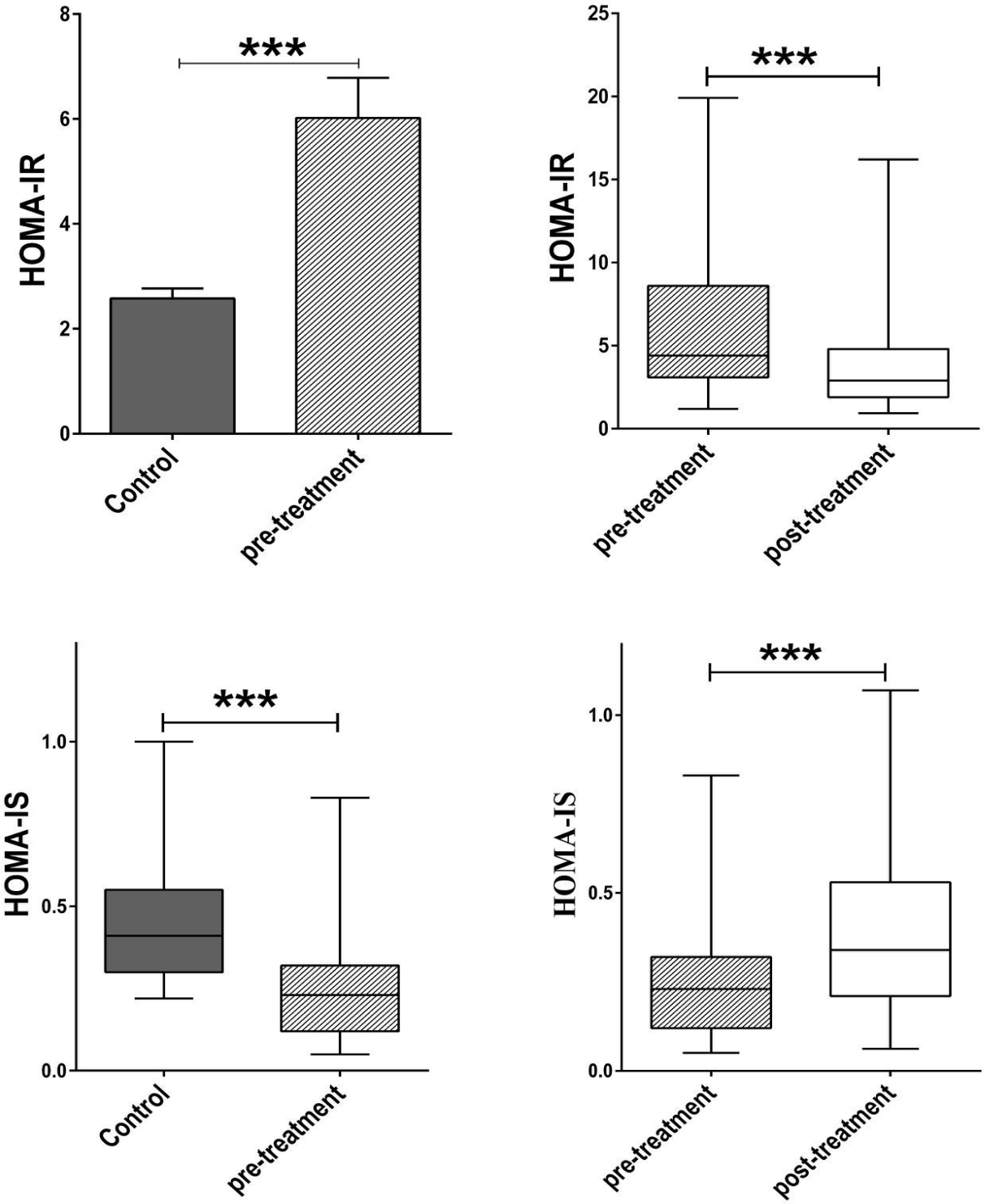

Figure 4. Impact of carbimazole on insulin resistance and insulin sensitivity in hyperthyroid patients and control subjects.

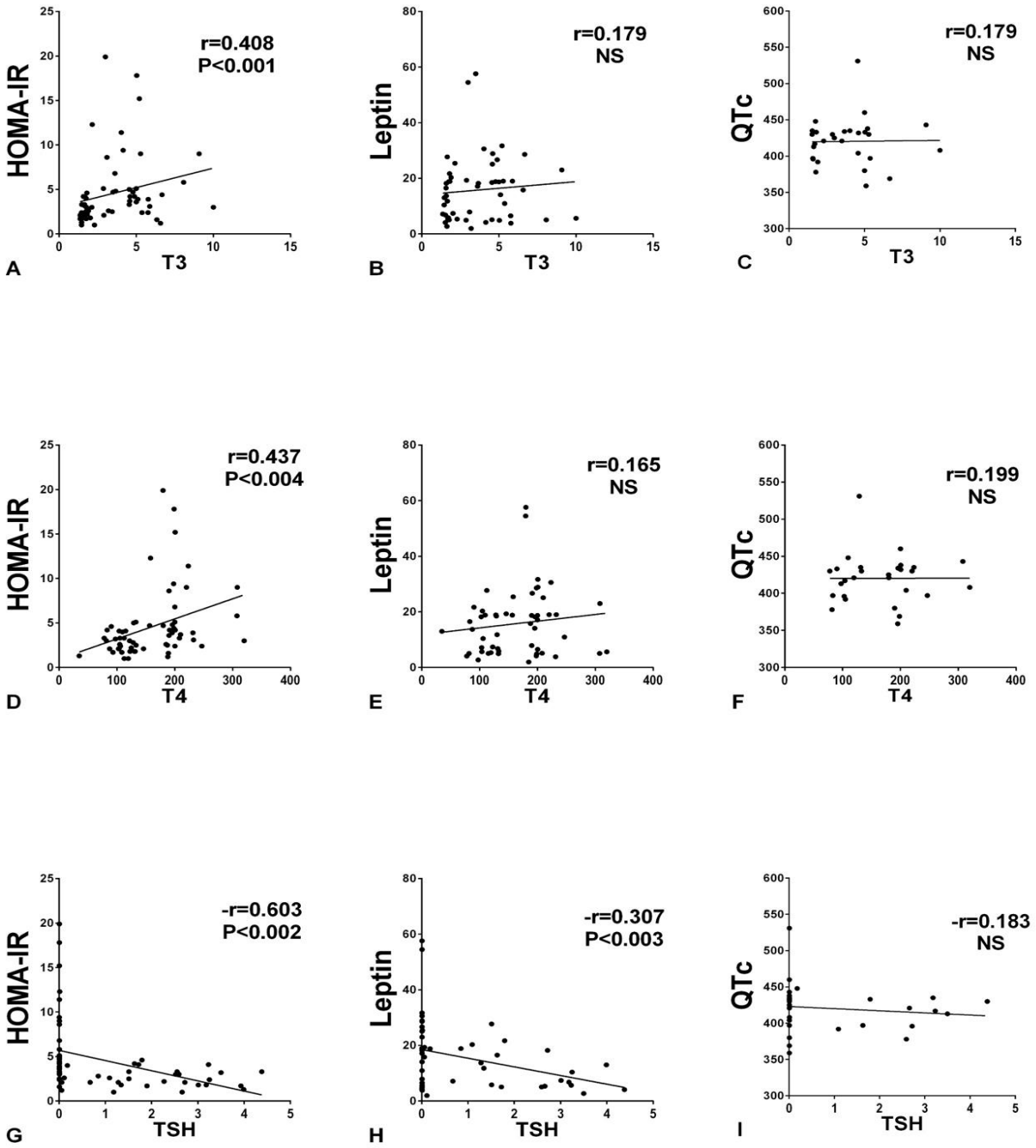

Figure 5. Spearman's correlations analysis between (A) Triiodothyronine (T3) and HOMA-IR, (B) Triiodothyronine (T3) and leptin, (C) Triiodothyronine (T3) and QTc, (D) Thyroxine (T4) and HOMA-IR, (E) Thyroxine (T4) and leptin, (F) Thyroid stimulating hormone (TSH) and QTc, (G) Thyroid stimulating hormone (TSH) and HOMA-IR, (H) Thyroid stimulating hormone (TSH) and leptin, (I) Thyroid stimulating hormone (TSH) and QTc.

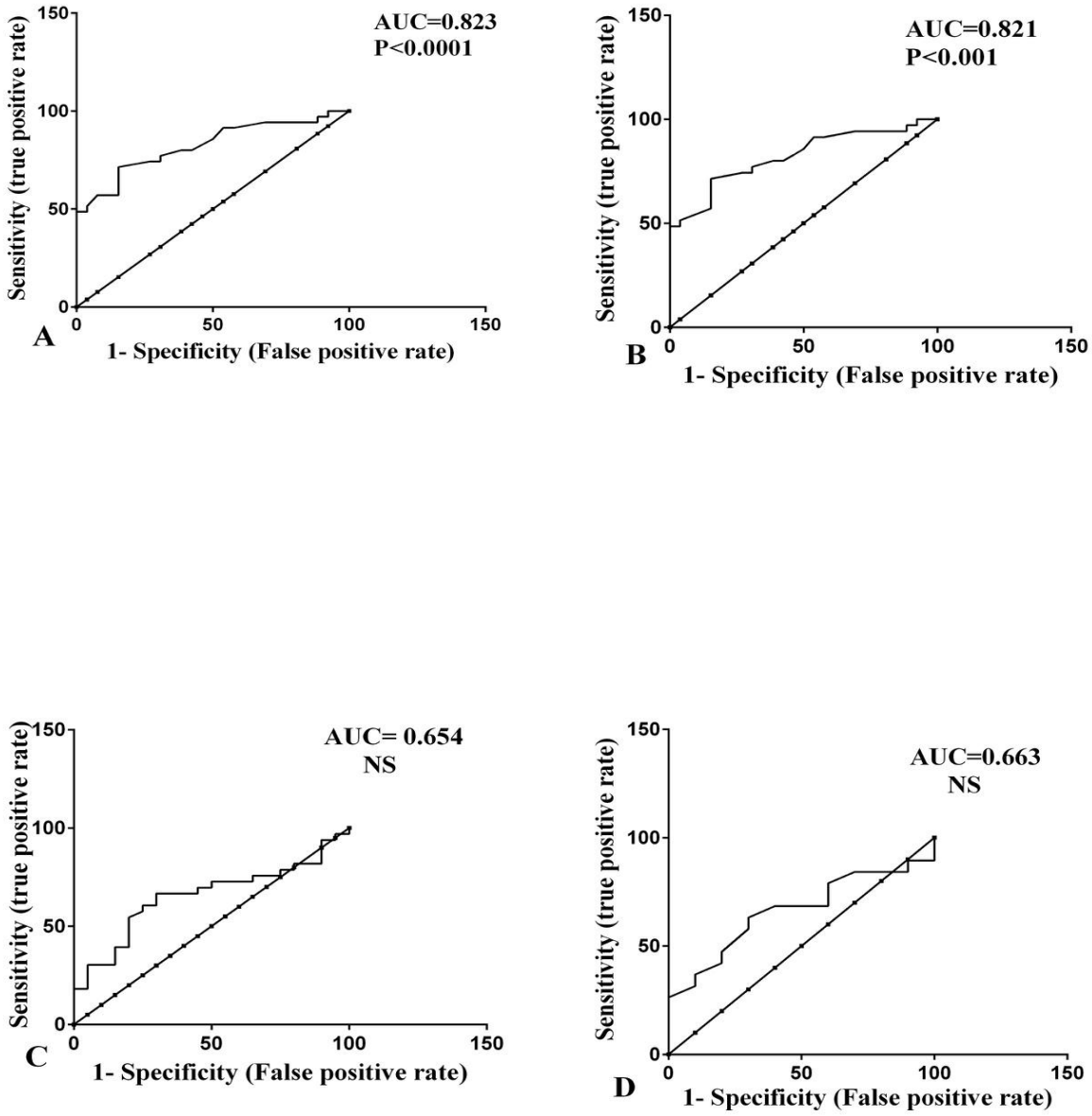

Figure 6. The ROC curves show: (A) The sensitivity and specificity of HOMA-IR, (B) The sensitivity and specificity of HOMA-IS, (C) The sensitivity and specificity of leptin and (D) The sensitivity and specificity of QTc in hyperthyroid patients. AUC: Area under the curve.

4. DISCUSSION

Antithyroid drugs are recommended for treatment of hyperthyroidism caused by overproduction of thyroid hormones in children, adults and pregnant women. They can be used as a long-term essential treatment for Graves' disease, with a duration of therapy that is considered to be 12 to 18 months, and can be given for longer durations up to 24 months in lower doses. A short-term ATD gave to prepare the patients with Graves' disease or toxic nodular goiter for thyroid surgery or radioactive ablation (Jastrzębska, 2015, Abraham et al., 2005).

It is documented that in hyperthyroidism disease, euthyroidism will be achieved after carbimazole therapy (Lizcano and Salvador, 2008, Dutta et al., 2012, Kansara et al., 2017) , similarly in our study all patients return to euthyroid state after carbimazole therapy.

Very few counted studies available that depend on carbimazole as ATD of choice for their study, opposite to that most studies depend on methimazole as ATD of choice. But, besides that carbimazole, which is a prodrug which gets converted into the active form methimazole, exerts same effects of methimazole with similar properties (Cooper, 2005), so we tried to mention studies that done on methimazole in our discussion.

In this clinical trial, there was a non-significant difference in serum leptin level in hyperthyroid patients compared to healthy control. Additionally, Spearman's correlation (weak correlation) show that decrease of TSH level associated with an increase in leptin level ($p<0.003$) while correlation between T_3 and T_4 and leptin was very weak and non-significant. However, reports available showing no alteration in serum leptin levels in thyroid dysfunction. Serum leptin concentrations either increased or unchanged in patients with hyperthyroidism. A study showed that thyroid hormone increases the expression of leptin mRNA and secretion of leptin in vitro adipocytes (Yoshida et al., 1998).

According to Baig *et al* (2003), serum levels of leptin in hyperthyroid female patients was lower than euthyroid control patients. (Al-Shoumer et al., 2000), also observed low leptin concentration of Arab women in Kuwait with hyperthyroidism, with an inverse relationship with T_3. Similarly, baseline leptin concentrations were significantly decreased in all hyperthyroid patients as compared with controls and non-significant correlation found between hyperthyroidism and leptin concentrations (Obermayer-Pietsch et al., 2001). Opposite to that, Studies show that serum leptin level increased in hyperthyroid patients compared to hypothyroid patients or healthy controls (Ozata et al., 1998, Nakamura et al., 2000, Dutta et al., 2012). Furthermore, some studies have found no correlation in serum leptin level in hyperthyroid patients when compared to control subjects (Valcavi et al., 1997, Sohn et al., 2015).The cause for this variability is unidentified, variation in leptin level may be due to different body weight or difference in thyroid hormone levels in hyperthyroid patients during the time of the study (Rosenbaum et al., 1996, Sreenan et al., 1997, Hsieh et al., 2002).

After 3 months of treatment with carbimazole leptin concentration significantly increased, as known Circulating leptin levels are directly in proportion to the amount of body fat (Park and Ahima, 2015), most of obese human subjects have elevated plasma levels of leptin associated to the size of their total adipose tissue mass (Hussain and Khan, 2017), and almost all female patients have weight gain after carbimazole therapy which may explain increase in leptin level post-treatment.

However, a study done by (Dutta et al., 2012) Dutta *et al* (2012), shows a decrease in leptin levels after 3 months of carbimazole therapy despite an increase in body weight after carbimazole therapy which they explain the decrease in leptin level may be due improvement in insulin resistance. Also serum leptin level in premenopausal females slightly decreased after methimazole therapy although a positive correlation found between serum leptin and %BF (body fat) (Braclik et al., 2008).

A study was done by Al-Shoumer et al., 2000, stated that after six months of therapy with carbimazole in female patients with hyperthyroidism there was non-significant change in serum leptin levels (Al-Shoumer et al., 2000). Another study that consists of 16 women and four men with hyperthyroidism treated with methimazole showed non-significant increase in leptin level post-therapy (Iglesias et al., 2003). Serum leptin in 21 female patients non-significantly decreased after two months of therapy with methimazole and 12 of these 21 patients were followed after 6 months of therapy and serum leptin was non-significantly increased compared to baseline measurements with significant increase in body weight (Nakamura et al., 2000), these findings suggest that antithyroid drugs in general has little or no effect on leptin level in humans, there may be another mechanism despite thyroid hormones that effect on serum leptin levels further investigations needed especially on genetic level.

In hyperthyroidism, decreased, normal, or even increased levels of plasma insulin have been reported. In the current study serum insulin levels and HOMA-IR were significantly higher than the healthy control group at baseline and significantly decreased after achievement of euthyroidism with carbimazole with improvement in insulin sensitivity , these results were consistent with other findings (Iglesias et al., 2003, Al-Shoumer et al., 2006, Chu et al., 2011, Dutta et al., 2012).

In our study, T_3 and T_4 were positively correlated with HOMA-IR, and TSH was negatively correlated with HOMA-IR, hyperthyroidism has been associated with insulin resistance, the mechanism of insulin resistance induced by thyrotoxicosis has not been completely explained. Furthermore, it is commonly recognized that leptin exerts an inhibitory effect on insulin secretion and leptin deficiencies are associated with hyperinsulinemia in humans. In which leptin directly affects pancreatic β-cell gene expression and leads to decrease insulin secretion (Seufert, 2004, Marroqui et al., 2012).

In the present study, there was non-significant change in QTc values in patients group pre-treatment compared to post-treatment with carbimazole and non-significant difference when compared to a healthy control group. And non-significant very weak correlation found between thyroid hormones and QTc interval (positive non-significant correlation between T3 and T4 with QTc interval while TSH shows a negative non-significant correlation), which hyperthyroidism may be associated with QTc interval prolongation.

QTc interval prolongation has been reported in many cases with hyperthyroidism along with positive correlation between QTc interval duration with FT_3 and FT_4 were founded while no correlation observed with TSH. Additionally, decreased the value of QTc interval after treatment with methimazole (Colzani et al., 2001, Owecki et al., 2006, van Noord et al., 2008, Lee et al., 2015).

Mechanism of hyperthyroidism induced QTc prolongation still not clear, there are hypothesis which states that increase in thyroid hormones may increase level of cardiac sodium/potassium adenosine tri-phosphatase (NA/K ATPase) leading to increase in intracellular K^+ level and causing membrane hyperpolarization and prolongation of the QTc interval (Awais et al., 2000, Colzani et al., 2001, Lee et al., 2015). These data's show us importance of evaluation of ECG during diagnosis of hyperthyroidism and throughout follow up and the evaluation of every electrocardiogram should also include interpretation of QT interval to determine arrhythmias and risk for their development and sudden death that may be associated with an abnormal QT interval.

However, during our study one hyperthyroid patient, QTc interval prolongation (531 ms) recorded in patient's ECG and after 3 months of carbimazole monotherapy there was significant decrease in QTc interval to normal values (436 ms) which may show the protective effect of carbimazole. A case report described by (Kulairi et al., 2017) Kulairi et al (2017), a 29-year-old male newly diagnosed with hyperthyroidism had a prolonged QTc interval of 509 ms after 3 months of treatment with propranolol and methimazole on ECG normal rhythm observed with normal QTC interval of 410 ms. However, no studies found to show effect of carbimazole on QTc interval in female hyperthyroid patients. Furthermore, studies that include a large number of populations are more necessary to determine effect of carbimazole on QTc interval.

5. CONCLUSIONS

From the results of the current study, following conclusions can be drawn: the level of serum insulin and HOMA-IR value increased significantly in hyperthyroid patients. Interestingly patients treated with carbimazole displayed a markedly reduction in the level of insulin and HOMA-IR value. The present new finding with respect to the ROC curve analysis of HOMA-IR suggested that it could be represent as a biomarker for hyperthyroid patients. Furthermore, a significant increase in leptin level observed after carbimazole therapy in female hyperthyroid patients and the ROC curve analysis of leptin suggested that it cannot be represent as a biomarker for hyperthyroid patients.

Conflict of Interest

The authors declare no conflict of interest.

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