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Original Article

Association between thyroid hormone levels with insulin resistance in obese euthyroid women with metabolic syndrome in Saudi Arabia: A cross-sectional study

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Abstract. *Background:* The obesity epidemic is a pressing global health concern, as obesity rates continue to rise worldwide. This study examines the relationship between thyroid hormone levels, insulin resistance and components of metabolic syndrome in euthyroid's. *Methods:* A pre-structured and pre-tested questionnaire was used to gather information and biochemical tests were performed using kits. The homeostatic model assessment (HOMA) ratio formula was used to quantify IR. *Results:* A total 100 obese women were clinically evaluated, from which 72 women were diagnosed with metabolic syndrome (MetS+). Body mass index (BMI), systolic blood pressure, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL-C) and thyroid-stimulating hormone (TSH) were statistically higher in MetS+ group. Even in euthyroids, TSH was positively associated with waist circumference and TC. TSH was also positively associated with HOMA-IR (r= 0.018*). FT_4 was negatively associated with TC (r = -0.007*), LDL-C (r=-0.084*) and HOMA-IR value (r= -0.187**). The difference between two levels within normal range of TSH (TSH <2.5μIU/mL and TSH ≥2.5 μIU/mL) in terms of age, TC, TG, HDL and LDL have been found to be significantly different. Using a cut-off value of 2.7 for HOMA-IR (> 2.7 resistant, < 2.7 sensitive) BMI, WC, TC, TG, LDL-C and TSH was higher in resistant group. *Conclusion:* Obese euthyroids exhibited a significantly positive correlation between HOMA IR values and TSH levels and significantly negative correlation between low normal FT4 and HOMA IR. It has also been established that thyroid function and lipid levels are related even in subjects classified as being euthyroid.

Keywords: Metabolic syndrome, insulin resistance, diabetes, thyroid hormone, obesity

Introduction

The obesity epidemic is a pressing global health concern, as obesity rates continue to rise worldwide. In addition to increasing the risk of health complications and premature death, obesity is the greatest contributing factor underlying the metabolic syndrome (MetS) (1). MetS is a chronic medical condition manifested by a cluster of symptoms (e.g., low high-density lipoprotein cholesterol (HDL-C) levels, high blood pressure (BP), high triglyceride (TG) levels, insulin resistance (IR), and other anthropometric and biochemical factors that are associated with developing cardiovascular disease and type 2 diabetes mellitus (2). IR basically refers to the inability of insulin to perform its function at the optimum concentration

required for its biological activity (3). The causes responsible for this inability can range from defective glucose output in the liver to impaired insulin uptake in the muscle (4).

Healthy thyroid activity is required to maintain the overall health of an individual. Several studies have described the effect of thyroid hormones on body mass index (BMI) (5, 6). Hypothyroidism leads to weight gain, while hyperthyroidism causes weight loss. Moreover, it has also been established that obesity affects thyroid gland function (7). Thyroid hormones have been found to be associated with insulin activity and regulate the metabolism of glucose. The dys-regulation of this pathway contributes to IR (8). Thyroid hormones regulated a variety of proteins involved in maintaining insulin sensitivity (9). The loss of insulin sensitivity, IR, is associated with obesity and has been used as a predictor of developing cardiovascular disease (CVD) and type 2 –diabetes (10). Maintaining glucose homeostasis involves the complex interplay between physiological pathways that regulate insulin secretion and modulate its activity (4). The American Association of Clinical Endocrinologists (AACE) (11) has set the guidelines for the identification of abnormal thyroid function and for the treatment of thyroid dysfunction in patients with abnormal serum levels of thyroid-stimulating hormone (TSH) (12). Subjects with both thyroid dysfunction and metabolic syndrome (MetS) are often witnessed in clinical practice (13). The possible role of TSH in adipogenesis has already been established and it has been found that even slightly raised serum TSH levels are related with an upsurge in the incidence of obesity (6). Among its various metabolic effectors, WC and BMI significantly and positively correlate with serum TSH levels (6). Therefore, the aim of this cross-sectional study was to identify associations between TSH, IR, and other clinically-relevant metrics in obese women with and without MetS in Saudi Arabia. This study involved the assessment of anthropometric, clinical, and biochemical characteristics of the subjects and compared the clinical and metabolic characteristics according to HOMA-IR subjects. It also assessed the associations between TSH levels and the subjects' clinical and biochemical characteristics, MetS diagnosis, and insulin sensitivity level.

Materials and Methods

Study design

The cross sectional study was carried out on 163 obese and overweight women aged 25 to 55 years. All of the patients had BMI ≥ 25 kg/m^2. The presence of medical conditions was assessed through self-report. A pre-structured and pre-tested questionnaire was used to gather demographic information and personal and family medical history. Informed consent was obtained from all participants.

Ethics approval and consent to participate

This study was conducted in compliance with the ethical principle of the Declaration of Helsinki. The study was approved by King Saud University (Reference #: KSU-SE-18-14) and study was in accordance with the Policy of Research Centre. The aim of this study was explained to all participants. Written consent was obtained from the respondents involved in this research and the study abided by the principle of voluntary participation. Blood was withdrawn by a qualified nurse and subjects were assured that the information given was entirely for scientific purposes and would be kept confidential.

Inclusion criteria

A total 100 subject in the age group of 25 to 55 years were recruited in the study.

Exclusion criteria

Subjects with history of polycystic ovary syndrome, chronic renal failure, thyroid disease, chronic hepatopathy or cancer and subjects taking antihypertensive drugs and statins, contraceptive drugs or under hormone replacement therapy (HRT), any medication known to interfere with glucose or insulin secretion and/or metabolism were excluded from the study (Fig.1).

Anthropometric measurements Height and Weight

Height and weight were measured in light clothing without shoes. Standing height was measured by a stadiometer and body weight by digital electronic weighing scale.

Body mass index (BMI)

BMI were calculated as weight in kilograms divided by the square of height in meters.

Waist circumferences

Waist circumferences were measured using a flexible measuring tape, midway between the xiphoid and the umbilicus during the mid-inspiratory phase.

Anthropometric measurements were carried out three times by a single tester.

Blood pressure

The average of two measurements of blood pressure (BP) with the subject in the sitting position was taken at a 2 to 3 min interval after resting for at least 15 min.

Biochemical parameters

Blood samples were drawn after an overnight fast. Serum samples were analyzed for fasting blood sugar (FBS), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) using commercially-available kits (Beckman-Coulter, USA). Serum insulin concentration was determined using

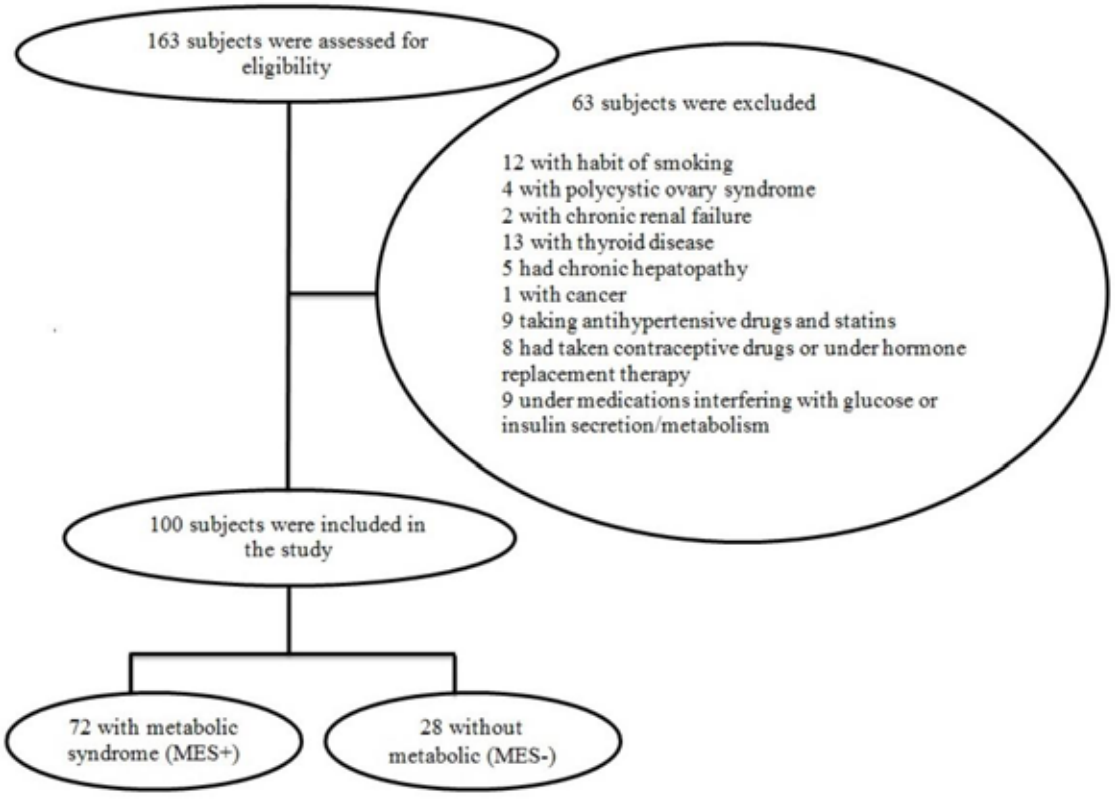

Figure 1. Flowchart schematic of study subject selection using the inclusion and exclusion criteria.

an electrochemiluminescence-based assay (Immulite 2000, USA). Serum thyroxine (FT_4), tri-iodothyronine (FT_3), and TSH levels were also determined by electrochemiluminescence-based immunoassay (Roche Diagnostics, Germany). All tests were performed according to the instructions given by manufacturer of the kits without any modification.

Definitions Euthyroidism

In this study Euthyroidism was defined as TSH (reference range, 0.35–5.5 μIU/mL), FT3 (reference range, 3.5–6.5 pmol/L) and FT4 (reference range, 11.5–22.7 pmol/L) within the normal reference range (14) without any thyroid medication.

Based on a large-scale epidemiological survey in 2003, National Academy of Clinical Biochemistry (NACB) suggested reducing the upper reference limit of TSH to 2.5 μIU/mL (15). Various related studies distributed the subjects within the normal range of TSH into TSH <2.5μIU/mL and TSH ≥2.5 μIU/mL groups (16, 17). Consequently, in this study also the subjects were divided into 2 groups according to TSH <2.5μIU/mL and TSH ≥2.5 μIU/mL.

HOMA-IR

The homeostatic model assessment (HOMA) ratio formula was used to quantify IR and it was calculated as follows:

HOMA-IR = *[fasting plasma insulin (μIU/ml) ×fasting plasma glucose (mmol/l)] / 22.5*

HOMA-IR cut-off value chosen was 2.7 (> 2.7 resistant, < 2.7 sensitive) (18).

Metabolic syndrome (MetS)

MetS was diagnosed according to standard protocol (19) based on the presence of the following criteria: 1) TG ≥ 150 mg/dL; 2) LDL-C < 130 mg/dL; 3) HDL-C < 40 mg/dL; 4) TC < 200 mg/dL; 5) FBS ≥ 100 mg/dL; 6) SBP ≥ 130 mmHg; 7) DBP ≥ 85 mmHg; 8) WC > 80 cm (Figure 2). Subjects with levels over the cut-off values (for at least two of the following traits and obesity was common trait in all subjects) were considered as MetS+. According to ATP III (20) Met S in women is defined as the presence of at least three of the mentioned traits: 1) abdominal obesity, defined as a waist circumference greater than 88 cm; 2) serum HDL less than ≤ 50 mg/dl; 3) serum triglycerides (TGs) ≥150 mg/dl; 4) fasting plasma glucose≥ 110 mg/dl and 5) BP ≥130/85 mm Hg (expert panel).

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) software package v25 (IBM, Chicago, IL, USA). Statistical comparisons between the MetS+ and MetS- groups were achieved

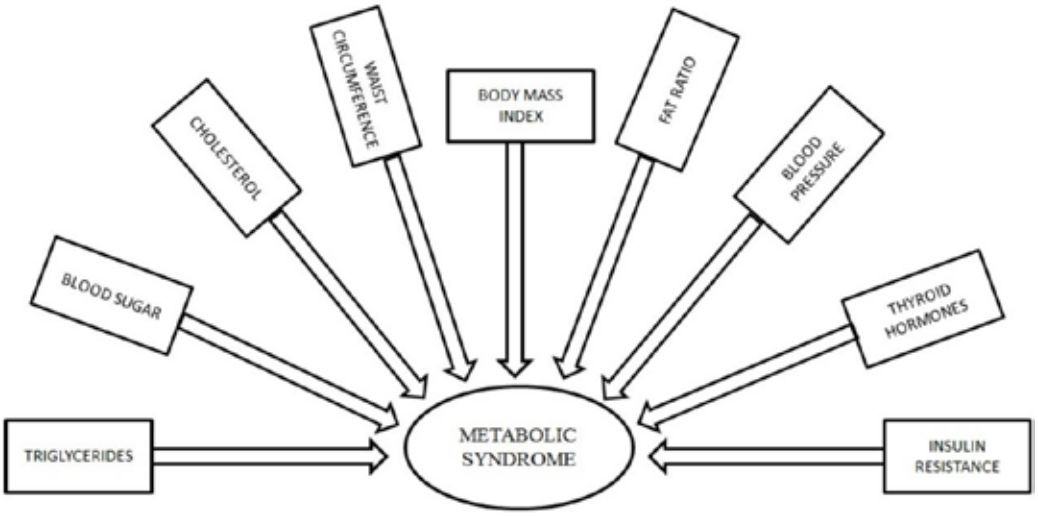

Figure 2. Components of metabolic syndrome

with the one-way analysis of variance (ANOVA). Significance assessments were carried out using Duncan's new multiple range tests. Values are expressed as means and standard deviations. We used hierarchical cluster analysis to assess the relationship between TSH levels and HOMA-IR values**.** Each experiment was repeated at least three times. A *P*-value of less than 0.05 was regarded as statistically significant.

Results

Anthropometric and biochemical characteristics of the metabolic syndrome positive (MetS+) and metabolic syndrome negative (MetS-) groups

Of the 163 individuals considered, 63 were eliminated based on exclusion criteria (Fig. 2). The study population consisted of the remaining 100 obese (BMI > 25 kg/m^2) women aged 25 to 55 years. Of these, 72 women were diagnosed as MetS+ and the remaining 28 were MetS-. The anthropometric and biochemical characteristics are presented in Table 1. BMI, SBP, TC, TG, HDL-C, FBS, TSH, and fasting insulin levels were statistically higher in the MetS+ group than the MetS- group. Similarly, the values for WC, fat ratio, LDL-C, FT_4, FT_3, and HOMA-IR were higher in the MetS+ group than the MetS- group; however, these differences were not statistically significant.

Pearson correlation coefficients (r) of TSH, FT_4 and FT_3 with demographic, anthropometric and components of metabolic syndrome

Even in euthyroid range, TSH was positively associated with WC (r=0.060*), TC (r=0.015**) and negatively associated with diastolic blood pressure (DBP) (r= -0.078*) (Table 2). TSH was also positively associated with HOMA-IR (r= 0.018*). FT_4 was negatively associated with TC (r = -0.007*), LDL-C (r=-0.084*) and with HOMA-IR value (r= -0.187**). FT_3 was positively associated with BMI (r = 0.570**) and fat ratio (r = 0.351*) (Table 2). Figure 3 represents the relationship between TSH level and metabolic syndrome. The difference between two levels within normal range of TSH (TSH <2.5μIU/mL and TSH ≥2.5 μIU/mL) in terms of age, TC, TG, HDL, and LDL has been found to be significantly different. TC

Table 1. Anthropometric and biochemical variables of the study subjects

Variables	MetS+ (*n*=72)	SD	MetS- (*n*=28)	SD	*P*-value
Age (years)	33.12	9.06	28.64	8.39	NS
Body mass index (kg/m^2)	32.12	4.89	29.41	5.98	<0.05
Waist circumference (cm)	89.38	7.93	80.44	2.34	NS
Fat ratio	39.24	6.60	24.62	4.35	NS
Systolic blood pressure (mmHg)	132.12	9.48	112.10	10.91	<0.001
Diastolic blood pressure (mmHg)	88.34	8.43	78.78	4.31	NS
Total cholesterol (mg/dl)	234.67	9.79	193.94	9.75	<0.001
Triglyceride (mg/dl)	167.83	8.90	151.41	8.26	<0.001
HDL-C (mg/dl)	34.27	7.08	58.21	4.33	<0.05
LDL-C (mg/dl)	130.42	11.37	125.72	11.45	NS
Fasting blood sugar (mg/dl)	109.55	10.47	94.70	8.12	<0.001
TSH (mIU/l)	2.38	1.52	1.38	1.02	<0.05
FT_4 (pmol/l)	11.99	2.81	10.56	2.46	NS
FT_3 (pmol/l)	6.22	1.70	5.47	2.47	NS
Fasting Insulin (μIU/ml)	12.42	5.09	5.10	1.42	<0.05
HOMA-IR	5.14	2.13	1.61	1.02	NS

Data is represented as mean ± standard deviation

HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TSH = thyroid stimulating hormone, FT4 = free thyroxine, FT3 = free triiodothyronine, HOMA I= homeostatic model assessment.

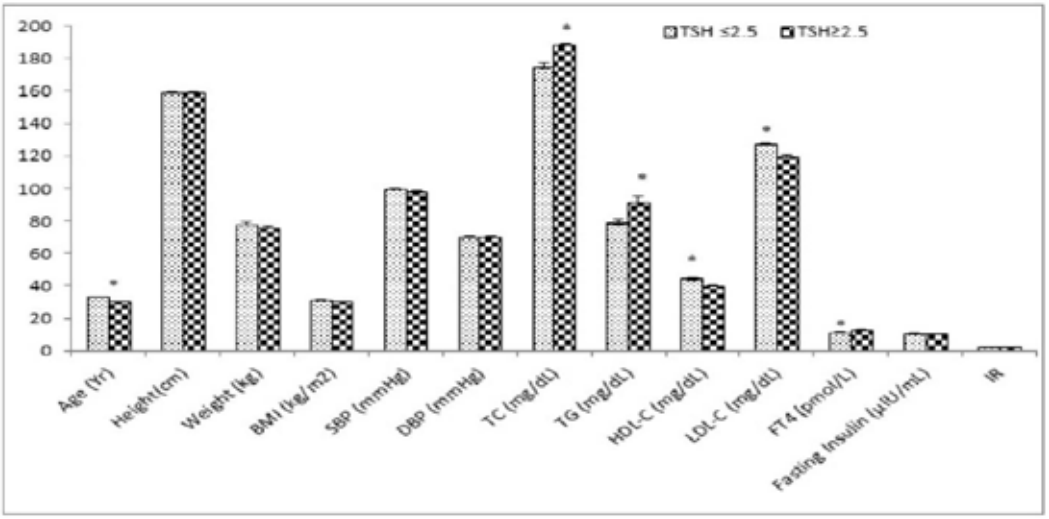

Figure 3. Comparison of clinical and metabolic characteristics of subjects based on TSH level.
***P < 0.**05. Significance assessments were carried out using Duncan's new multiple range tests.
BMI = body mass index, WC = waist circumference, SBP = systolic blood pressure, DBP = diastolic blood pressure, TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, FBG = fasting blood glucose, TSH = thyroid stimulating hormone, FT4 = free thyroxine, FT3 = free triiodothyronine.

and TG was significantly higher in TSH ≥2.5 µIU/mL group and HDL was more in TSH <2.5µIU/mL group.

Comparison between insulin-resistant and insulin-sensitive women in terms of the clinical and metabolic characteristics

The comparison between insulin-sensitive and insulin-resistant women in terms of the clinical and metabolic characteristics is presented in Figure 4. Using a cut-off value of 2.7 for HOMA-IR (> 2.7 resistant, < 2.7 sensitive), BMI, WC, TC, TG, HDL-C, LDL-C and FBS were higher in the resistant group than the sensitive one. Furthermore, hierarchical cluster analysis grouped the clinical and metabolic data according to HOMA-IR value revealed statistically significant association between these groups (Fig. 5).

Discussion

MetS describes a constellation of different metabolic irregularities, which are often associated with thyroid hormones and insulin resistance (IR). IR is defined as glucose homeostasis disorder comprising abridged sensitivity of muscles, liver, adipose tissue and other body tissues to insulin (21). It is common knowledge that excessive weight gain and the resulting obesity increases the likelihood of incurring MetS.

The present analysis established that HOMA-IR and TG values are comparatively higher in women that are MetS+ relative to their MetS- counterparts. Moreover, TSH was found to positively associate with WC and total cholesterol levels. The finding is in line with previous studies (22, 23). One of the risk factors for IR and hyperlipidemia is hypothyroidism which is associated with weight gain and concomitant changes to the other components that comprise MetS (24). Thyroid dysfunction especially subclinical hypothyroidism is closely associated with glucose metabolism (25). Even in hypothyroid MetS+ females; high TSH levels has been found to be associated with dyslipidemia (26) IR plays causative role in the development of MetS (27). Correlations between hypothyroidism and IR have been established before (28). Previous studies show positive correlation between TSH and

Table 2. Pearson correlation coefficients (r) of TSH, FT4 and FT3 with general, anthropometric and components of metabolic syndrome

Variables	TSH	FT_4	FT_3
Age (years)	-0.007	-0.187	-0.151
Body mass index (kg/m^2)	0.121	0.127	0.570**
Waist circumference (cm)	0.060*	-0.024	0.429
Fat ratio	0.084	0.091	0.351*
Systolic blood pressure (mmHg)	-0.057	-0.083	-0.020
Diastolic blood pressure (mmHg)	-0.078*	0.078	0.088
Total cholesterol (mg/dl)	0.015**	-0.007*	0.128**
Triglycerides (mg/dl)	0.238	0.126	0.218
HDL-C (mg/dl)	0.222	-0.156	0.141
LDL-C (mg/dl)	-0.029	-0.084*	-0.129**
Fasting blood sugar (mg/dl)	0.008	0.091	0.273
Fasting Insulin (µIU/ml)	0.023	0.189	0.238
HOMA-IR	0.018*	-0.187**	0.293

** Correlation is significant at the 0.001 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).
HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TSH = thyroid stimulating hormone, FT4 = free thyroxine, FT3 = free triiodothyronine, HOMA I= homeostatic model assessment.

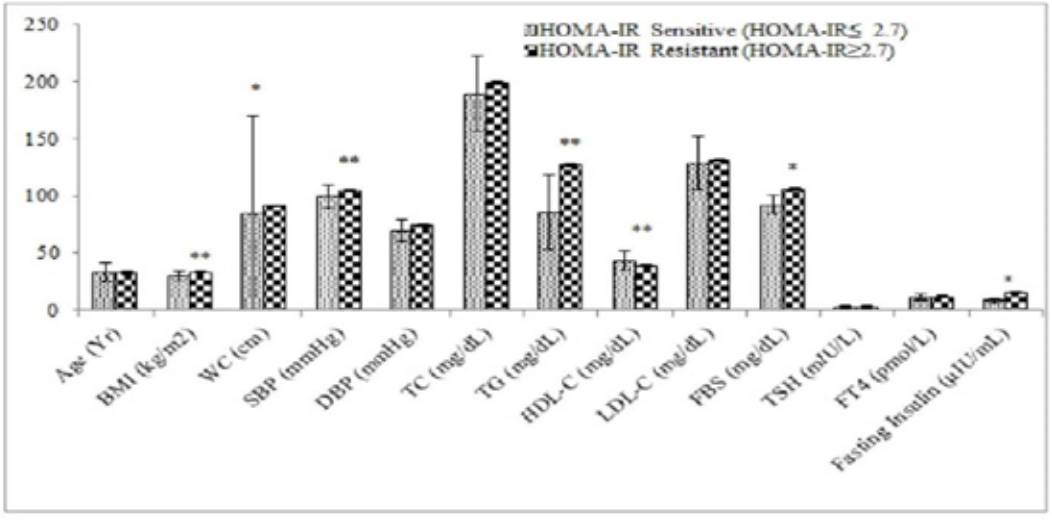

Figure 4. Comparison of clinical and metabolic characteristics of subjects according to HOMA-IR.
***p < 0.**05, **p < 0.001. Significance assessments were carried out using Duncan's new multiple range tests. BMI = body mass index, WC = waist circumference, SBP = systolic blood pressure, DBP = diastolic blood pressure, TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, FBS = fasting blood sugar, TSH = thyroid stimulating hormone, FT4 = free thyroxine, FT3 = free triiodothyronine.

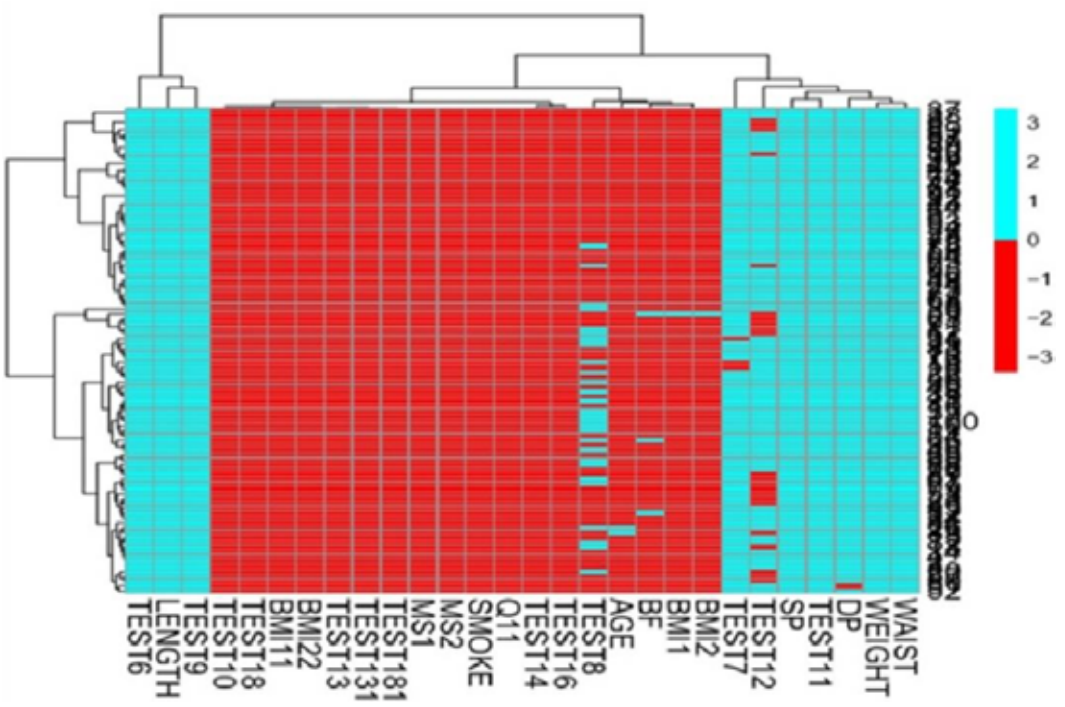

Figure 5. Hierarchical cluster analysis showing a significant correlation between HOMA-IR values and clinical and metabolic characteristics between both groups.

insulin and HOMA –IR (29, 30). Similar results are observed in this study in euthyroid. In a previous study TSH and IR were positively correlated independent of body status in obese children (31). Lekakais *et al.*, (30) mentioned that in hypothyroidism impairment of flow mediated endothelial vasodilation leads to IR.

The HOMA approach is a reliable, time-tested method for quantifying IR that is both well established and regarded in the field. The HOMA-based analysis of MetS+ and MetS- obese women described here provides empirical evidence that BMI positively correlates with IR, which supports the findings of a previous, independent study (32). Higher values of BMI and WC in HOMA-IR resistant group than sensitive group sustain the concept that obesity and particularly its visceral constituent should be considered as the principal causative factor in MetS (33). Macrophage infiltration with augmented production of cytokines and adipokines leads to oxidative stress and chronic "low-grade" inflammation which in turn affect insulin signaling in target cells (and binding of insulin to its receptor) leading to IR (34). TSH level was higher in HOMA –IR resistant group when compared with HOMA –IR sensitive group and as outcome, due to its morphogenic effect the possibility of proliferation of thyroid cells increases (29). Furthermore, the positive correlation between HOMA-IR values and TSH levels observed in the present study highlights the role played by the thyrotropin hormone in adipogenesis. These results are consistent with the findings of Racataianu *et al.*, and Vyakaranam *et al.*, (29, 35) and were further validated using hierarchical clustering. Even though the mechanisms by which IR may influence the thyroid are not fully implicated but the suspected mechanism can likely is the relationship between thyroid hormones and the adipokines released by visceral fat, especially leptin (36). Hyperinsulinemia and increased body fat with visceral fat mass inducing and aggravating IR, increases leptin's production. Leptin stimulates the hypothalamic-pituitary-thyroid axis to proliferate TSH secretion by interfering with the negative feedback regulation of thyroid hormones (37). Xu et al., (38) suggested that thyroid function might be one factor that affects body weight and the co-morbidities of obesity.

In the present study, FT_3 levels were positively associated with BMI. This is in accordance with a previous finding where associations between thyroid hormone levels and body weight and BMI were observed (39). Interestingly, the increase in FT_3 concentration is independent of other metabolic parameters and insulin sensitivity (22). In a study on 47 euthyroid subjects, it was found that concentration of FT3 was associated with hyerinsulinemia and insulin production (40). FT_3, alone or in combination with insulin, regulates the uptake and breakdown of glucose. The analysis described here revealed negative associations between FT_4 and HOMA-IR values which are quite similar to previous study (41). The reference range for FT4 is 11.5–22.7 pmol/L. In this study lower normal serum level of FT_4 has been observed even in MetS+ women. Roos *et al.*, (42) suggest that low normal FT_4 levels mediate the development of IR. A significant negative correlation has been found between thyroid hormone FT4 and TC as well as the atherogenic LDL-C within euthyroid which is similar to the results reported by Kavita and Nageshwari (43).

These outcomes incriminate that effect of thyroid function on lipid metabolism extends into the euthyroid range and subjects with low normal thyroid function can also be at greater CVD risk.

Conclusion

In conclusion obese euthyroid subjects exhibited a significantly positive correlation between HOMA IR values and TSH levels and significantly negative correlation between low normal FT4 and HOMA IR. It has also been established that thyroid function and lipid levels are related even in subjects classified as being euthyroid. These findings are consistent with an amplified CVD risk in subjects with low normal thyroid function. While further studies are required to explore the underlying mechanisms responsible for these correlations, they can serve as biomarkers that inform. In summary, the present study established associations between IR, the characteristic pathology of type 2 diabetes, and quantifiable clinical and metabolic factors.

Abbreviations

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; MetS: metabolic syndrome; BMI: Body mass index; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; FBS: fasting blood sugar; TSH: thyroid stimulating hormone; WC: waist circumference; CVD: cardiovascular disease; FT3: tri-iodothyronine; FT4: thyroxine

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Conflict of Interest: Each author declares that ghe or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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