

# Association between thyroid hormones, insulin resistance, and metabolic syndrome

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## ABSTRACT

**الأهداف:** دراسة الاتحاد بين هرمونات الدرقية ومقاومة الأنسولين ومتلازمة الاستقلاب لدى النساء سويات الدرقية.

**الطريقة:** تمت دراسة عدد 45 امرأة ليس لديها تاريخ طبي سابق في هذه الدراسة العرضية بقسم الغدد الصماء - مستشفى ميدوين - مدينة حيدرآباد - الهند، في الفترة ما بين أغسطس 2008م إلى سبتمبر 2008م. تم تقدير دهون الجسم بواسطة طريقة الممانعة الحيوية وتم تحليل عينات سكر الدم عند الصيام لحساب إجمالي الأيدوثيرونين الثلاثي (T3) والثايروكسين الكامل (T4) وهرمون تحفيز الدرقية (TSH) و الأيدوثيرونين الثلاثي (FT3) والدهون والأنسولين والجلوكوز (السكر الأحادي).

**النتائج:** بلغ متوسط عمر المشاركين  $32.6 \pm 9.6$  عاماً وبلغ مدخل كتلة الجسم (BMI) لعدد  $29.9 \pm 3.8$  كجم/متر مربع. تبين وجود دليل مقاومة الأنسولين ( $HOMA-IR > 3$ ) لدى (75%) و34 ومتلازمة الاستقلاب لدى (64%) 29 من المشاركات. أظهر (T3) علاقة إيجابية مع الدهون الثلاثية و الكلوسترول منخفض الكثافة LDL-C والأنسولين و ( $HOMA-IR$ ) وعلاقة سلبية مع دهون الجسم. بينما أظهر (TSH) علاقة إيجابية مع (BMI) والأنسولين و ( $HOMA-IR$ ) و الكلوسترول منخفض الكثافة LDL-C وعلاقة سلبية مع الكلوسترول عالي الكثافة ( $p < 0.05$ ). لدى (FT3) علاقة إيجابية إيجابية مع محيط الخصر وليس لدى (T4) علاقة بقاياسات متلازمة الاستقلاب.

**خاتمة:** أظهرت بياناتنا وجود اتحاد بين هرمونات الدرقية وبعض المكونات المحددة لمتلازمة الاستقلاب لدى النساء سويات الدرقية. يرتبط (T3) و (TSH) بشكل أكثر مع متغيرات متلازمة الاستقلاب من (FT3) و (T4). ان القيام بالمزيد من الدراسة لبيانات السكان أمر ضروري لتأكيد هذه النتائج.

**Objectives:** To determine the association between thyroid hormones, insulin resistance, and metabolic syndrome in euthyroid women.

**Methods:** Forty-five women with no past medical history were studied in this cross-sectional study at

the Department of Endocrinology, Medwin Hospitals, Hyderabad, India, from August 2008 to September 2008. The body fat was estimated using bio-impedance method, and fasting blood sample was analyzed for total triiodothyronine (T3), total thyroxine (T4), thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), lipid profile, insulin, and glucose.

**Results:** The mean age of the participants was  $32.6 \pm 9.6$  years with a body mass index (BMI) of  $29.9 \pm 3.8$  kg/m<sup>2</sup>. Evidence of homeostasis model assessment index for insulin resistance (HOMA-IR) more than 3 was seen in 34 (75%) and metabolic syndrome in 29 (64%) participants. Total T3 showed a positive correlation with triglycerides, low density lipoprotein-cholesterol (LDL-C), total cholesterol, insulin, HOMA-IR and negatively with body fat. Thyroid-stimulating hormone correlated positively with BMI, insulin, HOMA-IR, LDL-C and negatively with HDL-cholesterol ( $p < 0.05$ ). Free triiodothyronine correlated positively with waist circumference and T4 did not correlate with metabolic syndrome parameters.

**Conclusion:** Our preliminary data show an association between thyroid hormones and some components specific of the metabolic syndrome in euthyroid women. Total triiodothyronine and TSH correlated more with variables of metabolic syndrome than FT3 and T4.

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Thyroid hormones play an essential role in regulating energy balance, metabolism of glucose, and lipids. Thyrotropin directly induces adipogenesis and adipokine production, independent of control on energy balance.<sup>1-3</sup> Hypothyroidism is associated with obesity, dyslipidemia and increased atherosclerotic vascular disease.<sup>4</sup> A similar cluster consisting of obesity, dyslipidemia, diabetes and hypertension was proposed by Reaven<sup>5</sup> under the name "Metabolic syndrome" in 1988. Metabolic syndrome also leads to atherosclerotic vascular disease, and insulin resistance is the central pathophysiological phenomenon underlying this clustering.<sup>6</sup> The boundaries of metabolic syndrome are expanding with involvement of liver (non alcoholic fatty liver disease), ovary (polycystic ovarian disease) and other organs.<sup>7-9</sup>

Most subjects with metabolic syndrome are euthyroid and the data regarding the relationship between metabolic syndrome, insulin resistance, and thyroid function is scarce and conflicting.<sup>10,11</sup> In a study on 201 patients, free triiodothyronine (FT3) was shown to be associated with waist circumference, hyperinsulinemia and other components of metabolic syndrome.<sup>12</sup> The interaction with free thyroxine (FT4) is controversial with few studies showing association and others showing no relation with metabolic syndrome.<sup>13,14</sup> Free thyroxine concentration was found to be an independent risk factor for atherosclerosis in euthyroid subjects.<sup>15</sup> Insulin resistance modifies the relationship between serum thyrotropin (TSH) and cholesterol, such that patients with higher serum TSH and insulin resistance are at greatest risk of dyslipidemia.<sup>16</sup> We carried out this cross sectional study in euthyroid obese or overweight female participants to analyze the relationship between thyroid hormones and insulin resistance. In this study, we investigate the relationship between thyroid function, insulin resistance, and components of the metabolic syndrome.

**Methods.** A total of 45 overweight or obese females (40 premenopausal and 5 post-menopausal) were enrolled in this study from the staff of our hospital. The study design was a cross-sectional and was carried out at the Department of Endocrinology, Medwin Hospitals, Hyderabad, India from August 2008 to September 2008. Subjects with history of smoking, diabetes, hypertension, hyperlipidemia, thyroid disease or significant renal, hepatic and cardiac diseases were excluded. Subjects taking thyroid medications, lipid lowering drugs, oral contraceptives and any other drugs that influence glucose metabolism and insulin sensitivity were excluded from the study. All participants consumed normal meal with at least 150 g of carbohydrate for 3 days before the day of blood sample collection. We obtained an informed consent from all participants who

participated in this study and the study protocol was approved by the local hospital Ethics Committee.

Body weight was measured with light clothing and without foot wear to the nearest 0.1 kg. Standing height was measured with wall mounted stadiometer to the nearest 0.1 cm. The body mass index (BMI) was calculated as the weight in kilograms divided by square of the height in meters. Waist circumference was measured on bare skin as the narrowest circumference between the lower costal margin and the iliac crest in centimeters. After a resting period of 30 minutes, systolic and diastolic blood pressure were measured from the right arm. Blood pressure was obtained thrice from the same individual 30 minutes apart and the average was taken.

Body fat percentage was determined in the fasting state at the same time of the day by hand to hand bioelectric impedance analysis instrument (Omron HBF 306, Omron Corporation, Shimogo-ku, Kyoto, Japan). Anthropometric data such as height, weight, age, and gender were fed into the instrument and the device was held while both arms were stretched horizontally in front of the body. The subjects did not exercise or consume caffeine or alcohol prior to the measurement of body fat percentage.

**Biochemical measurements.** Fasting venous blood sample was collected from study participants between 08:30 and 10:00 h, after an overnight fast of more than 12 hours, centrifuged promptly, and separated sera stored at -20°C. Insulin was measured by a commercial radioimmunoassay kit (RIA insulin kit, Board of Radiaton and Isotope Technology, Navi Mumbai, India). The intra-assay coefficient of variance for insulin was 3.3 and inter-assay was 2.5%. The FT3 was measured by solid phase commercial radio immuno assay kit (Coat a count Free T3 kit, Siemens, USA) and TSH was measured by solid phase 2 site immunoradiometric assay by kit method (IRMAK-9, BRIT, Navi Mumbai, India). Assay for T3 and total thyroxine (T4) was carried out by radioimmunoassay method (RIAK, BRIT, Navi Mumbai, India). The normal reference range considered for the thyroid hormones is as follows: TSH: 0.27-4.2 mIU/L, T3: 0.7-2.4 nmol/L, T4: 5.5-13.5 µg/dL, and FT3: 1.5-4.7 pg/ml.

Fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were analyzed using enzymatic method with reagents supplied by Roche Diagnostics and Hitachi 911 analyzer (Roche Diagnostics). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation for those specimens with TG less than 4.5 mmol/L.<sup>17</sup>

Metabolic syndrome was defined according to the National Cholesterol Education Program (NCEP) Adult

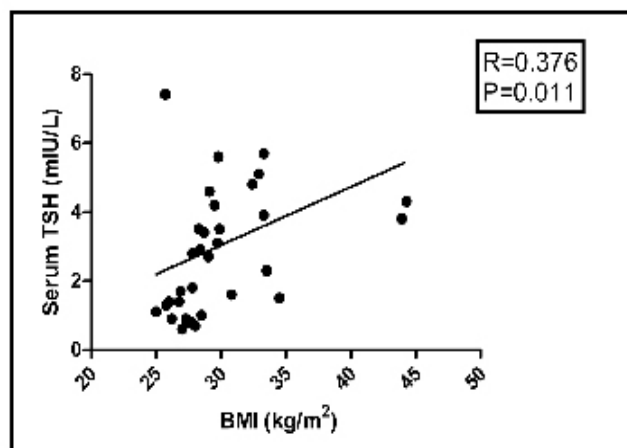
Treatment Panel III (ATP III) guidelines.<sup>18</sup> Euthyroidism is defined as the level of TSH and FT3 within the normal reference range. The homeostasis model assessment index for insulin resistance (HOMA-IR) was calculated as fasting insulin (mU/L) times fasting glucose (mmol/L) divided by 22.5. The HOMA-IR cut-off value used was 3 (more than 3 suggest insulin resistance and less than 3 as sensitive).<sup>19</sup> Body mass index between 25-29.9 kg/m<sup>2</sup> was considered as overweight and more than 30 kg/m<sup>2</sup> as obesity.

Data are presented as mean values  $\pm$  SD with total range of data. Relationships between continuous variables were assessed by Pearson's correlation. Spearman's correlation analyses was obtained for variables not having normal distribution and P values were reported for all statistical tests with a value of <0.05 considered to be significant. The statistical analysis was performed using Graphpad Prism Software, Version 5, manufactured by Graphpad Software, CA, USA.

**Results. Clinical and biochemical data.** Table 1 summarizes the clinical and demographic data of the participants. The mean age of the study population was  $32.6 \pm 9.6$  years and mean BMI of  $29.9 \pm 3.8$  kg/m<sup>2</sup>. Body fat percentage was  $38.2 \pm 5.8\%$  and the biochemical measurements are summarized in Table 2. Overall, 29 out of 45 (64%) satisfied the criteria for metabolic syndrome. The presence of 3 components of metabolic syndrome seen in 42%, 4 in 17% and all 5 in 4% of participants. The components of metabolic syndrome in decreasing order of occurrence are high waist circumference (81%), low HDL-C (74%), high TG (37%), elevated FBG (25%) and elevated blood pressure (10%). The mean HOMA-IR was  $6.4 \pm 4.3$  and 34 out of 45 (75%) participants had evidence of insulin resistance (HOMA-IR >3).

**Correlation analyses.** Total T3 showed positive correlation with TG, LDL-C, total cholesterol, insulin, HOMA-IR and negatively with body fat (Table 3). Thyroid-stimulating hormone showed positive correlation with BMI, insulin, HOMA, LDL-C and inverse correlation with HDL-cholesterol. Free triiodothyronine showed positive correlation with waist circumference. Total thyroxine level did not correlate with any component of metabolic syndrome. Table 3 summarizes the correlation analysis between thyroid hormones and components of metabolic syndrome.

**Discussion.** In this study, we have analyzed the correlation between thyroid hormones, insulin resistance and components of metabolic syndrome. Our data showed that thyroid hormones are related with majority of metabolic syndrome parameters. The correlation was stronger with T3 and TSH than with



**Figure 1** - Correlation between thyroid stimulating hormone and body mass index in study participants. R - correlation, P - probability value

**Table 1** - Clinical characteristics of patients.

Feature	Mean $\pm$ SD	Range
Age (years)	32.6 $\pm$ 9.6	18 - 56
Height (cm)	159.1 $\pm$ 8.3	142 - 174
Weight (Kg)	76.4 $\pm$ 13.1	55 - 130
Body mass index (kg/m <sup>2</sup> )	29.9 $\pm$ 3.8	25.7 - 44.3
Waist circumference (cm)	96.2 $\pm$ 8.5	72 - 126
Body Fat (%)	38.2 $\pm$ 5.8	6.5 - 50
Systolic BP (mm Hg)	132.5 $\pm$ 11.7	110 - 156
Diastolic BP (mm Hg)	79.4 $\pm$ 9.8	64 - 98
BP - blood pressure		

**Table 2** - Biochemical parameters of patients.

Feature	Mean $\pm$ SD	Range
Total T3 (nmol/L)	1.27 $\pm$ 0.45	0.7 - 2.1
Total T4 ( $\mu$ g/dL)	9.8 $\pm$ 4.1	1.8 - 14.8
Free T3 (pg/mL)	2.47 $\pm$ 0.44	1.6 - 3.1
TSH (mIU/L)	3.1 $\pm$ 1.7	0.6 - 7.4
Plasma glucose (mmol/L)	5.7 $\pm$ 1.7	3.7 - 9.9
Serum insulin ( $\mu$ U/mL)	24.4 $\pm$ 13.8	3.8 - 64
HOMA -IR	6.4 $\pm$ 4.3	0.6 - 21
Total cholesterol (mg/dL)	129.8 $\pm$ 48.5	62 - 255
HDL-cholesterol (mg/dL)	41.8 $\pm$ 7.7	28 - 59
Triglycerides (mg/dL)	112.1 $\pm$ 39.9	56 - 190
LDL-cholesterol (mg/dL)	91.1 $\pm$ 29.1	63 - 166

T3 - triiodothyronine, T4 - thyroxine, TSH - thyroid stimulating hormone, HOMA-IR - homeostasis model of assessment-insulin resistance, HDL - high density lipoprotein, LDL - low density lipoprotein

**Table 3** - Correlation (r) between clinical, biochemical factors and thyroid hormones.

Feature	Triiodothyronine (p-value)	Thyroxine (p-value)	Thyroid stimulating hormone (p-value)	Free triiodothyronine (p-value)
Systolic BP	r= -0.09346 (0.5414)	r= -0.04536 (0.7673)	r=0.1124 (0.4623)	r=0.08441 (0.5814)
Diastolic BP	r= -0.07098 (0.6431)	r= -0.0184 (0.2264)	r= -0.1216 (0.4253)	r=0.01412 (0.9267)
Waist circumference	r=0.273 (0.07)	r= 0.039 (0.797)	r= -0.0047 (0.998)	r=0.297 (0.047)*
Body mass index	r=0.205 (0.176)	r=0.207 (0.173)	r=0.376 (0.011)*	r=0.153 (0.316)
Body fat	r= -0.372 (0.012)*	r= -0.1119 (0.466)	r=0.218 (0.151)	r= -0.199 (0.190)
Total cholesterol	r=0.453 (0.002)*	r=0.253 (0.094)	r=0.273 (0.070)	r= 0.116 (0.448)
Triglycerides	r=0.356 (0.016)*	r=0.177 (0.245)	r=0.205 (0.177)	r= 0.120 (0.434)
LDL-cholesterol	r=0.360 (0.015)*	r= 0.141 (0.355)	r=0.306 (0.041)*	r=0.108 (0.478)
HDL-cholesterol	r= -0.174 (0.254)	r= -0.095 (0.533)	r= -0.466 (0.001)*	r= 0.112 (0.463)
Glucose	r=0.252 (0.095)	r=0.274 (0.069)	r= 0.039 (0.801)	r= 0.191 (0.209)
Insulin	r=0.416 (0.004)*	r=0.221 (0.144)	r=0.401 (0.006)*	r=0.218 (0.149)
HOMA-IR	r=0.377 (0.011)	r=0.231 (0.127)	r=0.346 (0.020)	r=0.227 (0.133)

\*Correlation is significant at 0.05 level (2-tailed), BP - blood pressure, HDL - high density lipoprotein, HOMA-IR - homeostasis model of assessment-insulin resistance, LDL - low density lipoprotein

FT3 and T4. Our study showed a significant positive correlation between T3 and insulin resistance ( $r=0.377$ ,  $p=0.011$ ). Total triiodothyronine is the biologically active hormone in the tissues and in our study; T3 has also been associated positively with total cholesterol, LDL-C and TG. Previous data suggest that both overt and subclinical hypothyroidism results in elevated triglycerides, low HDL-C and elevated LDL-C.<sup>20</sup> The observed discrepancy in our data could be due to sample being derived from obese females and not from general population and small size of the sample.

Thyrotropin level correlated positively with BMI in our data as shown in Figure 1. Obesity causes this apparent paradox of elevated thyroid hormones along with elevation in TSH level due to central and peripheral mechanisms. Obese persons have increased levels of leptin and pro-opiomelanocortin which directly stimulates thyrotropin releasing hormone (TRH) neurons in the paraventricular nucleus leading to increased TSH.<sup>21,22</sup> Subclinical hypothyroidism is associated with increase in lipid levels, endothelial dysfunction and increased risk of coronary artery disease.<sup>23</sup> Thyrotropin levels in our study data supports the similar assumption by showing a positive correlation with LDL-C and insulin resistance and negative correlation with HDL-cholesterol. This highlights that changes in TSH level in normal range are significantly associated with metabolic syndrome and insulin resistance.

Our study showed a positive association between FT3 and waist circumference. Waist circumference is an important parameter to assess the visceral fat status, and the majority of our study population (84%) had an

elevated waist circumference. In a study on 201 females, it was shown that FT3 was directly associated with BMI and waist circumference.<sup>12</sup> Such finding was not seen with FT4 and authors proposed that progressive central fat accumulation is associated with elevated FT3 and TSH levels independent of insulin resistance. Opinion is divided on the relationship of FT4 with the various metabolic syndrome components. Roos and Bakker<sup>13</sup> demonstrated an association between FT4 and lipids, metabolic syndrome. However, similar results were not observed in other large scale population data.<sup>11,14</sup> This observed difference could be due to differential expression of thyroid hormone receptor isoforms and in expression of iodothyronine deiodinases.<sup>24</sup>

Thyroxine did not show any correlation with any components of metabolic syndrome in our study population. This may be due to the fact that T3 is biologically more active than T4 and hence the changes are observed with levels of T3 in comparison to T4. The various components of metabolic syndrome are all well documented cardiovascular risk factors that co-occur in an individual more often than might be expected by chance. Our results indicate that elevated T3 and TSH are related to cardiovascular risk factors in the euthyroid range. Based on our study and previous published data, we postulate that elevation of TSH and free thyroid hormones indicate involvement of thyroid gland in insulin resistance.<sup>10,12,13</sup>

Our study is limited by small sample size, lack of testing for free thyroxine hormone and use of reliable technique such as dual energy x-ray absorptiometry (DEXA) for estimation of body fat. Even though,

our results indicate that thyroid hormones show correlation with components of metabolic syndrome in obese population, further cross-sectional studies and longitudinal studies with larger numbers of patients are required to confirm these findings.

In summary, we conclude that thyroid hormones have an association with some components of metabolic syndrome in euthyroid range. Total triiodothyronine and TSH were associated with more variables of metabolic syndrome than FT3 and T4. The results of this study have significant implications in view of additive role of thyroid dysfunction and metabolic syndrome towards atherosclerotic vascular disease. Further research is required to delineate this fascinating link between thyroid hormones and metabolic syndrome.

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