

1 **Thyroid hormone levels associate with insulin resistance in obese women with**
2 **metabolic syndrome in Saudi Arabia: A cross-sectional study**

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24

25

26 Abstract

27 **Background**

28 The obesity epidemic is a pressing global health concern, as obesity rates continue to
29 climb worldwide. The current study was aimed mainly to evaluate the correlation between
30 thyroid hormones and homeostatic model assessment of insulin resistance in Saudi obese women
31 with metabolic syndrome.

32 **Methods**

33 100 obese women aged 25 to 55 years were clinically evaluated, from which 72 women
34 were diagnosed with the metabolic syndrome and 28 without metabolic syndrome. Insulin
35 resistance was quantified using the homeostatic model assessment of insulin resistance method
36 and the resulting values were analyzed for association with demographic, clinical, and metabolic
37 parameters.

38 **Results**

39 This analysis revealed that body mass index, systolic blood pressure, and biochemical
40 parameters and fasting insulin showed statistically higher levels in the group with metabolic
41 syndrome compared to the group without metabolic syndrome. Similarly, values of waist
42 circumference, fat ratio, cholesterol, free thyroxine, free triiodothyronine and homeostatic model
43 assessment of insulin resistance results were higher in the group with metabolic syndrome as
44 compared to the group without metabolic syndrome. Correlation analysis revealed positive
45 association of thyroid-stimulating hormone with waist circumference ($P=0.01$), total cholesterol
46 ($P=0.002$), fasting insulin ($P=0.03$) and homeostatic model assessment of insulin resistance
47 results ($P<0.01$), and negatively associated with diastolic blood pressure ($P=0.013$) and age
48 ($P=0.05$). Free thyroxine was positively associated with triglyceride level ($P=0.003$) and
49 negatively associated with homeostatic model assessment of insulin resistance values ($P=0.035$)
50 and fasting insulin. Free triiodothyronine was positively associated with body mass index
51 ($P=0.032$) and waist circumference ($P= 0.006$) and negatively with age ($P=0.004$) and total
52 cholesterol ($P=0.001$).

53 Homeostatic model assessment of insulin resistance test revealed elevated level with
54 positive association of body mass index, waist circumference, biochemical parameters and

55 thyroid-stimulating hormone in insulin resistant obese women. Higher level of free
56 triiodothyronine was found to be associated with low insulin sensitivity.

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

58

59 **Introduction**

60 The obesity and overweight are associated to the risk of health complications and
61 premature death, obesity is the greatest contributing factor underlying the metabolic syndrome
62 (MetS) (Danaei et al., 2014). MetS is a chronic medical condition manifested by a cluster of
63 symptoms (e.g., low high-density lipoprotein cholesterol (HDL-C) levels, high blood pressure
64 (BP), high triglyceride (TG) levels, insulin resistance (IR), and other anthropometric and
65 biochemical factors) that are associated with developing cardiovascular disease and type 2
66 diabetes mellitus (Ford et al., 2005). A precursor to type 2 diabetes. IR basically refers to the
67 inability of insulin to perform its function at the optimum concentration required for its
68 biological activity (Harris et al., 1998; Ferrannini, 2004). This causes responsible for this
69 inability can range from defective glucose output in the liver to impaired insulin uptake in the
70 muscle (Farasat et al., 2011).

71 Healthy thyroid activity is required to maintain the overall health of an individual.
72 Several studies have described the effect of thyroid hormones on body mass index (BMI).
73 Hypothyroidism leads to weight gain, while hyperthyroidism causes weight loss (Hoogwerf and
74 Nutall, 1984). Moreover, it has also been established that obesity affects thyroid gland function
75 (Topsakal et al., 2012). Previous studies have associated thyroid hormones with insulin activity,
76 toward regulating the metabolism of glucose; the dysregulation of this pathway contributes to IR
77 (Ravi and Gokaldas, 2015). Thyroid hormones regulated a variety of proteins involved in

78 maintaining insulin sensitivity (Klieverik et al., 2009). The loss of insulin sensitivity, IR, is
79 associated with obesity and has been used as a predictor of developing cardiovascular disease
80 and type 2 diabetes (Naslund et al., 2000). Multiple studies have evidenced the cooperative
81 relationship between thyroid hormones and insulin in glucose metabolism (Lacobellis et al.,
82 2005; Chakrabarti et al., 2007). Maintaining glucose homeostasis involves the complex
83 interplay between physiological pathways that regulate insulin secretion and modulate its activity
84 (Farasat et al., 2011). The American Association of Clinical Endocrinologists (AACE) has
85 provided guidelines for the diagnosis of abnormal thyroid function and for the treatment of
86 thyroid dysfunction in patients with abnormal serum levels of thyroid-stimulating hormone
87 (TSH) (Gharib et al., 2004). The possible role of TSH in adipogenesis and IR has already been
88 established (Bastemir et al., 2007). Among its various metabolic effectors, WC and BMI
89 correlate positively with serum TSH levels (Knudsen et al., 2005); however, the relationship
90 between IR and TSH remains largely unexplored, particularly in the Saudi, female population
91 affected by MetS.

92 Therefore, the aim of this cross-sectional study is to identify associations between TSH,
93 IR, and other clinically-relevant metrics in obese women with and without MetS in Saudi Arabia.
94 The objectives of this study include: 1) to evaluate the anthropometric, clinical, and biochemical
95 characteristics of the study subjects; 2) to analyze these characteristics for correlations with
96 insulin sensitivity level; 3) to detect associations between TSH levels and the subjects' clinical
97 and biochemical characteristics, MetS diagnosis, and insulin sensitivity level.

98 Materials and Methods

99 Study subjects

100 The analysis was carried out on 163 obese and overweight women aged 25 to 55 years.
101 All of the patients had $BMI \geq 25 \text{ kg/m}^2$. The presence of medical conditions was assessed

102 through self-report. A pre-structured and pre-tested questionnaire were used to gather
103 demographic information and personal and family medical history. Informed consent was
104 obtained from all participants.

105 ***Inclusion criteria***

106 This study included women aged 25 to 55 years with BMIs over 25 kg/m² (Fig. 1).

107 ***Exclusion criteria***

108 Subjects with a history of smoking, polycystic ovary syndrome, chronic renal failure,
109 thyroid disease, chronic hepatopathy, or cancer as well as subjects taking antihypertensive drugs
110 and statins, contraceptive drugs, hormone replacement therapy, any medications known to
111 interfere with glucose and/or insulin secretion and/or metabolism were excluded from the study
112 (Fig. 1).

113 ***Demographic data***

114 A pre-structured and pre-tested questionnaire was used to gather self-reported
115 demographic information and individual and familial medical history.

116 ***Ethical considerations***

117 Informed consent was orally obtained from all participants before they gave voluntary
118 consent for this study and approved by IRB.

119 ***Anthropometric measurements***

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

121 ***Height and weight***

122 Height was measured without shoes and using a stadiometer. Body weight was morning
123 determined in lightweight clothing, with a digital scale.

124 ***Body mass index (BMI)***

125 BMI was calculated as the weight (kilograms) divided by the square of height (meters).

126 ***Waist circumference (WC)***

127 Subject's WC was measured using a flexible measuring tape, midway between the
128 xiphoid and the umbilicus during the mid-inspiratory phase.

129 ***Blood pressure (BP)***

130 Two BP measurements were taken with the subject in the seated position at a 2- to 3-
131 minute interval, after resting for at least 15 minutes. The average of these two readings was used
132 for all patients.

133 ***Biochemical parameters***

134 Blood samples were drawn after an overnight fast. Serum samples were analyzed for
135 fasting blood glucose (FBG), TG, total cholesterol (TC), low-density lipoprotein cholesterol
136 (LDL-C) and high-density lipoprotein cholesterol (HDL-C) using commercially-available kits
137 (Beckman-Coulter, CITY, STATE, USA). Serum insulin concentration was determined using an
138 electrochemiluminescence-based assay (Immulite 2000, CITY, STATE, USA). Serum FT₄, FT₃,
139 and TSH levels were also determined by electrochemiluminescence-based immunoassay (Roche
140 Diagnostics, CITY, Germany).

141 The homeostatic model assessment (HOMA) ratio formula was used to quantify IR
142 (Mathews et al., 1985).

143
$$\text{HOMA-IR} = [\text{fasting plasma insulin } (\mu\text{IU/ml}) \times \text{fasting plasma glucose } (\text{mmol/l})] / 22.5$$

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

145 ***Diagnosis of metabolic syndrome (MetS)***

146 MetS was diagnosed according to standard protocol (Grundy et al., 2005) based on the
147 presence of the following criteria: 1) TG \geq 150 mg/dL; 2) LDL-C $<$ 130 mg/dL; 3) HDL-C $<$ 40
148 mg/dL; 4) TC $<$ 200 mg/dL; 5) FBS \geq 100 mg/dL; 6) SBP \geq 130 mmHg; 7) DBP \geq 85 mmHg; 8)

149 WC > 80 cm; 9) TSH > 2.5 IU/mL. Subjects with levels over the cut-off values were considered
150 as MetS+ and subjects with levels under the cut-off values were considered to be MetS-.

151 **Statistical analysis**

152 All data were analyzed using the Statistical Package for the Social Sciences (SPSS)
153 software package v25 (IBM, Chicago, IL, USA). Statistical comparisons between the MetS+ and
154 MetS- groups were achieved with the one-way analysis of variance (ANOVA). Significance
155 assessments were carried out using Duncan's new multiple range test. Values are expressed as
156 means and standard deviations. We used hierarchical cluster analysis to assess the relationship
157 between TSH levels and HOMA-IR values. Each experiment was repeated at least three times. A
158 *P*-value of less than 0.05 was regarded as statistically significant.

159 **Results**

160 Of the 163 individuals considered, 63 were eliminated based on exclusion criteria (Fig.
161 1). The study population consisted of the remaining 100 obese (BMI > 25 kg/m²) women aged
162 25 to 55 years. Of these, 72 women were diagnosed as MetS+ and the remaining 28 were MetS-.
163 The anthropometric and biochemical characteristics are presented in Table 1. BMI, SBP, TC,
164 TG, HDL-C, FBP, TSH, and fasting insulin levels were statistically higher in the MetS+ group
165 than the MetS- group. Similarly, the values for WC, fat ratio, LDL-C, FT₄, FT₃, and HOMA-IR
166 were higher in the MetS+ group than the MetS- group; however, these differences were not
167 statistically significant.

168 Based on the Pearson's correlation coefficients (Table 2), TSH positively associated with
169 WC (*P* = 0.01) and TC (*P* = 0.002) and negatively associated with diastolic blood pressure
170 (DBP) (*P* = 0.013) and age (*P* = 0.05). TSH also positively associated with insulin (*P* = 0.03) and
171 HOMA-IR (*P* < 0.01). FT₄ positively associated with TG level (*P* = 0.003) and with HOMA-IR

172 value ($P = 0.035$). FT_3 positively associated with BMI ($P = 0.032$) and WC ($P = 0.006$) and
173 negatively with age ($P = 0.004$) and TC ($P = 0.001$).

174 The comparison between insulin-sensitive and -resistant women in terms of the clinical
175 and metabolic characteristics is presented in Figure 2. Using a cut-off value of 2.7 for HOMA-IR
176 (> 2.7 resistant, < 2.7 sensitive), BMI, WC, TC, TG, LDL-C, FBS, and TSH were higher in the
177 resistant group than the sensitive one. The positive association between IR and BMI ($P < 0.001$)
178 and WC ($P < 0.05$) was statistically significant. Similarly, TSH was significantly associated with
179 IR ($P = 0.03$). Higher FT_3 level associated with low levels of insulin sensitivity.

180 Furthermore, hierarchical cluster analysis grouped the clinical and metabolic data according to
181 HOMA-IR values and revealed statistically significant associations between these groups (Fig.
182 3).

183

184

186 Table 1. Anthropometric and biochemical characteristics (data are given as a mean and standard
187 deviation)

Variables	MetS+	MetS-	<i>P</i> -value
	(n = 72) (mean \pm SD)	(n = 28) (mean \pm SD)	
Age (years)	33.12 \pm 9.06	28.64 \pm 8.39	NS
BMI (kg/m ²)	32.12 \pm 4.89	29.41 \pm 5.98	< 0.05
WC (cm)	89.38 \pm 7.93	80.44 \pm 2.34	NS
Fat ratio	39.24 \pm 6.60	24.62 \pm 4.35	NS
SBP (mmHg)	132.12 \pm 9.48	112.10 \pm 10.91	< 0.001
DBP (mmHg)	88.34 \pm 8.43	78.78 \pm 4.31	NS
TC (mg/dl)	234.67 \pm 9.79	193.94 \pm 9.75	< 0.001
TG (mg/dl)	167.83 \pm 8.90	151.41 \pm 8.26	< 0.001
HDL-C (mg/dl)	34.27 \pm 7.08	58.21 \pm 4.33	< 0.05
LDL-C (mg/dl)	130.42 \pm 11.37	125.72 \pm 11.45	NS
FBG (mg/dl)	109.55 \pm 10.47	94.70 \pm 8.12	< 0.001
TSH (mIU/l)	2.38 \pm 1.52	1.38 \pm 1.02	< 0.05
FT ₄ (pmol/l)	11.99 \pm 2.81	10.56 \pm 2.46	NS
FT ₃ (pmol/l)	6.22 \pm 1.70	5.47 \pm 2.47	NS
Fasting insulin (μ IU/ml)	12.42 \pm 5.09	5.10 \pm 1.42	< 0.05
HOMA-IR	5.14 \pm 2.13	1.61 \pm 1.02	NS

188

189 Table 2. Pearson correlation coefficients (r) of TSH, FT₄, and FT₃ with demographic,
190 anthropometric, and MetS-associated factors

Variables	TSH	FT ₄	FT ₃
Age (years)	-0.007	-0.187	-0.151
BMI (kg/m ²)	0.121	0.127	0.570
WC (cm)	0.060*	-0.024	0.429
Fat ratio	0.084	0.091	0.351
SBP (mmHg)	-0.057	-0.083	-0.020
DBP (mmHg)	-0.078*	0.078	0.088
TC (mg/dl)	0.015**	-0.007*	0.128**
TG (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**
FBG (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

191 ** Correlation is significant at the *P*-values < 0.001 level (two-tailed)

192 * Correlation is significant at the *P*-values < 0.01 level (two-tailed)

193 NS

195 Discussion

196 MetS describes a constellation of different metabolic irregularities, which are often
197 associated with thyroid hormones and IR. The present study investigated the relationships

198 between thyroid hormones and IR in obese women diagnosed with MetS in Saudi Arabia. It is
199 common knowledge that excessive weight gain and the resulting obesity increases the likelihood
200 of incurring MetS. One of the risk factors for IR and hyperlipidemia is hypothyroidism.
201 Hypothyroidism is associated with weight gain and concomitant changes to the other
202 components that comprise MetS (Tarcin et al., 2012).

203 The present analysis established that HOMA-IR and TG values are comparatively higher
204 in women that are MetS+ relative to their MetS- counterparts. Moreover, TSH was found to
205 positively associate with WC and total cholesterol levels. The finding is in line with previous
206 studies (Pergola et al., 2007, Ayturk et al., 2009). Increases in TSH concentration, weight, and
207 TC level are likely indicative of subclinical hypothyroidism. This result serves as evidence for
208 the association between elevated TSH levels and obesity and MetS. Correlations between
209 hypothyroidism and IR have been thoroughly established by several earlier studies (Singh et al.,
210 2010; Pergola et al., 2007; Ravi and Gokaldas, 2015). The analysis described here revealed
211 positive associations between FT₄ and HOMA-IR values and fasting insulin levels. Low serum
212 levels of free T₄ were observed in MetS+ women. This strongly suggests that low FT₄ levels
213 mediate the development of IR. Thus, the association between thyroid hormone and HOMA-IR
214 cannot be discounted and requires further investigation. In the present study, FT₄ and TG levels
215 correlated positively, which is in contrast to one described a previous study (Kim et al., 2009).
216 Furthermore, a positive correlation was observed between FT₄ and MetS-associated variables
217 (Tarcin et al., 2012). Our results contradict the findings of Ayturk et al. (2009), who did not
218 detect any correlation between free thyroid hormones and MetS. The increases in TC levels and
219 LDL-C specifically are indicative of insulin sensitivity.

220 In the present study, increased FT₃ levels positively associated with increases in BMI.
221 This is in accordance with a previous finding where associations between free or total thyroid
222 hormone levels and body weight and BMI increases were observed (Roef et al., 2012).
223 Interestingly, the increase in FT₃ concentration was independent of other metabolic parameters
224 and insulin sensitivity; these results corroborate the findings of a previous study (Pergola et al.,
225 2007). FT₃, alone or in combination with insulin, regulates the uptake and breakdown of glucose
226 levels. A positive correlation between TG levels and HOMA-IR values was observed in MetS+
227 subgro

228 up in the present study. Some of the contradictory findings in the present study may stem
229 from the study design or variations in the health status of the study subjects.

230 The HOMA approach is a reliable, time-tested method for quantifying IR that is both
231 well established and regarded in the field. The HOMA-based analysis of MetS+ and MetS- obese
232 women described here provides empirical evidence that BMI positively correlates with IR, which
233 supports the findings of a previous, independent study (Geloneze et al., 2009). Moreover, the
234 positive association between HOMA-IR values and elevated TG and total cholesterol levels
235 nicely reflects its preponderance for MetS. Furthermore, the positive correlation between
236 HOMA-IR values and TSH levels observed in the present study highlights the role played by the
237 thyrotropin hormone in adipogenesis. These results are consistent with the findings of Bastemir
238 et al. (2007) and were further validated using hierarchical clustering.

239

240 **Declaration of interest**

241 The author declares that that is no conflict of interest that may prejudice the impartiality of the
242 present research.

244 **References**

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323 **Figures legends**

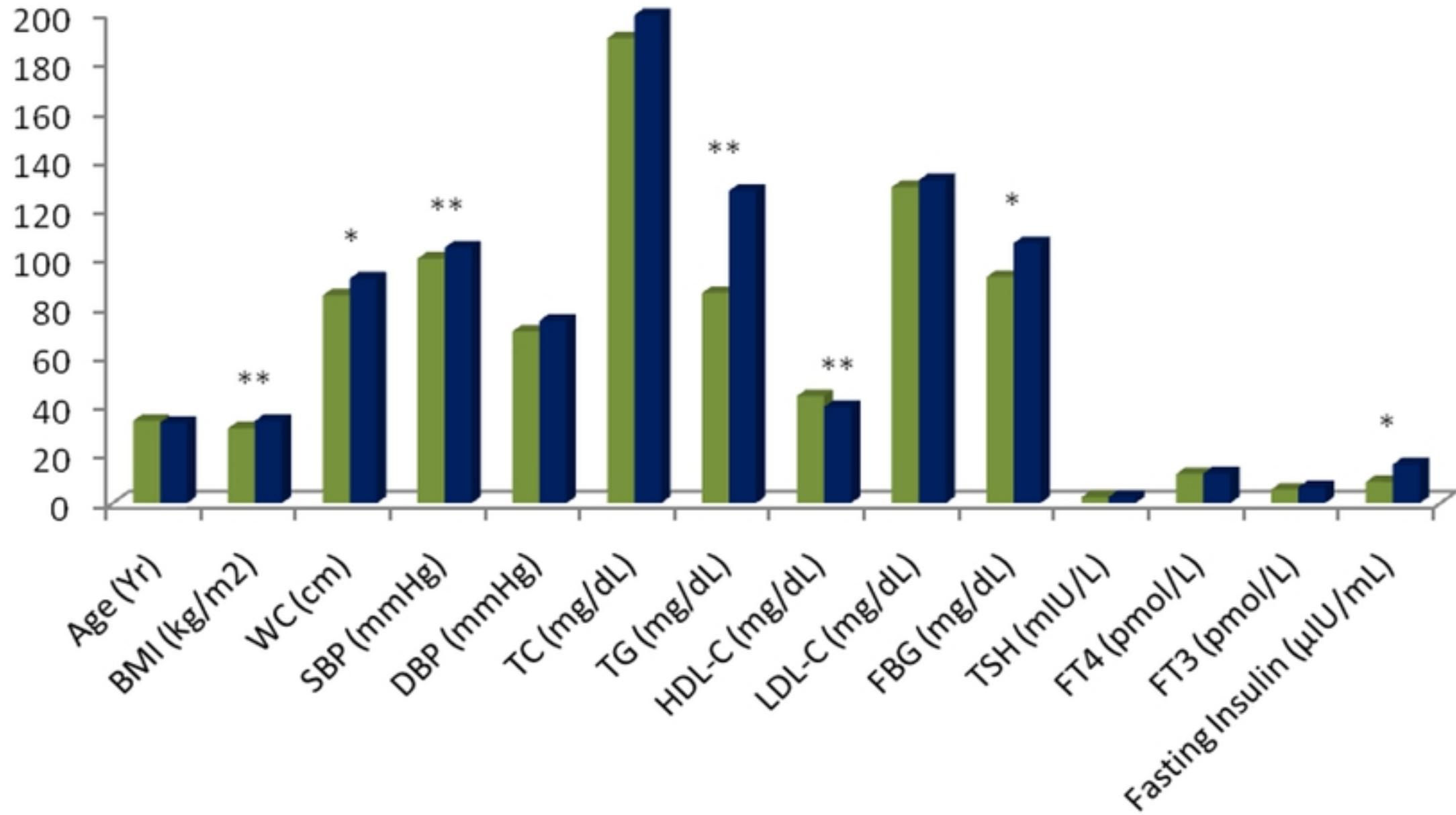
324 **Figure 1.** Flowchart schematic of study subject selection using the inclusion and exclusion
325 criteria

326 **Figure 2.** Comparison of clinical and metabolic characteristics according to HOMA-IR. Insulin-
327 sensitive (green, n = 21) and insulin-resistant (blue, n = 51) obese women. * $P < 0.05$, ** $P <$
328 0.001. BMI = body mass index, WC = waist circumference, SBP = systolic blood pressure, DBP
329 = diastolic blood pressure, TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol,
330 LDL-C = low-density lipoprotein cholesterol, FBG = fasting blood glucose, TSH = thyroid-
331 stimulating hormone, FT₄ = free thyroxine, FT₃ = free triiodothyronine.

332 **Figure 3.** Hierarchical cluster analysis showing a significant correlation between HOMA-IR
333 values and clinical and metabolic characteristics between both groups.



graphical abstract



Comparison of clinical and metabolic characteristics according to HOMA-IR

163 subjects were assessed for eligibility

63 subjects were excluded

12 with habit of smoking
4 with polycystic ovary syndrome
2 with chronic renal failure
13 with thyroid disease
5 had chronic hepatopathy
1 with cancer
9 taking antihypertensive drugs and statins
8 had taken contraceptive drugs or under hormone replacement therapy
9 under medications interfering with glucose or insulin secretion/metabolism

100 subjects were included in the study

72 with metabolic syndrome
(MetS+)

28 without metabolic syndrome
(MetS-)

Flowchart showing study subjects with inclusion and exclusion criteria

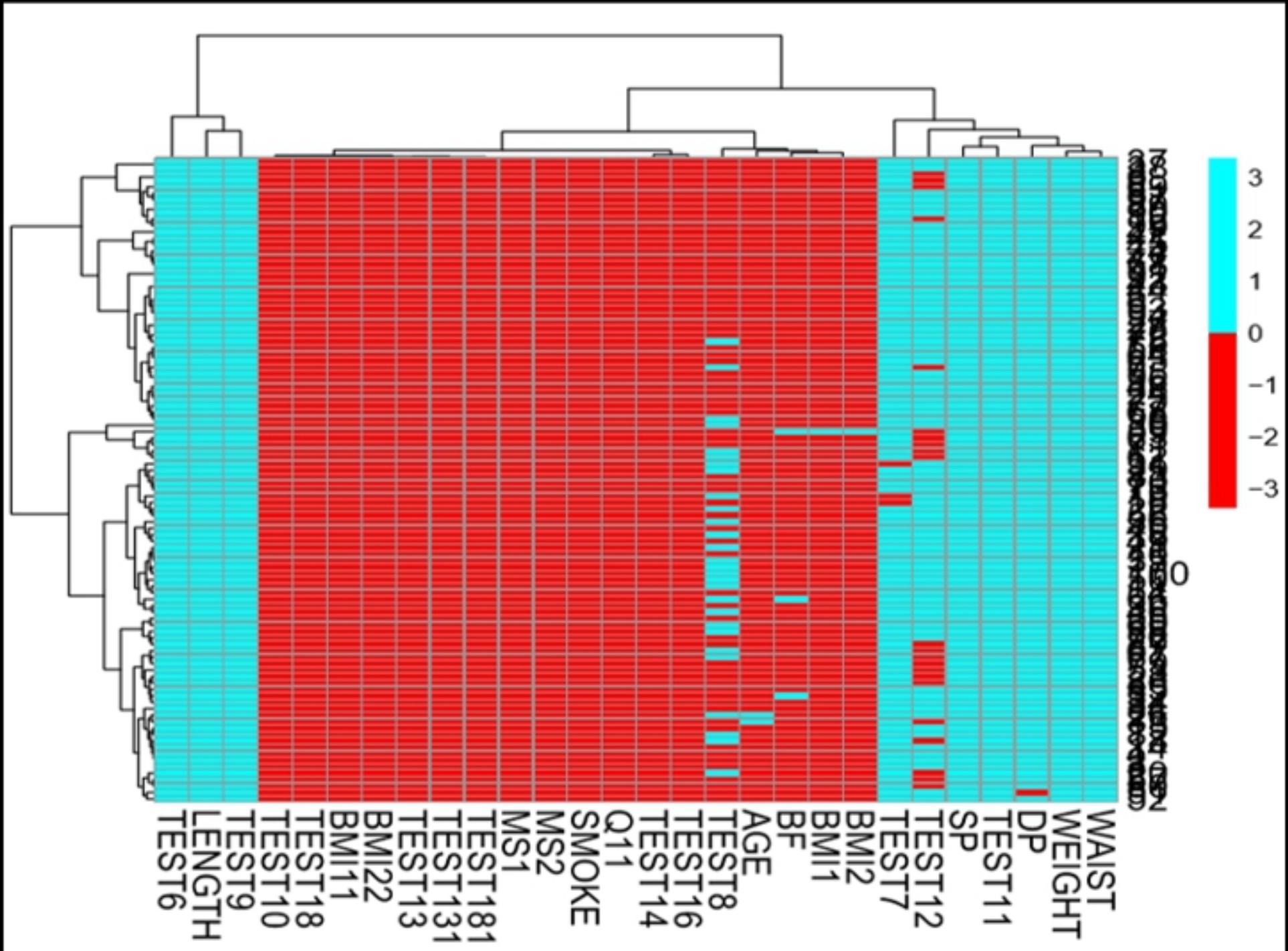


Fig.3 Shows a significant correlation among clinical a

Table 1. Anthropometric and biochemical variables in the study subjects (data are given as mean and standard deviation)

Variables	MetS+ (n=72)	MetS- (n=28)	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 glucose (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

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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**
Triglyceride (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 glucose (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).