Insulin Resistance and Cardiovascular Risk Factors in Patients With Mild and Severe Subclinical Hypothyroidism

Ramazan Gen, MD,* Esen Akbay,† and Kerem Sezer, MD†

Introduction: The aim of this study was to investigate insulin resistance in patients with mild and severe subclinical hypothyroidism (SH), and to explore the relationship between insulin resistance and cardiovascular risk factors.

Material and Methods: The study group consisted of 27 women with severe SH (body mass index [BMI], 28.35/3.92 kg/m²), 25 women with mild SH (BMI, 27.13/3.16 kg/m²), and 22 healthy women (BMI, 27.36/2.92 kg/m²). The mean systolic blood pressure, diastolic blood pressure, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), total cholesterol, LDL-cholesterol (LDL-C), triglyceride, thyroid-stimulating hormone (TSH), and high-sensitive CRP (hs-CRP) levels were higher in patients with severe SH than patients with mild SH and control subjects. The mean fasting insulin level, TSH level, LDL-C, and hs-CRP was higher in patients with mild SH than the control group. However, systolic blood pressure, diastolic blood pressure, and HOMA-IR were similar between patients with mild SH and those in the control group. In patients with severe SH, HOMA-IR was positively associated with TSH, total cholesterol, LDL-C, triglyceride, hs-CRP, and diastolic blood pressure but negatively associated with HDL-C. There was no correlation between HOMA-IR and waist circumference, W/H ratio, fT3, fT4, and systolic blood pressure in patients with severe SH. In patients with mild SH, HOMA-IR was positively correlated with TSH and hs-CRP, but there was no correlation between HOMA-IR and other parameters.

Conclusion: We conclude that severe SH was associated with increased insulin resistance and increased cardiovascular risk factors such as lipid abnormalities, hypertension, and hs-CRP. Our data also suggest that insulin resistance may play a role in mediating the effects of severe SH on diastolic blood pressure, lipid abnormalities, and low-grade inflammation. Mild SH is associated only with early insulin resistance, LDL-C, and low-grade inflammation.

Key Words: subclinical hypothyroidism, insulin resistance, cardiovascular risk factors

Subjects

The study group consisted of 52 women with SH. These patients were divided into 2 groups based on TSH levels.14 About 27 women had severe SH with TSH levels above 10 mIU/L (body mass index [BMI], 28.35 ± 3.92 kg/m²), 25 women had mild SH with TSH levels between 4.5 to 10 mIU/L (BMI, 27.13 ± 3.16 kg/m²), and 22 healthy women served as control subjects (BMI, 27.36 ± 2.92 kg/m²). The diagnosis of SH was based on basal serum TSH values >4 mIU/L and normal free triiodothyronine (fT3) and free thyroxine (fT4).14 Antithyroid-peroxidase and antithyroglobulin antibodies were determined in all patients with SH. All patients with SH were evaluated with ultrasoundography and scintigraphy. The cause of hypothyroidism was autoimmune thyroiditis. Patients entered the study only if they had SH for at least 3 months (as demonstrated by 2 thyroid hormonal profiles).

The Local Research Ethics Committee approved this study in accordance with the guidelines in The Declaration of Helsinki revised in 1989. Exclusion criteria for the study included known cardiovascular disease, neoplasms, current smoking, diabetes mellitus, renal impairment, medications that could cause thyroid hormone dysfunction, psychiatric conditions or their treatment. None of these women, SH, and controls was taking any medications for at least 3 months before the study, including oral contraceptives, glucocorticoids, ovulation induction agents, antidiabetic and anti-obesity drugs, or antihypertensive medication.

Anthropometric Evaluations

Before entering the study, a physical examination and appropriate laboratory tests were performed. Blood pressure (right arm) was measured after the participants had rested for at least 10 minutes. The BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m²). Weight, height, waist, and hip circumferences were measured. Waist circumference was obtained as the smallest circumference at the level of the umbilicus. Hip circumference was obtained as the widest circumference at the level of the buttocks.

Biochemical and Hormonal Analysis

In the study, blood samples were drawn after a 12 hour of overnight fast, for serum glucose, TSH, fT3, fT4, TC, triglyceride (TG), high-density lipoprotein (HDL-C), insulin, hs-CRP.

Assays for glucose, TC, HDL-C, TG were performed using a Cobas Integra 800 automated analyzer (Roche Diagnostics, Man-
Subclinical Hypothyroidism and Insulin Resistance

TABLE 1. Characteristics of Patients With SH and Controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients With Severe SH (n = 27)</th>
<th>Patients With Mild SH (n = 25)</th>
<th>Control (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>38.27 ± 2.52</td>
<td>37.19 ± 4.44</td>
<td>36.26 ± 5.44</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.25 ± 8.59</td>
<td>69.50 ± 9.64</td>
<td>70.54 ± 9.64</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.35 ± 3.92</td>
<td>27.13 ± 3.16</td>
<td>27.36 ± 2.92</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>84.23 ± 8.16</td>
<td>83.69 ± 7.24</td>
<td>83.77 ± 8.11</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.82 ± 0.06</td>
<td>0.83 ± 0.05</td>
<td>0.83 ± 0.03</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>123.10 ± 10.75*</td>
<td>117.55 ± 13.41</td>
<td>116.43 ± 12.81</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>80.48 ± 6.48*</td>
<td>72.36 ± 6.77</td>
<td>71.86 ± 7.62</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>87.79 ± 8.49</td>
<td>86.31 ± 9.06</td>
<td>85.94 ± 8.26</td>
</tr>
<tr>
<td>Fasting insulin (mIU/mL)</td>
<td>11.89 ± 4.21*</td>
<td>8.76 ± 2.21†</td>
<td>5.23 ± 1.34</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.54 ± 1.17*</td>
<td>1.89 ± 0.85</td>
<td>1.79 ± 0.95</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>189.61 ± 32.73*</td>
<td>168.33 ± 25.19</td>
<td>166.33 ± 27.19</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>55.68 ± 14.59</td>
<td>56.02 ± 13.91</td>
<td>54.02 ± 14.81</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>124.44 ± 23.47*</td>
<td>118.94 ± 22.31†</td>
<td>119.44 ± 11.31</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>158.97 ± 32.21*</td>
<td>113.22 ± 37.09</td>
<td>111.12 ± 36.02</td>
</tr>
<tr>
<td>Free T3 (pg/mL)</td>
<td>2.60 ± 0.70</td>
<td>2.66 ± 0.63</td>
<td>2.71 ± 0.63</td>
</tr>
<tr>
<td>Free T4 (ng/dL)</td>
<td>0.78 ± 0.13*</td>
<td>0.93 ± 0.14</td>
<td>0.98 ± 0.16</td>
</tr>
<tr>
<td>TSH (mIU/mL)</td>
<td>17.68 ± 2.71*</td>
<td>8.65 ± 0.77†</td>
<td>2.11 ± 0.77</td>
</tr>
<tr>
<td>hsCRP (mg/dL)</td>
<td>4.19 ± 0.74*</td>
<td>2.99 ± 0.15†</td>
<td>1.79 ± 0.12</td>
</tr>
</tbody>
</table>

**Comparison between severe SH and mild SH, P < 0.005.**
**Comparison between mild SH and control group, P < 0.005.**
SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HOMA, Homeostasis Model Assessment Model; IR, insulin resistance; Free T3, free triiodothyronine; Free T4, free thyroxine; TSH, thyrotropin; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; TC, total cholesterol; TG, triglyceride; hsCRP, high sensitive CRP.

Determining of Insulin Resistance

Insulin resistance was calculated by the HOMA-IR. HOMA-IR = fasting insulin (mIU/mL) × fasting glucose (mg/dL)/405.

Statistical Analysis

The SPSS package program (version 11.0, Chicago, IL) was used for statistical analysis. Data were presented as means ± SD. ANOVA test was used in comparison of groups. Relationships between variables were evaluated with Pearson correlation test. P value of <0.05 was taken to indicate statistical significance.

RESULTS

Descriptive characteristics for the patients with SH and control group are shown in Table 1. Age, height, weight, waist circumference, hip circumference and W/H ratio, BMI, fasting glucose, HDL-C, and FT3 values were similar between groups (P > 0.05). The mean systolic blood pressure (P = 0.016), diastolic blood pressure (P < 0.001), fasting insulin (P = 0.006), HOMA-IR (P = 0.007), TC (P < 0.001), LDL-C (P = 0.001), TG (P < 0.001), TSH (P < 0.001), and hs-CRP (P = 0.009) levels were higher in patients with severe SH than control subjects. The FT4 level were lower than in patients with severe SH than control subjects (P = 0.018). The mean systolic blood pressure (P = 0.038), diastolic blood pressure (P = 0.012), fasting insulin (P = 0.004), HOMA-IR (P = 0.009), TC (P < 0.001), LDL-C (P = 0.012), TG (P < 0.001), TSH (P = 0.011), and hs-CRP (P = 0.028) were higher in patients with severe SH than patients with mild SH. The mean fasting insulin level (P = 0.000), TSH level (P = 0.000), LDL-C (P = 0.042), and hs-CRP (P = 0.038) was higher in patients with mild SH than control group. But FT4 level, systolic blood pressure, diastolic blood pressure, HOMA-IR, were similar between patients with mild SH and control groups.

In patients with severe SH, HOMA-IR was positively associated with TSH (r = 0.280, P = 0.01), TC (r = 0.285, P = 0.009), LDL-C (r = 0.265, P = 0.016), TG (r = 0.309, P = 0.015), hs-CRP (r = 0.241, P = 0.028), and diastolic blood pressure (r = 0.384, P = 0.039), but negatively associated with HDL-C (r = −0.231, P = 0.036). However, there was no correlation between HOMA-IR and waist circumference, W/H ratio, FT3, FT4, and systolic blood pressure (P > 0.05). In patients with mild SH, HOMA-IR was positively correlated with TSH (r = 0.256, P = 0.021) and hs-CRP (r = 0.332, P = 0.032), but there was no correlation between HOMA-IR and other parameters (P > 0.05) in Table 2.

DISCUSSION

We show that insulin resistance is increased in patients with severe SH compared with patients with mild SH and healthy subjects. In patient with mild SH, only fasting insulin level is increased compared with healthy subjects. Sayed et al13 and Tuzcu et al6 found that HOMA-IR was the same in patients with mild SH and healthy subjects. They suggest that mild SH is associated with early insulin resistance.

Several reports in the literature give conflicting results for correlators between lipids and SH.16,11,13,18–21 We found that TC, LDL-C, and TG levels were significantly higher in patients with severe SH compared to those with mild SH. The results suggest that the conflicting results in the literature might reflect differences in the duration of thyroid dysfunction.
severe SH than in patients with mild SH and healthy subjects. HDL-C was the same as in healthy subjects. We also found that LDL-C was higher in patients with mild SH compared with healthy subjects. Some studies show that the lipid patterns are more abnormal in SH individuals with serum TSH greater than 10 mIU/L. 2,23 We confirmed these findings. One study suggests that insulin resistance may play a role in mediating the effects of mild hypothyroidism on serum lipids. 24 We found that TC and LDL-C were positively and HDL-C was negatively associated with HOMA-IR in patients with severe SH. We found no correlation between HOMA-IR and lipids in patients with mild SH.

An increased risk of hypertension is reported in some studies of patients with SH. 2,25 We found that mean systolic blood pressure and mean diastolic blood pressure were significantly higher in patients with severe SH than in patients with mild SH or in healthy subjects. Mean systolic blood pressures and mean diastolic blood pressures were the same in patients with mild SH and healthy subjects. Only diastolic blood pressure was significantly associated with HOMA-IR in patients with severe SH. Our findings suggest that insulin resistance may play a role in mediating the effects of severe SH on diastolic blood pressure.

The plasma level of hs-CRP is a strong, independent predictor of future cardiovascular events in women. 26 There are conflicting results about hs-CRP level in patients with SH. Many studies showed that CRP levels are significantly higher in subclinical hypothyroid patients than in controls. 6,7,27,28 In contrast, some studies found that CRP levels are the same in patients with SH and healthy subjects. 12,17,28,29 We show that hs-CRP levels are higher in patients with mild and severe SH than in healthy subjects. Previous study showed that insulin resistance is significantly associated with CRP. 29 We also found that HOMA-IR was positively associated with hs-CRP in patients with mild and severe SH.

CONCLUSION

We conclude that severe SH is associated with increased insulin resistance and increased cardiovascular risk factors such as lipid abnormalities, hypertension, and hs-CRP. Our data also suggest that insulin resistance may play a role in mediating the effects of severe SH on diastolic blood pressure, lipid abnormalities, and low-grade inflammation. Mild SH is associated with early insulin resistance, high LDL-C, and low-grade inflammation. There are many conflicting results about insulin resistance and other cardiovascular risk factors in patients with SH.

Study Limitation

The limitations for this study were the moderate size of the groups and the absence of data after the normalization of SH with levothyroxine treatment.

REFERENCES