The association of insulin resistance and metabolic syndrome in early androgenetic alopecia

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ABSTRACT

**Introduction:** Insulin resistance (IR), hyperinsulinaemia and concomitant metabolic syndrome (MS) are known to be independent risk factors for coronary arterial disease (CAD). The aim of this study was to examine the frequency of IR, hyperinsulinaemia and MS in individuals with early androgenetic alopecia (AGA).

**Methods:** The Hamilton-Norwood scale was used to grade AGA. The homeostasis model assessment of insulin resistance formula was used to detect IR, and a value above 2.7 was considered to show IR. According to the National Cholesterol Education Programme Adult Treatment Panel III-2001 diagnosis criteria, patients with three or more positive criteria were considered to have MS.

**Results:** In this study, we evaluated 80 patients with early AGA and 48 healthy participants. The serum level of insulin was higher in patients with early AGA compared to the healthy participants, although not significantly. IR was detected in 25 patients with early AGA and in six healthy participants. The difference between the groups was statistically significant. Although 20 patients with AGA were diagnosed with MS, it was only diagnosed in five healthy participants. The occurrence of MS was significantly higher in the AGA group than in the control group.

**Conclusion:** The prevalence of IR and MS was observed to have increased in early AGA patients. Hence, patients with early AGA should be followed up for CAD in the long term. Our results should be confirmed with prospective studies.

**Keywords:** androgenetic alopecia, insulin resistance, metabolic syndrome

INTRODUCTION

Insulin resistance (IR) can be defined as an impaired biological response to exogenous or endogenous insulin. It causes an insufficiency in insulin-stimulated glucose transport in the skeletal muscle and fat tissue, as well as a suppression of glucose production in the liver. The homeostasis model assessment (HOMA) method is performed with the help of a mathematical operation that allows for the quantitative assessment of IR. In contrast to other tests, it provides the basal IR. A homeostasis model assessment of insulin resistance (HOMA-IR) of more than 2.7 is considered to be in favour of IR.

Androgenetic alopecia (AGA) is an androgen-induced disorder that is characterised by hair loss in genetically predisposed men and women. It requires adequate androgens to be in circulation and a genetic predisposition. In AGA, androgens induce miniaturisation in follicles that are genetically predisposed to baldness. Such miniaturisation is observed in the frontotemporal area and vertex in men, and over the crown in women, as these areas are more sensitive to the effects of androgens. Some previous studies have shown early AGA to be related to coronary arterial disease (CAD). IR and hyperinsulinaemia are known to be independent risk factors for CAD. A relationship between IR and AGA has also been suggested, but only vaguely. Therefore, this study aimed to examine the association of early AGA with IR and Ms.

METHODS

This study was conducted at the Cumhuriyet University Health Services Practice and Research Hospital, Sivas, Turkey, between May 2006 and May 2008. Male patients who presented to the Internal Diseases Polyclinic were enrolled in the study as controls, while Faculty of Medicine students, research assistants and staff aged 20–50 years who had AGA symptoms before the age of 35 years and did not have known CAD or glucose metabolism disorder...
were enrolled as participants. This study was approved by the ethical and research committee of the Cumhuriyet University Medical Faculty. The study group consisted of 80 men with early AGA, and the control group was made up of 48 men without alopecia. Patient consent was obtained prior to the study. Those who displayed AGA symptoms after age 35 years, had glucose metabolism disorder or CAD, suffered from a disease with potential effects on hair physiology, were taking drugs that may cause IR, or were < 20 or > 50 years of age were excluded from the study.

Detailed anamneses were recorded for each individual, and physical examinations were performed. The Hamilton-Norwood scale was used for the grading of AGA, and all participants were assessed by the same doctor (Fig. 1). (12) Height and weight were measured, and the body mass index (BMI) was calculated by dividing the weight by the square of height (kg/m²). The participants' waist circumference (cm) was measured before food intake, parallel to the floor from the midline between the 12th costae lower boundary and the iliac crest. Blood pressure was measured using a sphygmomanometer on the right arm in a sitting position and after a 20-minute rest. The triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, total testosterone, free testosterone, sex hormone-binding globulin (SHBG), thyroid-stimulating hormone (TSH), fasting plasma glucose (FPG) and insulin levels of the patients were obtained from blood samples drawn after a 12-hour fast. The HOMA-IR formula was used to identify IR, and a value above 2.7 was considered to indicate IR. The mean fasting serum insulin and FPG concentration levels were obtained from blood samples drawn three times after five-minute intervals. IR was calculated using the following formula: fasting insulin level (µIU/mL) × fasting glucose level (mmol/L)/22.5. (3)

Based on the National Cholesterol Education Programme (NCEP) Adult Treatment Panel (ATP) III-2001 diagnosis criteria (waist circumference > 102 cm in male and 88 cm in female, a triglyceride value > 150 mg/dl, HDL < 40 mg/dl in male and 50 mg/dl in female, arterial blood pressure > 130/85 mmHg, FPG > 110 mg/dl), patients with three or more positive criteria were considered to have MS. (12)

The laboratory operations of the study were conducted at the Cumhuriyet University Faculty of Medicine Research and Practice Hospital’s Biochemistry and Nuclear Medicine Laboratories. FPG measurements were made using the Synchron System Plasma Glucose kit (Beckman Coulter, Brea, CA, USA) in the Synchron LX20 autoanalyser through the glucose oxidase/O₂ depletion method, and presented in mg/dl. Insulin measurements were made by the immunonasay method using the Abbott AxSYM System insulin kit (Abbott, Wiesbaden, Germany) in the Abbott AxSYM System tool. TG measurements were made using the Synchron System Triglyceride kit (Beckman Coulter, Brea, CA, USA) in the Synchron LX20 autoanalyser through the enzymatic/GPO-Trinder method. Total cholesterol and HDL were measured using the Synchron System Cholesterol and HDL Cholesterol kits, respectively (Beckman Coulter, Brea, CA, USA) in the Synchron LX20 autoanalyser through the enzymatic method and homogenous calorimetric method, respectively. LDL cholesterol measurements were made using the Friedewald formula (LDL = total cholesterol – [HDL + TG/5]). All the above parameters were presented in mg/dl. SHBG and total testosterone were measured using the Roche Hitachi Elecsys SHBG kit and testosterone reactive kit (Roche, Mannheim, Germany), respectively, in the Cobas tool through the electrochemiluminescence immunoassay method. Free testosterone measurements were taken using the Free Testosterone RIA kit (Diagnostic System Laboratories, Webster, TX, USA) in the DSL-4900 tool through the RIA method. Finally, TSH measurements were performed using the Architect TSH Kit (Diagnostic System Laboratories, Webster, TX, USA) in the Architect tool through the chemiluminescent microparticle enzyme immunological method.

The data was analysed using the Statistical Package for the Social Sciences version 14.0 (SPSS Inc, Chicago, IL, USA) through the test of significance between two means and the chi-square test. The arithmetic mean ± standard deviation, the number and percentage of participants were tabulated, and the margin of error was taken as 0.05. A p-value < 0.05 was considered to be statistically significant.
Table I. Distribution of demographic and laboratory parameters of the two groups in the study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>AGA group</td>
<td>Control group</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>36.28 ± 7.74</td>
<td>35.14 ± 6.54</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.96 ± 6.24</td>
<td>175.08 ± 5.18</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.61 ± 9.86</td>
<td>77.61 ± 10.44</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.69 ± 3.18</td>
<td>25.64 ± 3.02</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>96.36 ± 14.47</td>
<td>91.14 ± 10.57</td>
</tr>
<tr>
<td>Insulin (µIU/mL)</td>
<td>10.19 ± 8.92</td>
<td>8.13 ± 4.85</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>93.78 ± 14.70</td>
<td>92.37 ± 8.77</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>119.13 ± 12.54</td>
<td>119.37 ± 10.39</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74.78 ± 10.04</td>
<td>72.29 ± 9.28</td>
</tr>
<tr>
<td>Total testosterone (ng/ml)</td>
<td>3.71 ± 1.52</td>
<td>4.19 ± 2.18</td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td>13.79 ± 6.21</td>
<td>15.69 ± 5.13</td>
</tr>
<tr>
<td>Sex hormone-binding globulin (nM)</td>
<td>27.78 ± 13.75</td>
<td>31.59 ± 13.76</td>
</tr>
<tr>
<td>Low-density lipoprotein (mg/dL)</td>
<td>130.09 ± 42.93</td>
<td>124.26 ± 35.82</td>
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<tr>
<td>High-density lipoprotein (mg/dL)</td>
<td>37.23 ± 10.24</td>
<td>40.05 ± 9.66</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>146.40 ± 158.12</td>
<td>100.20 ± 46.63</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>198.71 ± 49.78</td>
<td>182.00 ± 37.49</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (µIU/ml)</td>
<td>1.32 ± 0.75</td>
<td>1.53 ± 1.12</td>
</tr>
</tbody>
</table>

* Denotes statistical significance.
SD: standard deviation; AGA: androgenetic alopecia

RESULTS
A total of 128 participants with early AGA were assigned to the study. The patient group consisted of 80 male subjects and the control group consisted of 48 healthy male subjects. The mean age of the participants in the patient group was 36.28 ± 7.74 years and that of the participants in the control group was 35.14 ± 6.54 years. The age difference between the groups was insignificant (p > 0.05). The groups were compared in terms of height, weight, BMI, FPG, systolic and diastolic blood pressure, total and free testosterone, SHBG, LDL, HDL and TSH. The differences between the groups were not found to be statistically meaningful (p > 0.05) (Table I). However, the differences between the groups with respect to TG, total cholesterol and waist circumference were statistically meaningful (p < 0.05).

The insulin level was 10.19 ± 8.92 µIU/mL in the patient group and 8.13 ± 4.85 µIU/mL in the control group. Although the values in the patient group were higher, the difference between the two groups was not statistically meaningful (p > 0.05). However, as shown in Table II, when patients were grouped according to the HOMA-IR > 2.7 cut-off value and IR was compared, 25 out of 80 patients (31.3%) in the early AGA group were found to have IR, whereas only 6 out of the 48 (12.5%) control patients were observed to have it. The difference between the groups was statistically meaningful (p < 0.05). When the AGA patient group was classified according to the Hamilton-Norwood scale, 24 (30%) patients were classified as stage III, 28 (35%) as stage IV, 11 (13.8%) as stage V and 17 (21.3%) as stage VI. The lowest stage found among the patients was stage III and the highest was stage VI. Stage IV was identified as the mean stage. When the stages were compared with regard to IR, the difference was statistically insignificant (p > 0.05) (Table III). When the groups were compared with respect to MS frequency, 20 (25%) patients in the AGA group and five (10.4%) participants in the control group were found to have MS, and the difference was statistically meaningful (p < 0.05) (Table IV).

DISCUSSION
An association between early AGA and serious cardiovascular incidents such as myocardial infarcts and fatal ischaemic heart disease has been documented; however, the underlying mechanism of this association is still not understood. In a previous study, the presence of androgen receptors in the arterial wall endothelium was shown to exist, but the direct effects of the androgens on vascular endothelium or functions remained unclear. Hyperinsulinaemia (fasting or postprandial) has been shown to be a risk factor for CAD in non-diabetic individuals. This association increases the risk of CAD independently from the presence of other cardiovascular risk factors such as obesity, hypertriglyceridaemia, hypercholesterolaemia, lack of physical activity, hypertension and cigarette use. Insulin increases the risk of CAD through many mechanisms, such as by increasing LDL receptor...
effectiveness in smooth muscle cells, fibroblasts and mononuclear cells, exogenous cholesterol intake, and arterial endogenous cholesterol and TG synthesis. At the same time, hyperinsulinaemia and IR accelerate the development of atherosclerosis, and prevent atherosclerotic plaque development and resorption. Insulin and insulin-like growth hormones also increase the risk of CAD by increasing collagen synthesis, which is an important component of atherosclerotic plaque.\(^\text{1,4}\) Data from these earlier studies suggests that IR, which leads to inflammation mediators and endothelial dysfunction, is the main mechanism for atherosclerosis.\(^\text{5}\) Insulin also increases the release of nitric oxide (NO) from the endothelium at the physiological levels. An increased risk of atherosclerosis in IR cases is thought to be related to the loss of insulin’s effects on NO expression.\(^\text{1,3}\)

Matilainen et al have shown that hyperinsulinaemia is significantly higher among men with early AGA.\(^\text{5}\) Ekmekçi et al conducted a partially similar study with 66 female participants, and compared IR and insulin sensitivity indices in 41 women with AGA against 25 healthy, non-obese women. Their results showed that IR is more common among women with AGA. However, they did not assess MS among these patients.\(^\text{18}\) Recently, González-González et al found that a relationship exists between IR and early baldness. Their study included 80 participants with AGA and 80 controls who were age- and weight-matched. Both groups comprised obese and non-obese cases. The HOMA-IR index was found to be significantly higher among both the obese and non-obese patients with AGA compared to the controls,\(^\text{17}\) which is similar to the findings of the current study, although we did not evaluate obese and non-obese cases as separate groups. In our study, we compared hyperinsulinaemia, IR and MS between 80 male patients aged 20–50 years who developed AGA before the age of 35 and 48 control males. When the groups were assessed with respect to their insulin levels, the men in the AGA group were found to have higher levels of insulin (10.19 ± 8.92 µIU/mL) than those in the control group (8.13 ± 4.85 µIU/mL), but the difference was not statistically meaningful (p = 0.144). When the groups were compared with respect to IR based on the HOMA-IR > 2.7 cut-off value, 25 (31.3%) patients in the patient group and 6 (12.5%) in the control group had IR; and the difference was statistically meaningful (p = 0.017).

The phenotypical pattern of AGA was defined systemically for the first time by Hamilton. This classification was later modified by Norwood and the non-existing types of hair loss were also included in the scale, which was extended from stage I to VII.\(^\text{11}\) When the patients in our study were grouped according to the Hamilton-Norwood scale, IR was identified in five patients in stage III (20.8%), 11 patients in stage IV (39.3%), four patients in stage V (36.4%), and five patients in stage VI (29.4%). When the stages were compared with respect to IR, the difference was not found to be statistically meaningful. This may be interpreted in two ways. Firstly, there may not be any correlation between IR and AGA stage, but the presence of alopecia alone is adequate to show IR. Secondly, this result may have been due to the smaller sample size within the stages.

The NCEP ATP III handbook mentions MS as a major cardiovascular risk factor.\(^\text{10}\) Individuals with MS are at an increased risk of coronary arterial calcification.\(^\text{18}\) The presence of MS has been associated not only with a three-fold risk increase for CAD and apoplexy, but also a five-fold risk increase for cardiovascular mortality.\(^\text{10}\) When all the participants in our study were assessed according to the NCEP ATP III-
2001 diagnostic criteria (they were considered to have MS if three or more of these criteria were met), 20 (25%) in the AGA group and 5 (10.4%) in the control group were identified as having MS. The difference between the groups was found to be statistically meaningful (p = 0.044).

Abdominal fat tissue is associated with serious metabolic disorders such as IR, hyperinsulinemia, hypertension, increased TG, glucose intolerance and diabetes mellitus. Some studies have pointed to abdominal fat tissue, calculated by measuring the waist-hip proportion, as an independent risk factor for CAD. The International Diabetes Federation has emphasized the strong correlation between abdominal obesity and IR, and suggests that this criterion be made compulsory for MS diagnosis. In our study, the two groups were compared with respect to waist circumference, and waist measurements of the AGA group (96.36 ± 14.47 cm) were found to be higher than those of the control group (91.14 ± 10.57 cm). The difference was statistically meaningful (p = 0.032).

In a meta-analysis conducted in 2003 by Shepherd et al, a 1 mmol/L increase in the TG value was shown to increase the possibility of CAD by 30% in men and by 69% in women. In 1996, Guzzo et al compared the serum lipid profile of 50 Hamilton III and IV vertex alopecia patients with a control group, and found no difference in HDL, LDL, total cholesterol, TG and total cholesterol/LDL ratios. In 1997, Şasmaz et al compared the serum total cholesterol, HDL, LDL, TG and lipoprotein A levels in 41 male vertex type AGA patients and 36 controls with normal hair texture. They found meaningfully higher levels of serum TG and lipoprotein A in the AGA group, and higher but not statistically meaningful total cholesterol and LDL cholesterol levels. Greger et al showed in 1990 that when castrated male monkeys were administered with dihydrotestosterone externally, their HDL cholesterol levels dropped. In another study, administering testosterone to monkeys resulted in an increase in total cholesterol and LDL cholesterol levels, and a decrease in HDL cholesterol levels. Animal experiments have also shown that androgens can cause hyperlipidaemia that pose a risk for CAD. In our study, the TG (146.40 ± 158.12 mg/dl) and total cholesterol (198.71 ± 49.78 mg/dl) levels in the patient group were higher than the TG (100.20 ± 46.63 mg/dl) and total cholesterol (182.0 ± 37.49 mg/dl) levels in the control group, and the difference was statistically meaningful (p < 0.05). There was no statistically meaningful difference in the LDL and HDL values.

In conclusion, more studies are required in order to objectively clarify whether early AGA causing CAD can be attributed to dyslipidaemia due to androgens, IR alone, or MS due to IR. As the risk factors for CAD, i.e. TG, total cholesterol, waist circumference, IR and MS level, are higher among early AGA patients, prospective studies should be conducted in which these patients are closely followed up in the long term, particularly for CAD.

REFERENCES


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