Available online at www.medicinescience.org

ORIGINAL RESEARCH

Medicine Science International Medical Journal

Medicine Science 2021;10(2):609-13

Early onset androgenic alopecia as the male phenotypic equivalent of polycystic ovarian syndrome is associated in high oxidative stress

Didem Dereli Akdeniz[1], Ibrahim Omeroglu[2]

[1]Izmir Economy University, Tepecik Teaching And Research Hospital, Department of Medical Endocrinology and Metabolic Diseases, Izmir, Turkey
[2]Izmir Economy University, Tepecik Teaching And Research Hospital, Department of Medical Gynecology and Obstetrics Specialist, Izmir, Turkey

Received 22 April 2021; Accepted 19 May 2021
Available online 20.05.2021 with doi: 10.5455/medscience.2021.04.127

Abstract

The genetic component of Polycystic ovarian syndrome (PCOS) proved to play an important role in its etiology. Early androgenetic alopecia (EAGA) is widely accepted as its male equivalent of PCOS if it starts before age of 30. In this study, we aimed to investigate metabolic and oxidative stress parameters of men with EAGA and compare them with healthy age-matched controls. Fasting glucose, fasting insulin, homocysteine, serum malondialdehyde (MDA), total antioxidant capacity (TAC), folic acid, and vitamin B12 were measured from the blood samples of thirty men with EAGA and 30 controls. Homeostasis model assessment (HOMA) results were used for the marker of insulin sensitivity. Alopecia classification was made by using the scale of Hamilton with Norwood modification. We demonstrated a significantly lower TAC activity ($p<0.01$), higher MDA levels ($p<0.01$) in patients with EAGA compared to controls. The EAGA group had insulin resistance but the control group did not (HOMA results were 3.34±0.47 vs 1.43±0.3). The homocysteine levels of the EAGA group were higher than controls (12.37±1.31 vs 9.33±2.12) which is another cardiovascular risk factor. The correlations in our study among HOMA, serum MDA levels, homocysteine, and alopecia scores were found positive in EAGA patients. We didn't find any correlations among those parameters in the control group. Because of these findings, men with EAGA should be followed for the long time risk factors like PCOS women. Insulin resistance and its results like metabolic syndrome, diabetes, and cardiovascular diseases, and oxidative damage are real but preventable risks.

Keywords: Early onset androgenetic alopecia, Polycystic ovary syndrome, insulin resistance, oxidative stress

Introduction

Polycystic ovarian syndrome (PCOS) was thought to be a gynecologic disorder and then accepted as a general endocrine and metabolic syndrome. It is characterized by irregular menses caused by anovulation, clinical (hirsutism /acne), with or without biochemical findings of high androgenic hormones, small-sized (<8mm) multiple cysts in ovaries, and some metabolic abnormalities in women who suffers from the syndrome. The shreds of evidence for the genetic component in PCOS etiology are strong. In the clinic, we see lots of patients with PCOS who clusters in the same families. It seems to be inherited through a polygenic autosomal type of mechanism. The PCOS women suffer from insulin resistance and this brings them the risks of diabetes, metabolic syndrome, and cardiovascular diseases (CVD) in the future. Oxidative stress (OS) which damages all the tissues plays a key role in the development of CVD, has also been demonstrated in PCOS women. The role of genetic in PCOS etiopathogenesis gives the scientific basis for a male PCOS equivalent. There is a strong possibility for inheriting the same responsible genes for PCOS in male relatives of those women [1].

Early androgenetic alopecia (EAGA) starts before age of 30 even sometimes before age of 20. It is a specific pattern of hair loss that starts from the temporal and occipital parts of the hair. EAGA and accompanied hypertrichosis in men may be the male synonym of PCOS in women. Men with EAGA mostly show similar abnormalities metabolic abnormalities like PCOS women and they may also be suffering because of elevated oxidative damage.

Material and Methods

This study was a prospective case-control hospital-based one and executed in Tepecik Teaching and Research Hospital Obstetrics and Gynecology department. The ethics committee of the hospital approved this study, and all participants gave written approval for participating in this study. Thirty men aged 18 - 30 years that have this specific type of hair loss (according to the classification of alopecia scale of Hamilton with Norwood they all had grade 4 or

***Coresponding Author:** Didem Dereli Akdeniz, Izmir Economy University, Tepecik Teaching And Research Hospital, Department of Medical Endocrinology and Metabolic Diseases, Izmir, Turkey E-mail: drdidemdereli@gmail.com

higher alopecia) were accepted as study patient group. Thirty age-matched men without any evidence of androgenetic alopecia were accepted as control.

The exclusion criteria for our study were

1. Men with Body mass index ³ 35 kg/m2Usage of medications that affect glucose metabolism

mass index ³ 35 kg/m^2 it should be mass index ≥ 35 kg/m^2

2. In the same raw 35 kg/m2Usage of medications that affect glucose it should be devided like=

3. Usage of any medications that affect skin or hormones for hair loss

4. Men with Body mass index ≥35 kg/m^2

5. Usage of medications that affect glucose metabolism

6. Patients who were using any antioxidant supplementations in the last 3 months

7. Special for the control group, men who have first-degree relatives with PCOS were excluded.

8. Special for the research group, men who do not have any first-degree relatives with PCOS were also excluded.

Detailed anamneses and family history were saved in their medical records for each participant. All individuals were assessed by the same physician. The weight of the patients was evaluated with the same Tanita BC-418 early in the morning before breakfast, their heights were also measured. The body mass index (BMI) was calculated using these results.

Blood samples were collected after ten hours overnight fast between 8 AM to 9 AM. The glucose oxidase technique was used to evaluate plasma glucose levels (Biobak Laboratory Supplies Trade, Ankara, Turkey).

Serum liver function tests [Serum glutamic oxaloacetic transaminase (SGOT), Serum glutamic pyruvik transaminase (SGPT) and glutamyl transferase (GGT)], kidney functions (creatinine and urea), and uric acid levels were measured by Olympus AU 2,700 analyzer.

The levels of insulin in plasma were measured by micro particle enzyme immunoassay (Abbott, Wiesbaden-Delkenheim, Germany). Insulin sensitivity was investigated by calculation of [fasting insulin (mU/ml) X fasting glucose (mg/dl)/22.5X18 = HOMA]. Results greater than 1.7 were accepted positive for insulin resistance and >2,7 was a high risk of diabetes mellitus.

Serum homocysteine levels were measured by high-performance liquid chromatography with the Hewlett-Packard 1100 Series System (Waldron, Germany).

Serum total antioxidant capacity (TAC) was assessed using ELISA Kit (TAC ELISA kit; LDN Labor Diagnostika Nord GmbH and Co KG, Germany). The spectrophotometric method was used to measure serum MDA by its reaction with thiobarbituric acid.

The Statistical Package for the Social Sciences (version 10.0 for Windows; SPSS, Inc., Chicago, IL) was used for statistical analyses. The normality tests were used to test the character of distributions of the data. If the distribution of the variables were normal, the student's two-tailed t-test with or without logarithmic transformation was used to compare all parameters. For the variables which didn't show normal disturbance even after log transformation Man-Whitney U test was performed. Relations between insulin sensitivities, degree of alopecia, metabolic and hormonal parameters were analyzed with simple linear regression analysis, and Pearson (r) correlation coefficients were presented. P values smaller than 0.05 were accepted as statistically significant.

Study design

One hundred twenty-four patients were evaluated on an outpatient basis in Tepecik Teaching and Research obstetrics and gynecology department. Figure 1 shows the patient enrollment protocol. Seventy-two patients with EAGA were evaluated for the patient group. In this group of patients, 24 did not have first-degree PCOS relatives, 5 of them did not accept to participate in our study, 7 had alopecia score <4, and 11 of them had body mass index (BMI)>35 kg/m2. And 8 were using antioxidant supplements. For the control group, we evaluated 52 medical students, assistants, and fellows without significant alopecia. Among the control group subjects 9 had PCOS relatives, 2 of them did not want to participate, 5 had BMI>35kg/m2, 11 were using antioxidant supplements and one of them was using beta-blockers.

The remaining 30 participants became our control group.

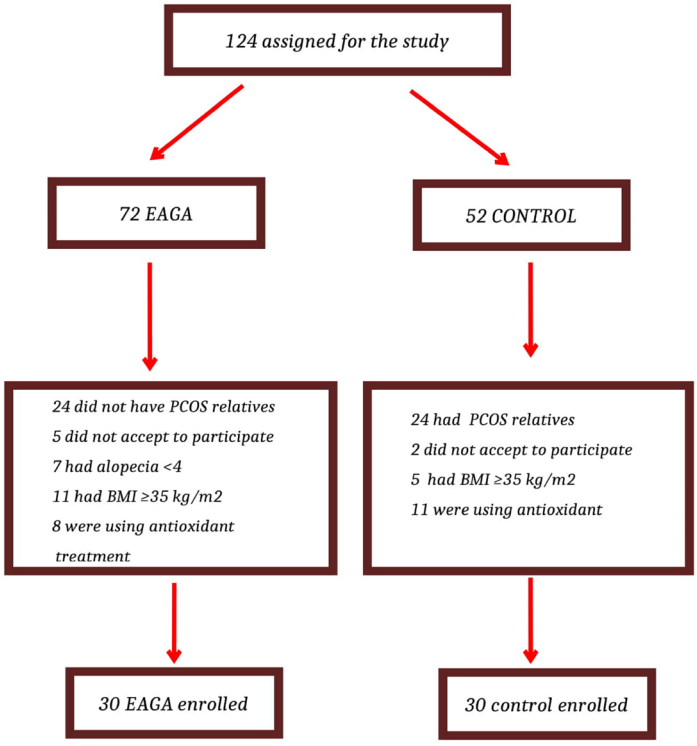

Figure1. Study Design

Results

The demographic and biochemical features and laboratory results of the studied groups are demonstrated in Table 1. The age in the EAGA group (as mean ± SD) was 24.83±2.41 years and it was 23.93±2.72 years in group 2. The difference was not statically significant (P=0.06). The calculated BMI is significantly high

in the EAGA group than in control group 2 (26.42±3.3 vs 25.7± 3.13 kg/m2 respectively P=0.03) The systolic blood pressures were similar in both groups but the diastolic blood pressure was high statistically in the EAGA group (8.28±0.41 vs 7.97± 0.29 P=0.01). The blood glucose in the fasting state (FBG) was significantly higher in Group-1 than Group-2 (96.93±4.23 mg/ dl vs 86.24±3.54 mg/dl respectively P<0.01). 5 patients in the EAGA group had impaired fasting glucose (IFG). We performed standard two-hour oral glucose tolerance test with seventy-five grams glucose (OGTT) to those patients and 3 had impaired glucose tolerance and 2 had normal results. None of the control group participants had IGF. We did not perform an OGTT to the control group as the FBG and HbA1c levels were normal in all control group patients. The HOMA index was higher and it was in the insulin-resistant range in all the patients in Group 1. That result was significantly higher than control group (3.44±0.54 vs 1.53±0.4 respectively P<0.01). There were only 7 participants whose HOMA index was higher than 1,7 (risky group) and no one had HOMA index greater than 2,7. The lipid profile parameters except HDL were significantly higher in EAGA but none of them needed antilipidemic treatment. HDL levels were similar in the two groups. The mean HbA1c value of EAGA was higher than control group (5.89±0.34vs5.29±0.28 respectively P<0.01). In the EAGA group, 1 patient had a diabetic HbA1c value but his OGTT was in the IGT range. Homocysteine values were higher in AGAE group than control group (12.64±1.42 vs 9.43±2.43 respectively P<0.01). MDA levels were significantly higher in group 1 showing a significant oxidative damage (7.33±0.29 vs 1.87±0.03 P<0.01). Total antioxidant capacity (TAC) was significantly lower in group 1 compared to group 2 (0.82±0.33 vs 1.12±0.35 P<0.01).

We investigated the correlation among insulin sensitivity, oxidative stress markers, and alopecia scores. The correlation between HOMA and alopecia score was significantly positive in Group-1 (Figure-2) but there was no correlation in Group-2. The correlation between HOMA and MDA levels was positive and strong in the EAGA group (r=0.71 p<0.001) (Figure-3). The correlation between HOMA and TAC was also significant but negative (r=-0.63 p<0.05). The correlation among homocysteine values and HOMA results was weakly positive but statistically significant (r=0.37 p=0.04).

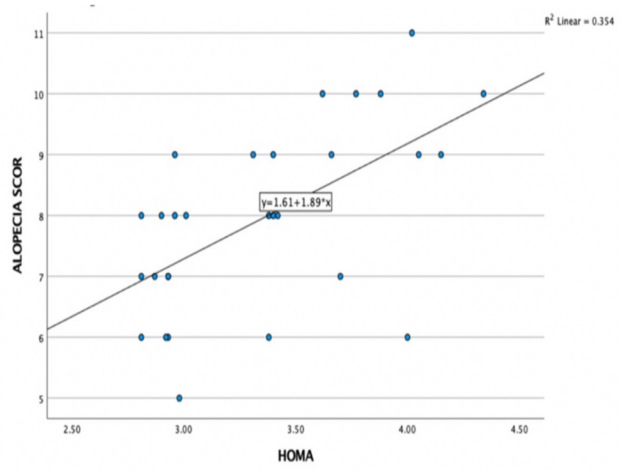

Figure 2. The Correlation of Alopecia Score and HOMA

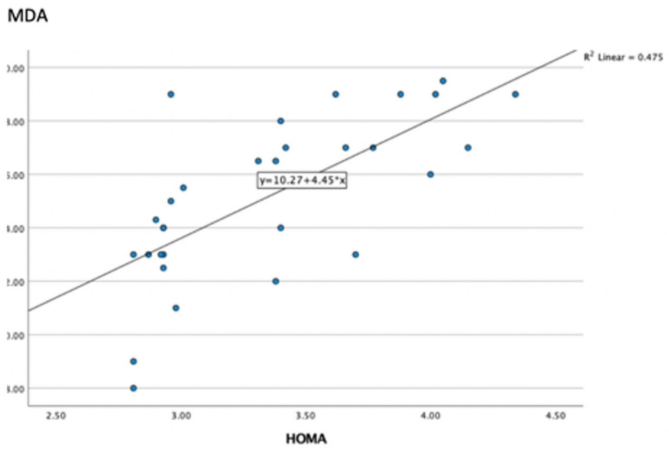

Figure 3. The Correlation of MDA and HOMA

Table 1. Demographic and biochemical results of the studied groups.

	Group-1	Group-2	p
Age (year)	24.83±2.41	23.93±2.72	P=0.06
BMI(kg/m²)	26.42±3,3	25.7±3.13	P=0.03
Systolic Blood Pressure (cm/Hg)	12.32±0.26	11.97±0.75	P>0.05
Diastolic Blood Pressure (cm/Hg)	8.28±0.41	7.97±0.29	P=0.01
fasting blood glucose (mg/dl)	96.93±4.23	86.24±3.54	P<0.01
Fasting Insulin (mIU/ml)	11.55±2.63	7.7±1.13	P<0.01
HOMA	3.44±0.54	1.53±0.4	P<0.01
T. Cholesterol (mg/dl)	229.81±13.32	191.63±13.71	P<0.01
TG (mg/dl)	255.66±42.82	175.7±33.99	P<0.01
HDL (mg/dl)	44.19±3.2	43.83±5.9	P=0.83
LDL (mg/dl)	141.40±11.92	118.23±14.32	P<0.05
Uric Asid (mg/dl)	6.3±1.07	5.1±0.44	P=0.83
Sgot (IU/L)	24.12±6.8	22±7,1	P=0.76
SGPT (IU/L)	38.3±6.9	25.1±8.2	P<0.05
Homocystein (±mol/L)	12.64±1.42	9.43±2.43	P<0.01
HBA1C	5.89±0.34	5.29±0.28	P<0.01
AGA Skor	7.88±1.2	1.44±0.3	P<0.01
TAC (mmol/L)	0.82±0.33	1.12±0.35	P<0.01
MDA (nmol/ml)	7.33± 0.29	1.87±0.03	P<0.01

Discussion

EAGA is like a symphonic melody of androgens, insulin sensitivity, and gens. Evaluating the metabolic profiles in these men is necessary to understand the etiopathogenesis of EAGA and to predict the future risks in this problem. Various studies proved the there are lots of similar findings in the hormonal abnormality styles of EAGA men with those women with PCOS. Now EAGA in men is widely accepted to be the phenotypic equivalent of PCOS. [3]. This brings those men a lifelong chronic disease risk burden.

There are a lot of studies showing the association of EAGA with insulin resistance and metabolic syndrome [2]. Although it is really difficult to compare the results of the sex hormone parameters in male and female patients, there are studies in the literature that reports similar hormonal changes in men affected by the EAGA as seen in PCOS [4]. It was found that this characteristic EAGA type is mostly present in male family members of PCOS women. This supports the hypothesis of the genetic component of this syndrome.

In this study, we investigated 30 EAGA men who have first-degree relatives with the diagnosis of PCOS and compared them with 30 age-matched men without EAGA and also without any female relatives with the diagnosis of PCOS.

In our study, we found significant increases in fasting blood glucose, fasting insulin, HOMA, and HbA1c results in EAGA men than the control group. Insulin resistance was reported frequently in men affected by the EAGA in the literature [5]. The brothers of PCOS women are shown to suffer from some metabolic problems such as a higher risk of insulin resistance, elevation in triglyceride levels, an elevation in blood pressure [6,7]. We found insulin resistance and other problems not only in brothers but in all first-degree male EAGA relatives of PCOS women. The combination of lower SHBG with higher free testosterone and metabolic problems in the EAGA men was reported in some studies. A case-control study on a Finnish population made of 125 men with EAGA and 104 controls, aged 19–50 years, found patients with early EAGA had elevated BMI with a twofold higher risk of developing insulin resistance when compared to controls [8]. In our study, we found higher BMI in the group of EAGA than controls. The interesting finding is that the insulin resistance was significantly higher than the control group even if the BMI effect is eliminated. According to this EAGA may be accepted as one of the predictors for the future diagnosis of hyperglycemia, insulin resistance than type 2 DM in young patients.

Framingham Offspring Study has demonstrated that insulin resistance and serum homocysteine level elevations are associated and may partially be the reason for increased risk of CVD [9]. The reason for elevated homocysteine is insulin inhibits the hepatic cystathionine β synthetase activity. In our study, we found significantly increased levels of homocysteine in the EAGA group and it was correlated with insulin levels this was similar to the study of AGA and coronary artery heart disease risk [10].

The correlation was not strong but homocysteine levels can be affected by nutrition factors like vitamin B12 and folic acid. It may be the reason for the weak correlation of our results as we did not investigate the nutritional status of our patients [10].

Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to detoxify the reactive intermediates or to repair the resulting damage.

Insulin resistance stimulates oxidative stress because of hyperglycemia and associated higher levels of free fatty acids. They lead to reactive oxygen species (ROS) production. In our study, we found a significantly elevated MDA level which is an important marker of oxidative stress. This finding is similar to the study of Erdogan et al. We also demonstrated a significantly decreased TAC in the EAGA group which will worsen the damage of the elevated oxidative end products like MDA [12,13].

The increased MDA level, a marker of lipid peroxidation observed in our study, in the plasma of the patients with androgenetic alopecia suggested that an increased oxidative stress was present in these patients. This finding is similar to the study of Prie et al. and this suggests early cell damage especially in the vessels [12].

There were few problems in our study; the parameters that we assess alopecia grade were subjective and our study group had a small sample size.

Conclusion

We found significantly increased levels of fasting blood glucose, fasting insulin, and HbA1c levels in the EAGA group. And we showed that they are under a high oxidative damage risk. These biochemical parameters are also similar to the metabolic abnormality of PCOS women. So we suggest that these men could be accepted as a phenotypic synonym of PCOS women. These young men have the same increased risks as women with PCOS, including insulin resistance, metabolic syndrome, diabetes, cardiac and vascular diseases, and also infertility. These risks need to be confirmed by some multicentered, large studies. And long term follow-up study results of men with EAGA are also needed to confirm these findings.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was a prospective case-control hospital-based one and executed in Tepecik Teaching and Research Hospital Obstetrics and Gynecology department.

References

1. Delcour C, Robin G, Young J. et al. PCOS and Hyperprolactinemia: what do we know in 2019? Clin Med Insights Reprod Health. 2019;13:1179558119871921.
2. Di Guardo F, Ciotta L, Monteleone M. et at. Male equivalent polycystic ovarian syndrome: hormonal, metabolic and clinical aspects. Int J Fertil Steril. 2020;14:79-83.
3. Guardoa F, Ceranab MC, D'ursoa G et al. Male PCOS equivalent and nutritional restriction: Are we stepping forward? Med Hypotheses. 2019;126:1-3.
4. Cannarella R, Condorelli RA, Mongioì LM, et al. Does a male polycystic ovarian syndrome equivalent exist? J Endocrinol Invest. 2018;41:49-57.
5. Arias-Santiago S, Gutiérrez-Salmerón MT, Buendía-Eisman A, et al. Sex hormone binding globulin and risk of hyperglycemia in patients with androgenetic alopecia. J Am Acad Dermatol. 2011;65:48-53.

6. Kaushal R, Parchure N, Bano G, et. al. Insulin resistance and endothelial dysfunction in the brothers of Indian subcontinent Asian women with polycystic ovaries. Clin Endocrinol (Oxf). 2004;60:322-8.

7. Norman RJ, Masters S, Hague W. Hyperinsulinemia is common in family members of women with polycystic ovary syndrome. Fertil Steril. 1996;66:942-7.

8. Tüttelmann F, Laan M, Grigorova M, er. al. Combined effects of in correlation analysis the variants FSHB-211G>T and FSHR 2039A>G on male reproductive parameters. J Clin Endocrinol Metab. 2012;97:3639–47.

9. Framingham Offspring Study. Fasting plasma homocysteine levels in the insulin resistance syndrome: the Framingham offspring study. Diabetes Care. 2001; 24:1403–10.

10. Sharma L, Dubey A, Gupta P. R, et. al. Androgenetic alopecia and risk of coronary artery disease. Indian Dermatol Online J. 2013;4:283–7.

11. Trüeb R.M. The impact of oxidative stress on hair. Int J Cosmet Sci. 2015;37:2:25-30.

12. Prie BE, Losif L, Tivig I, at. al. Oxidative stress in androgenetic alopecia. J Med Life. 2016;9:79-83.

13. Erdogan K. H. Bulur I, Kocaturk E. et al. The role of oxidative stress in early-onset androgenetic alopecia. J Cosmet Dermatol. 2017;16:527-30.