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Increase in subcutaneous adipose tissue in the frontal scalp may be associated with androgenetic alopecia and metabolic syndrome

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Abstract. – OBJECTIVE: Recent studies have suggested that androgenetic alopecia (AGA) may be associated with other disorders, especially metabolic syndrome (MetS). This study aimed to determine whether a connection exists between MetS and AGA based on the thickness of the subcutaneous adipose tissue in the scalp.

PATIENTS AND METHODS: This cross-sectional study included 34 participants with AGA who had MetS and 33 participants with AGA who did not have MetS. The Hamilton-Norwood scale was employed for classifying AGA and MetS was identified using the US National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III criteria). The body mass index (BMI), blood pressure, and lipid profiles of the participants were assessed. Hepatosteatosis and the thickness of the subcutaneous adipose tissue in the scalp were examined using ultrasonography.

RESULTS: Compared with the control group, the MetS+AGA group had higher BMI (p = 0.011), systolic blood pressure (p < 0.001), diastolic blood pressure (p < 0.001) and waist circumference (p = 0.003). Furthermore, the MetS+AGA group had a higher prevalence of dyslipidemia, hypertension (HT) and diabetes mellitus (DM) and higher rates of grade 6 alopecia than the control group (p = 0.019). Compared with the control group, those with MetS had thicker subcutaneous adipose tissue in the frontal scalp (p = 0.018).

CONCLUSIONS: The subcutaneous adipose tissue in the frontal scalp was thicker in individuals with AGA who had high Hamilton scores. The concomitance of AGA and MetS may be associated with a high increase in subcutaneous adipose tissue and less favorable metabolic parameters.

Key Words:
Androgenetic alopecia, Metabolic syndrome, Subcutaneous adipose tissue in the scalp.

Introduction

In addition to posing numerous risk factors, metabolic syndrome (MetS) is a metabolic disorder that increases the likelihood that diabetes and cardiovascular diseases will develop in the future. Its worldwide prevalence is estimated to be between 20% and 25% in the adult population. Current evidence suggests that MetS prevalence is steadily increasing like an epidemic, posing a growing threat to public health with each passing day[1]. In diagnosing MetS, the US National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III) consensus criteria are most commonly used[2].

Hepatosteatosis is referred to as non-alcoholic fatty liver disease (NAFLD) in the absence of additional factors, such as heavy alcohol consumption, that contribute to secondary hepatic fat buildup. NAFLD is certainly a significant contributor to cryptogenic cirrhosis and may progress to cirrhosis[3].

Androgenetic alopecia (AGA) is the non-scarring progressive miniaturization of the hair follicles, of which the distribution in women and men is generally determined by genetic predisposition[4]. The most common type of hair loss in men is AGA. This condition is characterized by the progressive loss of terminal hairs on the scalp in a specific pattern. The commonly involved locations are the vertex of the scalp, mid-scalp,

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anterior scalp, and temporal scalp. AGA is considered an androgen-dependent trait requiring a genetic predisposition. The interaction between these factors and other mechanisms that remain to be elucidated contributes to follicular miniaturization (the transition of larger, terminal hair fibers to small vellus hair fibers) in susceptible scalp areas. Male AGA often occurs after puberty, a stage associated with a significant increase in androgen production, supporting the idea that androgens play a crucial role in hair growth. The primary androgen responsible for causing and promoting male AGA is dihydrotestosterone (DHT)[5]. In scalp hair follicles, the 5-alpha-reductase enzyme can be found in two isoforms and mediates the conversion of testosterone to DHT: types 1 and 2. Although both isoforms play a role in AGA, the role of the type 2 isoform is greater. The type 2 isoform is found in the epididymis, vas deferens, seminal vesicles, and prostate, in addition to the outer root sheath of hair follicles. The sebaceous glands, epidermal and follicular keratinocytes, dermal papillae cells, and sweat glands all have the type 1 isoform. Intrinsic differences in hormone metabolism and hormone receptors may also contribute to AGA. The balding scalp of young men with AGA contains more androgen receptors and cellular 5-alpha-reductase than the non-balding scalp[6]. Furthermore, the rates of DHT production in men with AGA are higher than in men without this condition[7]. AGA is considered a heritable disorder, a concept supported by the results of familial studies[8,9]. Hair loss in AGA is caused by a shortening of hair follicles' anagen (growth) phase, rather than a complete cessation of hair growth in the affected areas[10]. The shortened anagen phase leads to the production of shorter, thinner vellus hair shafts, a process called follicular miniaturization. Follicular miniaturization is caused by a hormonally mediated process at the dermal papilla level of the hair follicle[11]. DHT binds to the androgen receptor at the cellular level and the hormone-receptor complex stimulates the genes causing the slow shrinkage of large, terminal follicles into smaller follicles with a condensed anagen phase[12,13]. The Hamilton-Norwood scale is used for the classification of AGA. This scale divides the clinical findings into seven stages and offers a visual depiction of the sequential stages of balding. It also describes a less common type A variant of hair loss in which men demonstrate only the progressive movement of the anterior hairline posteriorly.

In obesity-related insulin resistance, central or abdominal obesity, as well as ectopic fat deposition (e.g., in the muscle and liver), is a common condition. There is a relative deficiency of adipose tissue storage space in the usual fat depot sites, resulting in the deposition of fat in the muscle and liver, and abnormal distribution of adipose tissue underlying the development of insulin resistance. However, the exact mechanism is not fully understood. Previous scholars[14] have demonstrated a link between AGA and diseases related to insulin resistance (heart diseases such as myocardial infarction and ischemic heart disease). In a study investigating the relationship between AGA and mortality caused by diabetes mellitus (DM) and heart disease, patients with moderate or severe AGA were found to have a higher risk for mortality caused by DM or heart disease than those without AGA or with mild AGA[15].

In this study, men with AGA aged 18 to 65 years were examined to determine the relationship between the thickness of the subcutaneous adipose tissue in the scalp and MetS, a condition associated with insulin resistance.

Patients and Methods

This cross-sectional study included 67 participants with AGA aged between 18 and 65 years who presented to the Internal Diseases, Endocrinology, and Metabolic Diseases Clinic of Erzurum Ataturk University, Faculty of Medicine, between 2019 and 2020. The participants consisted of 34 male patients who met the MetS criteria and 33 voluntary male participants who did not. The Hamilton-Norwood Classification of Male Balding Scale was employed to classify the participants with regard to AGA. The inclusion criteria for the diagnosis of AGA were as follows: men aged between 18 and 65, a minimum of grade 3 alopecia on the Hamilton-Norwood scale, and the exclusion of other causes of alopecia by a dermatologist. MetS was diagnosed by an endocrinologist if at least three of the following conditions were met: abdominal obesity (waist circumference $\geq$ 102 cm for men), triglyceride $\geq$ 150 mg/dL or taking medication for high triglyceride, HDL cholesterol < 40 mg/dL for men or taking medication for low HDL cholesterol, blood pressure $\geq$ 130/85 mmHg or taking anti-hypertensive medication and fasting plasma glucose $\geq$ 100 mg/dL (5.6 mmol/L) or receiving treatment for high plasma glucose[2,16].

On the other hand, the exclusion criteria were as follows: causes of alopecia other than AGA (cicatricial alopecia, alopecia areata, traction alopecia), familial dyslipidemia, malignancies, autoimmune disease, receipt of corticosteroids and substance or alcohol use.

This study was approved by the Non-invasional Research Ethics Committee of Ataturk University (approval number: B.30.2.ATA.0.01.00/254; Decision: 90/30.05.2019) and written informed consent was obtained from all the participants.

Data Collection

The same author used calibrated devices to measure the height, body weight, and waist circumference of all participants in the study. An electronic scale was employed to measure each participant's weight to the closest 100 g while they were fasting, wearing only light clothing and not wearing shoes. Standing against the wall, height measurements were taken using a stadiometer to the nearest 0.5 cm during deep inspiration. Waist circumference was measured using a tape measure at the level of the umbilicus in a standing position at the end of the expirium. Measurements of the subcutaneous adipose tissue in the scalp and imaging of the liver were performed by the same radiologist. The subcutaneous adipose tissue in the scalp was measured via B-mode ultrasound using the 14-7.2-MHz linear probe of a Toshiba Aplio™ 500 (Tokyo, Japan) ultrasonography device. To prevent compression of the adipose tissue during the ultrasonography (USG) measurement, it was ensured that the probe only contacted the skin without applying pressure. After placing the probe perpendicularly on the skin, the distance between the junction of the skin and adipose tissue and the junction of the adipose tissue and muscle tissue was measured using an electronic caliper. The results were recorded in millimeters (mm). The measurements were taken from the same regions in all patients, from the right temporal region, the frontal region, and the vertex level. Figure 1 presents a sample measurement obtained from a participant.

Statistical Analysis

Statistical analysis was conducted using SPSS version 22 (IBM Corp., Armonk, NY, USA). The conformance of the variable to the normal distribution was evaluated (Kolmogorov-Smirnov) using both analytical and visual techniques, such as histograms and probability graphs. Categorical variables were expressed as frequencies and percentages. The Chi-squared test was employed to determine whether there was any difference between the groups in terms of quality variables. Continuous variables were expressed as mean and standard deviation or median and interquartile range depending on the normality of distribution. To determine whether there was any difference between the groups in terms of numerical variables, independent groups were examined using the *t*-test if parametric test conditions were satisfied, and the Mann-Whitney U test otherwise. Correlation coefficients and their significance were obtained using the Spearman's test in the investigation of relationships between non-normally distributed and/or ordinal variables. The two-tailed *p*-value that was considered statistically significant was < 0.05.

Results

Table I presents certain clinical and demographic characteristics of the participants. Of the 67 patients included in the study, 34 (50.7%) had AGA with MetS and 33 (49.2%) had AGA without MetS. The MetS + AGA group had a mean age of 48.8 ± 7.0 years, whereas the control group had a mean age of 45.3 ± 8.0 years; no statistically significant differences were observed between the groups ($p = 0.058$). The MetS + AGA group had higher body mass index (BMI, $p = 0.011$), systolic blood pressure ($p < 0.001$), diastolic blood pressure ($p < 0.001$), and waist circumference ($p= 0.003$) than the control group. Furthermore, the MetS + AGA group had higher rates of dyslipidemia, hypertension (HT), and DM (Table I).

Compared with the control group, the MetS + AGA group had higher rates of grade 6 alopecia ($p = 0.019$). However, in terms of the rates of grade 3, 4, 5, and 7 alopecia (Table II), no significant difference was observed between the groups.

A comparison was made between the MetS and control groups in terms of the subcutaneous adipose tissue thickness in the right temporal region [median (IQR, interquartile range): 9.5 mm (8-12) and 8 mm (7-11), respectively, $p = 0.162$], in the frontal region [median (IQR): 5 mm (5-7) and 5 mm (4-6), respectively, $p = 0.388$] and at the vertex [median (IQR): 6 mm (5-7) and 6 mm (4.5-6), respectively, $p = 0.420$] and no statistically significant difference was observed (Figure 2).

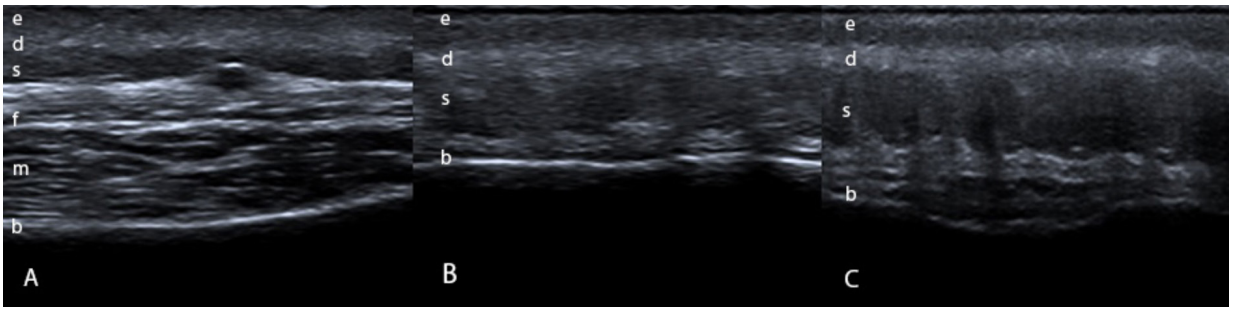

Figure 1. Sample measurement obtained from a participant. **A**, Right temporal; (**B**), frontal; (**C**), vertex; e, epidermis; d, dermis; s, subcutaneous adipose tissue; f, fascia; m, muscle; b, bone.

Table I. Comparison according to the clinical findings and laboratory results.

	Metabolic syndrome (n = 34)	Healthy controls (n = 33)	*p*-value
Age, years	48.8 ± 7.0	45.3 ± 8.0	0.058
Body mass index, kg/m^2	30.1 ± 3.5	27.7 ± 4.0	0.011
Systolic blood pressure, mmHg	140 (127.5-150)	120 (110-130)	< 0.001
Diastolic blood pressure, mmHg	90 (80-90)	70 (70-80)	< 0.001
Fasting blood sugar, mg/dL	94.6 ± 14.3	87.6 ± 9.6	0.132
Waist circumference, cm	106.4 ± 8.1	99.4 ± 10.5	0.003
High-density lipoprotein, mg/dL	39.0 ± 7.1	43.1 ± 8.2	0.096
Triglyceride, mg/dL	197 (128.5-262)	136 (96-187)	0.069
Dyslipidemia, n (%)	17 (50.0)	6 (18.2)	0.006
Hypertension, n (%)	13 (38.2)	2 (6.1)	0.002
Diabetes mellitus, n (%)	26 (76.5)	11 (33.3)	< 0.001
Hepatosteatosis, n (%)	34 (100)	30 (90.9)	0.072
Hamilton-Norwood scale	6.1 ± 1.0	5.5 ± 1.5	0.055
Average scalp subcutaneous adipose tissue thickness, mm	7 (6-8)	6.3 (5.7-7.8)	0.186

Depending on the normality of distribution, continuous variables were expressed as median and interquartile range or mean and standard deviation.

Table II. Comparison of the androgenic alopecia scores between the groups.

Norwood scale, n (%)	Metabolic syndrome (n = 34)	Healthy controls (n = 33)	*p*-value*
Grade 3	1 (2.9)	3 (9.1)	NS
Grade 4	2 (5.9)	7 (21.2)	NS
Grade 5	4 (11.8)	7 (21.2)	NS
Grade 6	12 (35.3)	2 (6.1)	Significant
Grade 7	15 (44.1)	14 (42.4)	NS

NS, non-significant. *A significant difference was observed between the groups ($p = 0.019$). The difference is due to those with grade 6 alopecia (according to the post hoc analysis results).

Using the Spearman correlation analysis, the thickness of the subcutaneous adipose tissue in the frontal region, right temporal region, and vertex of the scalp were compared to the degree of hepatosteatosis. No statistically significant difference was observed (Table III).

The relationship between the grade of alopecia with MetS and related comorbidities was investigated in the study population. No statistically

Table III. Correlation analysis of hepatosteatosis grade with Scalp subcutaneous adipose tissue thickness.

Subcutaneous adipose tissue (mm)	*r* value	*p*-value
Frontal	0.186	0.301
Right temporal	0.220	0.218
Vertex	0.034	0.850

mm; millimeter.

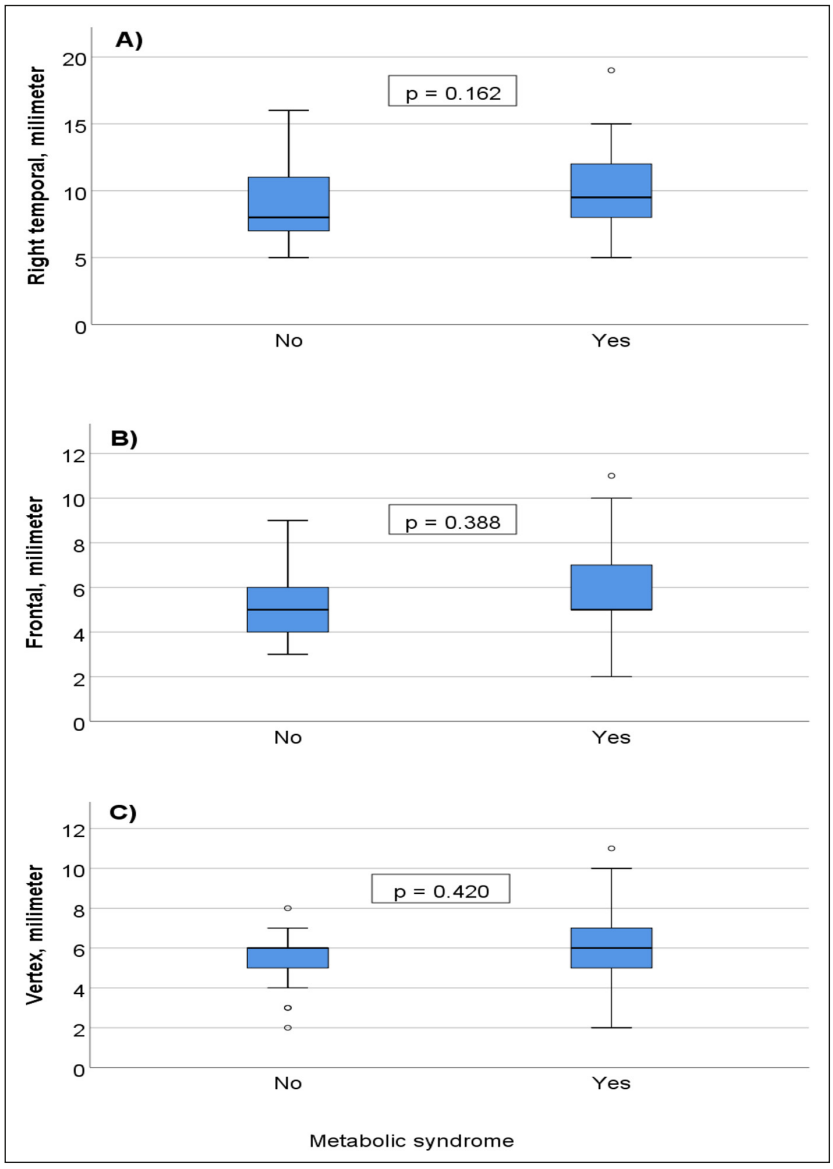

Figure 2. Comparison between the groups with and without MetS in terms of the subcutaneous adipose tissue thickness. **A**, Right temporal, (**B**) frontal, (**C**) vertex.

significant correlation was observed between the grade of alopecia and the frequency of the MetS, hepatosteatosis, DM, or HT (Table IV).

In the evaluation of the cases with the highest score on the Hamilton-Norwood classification of male balding, age was similar between the MetS and control groups ($p = 0.435$). The subcutaneous adipose tissue thickness in the MetS (n = 15) and healthy control (n = 14) groups as measured on ultrasound were respectively 5.7 ± 1.9 and 5.0±1.6 mm at the

Table IV. Association between the severity of alopecia and hepatosteatosis, MetS, T2DM, and high blood pressure.

	Norwood scale Grade 3 (n = 4)	Grade 4 (n = 9)	Grade 5 and above (n = 54)	*p*-value
Metabolic syndrome, yes n (%)	1 (25.0)	2 (22.2)	31 (57.4)	0.084
Diabetes, yes n (%)	2 (50.0)	4 (44.4)	31 (57.4)	0.752
Hypertension, yes n (%)	1 (25.0)	0*	14 (25.9)	0.223
Hepatosteatosis, yes n (%)	4 (100.0)	9 (100.0)	51 (94.4)	0.685

*No positive cases.

Table V. Comparison of age and subcutaneous adipose tissue thicknesses in the scalps of the study population and healthy controls with the highest scores on the Hamilton-Norwood scale.

	Metabolic syndrome (n = 15)	Healthy controls (n = 14)	*p*-value
Age, years	50.3 ± 7.0	48.1 ± 7.9	0.435
Frontal thickness, mm	6.3 ± 1.7	4.9 ± 1.2	0.018
Right temporal thickness, mm	10.3 ± 2.4	10.1 ± 3.0	0.795
Vertex thickness, mm	5.7 ± 1.9	5.0 ± 1.6	0.264
Average thickness, mm	7.4 ± 1.8	6.6 ± 1.4	0.193

vertex, 10.3 ± 2.4 and 10.1 ± 3.0 mm in the right temporal region and 7.4 ± 1.8 and 6.6 ± 1.4 at average values ($p = 0.264$, 0.795 and 0.193, respectively), without statistical significance; contrarily, the subcutaneous adipose tissue thickness in the frontal region was 6.3 ± 1.7 mm in the MetS group and 4.9 ± 1.22 mm in the healthy control group ($p = 0.018$), suggesting a statistically significant difference (Table V).

Discussion

This study examined the potential link between AGA and MetS, the thickness of the subcutaneous adipose tissue in the scalp, and insulin resistance and alopecia severity. The MetS group was found to have higher BMI, blood pressure, and waist circumference than the control group. Furthermore, the MetS group had higher rates of type 2 diabetes mellitus (T2DM). The data were consistent with our assumptions and the literature because MetS is characterized by abdominal obesity, insulin resistance, HT, and dyslipidaemia[17]. In this study, patients with MetS who had high Hamilton scores had significantly thicker subcutaneous adipose tissue in the frontal scalp than the other participants. In our study population consisting of male participants, the mean ages of those with and without MetS were not significantly different. Thus, the age variable was eliminated as a confounding factor in the comparison of the obtained data.

In terms of the Hamilton-Norwood Scale, no significant difference was observed between the MetS and control groups in this study. There are studies[18-21] showing an increased AGA risk in MetS.

Although previous data from the literature focused on the relationship between MetS and AGA, the relationship between alopecia severity (the Hamilton-Norwood scale) and MetS is unclear. Chakrabarty et al[22] reported that AGA severity was not associated with MetS. Contrarily, Agamia et al[21] reported higher rates of MetS in AGA, as well as a correlation between MetS and AGA severity. The effect of androgens plays a dominant role in the pathogenesis of both AGA and MetS and is undoubtedly the strongest link in their relationship. Hyperandrogenism severity is expected to have just as a strong relationship with MetS as with alopecia severity. However, previous literature data and the current results remain insufficient to elucidate the relationship between alopecia severity and MetS.

MetS is known to induce an increase in subcutaneous adipose tissue in the body, the mechanism of which was elevated insulin resistance and inflammation, as has been reported[16,17,23]. A previous meta-analysis[24] reported that AGA was associated with insulin resistance and MetS. Previous literature data indicated that both MetS and AGA induce an increase in subcutaneous adipose tissue through insulin resistance. In this context, the concomitance of MetS and AGA is expected to accelerate the increase in subcutaneous adipose tissue. This study determined that participants with MetS who had high Hamilton scores had significantly thicker subcutaneous adipose tissue in the frontal scalp than the other participants. According to the aforementioned mechanism, an increase in adipose tissue may be an expected finding in the concomitance of MetS and severe AGA. Gopinath et al[20] reported a higher risk for abdominal obesity and low HDL in individuals with AGA than in controls. Yang et al[25] stated that BMI increased as the severity of AGA increased and that early-onset AGA increased the risk of obesity. Previous data from the literature indicated a correlation between AGA and obesity and increased adipose tissue[20,24,25]. In the literature, studies on the increase of subcutaneous adipose tissue in the scalp and AGA are scarce. This study demonstrated that subcutaneous tissue thickness was associated with a high Hamilton score, particularly in the frontal

region. The present data suggest that the measurement of frontal subcutaneous adipose tissue is useful in the evaluation of the metabolic risk of individuals with AGA who had high Hamilton scores. We think that the subject matter can be further explained by future studies that will focus on the relationship between increased subcutaneous adipose tissue in the scalp and the metabolic risk of individuals.

In Western industrialized nations, where the key risk factors for NAFLD, central obesity, T2DM, dyslipidemia, and MetS are prevalent, NAFLD is the most prevalent liver ailment[26]. It has been reported[27] that NAFLD has a worldwide prevalence of 6% to 35% (median 20%). Of the 2,133 subjects from the USA, 30% and 32% who reported moderate and no alcohol intake, respectively, had hepatosteatosis. The prevalence of NAFLD in the Asia-Pacific regions was estimated to range from 5% to 30% depending on the studied population[28]. With rates of 100% in the MetS group and 90.9% in the healthy control group, the rates of hepatosteatosis in this study were significantly higher than those reported in the literature. These rates indicate that the patients in our region need to be screened more thoroughly for hepatosteatosis.

Previous literature data have associated AGA with an elevated risk for cardiovascular disease[29]. In addition, AGA was reported to increase the risk of HT, obesity, dyslipidemia, insulin resistance, and atherosclerosis[30]. MetS is also known to be among the causes of the pathological conditions specified above. This study investigated the effect of concomitant AGA and MetS on metabolic parameters, especially hepatosteatosis and subcutaneous adipose tissue thickness. HT, diabetes, and obesity were more common in the group with concomitant MetS and AGA than in the group with alopecia alone. In addition to these expected results, this study focused on the increase in the subcutaneous adipose tissue in the scalp and the change in the degree of hepatosteatosis. No significant correlation was observed between the concomitance of AGA and MetS, scalp subcutaneous adipose tissue thickness, and hepatosteatosis degree. We think that the relationship between AGA and metabolic disorders such as hyperinsulinemia, insulin resistance, and dyslipidemia, although have been studied in previous research, remains unclear. Prospective studies that will include large populations are warranted to elucidate the subject matter.

Limitations

The first limitation of the study is that it is cross-sectional and single-centered. The absence of data regarding the duration of MetS and dietary characteristics may have influenced the results, particularly those concerning hepatosteatosis and subcutaneous adipose tissue thickness. This study was conducted on a small population and may not be reflective of the entire population.

Conclusions

The results of the present study indicated that HT, obesity, and T2DM are more common in individuals with AGA and MetS than those with AGA alone. The subcutaneous adipose tissue in the frontal scalp was thicker in individuals with AGA who had high Hamilton scores. The association between AGA and MetS may be associated with a higher increase in subcutaneous adipose tissue and more negative metabolic parameters. Future studies are warranted to demonstrate the relationship between the subcutaneous adipose tissue thickness in the frontal scalp and more negative metabolic outcomes.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

R.D researched the data, contributed to the discussion, and wrote the manuscript. A.B, S.C, E.C, F.M, GT, and B.Y E.O conducted the research and contributed to the discussion. İ.C and H.B drafted the manuscript and made critical revisions to the manuscript. T.D contributed to data analysis. All authors read and approved the final manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this article.

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Ethics Approval

This study was approved by the Research Ethics Committee of Medical Faculty, Erzurum Ataturk University (Num-

ber: B.30.2.ATA.0.01.00/254; decision: 90/30.05.2019). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent

Written informed consent was obtained from each patient included in the study.

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