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A Cross-sectional Study of Plasma Trace Elements and Vitamins Content in Androgenetic Alopecia in Men

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Abstract
Androgenetic alopecia (AGA) is the most common variant of male pattern baldness in which occurrence and development of multiple genetic, hormonal, and metabolic factors are involved. We aimed to estimate plasma element content (Mg, Ca, Zn, Cu, Se, Fe), vitamin status (B12, D, E, and folic acid) in patients with AGA using direct colorimetric tests or atomic absorption spectrometry, and the influence of these parameters in the formation of various hair loss patterns. The study included 50 patients with I–IV stages of AGA divided into two groups with normal and high levels of dihydrotestosterone compared with 25 healthy individuals. The presence of two patterns of pathological hair loss in the androgen-dependent (parietal) and androgen-independent (occipital) areas of the scalp was confirmed. It was shown that all patients with AGA have a deficiency of elements (Zn, Cu, Mg, Se) and vitamins (B12, E, D, folic acid). However, the hair loss rate was not due to their content. A positive interrelation between quantitative trichogram parameters in the occipital region and iron metabolism in pairs "hair density vs Fe" and "hair diameter vs ferritin" was shown. In turn, in the parietal region, an inverse correlation of hair diameter with plasma Cu level was found, the most pronouncing in patients with high levels of dihydrotestosterone. The obtained results indicate the importance of multiple micronutrient deficiencies in the AGA occurrence accompanied by the existence of two different hair loss patterns, differently related to the content of certain trace elements and androgens in the blood.

Keywords Androgenic alopecia · Hair loss pattern · Trace elements · Vitamins · Dihydrotestosterone

Introduction

Androgenetic alopecia (AGA), also known as male pattern baldness, is a pathological condition with varying degrees of severity, age of onset, and localization of hair loss [1]. An important role in the development of AGA is attributed to androgen steroid hormones that act directly in the hair follicle and inhibit scalp hair growth but stimulate beard growth. This condition is known as the androgenic paradox [2]. Besides the decrease in the level of sex hormones, the incidence of AGA increases with age and by the age of 80, it can affect 90% of the European population [3]. Based on these findings, suggestions about androgen-dependent and androgen-independent patterns of hair loss with different significance of hormonal factors were made [4]. The fact that the pharmacological modulation of androgen activity in AGA treatment has shown limited effectiveness also indicates a restricted role of androgens in pathological hair loss [5].

In this regard, there is an increasing interest in non-hormonal factors that play a role in AGA pathogenesis and their relationship with hormonal status [6]. In particular, micronutrients (trace elements, vitamins, and essential amino acids), a number of which have shown a positive effect on the growth and strengthening of hair roots capture the attention of researchers [7–11]. The regular use of food supplements, a topical L-carnitine tartrate, zinc, niacin, branched chain amino acids, and biotin treatment, led to a decrease in the rate of hair loss and an increase in the anagen/telogen ratio in individuals with AGA [12]. These data are also supported by studies that demonstrated that the Mediterranean diet—fresh herbs and vegetables—reduces the risk of AGA development in men

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[6], including due to the effect on low-grade inflammation observed in alopecia [13]. Deficiency of micronutrients, such as iron, selenium, zinc, folic acid (FA), and vitamins A, B, C, D, can be a modifiable risk factor associated with the AGA development, prevention, and treatment [14]. The role of micronutrients is also confirmed in our recent study [15]. It was shown that patients with a low level of genetic risk of AGA development have more non-genetic factors involved in the development of alopecia including deficiency of Mg, Cu, Zn, Se, and vitamins D, E, FA, as compared with people with a high level of genetic risk [16]. At the same time, the relationship between the level of androgens and micronutrients in patients with AGA remains unclear.

The aim of the present study was to assess the trace element content and vitamin status in patients with AGA and to define their influence on the formation of androgen-dependent and androgen-independent hair loss patterns.

Materials and Methods

Patients

In a case-control study, fifty patients with AGA and a control group of healthy volunteers ($n = 25$) aged 18 to 55 (26.2 ± 5.3) years and body mass index from 19 to 25 were recruited. All individuals included in the study provided written informed consent to participate in the research. The study was carried out in accordance with the rules of the Helsinki Declaration of 1975 [17] and its later amendment. The protocol was approved by the Local Ethics Committee of the State Research Center of Dermatovenereology and Cosmetology (protocol no. 7, 10/31/2017) and complies with the standards of good clinical practice and evidence-based medicine.

Patients had the early stages (1–4) of AGA according to the Norwood-Hamilton scale. There are seven stages of male pattern baldness based on this scale: from minimal or no recession of the hairline (stage 1) to the most severe stage when only a band of hair going around the sides of the head remains (stage 7) [18–20]. At stage 4, "the frontotemporal recession is more severe than in type III and there is sparse hair or no hair on the vertex. The two areas of hair loss are separated by a band of moderately dense hair that extends across the top. This band connects with the fully haired fringe on the sides of the scalp [18].

All participants had a constant lifestyle and food consumption patterns within 3 months before and during the study. Exclusion criteria used to select subjects for participation were smoking; presence of skin diseases in the acute stage; gastrointestinal tract diseases; a history of mental illness; alcohol or drug addiction; presence of other acute or chronic inflammations; presence of endocrine diseases—patients were examined in order to exclude the presence of thyroid diseases, diabetes mellitus, obesity, etc.; vitamin, mineral and other dietary supplements/drugs taken for any reason, within 3 months before the study. Additional exclusion criteria for a group of patients with AGA were other forms of alopecia and hair loss as a complication of another pathological condition. Based on the results of the androgens level analysis (see below), this group (total group) was further divided into subgroups with normal and elevated levels of dihydrotestosterone (DHT). Inclusion criteria in the control group were as follows: normal trichogram (hair density more than 250/cm^2, hair diameter more than 54 μm, no more than 10% of hair in telogen), absence (at the time of the study) of pronounced signs or documented diseases, and absence of clinical signs of alopecia in parents and close relatives. The additional inclusion criterion was the normal level of androgens (dihydrotestosterone) in the range of 250–990 pg/ml. Patients were examined by a dermatologist, trichologist, and andrologist, and in case of abnormalities in blood tests, they were additionally examined by a general practitioner, endocrinologist, and urologist. However, these patients were not included in the study.

Trichographic Analysis

The quantitative characteristics of hair were assessed with trichogram and phototrichogram data using an Aramo SG micro camera (Aram HUVIS Co. Ltd., Republic of Korea). The images obtained were processed by the professional software Trichoscience PRO v. 1.4 (Russia). The number of hairs was determined in 0.1 ± 0.004 cm^2 areas in the androgen-dependent (parietal) and androgen-independent (occipital) zones using a × 60 lens. The diameter of the hair was measured using a × 200 lens. Before performing a phototrichogram, the hair was cut to a length of 0.2–0.3 mm in areas of 8–10 mm^2 and 48 h later, a black Igora Bonacrom colorant (Schwartzkopf, Germany) was applied. The dye was washed off after a 10-min exposure and the stained zones were analyzed using a × 60 lens. The calculation of the number of hairs per 1 cm^2 (hair density) was performed out automatically.

Analysis of Hormones, Vitamins, and Minerals

Five milliliters of blood was drawn in Vacutainer tubes with 0.5M EDTA. Plasma was separated by centrifugation at 3000*g* for 10 min and used for further analysis. Plasma DHT levels were determined by enzyme-linked immunosorbent assay using a Multiskan Ascent microplate photometer (ThermoScientific, USA) and reagent kits manufactured by DRG Instruments GMbH (Germany).

The concentration of elements (Mg, Ca, Zn, Cu, Fe) as well as iron-binding protein ferritin in plasma was assessed using direct colorimetric tests using a KONELAB 20XTi biochemical analyzer (ThermoScientific, USA), ferritin kit (22934,

BioSystems, Spain), and respective controls. Copper Assay Kit based on the 3,5-DiBr-PAESA method without deproteinization—for Cu (with sensitivity 0.5 μmol/L); Zinc Assay Kit based on the 5-Br-PAPS method—for Zn (0.6–306 μmol/L); Magnesium Assay Kit based on the Xylidyl Blue-I method for Mg; Calcium Assay Kit based on the cresolphthalein complexone method—for Ca (Sentinel, Italy); and Iron B Chromazurol Assay Kit (BioSystems, Spain) were used for analysis. Laboratory quality control was performed using certified reference material of human serum (Clin Chem Control 1, №16150, Clin Chem Control 2, №16250, Sentinel, Italy)

For estimation of Se level, flame atomic absorption spectrometry (FAAS) using the AA-7000 platform (Shimadzu, Japan) was used according to the manufacturer's instructions. One hundred microliters of sample was prepared according to Subramanian et al. [21] by acidic digestion (6 M HCl) and subsequence dissolving in 0.1 M HNO_3. Laboratory quality control was performed using certified reference material of human serum (Seronorm Trace Elements, Serum Level 1, 0903106, Sero AS, Norway). The results obtained from the certified reference material used were compared with the certified values for estimating the accuracy (recovery rates) and precision (expressed as the relative standard deviation). The atomic absorption signal was shown by the peak area viewed in the calibration curve. The detection limit for each metal was calculated as 3 × standard deviation of the mean of the 10 blanks determinations. The recovery rate for the studied element varied in a range of 90–106%. The relative standard deviation was less than 20%.

The concentration of vitamin D (in the form of 25 (OH)-D3) was determined by enzyme-linked immunosorbent assay and immunoluminescent analysis, as well as high-performance liquid chromatography-mass spectrometry at EVOQ TQ MS with an electrospray ionization (ESI) probe (BrukerDaltonics GmbH, Germany) for vitamin B12, E, and FA in accordance with the manufacturer's instructions. Water-soluble and fat-soluble vitamins were analyzed using two separate chromatography methods both employing an ACE 3 C18, 100 × 2.1 mm column (Advanced Chromatography Technologies Ltd, Aberdeen, Scotland). Water-soluble vitamin LC-MS method: 15 mM formic acid, adjusted to pH 3.8 with ammonia (phase A) and MeOH (phase B), with flow rate of 0.4 mL/min in ESI positive mode. B gradient of 0 min, 1% B; 3 min, 25%; 6 min, 50%; 7 min, 1%; 9 min, 1%. Fat-soluble vitamin LC-MS method: isocratic method consisting of 100% MeOH/MeCN (90:10 v/v), with flow rate 1 mL/min for 8 min.

Statistical Analysis

The data obtained were processed using the statistical software package STATISTICA 13.0 (StatSoftInc., USA) [22]. Group-by-group comparison of data was evaluated using the Mann-Wintney *U* test. Differences between groups were considered statistically significant at $p < 0.05$. The Spearman correlation analysis was performed to reveal the interrelation between the levels of the micronutrients and the trichogram parameters. The contribution of the studied parameters to the patterns of hair loss was assessed by a factor analysis application.

Results

The Content of Trace Elements and Vitamins in Healthy Individuals and Patients with AGA, Including Those with Normal and Elevated Levels of DHT

Given the level of DHT, all patients with AGA were divided into subgroups with an increased ($n = 19$) and normal ($n = 31$) content of this hormone (Table 1).

As it is seen from the data presented in Table 1, patients with AGA had different quantitative characteristics of the scalp hair: 37% decrease in hair density and 30% fall in average hair diameter in comparison with control values were found in the parietal region. The respective parameters were 21 and 10% lower in the occipital zone. This trend continued in the subgroups with elevated and normal levels of DHT. At the same time, there were no differences between the subgroups in the studied trichogram parameters.

The content of elements and vitamins in plasma was compared between total group of patients with AGA, subgroups with normal and elevated levels of DHT, and healthy controls (Table 2). The data obtained showed that patients with AGA had higher levels of DHT on average by 22.1% ($p = 0.029$) as compared with healthy controls. Patients with AGA, regardless of the level of DHT, were characterized by a multiple deficiency of trace elements, metals, and vitamins in comparison with healthy individuals. In particular, zinc content was reduced by 21.4% ($p = 0.003$), copper by 42.1% ($p < 0.001$), magnesium by 10% ($p = 0.005$), selenium by 30% ($p = 0.002$), vitamin B12 by 15.5% ($p = 0.012$), and vitamin D by 53.3% ($p < 0.001$). However, no significant differences in trace elements and vitamins were detected between groups with normal and elevated DHT levels. The only exception was a difference in FA levels, which was reduced in patients with AGA—and more pronounced decrease was in patients with elevated levels of DHT by 66% ($p = 0.034$) versus 39% ($p = 0.047$) in a subgroup with a normal level of DHT compared with the controls. There was no significant difference in Ca, Fe, and ferritin content among all the groups studied, including the control one.

Table 1 Trichogram data of patients with AGA with elevated and normal levels of DHT

Parameter	Healthy controls (n = 25)	Androgenic alopecia		
		Total (n = 50)	Normal DHT level (n = 31)	Elevated DHT level (n = 19)
Hair density (number of hairs per cm^2) in parietal region	298 (285–310)	188 (150–201)[a]	181 (149–201)[b]	192 (181–205)[c]
Hair density (number of hairs per cm^2) in occipital region	320 (315–350)	252 (206–264.5)[a]	255 (204–264)[b]	229 (210–267)[c]
Average hair diameter (μm) in parietal region	60 (58–61)	42 (39–45)[a]	42 (38–45)[b]	41.5 (41–44)[c]
Average hair diameter (μm) in occipital region	62 (61–63)	56 (54–58)[a]	56 (54–58)[b]	55.5 (54–59)[c]

Data expressed as median (25–75)

[a] $p < 0.05$ when total population with AGA and control group are compared

[b] $p < 0.05$ when patients with AGA and normal DHT level and control group are compared

[c] $p < 0.05$ when patients with AGA and elevated DHT level and control group are compared

Association Between the Trichogram Parameters and the Content of Trace Elements and Vitamins in Patients with AGA

Surprisingly, despite of explicit differences in the content of Zn, Mg, Se, vitamins B12, E, D, and FA between the total group and healthy controls, none of these micronutrients showed a correlation with the severity of hair loss process, estimated by trichogram data and the corresponding AGA progression from I to IV stages according to Norwood-Hamilton scale.

In contrast, parameters of iron metabolism (Fe and ferritin), which were non-significant when distinguishing between individuals with AGA and controls, showed a positive correlation with some parameters of the trichogram. In particular, a positive correlation between "hair density–Fe" ($r = 0.36$; $p < 0.05$) (Fig. 1) and "hair diameter–ferritin" ($r = 0.39$; $p < 0.05$) (Fig. 2) in all patients with AGA in the hormone-insensitive (occipital) region was revealed. Both parameters of iron metabolism were also positively correlated with each other ($r = 0.37$; $p < 0.05$) and, in addition, with the content of FA ($r = 0.40$; $p < 0.05$ for Fe and $r = 0.32$, $p < 0.05$ for ferritin). This fact indirectly indicates a higher significance of the described effect in the subgroup with the normal content of DHT, since there was a negative correlation between FA and the level of DHT ($r = -0.43$, $p < 0.05$). However, the dependence of

Table 2 Plasma trace elements, metals, and vitamins in AGA patients with elevated and normal levels of DHT

Parameter	Healthy controls (n = 25)	Androgenic alopecia		
		Total (n = 50)	Normal DHT level (n = 31)	Elevated DHT level (n = 19)
Dihydrotestosterone, pg/mL	632.2 (547.1–742.5)	771.7 (541–1413.4)[a]	589.9 (491.7–718)	1575 (1166.7–2347)[cd]
Zn, μmol/L	14 (12–15)	11 (9–14)[a]	11.5 (9–14) [b]	10.6 (9–13.9)[c]
Cu, μmol/L	19 (17–20)	11 (9.9–13.3)[a]	10.2 (9.3–13) [b]	11.5 (10–13.4)[c]
Mg, mmol/L	1 (0.9–1)	0.9 (0.8–1)[a]	0.8 (0.7–1) [b]	0.9 (0.8–1)[c]
Ca, mmol/L	2.4 (2.3–2.5)	2.4 (2.3–2.5)	2.3 (2.3–2.4)	2.4 (2.4–2,5)[cd]
Fe, μmol/L	26 (19–28)	21.4 (18–28.6)	22.7 (18–29)	20.6 (15.5–25)
Ferritin, ng/mL	198 (125–265)	160 (98–230)	168.5 (98–285)	153 (76.9–200)
Se, μmol/L	1 (0.9–1)	0.7 (0.5–1)[a]	0.7 (0.6–1)[b]	0.6 (0.5–1)[c]
Vitamin B12, pg/mL	369 (290–741)	312 (199–403)[a]	315 (200–403)[b]	294 (165–409)[c]
Vitamin E, μg/mL	9 (8–13)	5.4 (4–10.5)[a]	6.5 (4.9–11)[b]	4.2 (4–10)[c]
Vitamin D, ng/mL	45 (35–59)	21 (19–35)[a]	20.5 (18–32)[b]	24 (19–37.8)[c]
Folic acid, ng/mL	10 (9–12)	4.7 (3–9)[a]	6.1 (3–11)[b]	3.4 (3–6)[cd]

Data expressed as median (25–75)

[a] $p < 0.05$ when total population with AGA and control group are compared

[b] $p < 0.05$ when patients with AGA and normal DHT level and control group are compared

[c] $p < 0.05$ when patients with AGA and elevated DHT level and control group are compared

[d] $p < 0.05$ when patients with normal and elevated DHT level are compared

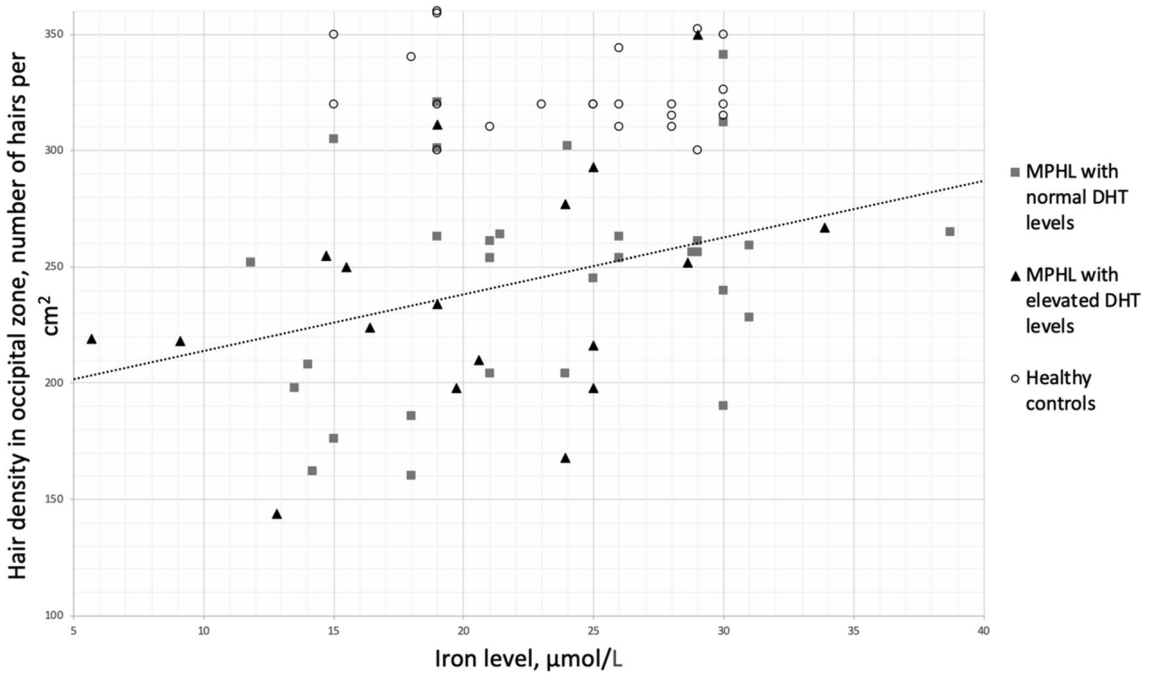

Fig. 1 Relationship between the level of iron and the hair density in the occipital region

trichogram parameters on the content of Fe and ferritin was significant in both subgroups regardless of the level of DHT, which indicates the universal role of Fe and ferritin in hair growth in the occipital region.

In turn, for some characteristics of the trichogram (primarily the hair diameter), the relationship with the plasma Cu content in the androgen-dependent (parietal) region was shown. It is notable that in the entire analyzed sample, the relationship between the Cu content and hair diameter was positive ($r = 0.44$; $p < 0.05$), i.e., more copper means thicker hair. In the case of AGA, this relationship was inverted and became negative ($r = -0.391$; $p < 0.05$), i.e., more copper means thinner hair. This inversion was most pronounced in patients with elevated levels of DHT ($r = -0.65$; $p < 0.05$)

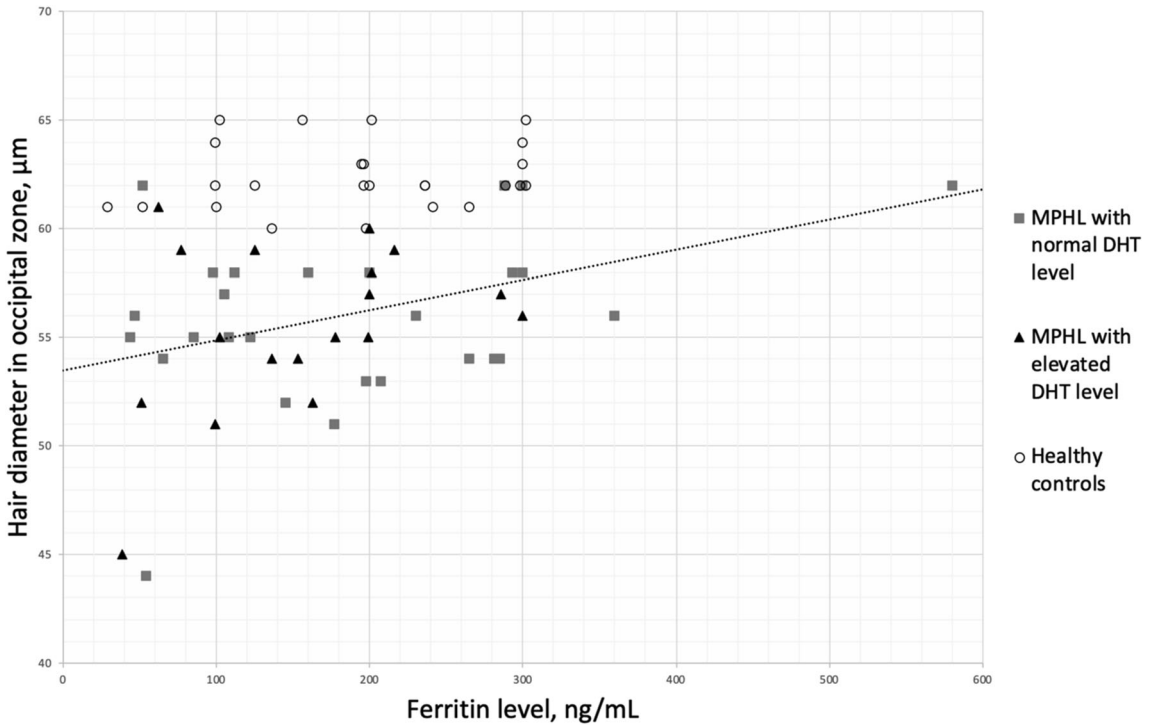

Fig. 2 Relationship between the level of ferritin and hair diameter in the occipital region

(Fig. 3) with a negative but less significant coefficient in the subgroup with a normal level of DHT ($r = -0.29$; $p < 0.05$).

Identification of Hair Loss Patterns Depending on the Hormones, Trace Elements, and Vitamin Content in Patients with AGA

The application of factor analysis to all the data obtained allowed to identify two main clinical and laboratory patterns of hair loss in the occipital and parietal regions in patients with AGA.

The first of them with an eigenvalue of more than 3.0 which explains 12.17% of the variance was described as a "pattern of hair loss in the occipital region" (factor 1) (Fig. 4a). The greatest contribution to pattern formation estimated by the values of factor loading was due to the corresponding parameters of the trichogram (hair density and hair diameter in the occipital region), the content of Fe, ferritin, and FA. At the same time, it was inversely related to DHT—the factor loading of (minus) − 0.524—which characterizes this pattern as androgen-independent.

The second relevance factor (the eigenvalue is more than 2.5; the percentage of explained variance is 10.35%) was the "pattern of hair loss in the parietal region" (factor 2). Factor analysis showed positive loadings for multiple parameters of trichogram, mainly in the parietal region, as well as a small but positive loading for DHT level (0.105). The most significant negative value (− 0.683) was shown for Cu (Fig. 4b).

Discussion

The results of the study showed that the occurrence and progression of AGA happen together with a multiple deficiency of such elements and vitamins like zinc, copper, magnesium, selenium, vitamins B12, E, D, and FA. Consequently, the quantity and quality of human hair are closely related to the nutritional factor, since metabolism in tissues with high biosynthetic activity, such as the hair follicle, requires adequate accessibility of both substrates and trace elements and vitamins [23, 24]. Obesity is an important condition with the micronutrient deficiency and possible cause of hair loss may be due to an increased fat deposition, inadequate intake relative to body mass, decreased bioavailability or impaired metabolism of micronutrients [25, 26]. At the same time, some studies indicate that even normal-weight people may have deficiency, most probably because of an unbalanced diet [26]. In addition to dietary factors, the causes of a decrease in the level of trace elements and metals in AGA can be environmental pollution, psycho-emotional stress, and depression [27, 28]. This statement is confirmed by the study of Iyanda et al. which showed a decrease in serum zinc, copper, selenium, manganese, and magnesium levels in AGA in smokers [29]; a decrease in serum Zn levels and the development of its extracellular dyshomeostasis under psychological stress [30]; and the correlation of severity and prognosis of depression with trace elements imbalance [31].

We clarified the importance of trace elements, metals, and vitamin deficiency in the formation of two hair loss patterns in

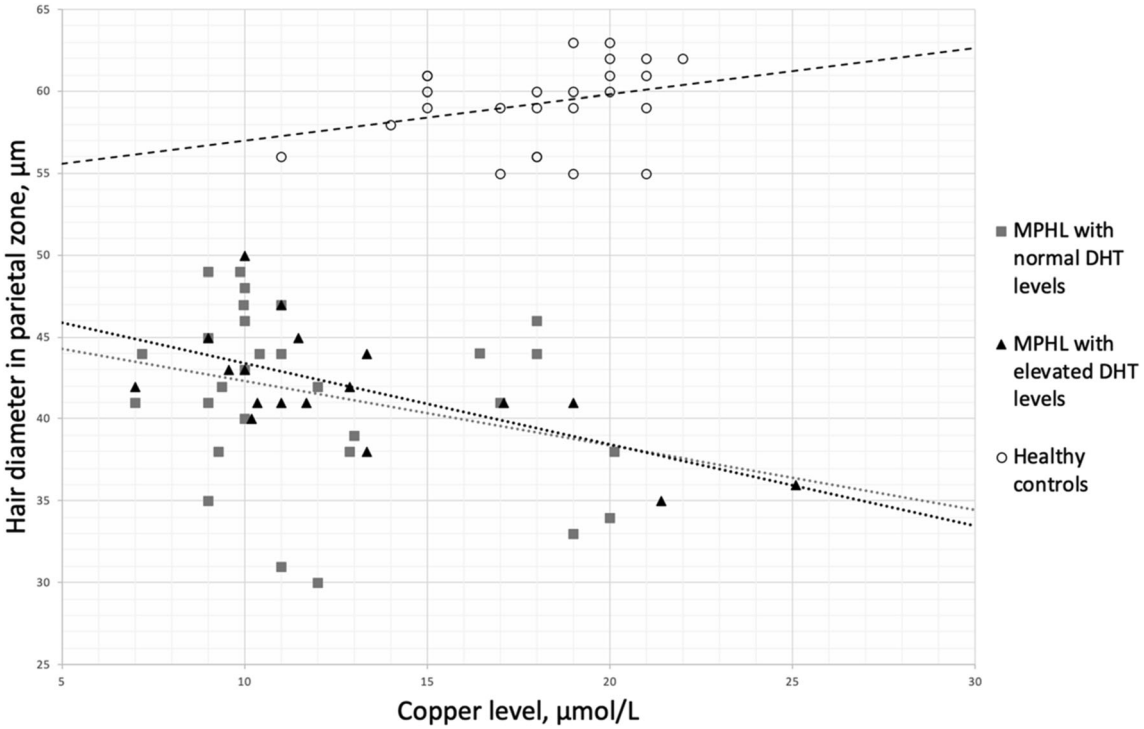

Fig. 3 The relationship between the level of copper and the diameter of the hair in the parietal zone

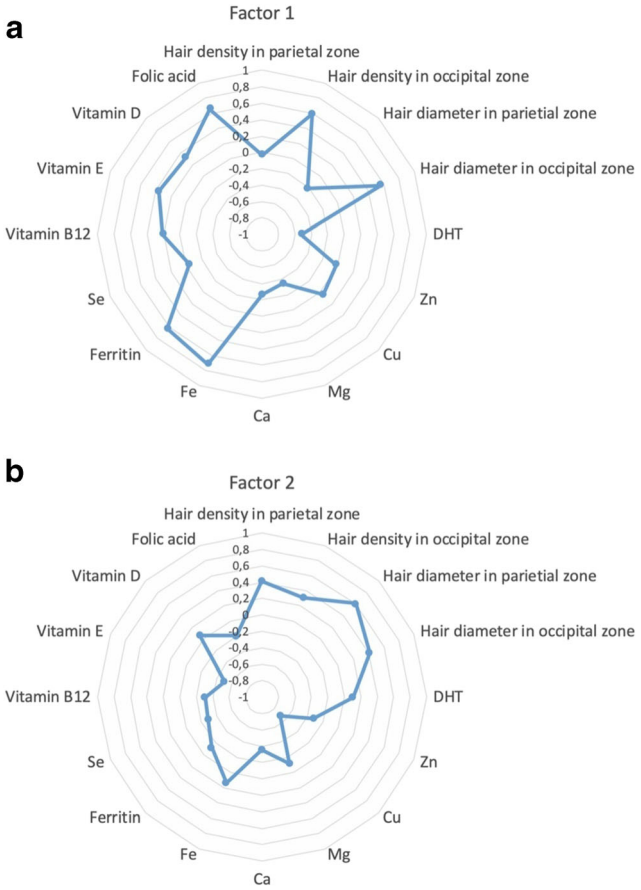

Fig. 4 Diagram showing the contribution of various parameters to hair loss patterns in patients with AGA. (a) Factor 1—pattern of hair loss in the occipital region. (b) Factor 2—pattern of hair loss in the parietal region

AGA corresponding to androgen-dependent and androgen-independent types of baldness. It is believed that the androgen-dependent type of hair loss is directly related to the effect of DHT, the number, distribution of receptors, and the presence of a genetic predisposition [1]. In turn, according to another hypothesis, the androgen-independent pattern of hair loss may be associated with inflammation due to chronic scalp tension transmitted from the galea aponeurotica and deficiency of essential trace elements and vitamins [32].

The results of a factor analysis confirmed this concept showing the greatest contribution of Fe, ferritin, and FA to the hair loss in the androgen-independent occipital region. At the same time, the role of some trace elements turned out to be significant for hair loss mainly in the androgen-dependent parietal region, where the quantitative trichogram parameters were inversely related to the copper level. This fact confirms the assumption that there are more complex mechanisms for the development of this condition with a significant role of non-hormonal factors acting in combination with hormonal and genetic risk factors which, however, requires further study [33–35].

Iron and ferritin are considered as significant factors in AGA in a large number of studies. Kantor et al. show that the average serum ferritin concentration in patients with AGA was significantly lower compared with the control (23.8 versus 62.3 ng/ml, respectively) [36]. Shetty et al. indicated a correlation between blood ferritin and telogen effluvium, female pattern hair loss, and alopecia areata [37]. Ullah et al. revealed an association between low serum ferritin and telogen effluvium [38]. Possible mechanisms for the participation of iron in the AGA pathogenesis include limitation of the availability of both the iron-dependent cofactor ribonucleotide reductase (an enzyme restricts the rate of DNA synthesis and, consequently, the proliferation of cells) and iron-dependent coenzymes of stearyl coenzyme A desaturase which provides the formation of polyene fatty acids necessary for adequate transmembrane transport and cells response to regulatory molecules [36]. Since the cells of the hair follicle matrix are one of the fastest dividing cells in the body, they can be extremely sensitive even to a slight decrease in Fe availability which leads to decrease in hair growth in the presence of Fe deficiency [39].

FA was another factor significant for determining the quantitative parameters of trichogram in the androgen-independent occipital region. Its correlation with the Fe and ferritin content can be partially determined by their joint participation in the process of hematopoiesis and oxygen access to the hair follicles [40]. Another mechanism that implements the improvement of the oxygen supply to the hair follicle by FA and its active metabolite 5-methyltetrahydrofolate may be an improvement in the bioavailability of nitric oxide by increasing the activity of endothelial nitric-oxide synthase and nitric oxide production [41]. Direct removal of superoxide radicals, which ultimately improves blood supply and, consequently, the oxygen supply of tissues with high activity, is also possible [41].

Other processes which are significant for the development of the hair follicle and require the participation of FA are DNA replication [42] and activation of poly (ADP-ribose) polymerase (PARP), which is a single-strand break DNA repair enzyme [43].

The third probable mechanism of folate involvement in the AGA pathogenesis is the direct and indirect antioxidant action of FA and its active form [44]. In the fetal undifferentiated cell model, the use of FA reduced the level of mitochondrial reactive oxygen species (ROS), affected the genes that regulate the morphology and activity of mitochondria, and increased ATP formation [45]. The latter circumstance may also explain the more pronounced FA deficiency in AGA patients with elevated levels of DHT, since the effect of DHT can be blocked by antioxidants due to a decrease in the production of ROS-mediated synthesis of TGF-β1 [46]. According to current beliefs, androgens stimulate the secretion of hair growth–inhibiting factors, such as transforming growth factor-beta 1 and 2 (TGF-β1/β2) and dickkopf 1 (DKK-1) in AGA [47, 48].

Copper is also considered to be an important factor in the development of AGA [49]. Moreover, the role of copper shown in this work is rather ambiguous. We found that besides copper deficiency in patients with AGA, an inverse relationship between the quantitative trichogram parameters and Cu content was present. Two correlations characterized this effect: a positive dependence was found in healthy individuals (more copper–thicker hair), while in patients with AGA, this relationship was negative (more copper–thinner hair); this inversion was most pronounced in patients with increased levels of DHT. There is no unambiguous explanation for this paradox. However, the fact that copper plays an important role in redox systems [50] and oxidative stress as one of the causes of hair loss has been proven by many studies [51, 52] allows to explain this paradox by an imbalance in the prooxidant/antioxidant processes. In healthy individuals, where the level of free radical processes is at the physiological level, Cu develops its positive effect. In AGA with an increased DHT, the prooxidant effect of copper is embodied. Being a chemical element with a variable valency, it can lead to the formation of ROS, especially under the condition with the deficiency of TE and vitamins with antioxidant activity [53].

Vitamin D is essential for hair growth and exerts its effects by binding to a nuclear vitamin D receptor [54]. However, data about serum vitamin D levels and a receptor action in the AGA development are still contradictory and insufficient [54–56]. In our study in patients with AGA, decreased vitamin D levels regardless of DHT levels were found. This result corresponds to a systematic review and meta-analysis data showed that vitamin D deficiency was widespread among patients with alopecia—but there was no association between a blood 25(OH)D level and the degree of hair loss [57]. In another study, Sanke et al. revealed that low levels of vitamin D were correlated with the AGA severity [58]. Selenium is another important TE which provides a strong antioxidant effect and is present in selenoproteins (glutathione peroxidase, selenoprotein P, MSRB1, deiodinases, etc.) in the form of selenocysteine [59, 60]. Low Se levels may be associated with oxidative stress and damage, and interruption of hair growth cycles [61]. Some studies indicate the presence of Se deficiency combined with Fe, Zn, and vitamins in individuals with hair loss that is in agreement with the obtained data [62, 63]. However, despite an almost 50% decrease in serum levels, factor analysis did not reveal a significant contribution of vitamin D and Se in AGA development. So large-scale studies are required for the final solution of this issue.

In conclusion, it should be noted that this study develops and complements the idea of the pathogenetic significance of the metabolic pathways in the hair follicle, due primarily to the body's supply with essential nutritional factors: TE, vitamins, and essential amino acids. Consequently, monitoring of micronutrient level before the treatment and their early correction in addition to pharmacotherapy is a necessary step in the management of this condition. The presence of various patterns of hair loss requires more in-depth studies to develop more effective and personalized prevention and conservative AGA treatment strategies, which implies only two FDA-approved medications: the potassium channel opener minoxidil and the DHT synthesis inhibitor finasteride.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest

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