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Evaluation of Serum Zinc Level in Patients with Pattern Hair Loss (A Case-Controlled Study)

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ABSTRACT
Background: Although androgenetic alopecia affects both males and females, trace elements may play as crucial impact.
Objectives: To evaluate serum zinc in patients with pattern hair loss (PHL) and to compare the findings with normal controls.
Patients and Methods: This study is a cross sectional observational case control study conducted at outpatient clinic of Dermatology, Andrology and STDs Department, Mansoura University hospital in the period between May 2022 and May 2023. The study included 100 subjects, divided into two groups: the first consisted of 50 patients (Male and female) with pattern hair loss and the second was 50 subjects (control group). The serum zinc assay was done for all participants.
Results: The mean serum zinc level in the cases group was 75.36±19.29 and 71.73±20.19 in the control group, with no statistically significant difference between the two groups (p= 0.360). Low zinc levels were found in 56% of cases and 60% of controls, with no significant difference between the two groups (p= 0.685). There was no significant variation in serum zinc levels across the different degrees of hair loss in either male or female patients. The best cutoff point of serum zinc level to identify patients with PHL was less than 68.85. This value showed mild sensitivity and specificity with no significant value (p= 0.261). **Conclusion:** Zinc deficiency cannot be viewed as a direct etiologic component in the development of androgenic alopecia and not all androgenic alopecia patients may benefit from obtaining nutritional supplements. There is disagreement on the function of supplementing with zinc.
Keywords: Androgenetic alopecia, Zinc.

INTRODUCTION

A distinctive distribution of follicular miniaturisation to vellus hair fibres on the scalp and a progressive loss of terminal hair are the hallmarks of PHL, a nonscarring type of hair loss [1]. About 30 million women and 50 million men in the US suffer from female pattern hair loss (FPHL) and male pattern hair loss (MPHL) accordingly [2]. There is a 50% probability of development of MPHL in males over 50, while around 40% of women acquire FPHL by the age of 50 [3].

The three primary phases of the hair follicle cycle are traditionally referred to as anagen, which is active hair growth, catagen, which is hair growth halt, and telogen, which is follicular rest [4].

But in MPHL and FPHL, this cycle's anagen phase gets smaller with each cycle, while the telogen phase stays the same or even gets longer. This results in smaller follicles and less hair growth [5]. Hair eventually thins and becomes too short to successfully project through the scalp's surface, leaving an empty follicular pore as a result of the gradual reduction in the anagen phase and the early transition from the anagen to the catagen phase [6].

The only recognised therapies for MPHL and FPHL approved by the Food and Drug Administration are topical minoxidil and oral finasteride [7]. Other treatment options may include low-dose oral minoxidil, low-level laser therapy and PRP therapy [8]. Nevertheless, a variety of adverse effects of these treatments significantly affect how well patients comply with their treatment [9].

Zinc is a crucial trace element that is involved in many biological processes, such as the creation of DNA, the expression of genes, the regulation of hormones, enzymatic activities, and cell division [10]. Zinc has a strong anti-regression effect on hair follicles and speeds up their recovery in relation to hair loss. More precisely, acrodermatitis enteropathica, which causes hair loss, is mostly caused by temporary zinc insufficiency [11].

The purpose of this study was to compare blood zinc levels in individuals with PHL to normal controls.

PATIENTS AND METHODS

This study is a cross sectional observational case control study conducted at outpatient clinic of Dermatology, Andrology and STDs Department, Mansoura University Hospital in the period between May 2022 and May 2023. The study included 100 subjects into two groups: the first consisted of 50 patients (Male and female) with PHL and the second was 50 subjects (control group).

The required sample size was calculated using the IBMª SPSSª Sample Powerª version 3.0.1 (IBMª Corp., Armonk, NY, USA). With considering serum zinc level as the main outcome, based on intensive literature review, the mean serum zinc level in the control group was 128.4 µg/dl (SD 41.4) in the study conducted by **Dhaher *et al.*** [12] versus 56.6 µg/dl (SD 14.2) in the AGA group. This difference between the groups was taken for calculating the

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sample size. At 95% level of significance and power of 80%, the minimal required sample size calculated was at least 36 in each group.

Exclusion criteria included individuals with serious health issues, such as heart and kidney disorders. Symptoms of zinc deficiency as chronic diarrhea, changes in their nails, loss of appetite and impotence must be also excluded.

Clinical confirmation of the PHL diagnosis was obtained based on the following factors: A negative hair pull test, slow development of hair loss at the fronto-vertical site, visual confirmation of short, thin hairs present in the vertex, and confirmation by dermoscopic examination: More miniaturised thin vellus hairs, particularly in the frontoparietal region, and a greater preponderance of single hair pilosebaceous units in the frontal area as opposed to the occipital area are associated with a shift in hair shaft diameter diversity of more than 20%. All the participants provided details of their name, age, sex, duration of the lesion, progression of the lesion, previous medication or intervention, symptoms of zinc deficiency as chronic diarrhea, changes in their nails, loss of appetite and impotence, family history of similar conditions.

Clinical assessment of individuals to look for indications of chronic illnesses: Assessment of the patients was conducted by clinical photographs using a digital camera, dermoscopy and patient-self assessment scores.

We used Hamilton-Norwood scale to categorize male PHL. The scale splits clinical data into seven stages and provides a visual representation of balding progression. A type of hair loss in which men only show a gradual shift of the hairline from the front to the back [13].

Also, Sinclair scale is used for FPHL. In which FPHL is divided into four levels of intensity on the basis of normal scalp which consider grade 1 [14].

The KONELAB 20XTi biochemical analyzer (Thermo Scientific, USA) was utilised to assess the amounts of serum zinc by direct colorimetric assays. The standard range for serum zinc is between 70 and 150 µg/dL. Following a 12-hour fast, 5 millilitres of venous blood—free of anticoagulant—were drawn from each participant in a plain tube. The samples were allowed to coagulate for thirty minutes at room temperature, after which they were centrifuged for fifteen minutes at 250 g. The resulting serum was then kept at -20°C until analysis.

Ethical approval:

Mansoura Medical Ethics Committee of Faculty of Medicine gave its approval to this study on 31/08/2022. Its approval code is MS.22.07.2076. All participants gave written consent after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis: Using SPSS V. 22.0 for Windows®, the gathered data were coded, processed, and examined. Using the Shapiro Wilk test, data were examined for normal distribution. Relative percentages and frequencies were used to display the qualitative data. The difference between the qualitative variables was calculated using the Chi square test (χ^2). Quantitative data were presented as mean ± standard deviation (SD), median, and range. For regularly distributed quantitative variables (parametric data), the independent samples t-test was employed for comparison between two independent groups; for non-normally distributed data (non-parametric data), the Mann-Whitney U test was utilised. The relationship between quantitative data for more than two groups was evaluated using analysis of variance (ANOVA). When it is equal to or less than 0.05, a significant p-value is taken into account.

RESULTS

The mean age of the cases group was 32.40 ± 10.44 years and the mean age in the control group was 34.98 ± 9.53 years with no significant difference between the two groups (p= 0.223). There was higher prevalence of female gender in the control group compared to the cases group (80% versus 62% respectively) with no significant difference between the two groups (p= 0.047). There was no significant difference between the two groups regarding the height, weight, BMI and the marital status. The mean BMI was 28.87 ± 5.63 kg/m2 and 29.97 ± 5.29 kg/m2 in the cases and the control group respectively. The mean disease duration in the cases group was 3.5 ± 2.94 years and the median age was 2 years with rage between 6 months and 10 years (Table 1).

Table (1): Demographic data analysis for the two study groups

	Groups				**Test of significance**
	Cases group (N=50)		**Control group (N=50)**		
Age (years)	32.40 ± 10.44		34.98 ± 9.53		t= - 1.225 p = 0.223
Sex					
Male	19	38%	10	20%	χ2= 3.934 P= 0.047*
Female	31	62%	40	80%	
Weight (Kg)	76.92 ± 16.42		81.42 ± 13.66		t= - 1.490 p = 0.139
Height (cm)	163.30 ± 8.14		165.12 ± 7.52		t= - 1.161 p = 0.249
BMI (Kg/m^2)	28.87 ± 5.63		29.97 ± 5.29		t= - 1.002 p = 0.319
Marital status					
Single	14	28%	14	28%	χ2= 0 P= 1
Married	36	72%	36	72%	
Disease duration (Years)					
Mean ± SD	3.5 ± 2.94				
Median (Range)	2 (0.5-10)				

P: probability. *: statistically significant (p< 0.05)
T= independent samples t-test, χ2= Chi-square test

In male patients in the cases group, the Hamilton classification was used for local hair grading. The most common grade was grade 2. In the female patients, the Sinclair scale was used for local hair grading. The most common grade was grade 3 (Table 2).

Table (2): Analysis of Grading of local hair examination in the cases group

	Cases group (N=50)	
Male cases (n=19) [Hamilton classification]		
Grade 1	**1**	**5.3 %**
Grade 2	**7**	**36.8 %**
Grade 3	**5**	**26.3 %**
Grade 4	**1**	**5.3 %**
Grade 5	**3**	**15.8 %**
Grade 6	**1**	**5.3 %**
Grade 7	**1**	**5.3 %**
Female cases (n=31) [Sinclair scale]		
Grade 2	**9**	**29 %**
Grade 3	**12**	**38.7 %**
Grade 4	**7**	**22.6 %**
Grade 5	**3**	**9.7 %**

Regarding dermoscopic examination, the most common findings were yellow dots (82%). Vellus hair in relation to terminal hair with > 10% was reported in 46 patients (92%) (Table 3).

Table (3): Analysis of dermoscopic findings in the cases group

	Cases group (N=50)	
Hair diameter diversity more than 20%	50	100%
Follicular unit		
Single	22	44%
Double or triple	28	56%
Peribulbar cast	17	34%
Yellow dots	41	82%
Brown follicular pigmentation	8	16%
Vellus hair in relation to terminal hair > 10%	46	92 %

Regarding serum zinc level, there was no statistically significant difference between the two groups (Table 4).

Table (4): Analysis of zinc level in the two study groups

	Groups				**Test of significance**
	Cases group (N=50)		**Control group (N=50)**		
Serum zinc	75.36 ± 19.29		71.73 ± 20.19		t= 0.919 p = 0.360
Zinc level					
Low	28	56%	30	60%	χ2= 0.164 P= 0.685
Normal	22	44%	20	40%	

P: probability.
T= independent samples t-test, χ2= Chi-square test

There was no significant difference between the different grades of local hair affection either in male or female patients regarding the serum zinc level (Table 5).

Table (5): Analysis of serum zinc level according to the Grading of PHL group.

Grading of local hair examination	**Number**	**Zinc level**	**Test of significance**
Male patients (n=19) **[Hamilton classification]**			
Grade 1	**1**	90.1	F= 1.040 P= 0.447
Grade 2	**7**	79.97 ± 20.49	
Grade 3	**5**	89.26 ± 18.95	
Grade 4	**1**	76.7	
Grade 5	**3**	69.25 ± 3.54	
Grade 6	**1**	115	
Grade 7	**1**	71.4	
Female patients (n = 31) **[Sinclair scale]**			
Grade 2	9	75.57 ± 17.58	F= 0.358 P= 0.784
Grade 3	12	67.38 ± 19.73	
Grade 4	7	69.63 ± 15.01	
Grade 5	3	75 ± 32.53	

F: One-way anova

The best cutoff point of serum zinc level to identify patients with PHL was less than 68.85. This value showed mild sensitivity and specificity with no statistically significant value (Table 6 and figure 1).

Table (6): predictive value of serum zinc in differentiating cases from controls.

Diagnostic criteria	Zinc level
AUC	0.565
Cutoff point	**< 68.85**
P	**0.261**
Sensitivity	**60%**
Specificity	**54%**
NPV	**58%**
PPV	**64%**
Accuracy	**58%**

AUC: Area under curve
PPV: positive predictive value
NPV: Negative predictive value

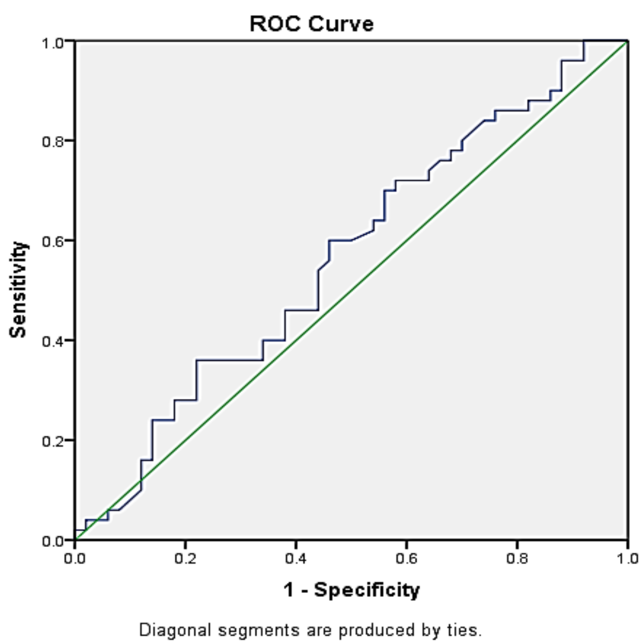

Figure (1): ROC curve for serum zinc in differentiating cases from controls.

DISCUSSION

The study found that there was no statistically significant difference (p=0.223) in the mean age of the two groups: the cases group's mean age was 32.40 ± 10.44 years, while the control group's mean age was 34.98 ± 9.53 years. 38% of the patients were males and 62% of the cases were females.

Prie *et al.* [15] observed similar findings, stating that there was no significant difference in the age or sex between the two groups, with the patients' age being 35.40 ± 9.35 years and the control group's age being 32 ± 8.78 years.

Regarding height, weight, BMI, and marital status, there was no statistically significant difference between the two groups in the current study. In the case group, the mean BMI was 28.87 ± 5.63 kg/m^2, while in the control group, it was 29.97 ± 5.29 kg/m^2.

Our findings corroborated those of **Arias-Santiago *et al.*** [16], who reported that there were no appreciable variations in mean weight, BMI, or total testosterone levels between AGA patients and controls.

However, our findings were at odds with those of research by **Chao-Chun Yang *et al.*** [17], which found that males with male-pattern AGA, particularly those with early start AGA, had more severe hair loss when their BMI was higher.

This discrepancy might be attributed to differences in the sample size and inclusion criteria for study cases.

In the current study, in male patients in the cases group, **the Hamilton classification** was used for local hair grading. There was one patient with grade 1 (5.3%), 7 patients with grade 2 (36.8%), 5 patients with grade 3 (26.3%), one patient with grade 4 (5.3%), 3 patients with grade 5 (15.8%), one patient with grade 6 (5.3%) and one patient with grade 7 (5.3%). In the female patients, the Sinclair scale was used for local hair grading. There were 9 patients with grade 2 (29%), 12 patients with grade 3 (38.7%), 7 patients with grade 4 (22.6%) and three patients with grade 5 (9.7%).

In the research done by **Erdogan *et al.*** [18]**,** 72.7% of patients were in stage 3 of the Hamilton-Norwood scale, and 27.3% were in stage 4. According to the Hamilton-Norwood classification, **Gok and her colleagues**[19] found that, out of the 74 AGA patients included in their study, 24 (32.4%) were in stage 2, 26 (35.1%) were in stage 3, 17 (23%) were in stage 3V, 1 (1.4%) was in stage 5, and 6 (8.1%) were in stage 7.

In the current study, the main dermoscopic feature was hair diameter diversity that was detected in all the cases. Vellus hair in relation to terminal hair with > 10% and was reported in 46 patients (92%). There were 22 patients with single follicular unit (44%) and there were 28 patients with double or triple follicular unit (56%). Peribulbar cast was reported in 17 patients (34%), yellow dots was reported in 41 patients (82%) and brown follicular pigmentation in 8 patients (16%).

This was in line with the research by **Hofny *et al.*** [20] who found that trichoscopic findings in all 35 (100%) patients with AGA was hair shaft diversity greater than 20%, 30 (85.7%) patients had short vellus hair, 16 (45.7%) patients had peripilar sign, and yellow dots were presented in 11 (31.4%) patients.

In the current study, there was no statistically significant difference between the two groups (p= 0.360) regarding the level of serum zinc. The mean serum zinc level in the cases group was 75.36 ± 19.29 and the control group's mean serum zinc level were 71.73 ± 20.19. Although there was no statistically significant difference between the two groups (p=0.685), low zinc levels were found in 56% of the cases and 60% of the control group, respectively.

Yellow dots are characteristically seen in the advanced stages of MPHL and FPHL [21]. In our study, yellow dots were seen in 82% of the cases.

The current results came in accordance with **Aly** [22] who conducted a study to evaluate the serum levels of zinc and iron in male and female patients with AGA and to compare the findings with normal controls. They included 60 AGA patients (30 males and 30 females) and 40 healthy volunteers (20 males and 20 females). The serum zinc (µg/dL) and iron (µg/dL) levels were statistically significantly lower in female AGA patients compared to controls. The male AGA (MAGA) group's serum levels of iron and zinc were not significantly different from those of the control group.

This agreed with **Ozturk *et al.*** [23] who included 100 controls and 116 individuals with male pattern androgenetic alopecia. They looked into the zinc concentration in the hair, serum, and urine of MAGA patients and compared the results with those of the control group. They discovered that only the zinc level in the hair of MAGA patients was considerably lower than the control group, while the zinc levels in the serum and urine showed no changes.

Also, opposite to the current results, in research headed by **Aiempanakit *et al.*** [24]**,** 114 participants were enrolled: 57 patients with androgenetic alopecia (case group) and 57 age- and gender-matched individuals without alopecia (control group). Mean plasma zinc levels in the case group were found to be lower in both men and females than in the control group (males: 59.40 ± 12.73, 64.81 ± 10.19 µg/dL, P = 0.09; females: 54.13 ± 9.69, 62.27 ± 11.89 µg/dL respectively, P = 0.005).

A recent analysis that comprised eight case-control studies that enrolled 372 age- and sex-matched controls and 516 patients with AGA; there was a significant difference in blood zinc levels between patients with AGA and controls [difference in means (MD) = −18.915, 95% confidence interval (CI) = −26.879 to −10.951, p < 0.001] [25].

On the other hand, the current results disagreed with **Dhaher *et al.*** [12]. The subjects were split up into two groups: the first included 27 women with FPHL, and the second included a control group of 28 age-matched healthy women. The study findings indicated that there was a significant difference (P<0.05) in the mean serum zinc concentration levels between the women with FPHL and the control group (65.6±14.2 µg/dl and 128.4±41.4 µg/dl, respectively).

The current results contradicts those of **Kil *et al.*** [26] who carried out a research including 312 patients with alopecia areata, MPHL, FPHL, and telogen effluvium (TE) as well as 30 healthy controls. Significantly less than the control group (97.94±21.05 µg/dl), the mean serum zinc level was 84.33±22.88 (p=0.002).

Although the precise association between Zn and AGA is still unknown, few examples indicate that zinc supplementation can effectively alleviate hair loss [27]. Regular use of zinc and L-carnitine in the form of dietary supplements and topically applied as a lotion can successfully slow the progression of AGA [28].

In our study, regarding the blood zinc level, neither the male nor female patients' grades of local hair affection differed statistically significantly in the current investigation. This come in accordance with previous results that showed that zinc level showed no statistically significant difference between the different grades of androgenic alopecia in their studies [23, 26].

In our study the best cutoff point of serum zinc level to identify patients with PHL was less than 68.85. This value showed mild sensitivity and specificity with no statistically significant value (p= 0.261).

Kondrakhina *et al.* [29] reported that AGA in men with a serum zinc concentration of ≦65.4 µg/dL is more resistant to topical minoxidil and mineral correction than that in those whose serum zinc concentration was above the cutoff.

LIMITATIONS

- All patients were obtained from outpatient clinic of Mansoura Hospital, therefore there is lack of generalisation of the results.
- Short duration of the study.
- The study did not include patients under therapy, so zinc supplementations were supposed to be taken and detect clinical and dermoscopic changes after therapy.
- Single hair analysis by fluorescence spectrometry also was supposed to be done to detect changes in hair zinc.

CONCLUSION

It is not possible to identify zinc deficiency as a direct causative component in the pathophysiology of androgenic alopecia, and not all individuals with this condition will benefit from taking dietary supplements. The role of zinc supplementation is also open to debate**.**

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