

Serum ferritin levels in non-scarring alopecia of women: a case-control study

Muzamil A Chisti[†], Qazi Masood*, Iffat H Shah*, Dilshad Khan*, Imran Majid*, Seema Qayoom**, Samreen Shah*

[†]Department of Dermatology, King Faisal specialist hospital & research centre Riyadh, KSA

*Department of Dermatology, STD & Leprosy Government Medical College Srinagar, J & K India

**Department of Dermatology, Sheri Kashmir Institute of Medical Sciences, Medical College, Srinagar, J&K India

Abstract *Background* Iron deficiency in the etiology of hair loss has been studied for more than 45 years. However, contradictory reports have been published and almost all the studies conducted so far are based on observational methodology.

Objective To find out if any real association exists between the iron deficiency and alopecia.

Patients and methods One hundred consecutive, clinically typical female patients (14-54 years) with nonscarring alopecia i.e. alopecia areata, androgenetic alopecia and telogen effluvium and an equal number of age- and sex-matched controls were included in the study. Both groups were evaluated for serum ferritin and other important parameters of iron status.

Results Mean serum ferritin value of cases was significantly lower than that of the controls ($p=0.005$). Patients with alopecia areata and androgenetic alopecia had significantly lower values of serum ferritin ($p=0.011$ and 0.015 , respectively), but there was no significant difference in telogen effluvium cases and controls ($p=0.348$). The values of hemoglobin, hematocrit, MCV, MCH and transferring-saturation were significantly lower in cases but had significantly higher TIBC values than controls.

Conclusion There is a definite association of decreased serum ferritin levels and nonscarring alopecia in women. The iron stores of female patients with nonscarring alopecias should be built for the optimum response to treatment as the proposed triggering factor can be abolished.

Key words

Serum ferritin, alopecia areata, androgenetic alopecia, telogen effluvium.

Introduction

Hair has no vital function in humans yet its cosmetic and psychological importance is immense, as is evident from the concern of a person who is losing hair. In women the loss

of hair from scalp is even more distressing than growth of the body or facial hair in excess of the culturally acceptable norms. Berg has expressed a woman's concern about her hair very well. "Woman is herself constantly doing something to her hair. She even carries a little mirror everywhere with her with the principal object of looking at her hair to see that it is right. Obviously it is a source of anxiety to her".¹

The hair follicles in humans show a cyclical activity. The phases of hair cycle include anagen (86%), catagen (1%), telogen (13%).² Release of the dead hair from the follicle

Address for correspondence

Dr. Muzamil Amin Chisti

Assistant Consultant

Department of Dermatology (MBC 46-1)

King Faisal Specialist Hospital and Research Centre

P.O. Box 3354, Riyadh 11211, KSA

Phone No. +966 442 4608

Fax No. +966 1 442 4603

Email: janphiny@gmail.com.

(exogen) occurs either late in telogen or early in anagen. Besides, these phases another phase of hair growth cycle has been described which is called as the kenogen.³

Alopecia by definition is the absence of hair from a normally hairy area, and it affects more than 25% of women in developed countries.⁴ Like other organs of body, hair also needs adequate nutrition for its proper growth and development, and hair is affected in various nutritional deficiencies.^{5,6} In humans the association of nutrition with skin and hair changes emanates primarily from studies on protein-energy malnutrition.^{5,6} Besides protein-energy malnutrition, various micronutrients have also been studied as etiological factors of hair loss.^{7,8}

Iron deficiency is the most common deficiency disorder in the world, and at the present time, is the one nutritional deficiency disorder, that still persists in developed countries.^{9,10} Ferritin is present in plasma in trace amounts, and the serum concentration correlates well with the amount of iron stores.¹¹

Iron deficiency in the etiology of hair loss has also been studied for more than 45 years. Ever since Hard⁷ in 1963 demonstrated the importance of non-anemic iron deficiency as an etiologic factor in diffuse loss of scalp hair in women, there have been many contradictory reports regarding the association of decreased iron stores with alopecia.

The overall nutritional status of the people in this part of the world is poor and the prevalence of overt iron deficiency is high in our population,^{9,12} more so in women. It seems likely that the iron reserves even in non-anemic individuals may be low. Besides, consumption of a lot of tea further decreases the iron reserves in the body of individuals with borderline iron reserves.¹³ Keeping in view the above mentioned facts, the

contradictory reports regarding the association of iron deficiency and hair loss and a good number of female alopecia patients that we see in our hospital, it seemed interesting to study if there is really an association between the serum ferritin levels and various types of alopecias.

There are only two published studies in the literature that use analytical methodology for drawing inferences. All the other studies relied on observational methodology rather than standard statistical tests.^{7,14-17} Besides this, no previous study has evaluated all the important parameters of iron status in patients with alopecia.

Patients and methods

The study was approved by the institutional ethical committee. In all study subjects, written consent was taken before their inclusion in the study. The study group comprised of one hundred consecutive premenopausal female patients of alopecia aged between 14 and 54 years presenting to our outpatient department. It included clinically typical cases of commonest types of alopecias (androgenetic alopecia, telogen effluvium and alopecia areata). The diagnosis of various types of alopecias was made on grounds of history and clinical examination only, by the same experienced dermatologist.

Equal number of age- and sex-matched controls were taken. The control group comprised of the patients who presented to our outpatient department for some other dermatological abnormality not directly related to increased hair loss and iron deficiency. None of these patients gave a history of increased hair loss or had alopecia clinically. An informed consent was taken from all cases and controls.

The patients of androgenetic alopecia were classified according to Ludwig's pattern into grade I to III,¹⁸ while the diagnosis was made by comparing the part width on the crown and occiput and by finding a typical "Christmas tree" pattern of hair loss.¹⁹

Besides a detailed history and thorough local and relevant systemic examination for the diagnosis of various types of alopecias, the baseline investigations including, hemogram, ESR, thyroid function tests, serum iron and total iron-binding capacity (TIBC), serum ferritin levels by standard enzyme-linked immunosorbent assay (ELISA) method were also carried out in the patients. Liver function tests, kidney function tests and antinuclear antibody tests were performed wherever necessary.

The patients with scarring alopecia, congenital alopecia, hair shaft disorders, abnormal thyroid function tests, any gross (clinically evident) systemic disease, ESR of more than 30mm 1st hour, postmenopausal women, patients who had taken iron, vitamin B₁₂, folic acid or multivitamin supplements for at least 3 months before inclusion in the study, who had pregnancy in the preceding 1 year and patients on anticoagulants, antithyroid drugs, antimetabolic drugs, and oral contraceptives were excluded from the study. Patients with any form of acute inflammatory condition were also not included in view of serum ferritin being raised during such events.

5ml of venous blood was collected, out of which 2ml was sent in EDTA vial for CBC analysis and serum was obtained from the rest which was stored at -20⁰ C till the assay was done. Complete blood counts were performed using completely automatic hematology analyzer (Sysmex KX-21®). Serum iron and TIBC were estimated on Hitachi-912®, autoanalyzer, using a commercially available kit, manufactured by M/S Roche

Diagnostics®, Roche Diagnostics Corporation®, Indianapolis IN, USA and Randox Laboratories®, United Kingdom, respectively. The expected values of serum iron were 50-160 µg/dl²⁰ while expected values of TIBC were 145-399µg/dl.²¹

Serum transferrin saturation was calculated and values more than or equal to 15% were considered normal and less than 15% were taken as having decreased iron stores.

Serum ferritin was measured by enzyme immunoassay (EIA) test, based on sandwich ELISA. The necessary reagents for the test were obtained in a kit manufactured by Monobind, Inc. USA® and the absorbance in each well was read at 450nm using a microplate reader- Multiskan® (manufactured by Labsystems®) and the readings of serum ferritin were obtained.

The statistical analysis of the data was done using students' t test for the difference of means, chi-square test and Fisher's exact test for ratios. These tests were referenced for *p* values and *p* value of less than 0.05 was taken to be significant.

The analysis of the data was performed by using SPSS computer program (Statistical Package for Social Sciences, SPSS Inc. Chicago, USA.) version 10.0.

Results

The age range of cases and controls in our study was 14-54 years [mean 26.6±7.25 years (cases) and 26.83±9.97 years (controls)], *p*>0.05. Amongst 100 patients of alopecia, 46 had alopecia areata, 25 had androgenetic alopecia and 29 were suffering from telogen effluvium.

In our study we found that the mean values of hemoglobin (12.39±1.40g/dl c.f.

12.84±0.96g/dl; $p=0.011$), hematocrit (38.95±4.18% c.f. 40.92±2.65%; $p=0.000$), MCV (88.67±4.15fl c.f. 90.81±1.79fl; $p=0.000$), MCH (28.85±2.27pg c.f. 30.25±1.56pg; $p=0.000$) and transferrin saturation (18.38±4.68% c.f. 23.83±19.10%; $p=0.000$) were significantly lower than the control group. It was also seen that the value for TIBC (383.30±105.56µg/dl c.f. 321.83±76.81µg/dl; $p=0.000$) was significantly higher than the controls (**Table 1**). There was also significant number of patients who had abnormal peripheral blood film ($p=0.005$) as shown in (**Table 2**). However, there was no significant difference in RBC count ($4.21±0.50×10^6$ c.f. $4.19±0.46×10^6$; $p=0.748$), MCHC (31.35±1.80g/dl c.f. 31.81±1.57g/dl; $p=0.072$), ESR (10.31±4.41mm c.f. 9.30±3.23mm; $p=0.067$) and serum iron (56.61±29.04 µg/dl c.f. 63.61±22.02µg/dl; $p=0.063$) (**Table 3**). This shows that although the mean serum iron of patients is on the lower side of the reference range (50-160 µg/dl),²⁰ there was no statistically significant difference between cases and controls.

A significant difference ($p=0.005$) in the mean serum ferritin levels was seen in the cases (20.47±17.50ng/ml) and controls (27.87±17.51ng/ml) as shown in (**Table 4**). As ferritin levels accurately reflect the body iron stores,²² so there is a significant difference in patients and controls as far as their body iron stores are concerned.

On analyzing the data further, it was concluded that the mean ferritin levels of patients with alopecia areata (19.71±18.56ng/ml) and androgenetic alopecia (15.23±9.27ng/ml) were significantly lower than that in the controls ($p=0.011$ and 0.015, respectively), whereas the mean ferritin level of patients with telogen effluvium (24.13±19.75ng/ml) was not significantly

different from that of controls ($p=0.348$) [**Table 4**]. The data was further analyzed and the subgroups of various alopecias were evaluated for any difference in mean serum ferritin levels. It was found that the mean ferritin levels in patients with both Ludwig's grade I (16.86±11.33ng/ml) as well as grade II (13.59±7.73ng/ml) were significantly lower than in controls ($p=0.017$ in each group). While in cases having telogen effluvium (both acute and chronic), it was seen that there was no significant difference in mean ferritin levels between cases and controls, $p=0.945$ and 0.346 for acute and chronic telogen effluvium, respectively (**Table 4**).

We further analyzed the data using the serum ferritin value of 20ng/ml as the lower limit of normal and it was found that a significantly higher number of patients had ferritin levels of less than 20ng/ml (63% c.f. 38% of controls; $p=0.000$) [**Table 5**]. It was also seen that a significant number of patients with alopecia areata (65.2% c.f. 38% of controls; $p=0.002$) and androgenetic alopecia (68% c.f. 38% of controls; $p=0.012$) had serum ferritin levels below 20ng/ml as depicted in **Table 5**.

As regards telogen effluvium, no significant difference was found in the number of patients with serum ferritin levels less than 20ng/ml when compared with those of controls ($p=0.099$). Further analysis of the data revealed that a statistically significant number of patients with chronic telogen effluvium (77.3%) had serum ferritin levels below 20ng/ml ($p=0.031$). On the other hand no significant difference was seen in the number of patients of acute telogen effluvium ($p=0.558$) with serum ferritin levels below 20ng/ml when compared with that of controls.

Table 1 Comparison of various red cell indices between cases and controls.

	Cases	Controls	T value	p' value
Hb (gm/dl)	12.39±1.40	12.84±0.96	2.59	0.011*
TEC (million)	4.21±0.50	4.19±0.46	0.323	0.748
Hct (%)	38.95±4.18	40.92±2.65	3.676	0*
MCV (fl)	88.67±4.15	90.81±1.79	4.57	0*
MCH (pg)	28.85±2.27	30.25±1.56	4.93	0*
MCHC (gm/dl)	31.35±1.80	31.81±1.57	1.82	0.072
ESR (mm)	10.3±4.4	9.3±3.23	1.85	0.067

Hb=hemoglobin, TEC=total erythrocyte count, Hct=hematocrit, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration. * Statistically significant.

Table 2 Comparison of cases and controls with abnormal peripheral blood film.

Peripheral blood film	Normal %	Abnormal %	$\chi^2_{1df}=8.04$	p' value
Cases	63	37		
Controls	81	19		

Table 3 Comparison of mean serum ferritin levels in cases and controls.

Study group	Number	Mean±S.D. (ng/ml)	t' value	p' value
Alopecia areata	46	19.71±18.56	2.57	0.011*
Androgenetic alopecia	25	15.23±9.27	2.45	0.015*
Telogen effluvium	29	24.13±19.75	0.842	0.328
Total cases	100	20.47±17.50	2.91	0.005*
Controls	100	27.87±17.51		

* Statistically significant.

Table 4 Table showing comparison of mean serum ferritin levels in cases (subgroups) and controls.

Study Group	Number	Mean±S.D (ng/ml)	t' value	p' value
Grade I androgenetic alopecia	16	16.86±11.33	2.43	0.017*
Grade II androgenetic alopecia	9	13.59±7.73	2.42	0.017*
Acute telogen effluvium	20	27.57±16.89	0.7	0.945
Chronic telogen effluvium	9	21.86±27.76	0.946	0.346
Controls	100	27.87±17.51		

* Statistically significant.

Table 5 Comparison of cases and controls in relation to serum ferritin levels.

Study group	< 20ng/ml		> 20ng/ml		p' value
	N (%)	N (%)	N (%)	N (%)	
Alopecia areata	30(65.20)	16(34.80)	$\chi^2_{1df}=9.38$		0.002*
Androgenetic alopecia	17 (68.00)	8 (32.00)	$\chi^2_{1df}=7.31$		0.012*
Telogen effluvium	16 (55.20)	13 (44.80)	$\chi^2_{1df}=2.72$		0.099
Acute	9 (45.00)	11 (55.00)	$\chi^2_{1df}=0.343$		0.558
Chronic	7 (77.80)	2 (22.20)	Fisher's exact test		0.031*
Total cases	63(63)	37(37)	$\chi^2_{1df}=12.5$		0*
Control	38(38.00)	62(62.00)			

* Statistically significant.

Discussion

The present case-control study was designed to see if there is any association between low serum ferritin values and three most common types of non-scarring alopecias (alopecia areata, androgenetic alopecia and telogen effluvium) with typical clinical presentation.

Besides being one of the few studies using analytical methodology, this study also assumes significance as we have determined the parameters in the subgroups of patients with different types of alopecia (androgenetic alopecia–Ludwig's grade I-III and telogen effluvium – acute and chronic), while in the previous studies, researchers have clubbed

them together¹⁴ which might have affected the results of these studies.

In our study, we found that the mean values of hemoglobin, hematocrit MCV, MCH and transferrin saturation were significantly lower than the control group while as the value for TIBC was significantly higher than the controls thereby depicting depleted iron status in patients.

A significant difference ($p=0.005$) in the mean serum ferritin levels was seen in the cases and controls. As ferritin levels accurately reflect the body iron stores,²² so there is a significant difference in patients and controls as far as their body iron stores are concerned.

We also found that patients with alopecia areata and androgenetic alopecia had significantly lower serum ferritin levels than controls, however, the serum ferritin levels of patients with telogen effluvium was not significantly different from that of controls ($p=0.348$).

Our study is in close approximation to the study conducted by Kantor *et al.*¹⁴ who showed that the mean ferritin levels in women with androgenetic alopecia and alopecia areata were significantly lower than those without alopecia, while as there was no difference in the mean ferritin levels of telogen effluvium, alopecia totalis and alopecia universalis patients, when compared with those of controls.

Reduced serum ferritin levels were also seen in patients with diffuse alopecia in studies conducted by Rushton *et al.*²³ and Van Neste and Rushton.⁴

White *et al.*¹⁷ demonstrated similar findings in patients with alopecia areata.

Positive association of low serum ferritin and alopecia in women was also reported by Kantor *et al.*²⁴ and Headington.²⁵

Sinclair¹⁶ has contradicted the above observation and is of the view that there is no clear association between low serum ferritin levels and alopecia. However, the lower limit of serum ferritin level was taken as 20ng/ml whereas in other studies it was taken from 40-70ng/ml.

In a recent retrospective study conducted by Olsen *et al.*,²⁶ they took 15ng/ml as a cutoff level and found that the incidence of iron deficiency is not more in patients with female pattern hair loss and chronic telogen effluvium.

This lower limit is a matter of hot debate for the present day trichologists world over. Rushton and Ramsay²⁷ demonstrated that women with androgenetic alopecia responded best to treatment with antiandrogen cyproterone acetate and ethinyl estradiol when their serum ferritin level was above 40ng/ml.

In another study conducted by Rushton,²⁸ it was found that the optimal hair growth potential is considered to exist when specific parameters for biochemical variables are operating. These include red blood cell and serum folate concentrations within normal range, serum vitamin B₁₂ levels between 300 and 1,000ng/l, hemoglobin levels greater than 13.0gm/dl and serum ferritin concentration of 70ng/ml or greater.

It was also argued by Rushton *et al.*²⁹ that the reference range used by Sinclair¹⁶ for serum ferritin has been derived from a population containing a high proportion of iron deficient women.

Ours being a similar type of population where the prevalence of iron deficiency is high

particularly among women,⁹ we further analyzed the data using the serum ferritin value of 20ng/ml as the lower limit of normal, and it was found that a significantly higher number of patients had ferritin levels of less than 20ng/ml ($p=0.000$). It was also seen that a significant number of patients with alopecia areata ($p=0.002$) and androgenetic alopecia ($p=0.012$) had serum ferritin levels below 20ng/ml.

As regards telogen effluvium, no significant difference was found in the number of patients with serum ferritin levels less than 20ng/ml when compared with those of controls ($p=0.099$). Further analysis of the data revealed that a statistically significant number of patients with chronic telogen effluvium (77.3%) had serum ferritin levels below 20ng/ml ($p=0.031$). On the other hand no significant difference was seen in the number of patients of acute telogen effluvium with serum ferritin levels below 20ng/ml when compared with those of controls.

This difference in the results obtained as regards chronic telogen effluvium patients while taking the lower limit of serum ferritin as 20ng/ml can be explained on the basis of the "threshold hypothesis" as proposed by Kantor *et al.*¹⁴ which states that the decreased iron stores lower the threshold for developing different types of alopecia. They proposed that in patients with a very strong genetic predisposition to developing alopecia, it is possible that low body iron stores are not important in triggering these disorders. In comparison, in those individuals with a mild hereditary predisposition or with the presence of other triggering factors, low iron stores may lower their threshold to the point where they develop alopecia. Theoretically it will be this subgroup of patients who are best candidates for iron therapy. Lastly, in those individuals without a hereditary predisposition or without

other triggering factors, low iron stores would not cause alopecia.

The observation made in our study further strengthens this hypothesis, and it is possible that these patients of chronic telogen effluvium have a mild genetic predisposition to develop alopecia and the event is triggered when their serum ferritin falls below the threshold level. We recommend that the iron stores of female patients with non-scarring alopecias should be built for the optimum response to treatment as the proposed triggering factor can be abolished.

Limitations

Power analysis was not done prior to starting the study and the sample size was taken as per the previously published studies. The small sample size is another limitation of our study and further studies with a larger sample size will further validate our data.

References

1. Guy WB, Edmundson WF. Diffuse cyclic hair loss in women. *Arch Dermatol* 1960;**81**:205-7.
2. Barman JM, Astore I, Pecaro V. The normal trichogram of adult. *J Invest Dermatol* 1965;**44**:233-6.
3. Guarrera M, Rebora A. Kenogen in female androgenetic alopecia. *Dermatology* 2005;**210**:18-20.
4. Van Neste DJ, Rushton DH. Hair problems in women. *Clin Dermatol* 1997;**15**:113-25.
5. Bradfield RB, Cordario A, Graham GG. Hair root adaptation to marasmus. *Lancet* 1969;ii:1395-6.
6. Bradfield RB, Bailey MA. Hair root response to under nutrition. In: Montagna W, Dobson RL, eds. *Hair Growth*. Oxford: Pergamon; 1969. P. 109-19.
7. Hard S. Non-anemic iron deficiency as an etiological factor in diffuse loss of hair of the scalp in women. *Acta Derm Venereol* 1963;**43**:562-9.
8. Rushton DH. Nutritional factors and hair loss. *Clin and Exp Dermatol* 2002;**27**:396-404.

9. Bentley ME, Griffiths PL. The burden of anemia among women in India. *Eur J Clin Nutr* 2003;**57**: 52-60.
10. Looker AC, Dalman PR, Carroll MD *et al*. Prevalence of iron deficiency in United States. *JAMA* 1997;**277**:973-76.
11. Bellotti V. Characteristic of a ferritin binding protein present in human serum. *Br J Hematol* 1987;**65**:489.
12. Chakarvati I, Ghosh K. Micronutrient malnutrition- present status and future remedies. *J Indian Med Assoc* 2000;**98**:539-42.
13. Temme EH, Van Hoydonck PG. Tea consumption and iron status. *Eur J Clin Nutr* 2002;**56**:379-86.
14. Kantor J, Kessler LJ, Brooks DG, Cotsarelis G. Decreased serum ferritin is associated with alopecia in women. *J Invest Dermatol* 2003;**121**:985-8.
15. Boffa MJ, Wood P, Griffiths CE. Iron status of patients with alopecia areata. *Br J Dermatol* 1995;**132**:662-4.
16. Sinclair R. There is no clear association between low serum ferritin and chronic diffuse telogen hair loss. *Br J Dermatol* 2002;**147**:982-4.
17. White MI, Currie J, Williams MP. A study of iron status of patients of alopecia areata. *Br J Dermatol* 1994;**130**:261-3.
18. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in female sex. *Br J Dermatol* 1977;**97**:247-54.
19. Miller JJ. Medical Pearl: Comparing crown part width to occipital part width to diagnose female pattern hair loss. *J Am Acad Dermatol* 2005;**53**:331-2.
20. De Jong G, van Dijk JP, van Eijk HG. The biology of transferrin. *Clin Chim Acta* 1990;**190** (1-2):1-46.
21. Ferrucis C. Improved direct specific determination of serum iron and TIBC. *Clin Chem* 1980;**26**:327-31.
22. Jacobs A. Serum ferritin and iron stores. *Fed Proc* 1977;**36**:2024-27.
23. Rushton DH, Ramsay ID, James KC *et al*. Biochemical and trichological characterization of diffuse alopecia in women. *Br J Dermatol* 1990;**123**:187-97.
24. Kantor J, Jay K, Brooks D, Cotsarelis G. Decreased serum ferritin is associated with alopecia in women: a case controlled study. *J Invest Dermatol* 2001;**117**:435.
25. Headington J. Telogen effluvium: New concepts and review. *Arch Dermatol* 1993;**129**:356-63.
26. Olsen EA, Reed KB, Cacchio PB, Caudill L. Iron deficiency in female pattern hair loss, chronic telogen effluvium and control groups. *J Am Acad Dermatol* 2010;**63**:991-9.
27. Rushton DH, Ramsay ID. The importance of adequate serum ferritin levels during oral cyproterone acetate and ethinyl oestradiol treatment of diffuse androgen-dependent alopecia in women. *Clin Endocrinol* 1992;**36**:421-7.
28. Rushton DH. Management of hair loss in women. *Dermatol Clin* 1993;**11**:47-53.
29. Rushton DH, Dover R, Norris MJ. Is there really no association between low serum ferritin and chronic diffuse telogen hair loss? *Br J Dermatol* 2003;**148**:1270-90.