

Iron Status in Diffuse Telogen Hair Loss among Women

Mojdeh Moeinvaziri¹, Parvin Mansoori¹, Koorosh Holakooee²,
Zahra Safaee Naraghi¹, Ali Abbasi³

¹Department of Dermatology, Tehran University of Medical Sciences, Razi Hospital;

²Department of Epidemiology, Institute of Public Health Research, Tehran University of Medical Sciences, Tehran, Iran; ³Department of Epidemiology, University Medical Center Groningen, Groningen, The Netherlands

Corresponding author:

Ali Abbasi, MD
Hanzeplein 1
P.O. Box 30.001
9700 RB Groningen
The Netherlands
a.abbasi@epi.umcg.nl

Received: April 15, 2009

Accepted: October 15, 2009

SUMMARY The relationship between iron body status and different types of hair loss has been investigated in a number of studies, however, with relatively discrepant findings. Therefore we conducted an analytical case-control study to assess whether diffuse telogen hair loss in women of child-bearing age (15 to 45 years old) is associated with iron deficiency. Using the analytical case-control methodology, we studied 30 consecutive women with documented diffuse telogen hair loss in comparison with 30 women without hair loss. Study subjects had no history of nutritional supplement intake or chronic underlying diseases, and had normal thyroid function and inflammatory profiles. Biochemical investigations were performed in all study women. The mean ferritin level and transferrin saturation was statistically significantly lower in patients with diffuse telogen hair loss than in subjects without hair loss (16.3 ± 12.6 vs. 60.3 ± 50.1 , ng/mL; $P < 0.0001$ and 20.3 ± 9.7 vs. 28.3 ± 11.8 percent; $P = 0.006$, respectively). Also, total iron binding capacity was significantly higher in patients than in control group (367.8 ± 58.2 vs. 319.2 ± 60.1 $\mu\text{g/dL}$; $P = 0.004$). Of nine patients with iron deficiency anemia (Hb < 12 g/dL), eight patients had telogen hair loss (odds ratio: 10.5, 95%CI: 1.2-90.7; $P = 0.013$). Odds ratio (95% confidence interval) for diffuse telogen hair loss was 21.0 (4.2-105.0) at serum ferritin levels ≤ 30 ng/mL. Women with iron deficiency status are at a risk of telogen hair loss. The important role of serum ferritin in hair loss is becoming more evident. In women without systemic inflammation or other underlying disorders, serum ferritin levels below or equal to 30 ng/mL are strongly associated with telogen hair loss.

KEY WORDS: hair loss, telogen, anemia, ferritin, iron deficiency

INTRODUCTION

The precise prevalence of hair loss in the general female population is unknown, but diffuse hair loss lasting for more than 6 months in women is a common presentation to dermatologists. Hair loss affects over 25% of women in developed coun-

tries. Of hair disorders, telogen effluvium as an abnormality of hair cycling results in excessive loss of telogen hairs, and is one of the most common causes of diffuse hair loss among women. Many cases of telogen effluvium are subclinical, so

the true incidence in the community is unknown. Women are overrepresented among those that present for medical attention. Also, a large number of women that complain of persistent increased hair shedding will have sought professional help but without much success. Too often, they are dismissed because the hair loss is not obvious (1-4). Despite the prevalence of telogen hair loss, few epidemiological studies have addressed the etiology of and risk factors for this hair loss. The common precipitating events include childbirth, fever, and medications, although precipitating factors are often not discernable. In many cases, no cause can be found (5,6).

Dermatologists commonly assess serum iron status in women because of the assumption that iron deficiency causes alopecia. Observational data have suggested that alopecia in women may be associated with decreased body iron stores. Some studies have suggested that decreased body iron stores (as measured by serum ferritin) may be associated with telogen effluvium (5,7,8). Two observational studies evaluated the association between decreased ferritin levels and androgenic alopecia (AA) and came to opposing conclusions, although both studies were limited by their methodology, which relied on published norms for ferritin and hemoglobin that were drawn from other laboratories and populations (9,10). Only one study utilized standard epidemiologic methodologies to evaluate the relationship between alopecia and decreased iron stores in women (11). Therefore, we conducted a case-control study with analytical methodology to determine whether women with hair loss have lower serum ferritin levels and higher prevalence of iron deficiency or anemia as compared to controls. Also, the role of serum ferritin in diagnosing diffuse telogen hair loss was evaluated with respect to its cut-off points.

SUBJECTS AND METHODS

The study included 30 consecutive women that presented between February 2005 and March 2006 with diffuse telogen hair loss for 6 months or longer. All women underwent extensive screening at Hair and Skin Clinic, Razi Hospital, Tehran University of Medical Sciences. To determine the sample size in this case-control study, we considered a 1:1 ratio of numbers in each case and control group. The α (probability of detecting a false effect) and β (probability of detecting a real effect) values were 0.05 and 0.20, respectively. Therefore, the minimum sample size was calculated to be 28 subjects in each group, considering a value of 0.05 for difference between groups.

The case group consisted of women of child-bearing age, 15 to 45 years old. Women were not included if they had a history of surgical operation, pregnancy, lactation, chronic systemic disease, weight loss, being on low-calorie diet, or used medications that may be associated with hair loss in the last 6 months. Also, women with elevated erythrocyte sedimentation rate (ESR), i.e. $ESR > (age+10)/2$ mm/h, indicating nonspecific inflammation that could also raise ferritin and invalidate its use as a marker of iron status, were excluded.

All patients were evaluated by a dermatologist to make the diagnosis of telogen hair loss by history and physical examination. All patients had a 4-mm punch biopsy taken from the vertex of the scalp. The sectioned biopsy was used to calculate the ratio of vellus to terminal hair. The diagnosis of telogen hair loss was made if patients had increased shedding by history (more than 100 numbers/daily) or physical examination (more than 2 telogen hair-shed in light pull test). It was documented by dermatopathologist reports (microscopically specific morphology of a shed telogen hair). Biochemical investigations included thyroid function tests, complete blood count, renal and liver function tests, and iron studies (serum iron, ferritin, and total iron binding capacity (TIBC)). All patients were euthyroid. The thyroid function was measured by testing the levels of thyroid stimulating hormone (TSH) and thyroxine (T4).

Control group without hair loss were recruited from the women screened at the same clinic. Control group consisted of women having neither history of alopecia nor clinical findings suggesting hair loss. These women were volunteers that presented for dermatologic problems other than hair loss.

Duration of hair loss was not taken into account when determining whether women with diffuse telogen hair shedding had lower ferritin and iron levels than controls. A trained general physician collected information on all study subjects by filling-out a well-designed questionnaire. Then data on all study subjects were analyzed and demographics, medical history, clinical examinations and laboratory test results recorded.

An informed consent was obtained from all study subjects. The study was approved by the institutional Review Board, overseeing the participation of human subjects in research at Tehran University of Medical Sciences. This study design was in line with the principles outlined in the Declaration of Helsinki.

Results were reported as mean \pm standard deviation (SD) or median (interquartile range [IQR])

for continuous variables and percentages for dichotomous variables. The groups were compared by using Student's *t*-test for continuous variables and χ^2 -test for dichotomous variables. Mann-Whitney *U* test was employed for skewed continuous data (examined by Kolmogorov-Smirnov and Shapiro-Wilk tests). By using logistic regression analyses, odds ratio (OR) and 95% confidence intervals (CI) were calculated for cut-off points of hemoglobin and serum ferritin levels. The study was done with a power of 80%. *P* values of 0.05 or less were considered statistically significant. All statistical analyses were carried out by use of SPSS (Chicago Inc., version 13).

RESULTS

The mean age in 60 study women (case and control) was 28.8 ±8.3 years. The mean age was similar in both case and control groups (28.1±8.5 vs. 29.4±8.2, respectively; *P*=0.441), suggesting that any differences in ferritin levels between subjects with and without telogen hair loss were not due to age difference. The values of TSH, T4 and ESR were not significantly different between the women with and without telogen hair loss either. Laboratory profiles of patients with telogen hair loss and control subjects are shown in Table 1.

Student's *t*-test showed the mean serum ferritin levels to be statistically significantly lower in patients with telogen hair loss than in those without

hair loss (Table 1). There was no statistically significant difference in the mean serum iron levels between patients with and those without telogen hair loss. However, the patients with telogen hair loss had significantly lower mean saturation of transferrin than controls. The mean TIBC was statistically significantly higher in patients with telogen hair loss than in controls (Table 1). Comparison of whole blood count yielded similar values in the case and control groups for all parameters except for platelet count (significantly higher in patients with hair loss) and mean corpuscular hemoglobin concentration (significantly lower in patients with hair loss). Diffuse telogen hair loss was present in eight of nine women with laboratory anemia (i.e. hemoglobin less than 12 g/dL). The odds of having telogen hair loss was significantly higher in anemic women than in those free from anemia (*P*=0.013). Serum ferritin level ≤10 ng/mL as the lower limit of normal based on reference sample groups was found in ten (33.3%) women with diffuse telogen hair loss and in only two (6.7%) women without hair loss (*P*<0.0001). Moreover, the odds ratio for telogen hair loss was 21.0 (95% CI, 4.2-105.0) at serum ferritin level ≤30 ng/mL (Table 2).

DISCUSSION

Only one recently published study used analytical methodology to address the relationship between ferritin level and alopecia in women (11).

Table 1. Biochemical profiles and complete blood count indices in women with diffuse telogen hair loss and control women

Variable	Women without hair loss (n=30)	Women with telogen hair loss (n=30)	<i>P</i> value
TSH, median (IQR), mU/L	1.5 (1.0-2.4)	1.2 (0.6-2.4)	0.391 ^I
T4, median (IQR), µg/dL	8.1 (6.7-13.9)	7.4 (6.4-12.4)	0.442 ^I
ESR, median (IQR), mm/h	15 (8.5-19.5)	11.5 (7.7-17.7)	0.704 ^I
WBC, median (IQR), ×10 ³ /mm ³	5.5 (4.7-6.2)	5.1 (4.2-6.2)	0.384 ^I
RBC, mean (SD), ×10 ⁶ /mm ³	4.5±0.3	4.4±0.3	0.570 ^{II}
Hb, median (IQR), g/dL	12.9 (12.6-13.4)	12.6 (11.8-13.4)	0.102 ^I
Hct, median (IQR), %	39.2 (38.0-39.8)	38.1 (35.7-40.2)	0.186
MCV, median (IQR), fL	88.3 (86.2-90.6)	88.2 (84.1-91.3)	0.976 ^I
MCH, median (IQR), pg/cell	29.7 (27.9-30.2)	29.1 (27.3-30.3)	0.467 ^I
MCHC, mean (SD), %Hb/cell	33.4±0.6	32.9±0.6	0.010 ^{II}
Plt, mean (SD), ×10 ³ /mm ³	232.5±48.3	261.6±52.5	0.044 ^{II}
Serum iron, mean (SD), µg/dL	87.8±33.4	77.0±38.8	0.251 ^{II}
TIBC, mean (SD), µg/dL	319.2±66.1	367.8±58.2	0.004 ^{II}
Serum ferritin, mean (SD), ng/mL	60.3±50.1	16.3±12.6	<0.001 ^{II}
Transferrin saturation, mean (SD), %	28.3±11.8	20.3±9.7	0.006 ^{II}

IQR, interquartile range; TSH, thyroid stimulating hormone; T4, thyroxine; ESR, erythrocyte sedimentation rate; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; MCV, mean cell volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; Plt, platelet; ^IMann-Whitney *U* test was used for skewed continuous data; ^{II}Student's *t*-test was used for continuous data with normal distribution.

Table 2. Odds ratio for cut-offs of hemoglobin and serum ferritin in women with diffuse telogen hair loss compared with control women

	Women without hair loss (n=30)	Women with telogen hair loss (n=30)	OR (95%CI) ¹
Hb ≥12 mg/dL	29	22	1.00
Hb <12 mg/dL	1	8	10.5 (1.2-90.7)
Serum ferritin >10 ng/L	28	20	1.00
Serum ferritin ≤10 ng/L	2	10	7.0 (1.4- 35.5)
Serum ferritin >30 ng/mL	18	2	1.00
Serum ferritin ≤30 ng/mL	12	28	21.0 (4.2-105.0)

OR, odds ratio; CI, confidence interval; Hb, hemoglobin; ¹P<0.001.

Other previous studies relied on observational methodologies rather than statistical tests to draw their conclusions (3,7,9,10). The present investigation was one of the largest studies of iron status and telogen hair loss in women, particularly as earlier studies included both male and female subjects, with the size of control group without hair loss ranging from zero (chronic telogen effluvium/AA and alopecia areata) to 11 (various types of hair loss, n=15) and 20 (diffuse alopecia) (7-10,12). Only one case-control study compared 43 female subjects with AA or diffuse alopecia (as a variant of AA), having a relatively large age-matched control group (n=46) and excluding cases with pregnancy, thyroid problems, acute febrile disease, hyperandrogenism, chronic disease, or use of medications. In this study, there was no association between iron deficiency and hair loss (13).

Furthermore, we evaluated both patients with telogen hair loss and control group for chronic systemic disease, weight loss, diet, prior operation, pregnancy and lactation, use of certain medications, and dysfunctional thyroid through clinical and laboratory examination, as they might be associated with hair loss or could raise serum ferritin; thus we ruled out the possibility that the ferritin level in the controls was elevated due to these common disorders. The mean serum ferritin level in our women without hair loss (60.3 ng/mL) closely approximated the mean ferritin level in normal women (54.9 mg/L), as reported from a large population-based study in more than 10,000 individuals (14).

Except for serum iron and hemoglobin concentration, serum ferritin, transferrin saturation and TIBC suggested iron deficiency status in many women with alopecia. However, these levels generally were within the normal range among women with hair loss. In other words, the women with serum ferritin ≤30 ng/mL were at a significant risk of

developing telogen hair loss, as 93.3% of patients with telogen hair loss had this level of serum ferritin. Among women with laboratory anemia, 88.9% had diffuse telogen hair loss. All women with iron deficiency anemia had serum ferritin level lower than 30 ng/mL. Generally, serum ferritin is directly related to intracellular ferritin and thus to total body iron stores (15). Only iron deficiency causes very low serum ferritin concentrations; therefore, low serum ferritin level is very specific for iron deficiency (16). Although many laboratories use serum ferritin levels of 10 to 15 ng/mL as the lower limits of normal based on reference sample groups, it has a sensitivity of only 59% and specificity of 99% for diagnosing iron deficiency. In women of childbearing age, using a cut-off of 10-15 ng/mL yields a sensitivity of 75% and specificity of 98%, while a cut-off of 30 ng/mL yields a sensitivity of 92% and specificity of 98% (17,18). Investigators consider serum ferritin to be the most powerful screening tool for iron deficiency. One large review concludes that serum ferritin has a greater predictive value than other tests of iron status, such as transferrin saturation and erythrocyte zinc protoporphyrin (19). In iron overload, ferritin is increased. Ferritin is also an acute phase reactant and is elevated in anemia of chronic disease (20,21).

Iron deficiency has been commonly listed as a possible cause of telogen effluvium; however, this still remains controversial (22,23). A recent case-control study found the mean serum ferritin levels in women with AA and alopecia areata to be significantly lower as compared with normal controls. However, the lack of lower ferritin levels in patients with telogen effluvium might be related to its multifactorial nature. Medications, fevers, rapid weight loss, and numerous other factors may cause telogen effluvium (3,5). As all patients with telogen effluvium were included, it is possible that a subset of women with telogen effluvium triggered by low iron body stores were not detected (11).

Thus, our strong correlation between iron status and telogen hair loss could be reasonable as we selected otherwise healthy women with diffuse alopecia. In another study, iron deficiency anemia and iron deficiency were found in 14% and 71% of female subjects, respectively. However, no statistical comparison with a population-based study is reported (9). A prospective cohort study of female subjects with diffuse telogen hair loss found that 12 (6%) subjects had serum ferritin levels less than or equal to 20 ng/mL. In five women, iron deficiency was considered on differential diagnosis of their hair loss; none of these women responded to iron replacement therapy (12). In contrast, another prospective controlled study in premenopausal women with diffuse AA revealed a significant increase in the mean total hair density and meaningful hair densities in treatment group patients with serum ferritin levels >40 ng/mL. Treated patients with serum ferritin levels ≤40 ng/mL showed no significant change in the mean total and meaningful hair densities (24). These findings are consistent with a previous study in premenopausal women with diffuse alopecia, where 72% had serum ferritin levels below the lowest level recorded in controls (40 ng/mL) (8). Also, in a prospective double-blind, placebo-controlled study in women with chronic telogen effluvium, subjects receiving 72 mg of iron and 1.5 g of L-lysine daily for 6 months showed a serum ferritin level increase, from 41.3 to 68.9 ng/mL and a 31% reduction in the amount of hair shed (4).

The deleterious effects of iron deficiency are partly due to impaired oxygen delivery to the tissues and to a deficiency of iron-containing compounds (25). From a biologic point of view, hair follicle matrix cells as the most rapidly proliferating cells in the body appear to have lower levels of ferritin and higher levels of free iron (26,27). Another likely mechanism for the possible effect of iron on hair growth stems from its requirement as a cofactor for ribonucleotide reductase, the rate-limiting enzyme for DNA synthesis. Iron depletion could prevent proper function of this enzyme, resulting in inhibition of proliferation (28).

Although we demonstrated a strong association between low ferritin levels and diffuse telogen hair loss, the causality between low iron stores and alopecia was not demonstrated *per se*. As ferritin levels accurately reflect body iron stores, our study clearly demonstrated the association between low iron stores (i.e. iron deficiency status and/or anemia) and telogen hair loss. More detailed cohort and interventional studies are

necessary to assess the role of iron in diffuse hair loss, especially in women during childbearing years. Currently, there is insufficient evidence to recommend iron supplementation therapy for patients with alopecia and iron deficiency in the absence of iron deficiency anemia. The decision to do either should be based on clinical judgment.

Assessment of iron status in women plays a significant role in telogen hair loss and it may be important both in designing new therapies and in generating hypotheses to better elucidate the biochemical underpinnings of this disorder. From these findings, we recommend universal screening for iron deficiency in patients with hair loss, especially among high risk women. Although serum ferritin is very specific in diagnosing iron deficient condition, other iron indices including TIBC and transferrin saturation are considered consistently reliable indicators of iron deficiency in otherwise healthy women with telogen hair loss. While independent confirmation is awaited, it would seem appropriate to consider the nutritional status of women with telogen hair loss. Further, there appears to be a minimum ferritin concentration required to optimize treatments in diffuse hair loss. What level of serum ferritin to use is still not fully resolved; and the level of supplementation or dietary change needed to maintain serum ferritin levels above this optimal level is the subject of continuing research.

References

1. Van Neste DJ, Rushton DH. Hair problems in women. *Clin Dermatol* 1997;15:113-25.
2. Eckert J, Church RE, Ebling FJ, Munro DS. Hair loss in women. *Br J Dermatol* 1967;79:543-8.
3. Harrison S, Sinclair R. Telogen effluvium. *Clin Exp Dermatol* 2002;27:389-95.
4. Rushton DH. Nutritional factors and hair loss. *Clin Exp Dermatol* 2002;27:396-404.
5. Headington J. Telogen effluvium: new concepts and review. *Arch Dermatol* 1993;129:356-63.
6. Kligman A. Pathological dynamics of reversible hair loss in humans. I. Telogen effluvium. *Arch Dermatol* 1961;83:175-98.
7. Hard S. Non-anemic iron deficiency as an etiologic factor in diffuse loss of hair of the scalp in women. *Acta DermVenereol* 1963;43:562-9.
8. Rushton DH, Ramsay ID, James KC, Norris MJ, Gilkes JJ. Biochemical and trichological characterization of diffuse alopecia in women. *Br J Dermatol* 1990;123:187-97.

9. White MI, Currie J, Williams MP. A study of the tissue iron status of patients with alopecia areata. *Br J Dermatol* 1994;130:261-3.
10. Boffa MJ, Wood P, Griffiths CE. Iron status of patients with alopecia areata. *Br J Dermatol* 1995;132:662-4.
11. Kantor J, Kessler LJ, Brooks DG, Cotsarelis G. Decreased serum ferritin is associated with alopecia in women. *J Invest Dermatol* 2003;121:985-8.
12. Sinclair R. There is no clear association between low serum ferritin and chronic diffuse telogen hair loss. *Br J Dermatol* 2002;147:982-4.
13. Aydingoz IE, Ferhanoglu B, Guney O. Does tissue iron status have a role in female alopecia? *J Eur Acad Derm Venereol* 1999;13:65-7.
14. Beutler E, Felitti V, Ho NJ, Gelbart T. Relationship of body iron stores to levels of serum ferritin, serum iron, unsaturated iron binding capacity and transferrin saturation in patients with iron storage disease. *Acta Haematol* 2002;107:145-9.
15. Brittenham GM. Disorders of iron metabolism: iron deficiency and overload. In: Hoffman R, ed. *Hematology: basic principles and practice*. 3rd edn. New York: Churchill-Livingstone; 2000. pp. 397-428.
16. Trost LB, Bergfeld WF, MD, Calogeras E. The diagnosis and treatment of iron deficiency and its potential relationship to hair loss. *J Am Acad Dermatol* 2006;54:824-44.
17. Schrier SL. Causes and diagnosis of anemia due to iron deficiency. Available from: www.UpToDate.com. Accessed April 18, 2005; last updated November 6, 2003.
18. Centers for Disease Control (CDC). Recommendations to prevent and control iron deficiency in the United States. *Morb Mortal Wkly Rep* 1998;47:1-36.
19. Guyatt GH, Oxman AD, Ali M, Willan A, McIlroy W, Patterson C. Laboratory diagnosis of iron-deficiency anemia: an overview. *J Gen Intern Med* 1992;7:145-53.
20. Schrier SL, Bacon BR. Pathophysiology and diagnosis of iron overload symptoms. 2004. Available from: www.UpToDate.com. Accessed April 23, 2004; last updated January 9, 2004.
21. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;352:1011-23.
22. Dawber RPR, Simpson NB, Barth JH. Diffuse alopecia: endocrine, metabolic and chemical influences on the follicular cycle. In: Dawber RPR, ed. *Diseases of the hair and scalp*. 3rd edn. Oxford: Oxford University Press; 1997. p. 129.
23. Sinclair R. Diffuse hair loss. *Int J Dermatol* 1999;38(Suppl 1):8-18.
24. Rushton DH, Ramsey 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.
25. Hallberg L. Iron absorption and iron deficiency. *Hum Nutr Clin Nutr* 1982;36:250-78.
26. Larsson LG, Ivhed I, Gidlund M, Pettersson U, Vennstrom B, Nilsson K. Phorbol ester-induced terminal differentiation is inhibited in human U-937 monoblastic cells expressing a V-Myc oncogene. *Proc Natl Acad Sci U S A* 1988;85:2638-42.
27. Liao G, Chan LM, Feng P. Increased ferritin gene expression is both promoted by cAMP and a marker of growth arrest in rabbit vascular smooth muscle cells. *J Biol Chem* 1991;266:1819-26.
28. Elledge SJ, Zhou Z, Allen JB. Ribonucleotide reductase: regulation, regulation, regulation. *Trends Biochem Sci* 1992;17:119-23.