ORIGINAL ARTICLE
See related Commentary on pages xiii and xvii

Decreased Serum Ferritin is Associated With Alopecia in Women

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Alopecia in women is a common problem, and conflicting observational data have failed to determine whether an association exists between alopecia and iron deficiency in women. We therefore utilized an analytical cross-sectional methodology to evaluate whether common types of alopecia in women are associated with decreased tissue iron stores, as measured by serum ferritin. We studied patients with telogen effluvium ($n = 30$), androgenetic alopecia ($n = 52$), alopecia areata ($n = 17$), and alopecia areata totalis/universalis ($n = 7$). The normal group consisted of 11 subjects without hair loss from the same referral base and source population as those patients with alopecia. We analyzed the data utilizing the unpaired Student's *t* test assuming unequal variances with an α adjustment for multiple comparisons to assess whether the mean ages, ferritin levels, and hemoglobin levels of women without hair loss differed from the means in each alopecia group. The mean age of patients and normals did not differ significantly. We found that the mean ferritin level (ng per ml [95% confidence intervals]) in patients with androgenetic alopecia (37.3 [28.4, 46.1]) and alopecia areata (24.9 [17.2, 32.6]) were statistically significantly lower than in normals without hair loss (59.5 [40.8, 78.1]). The mean ferritin levels in patients with telogen effluvium (50.1 [33.9, 66.33]) and alopecia areata totalis/universalis (52.3 [23.1, 81.5]) were not significantly lower than in normals. Our findings have implications regarding therapeutics, clinical trial design, and understanding the triggers for alopecia. ***Key words: hair/iron/hemoglobin/female. J Invest Dermatol 121:985–988, 2003***

Hair loss affects over 25% of women in developed countries (Van Neste and Rushton, 1997). Three hair disorders, androgenetic alopecia (AGA), telogen effluvium (TE), and alopecia areata (AA) account for almost all cases of nonscarring alopecia in women (Eckert *et al*, 1967; Van Neste and Rushton, 1997). Despite their prevalence, few epidemiologic studies have addressed the etiology of and risk factors for these hair disorders (van der Steen *et al*, 1992; Garcia-Hernandez and Rodriguez-Pichardo, 1999). Dermatologists commonly assess serum iron status in women because of the assumption that iron deficiency causes alopecia. Little objective evidence supports this practice, however.

TE, or hair shedding, results from the synchronous transition of hair follicles from the growing stage of the hair cycle (anagen) to the resting stage of the hair cycle (telogen) (Headington, 1993; Harrison and Sinclair, 2002). Common precipitating events include childbirth, fever, and medications, although precipitating factors are often not discernable (Paus and Cotsarelis, 1999). TE lasting greater than 6 mo is referred to as "chronic TE" (Whiting, 1996). AGA in women, as in men, is thought to be an androgen-driven process that causes miniaturization of genetically predisposed hair follicles, and results in a pattern of hair loss involving the superior scalp (Ludwig, 1977). AA is an autoimmune process associated with lymphocytic infiltrates surrounding affected hair bulbs (Gilhar *et al*, 1998; Bertolino, 2000).

Observational data have suggested that alopecia in women may be associated with decreased body iron stores (Hard, 1963; Rushton *et al*, 1990; Van Neste and Rushton, 1997). Some studies have suggested that decreased body iron stores (as measured by serum ferritin) may be associated with TE (Van Neste and Rushton, 1997). Two observational studies evaluated the association between decreased ferritin levels and 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 (White *et al*, 1994; Boffa *et al*, 1995). No studies have utilized standard epidemiologic methodologies to evaluate the relationship between alopecia in women and decreased iron stores. Therefore, our goal was to determine whether women with hair loss have lower serum ferritin levels compared to controls using an analytical methodology.

METHODS

Patients with hair loss were obtained by selecting 108 consecutive patients with the diagnosis of AGA, TE, AA, or alopecia areata totalis/universalis (AAT/U) treated at the University of Pennsylvania hair and scalp clinic. All patients were evaluated by one dermatologist (GC). All diagnoses were made by history and physical examination. The diagnosis of AGA was made as described by Olsen (1999). In general, these women had widening of the midline hair part and preservation of the anterior hair line. The diagnosis of TE was made if the patients had increased shedding by history or physical examination. For the purposes of this portion of the study, i.e., to determine whether women with hair shedding of any kind had lower ferritin levels than controls, the duration of the hair loss was not taken into account. The diagnoses of AA, AAT, and AAU were also made by history

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Abbreviations: AA, alopecia areata; AAT/U, alopecia areata totalis/universalis; AGA, androgenetic alopecia; TE, telogen effluvium; TSH, thyroid stimulating hormone.

and physical examination, as described previously (Madani and Shapiro, 2000). All patients were euthyroid, as measured by thyroid stimulating hormone (TSH) levels. We abstracted data, including serum ferritin, hemoglobin, and erythrocyte sedimentation rate, from the records of all patients. This population included a total of 52 patients with AGA, 30 patients with TE, 17 patients with AA, and seven patients with AAT/U. Two patients were excluded because they had elevated erythrocyte sedimentation rates (>30 mm per h), which may indicate nonspecific inflammation that could also raise ferritin and invalidate its use as a marker of iron status.

To obtain normal patients without hair loss, we sampled individuals screened in the Hospital of the University of Pennsylvania Division of Medical Genetics. This group consisted of patients having neither of the common mutations in the HFE-1 gene for hereditary hemochromatosis. These women were either spouses of patients with hemochromatosis (two), healthy relatives of patients with hemochromatosis (two) or "walk-in" patients (seven) evaluated at the University of Pennsylvania Health System, and reflect a similar referral base and source population as those seen in the hair loss clinic. We abstracted the charts of all women and recorded patient age, medical history, serum ferritin, and hemoglobin. None of these women volunteered information regarding a history of alopecia. Of the 13 normals abstracted, one was excluded due to incomplete records and one was excluded due to a history of elevated serum ferritin and the subsequent diagnosis of hyperferritinemia/cataract syndrome, leaving a total of 11 normals for analysis.

Prior to statistical analyses, patients were coded as having AGA, TE, AA, or AAT/U, as described in their medical chart. Given the nature of these disorders, patients could be coded as having more than one disorder, although no patients were coded as having both AA and AAT/U. Data were first evaluated utilizing the unpaired Student's *t* test assuming unequal variances with an α correction for multiple comparisons in order to assess whether the mean ages of patients without hair loss differed from the mean age of each individual alopecia group. Unequal variances were assumed in order to take a conservative statistical approach. As we compared multiple means to a single mean (for the normal group), we adjusted the α for each individual *t* test to reflect these multiple comparisons. Thus, an available α of 0.05 in total could be spent on all comparisons. The *t* test with α correction was then used to determine whether the ferritin level in each of the individual alopecia groups was lower than the mean ferritin level in normals. We also used the *t* test with α correction to evaluate whether the mean hemoglobin levels of patients with alopecia were significantly lower than normals. One-sided p-values utilizing the traditional cutoff of $p \leqslant 0.05$ were utilized in order to determine statistical significance, with the 0.05 divided over all comparisons as noted above. Reporting the one-sided p-values is appropriate as the clinical question we are addressing is whether the mean ferritin and hemoglobin levels in patients with alopecia are *lower* than in normals. We conducted a secondary analysis utilizing the *t* test to compare mean ferritin levels in women aged 40 and under.

This study was approved by the Institutional Review Board of the University of Pennsylvania. Statistical analyses were conducted using Stata 6.0 for Windows NT (College Station, TX).

RESULTS

The mean and median ferritin levels, hemoglobin levels, and ages of patients with alopecia and of the normals with 95% confidence intervals and ranges are listed in **Table I**. The ages of patients with hair loss and normals did not differ significantly. This suggests that any differences in ferritin levels between patients with alopecia and those without alopecia are not secondary to differences in age.

Using the *t* test, we found that the mean ferritin levels in patients with AGA or AA were statistically significantly lower than levels in women without hair loss (**Table I**). The ferritin levels in patients with TE or AAT/U were not statistically significantly lower than in normals. The mean hemoglobin levels in patients with AGA, TE, AA, or AAT/U were not statistically significantly lower than in normals (**Table I**).

Because previous investigators raised the possibility that younger women as a group are more commonly iron deficient and that this may spuriously imply a relationship between hair loss and mild iron deficiency, we performed a secondary analysis of women aged 40 and under to determine whether the significant difference in ferritin levels persisted in younger women who were less likely to be postmenopausal. This analysis demonstrated that ferritin levels in patients with AA, TE, and AGA were significantly lower than those in normals in this age group. Hemoglobin was also lower in women less than 40 with TE compared to controls.

DISCUSSION

This is the first study that utilizes an analytical methodology to address the relationship between ferritin levels and alopecia in women. Previous studies relied on observational methodologies, rather than statistical tests, in order to draw their conclusions (Hard, 1963; White *et al*, 1994; Boffa *et al*, 1995; Harrison and Sinclair, 2002). This investigation is also one of the largest studies to address iron status and alopecia in women, particularly as many

Table I. Mean age, hemoglobin, and ferritin values with 95% confidence intervals for each group and for subjects 40 y old or less

	Mean age ($\pm$95% CI) Median (range)	Mean hemoglobin ($\pm$95% CI) Median (range)	Mean ferritin ($\pm$95% CI) Median (range)
All subjects			
Normals ($n=11$)	41.9 (36.4, 47.5)	13.5 (12.7, 14.4)	59.5 (40.8, 78.1)
	40 (24–52)	13.7 (11.9–14.5)	58.0 (27.0–117.0)
AGA ($n=52$)	44.3 (40.6, 48.1)	13.3 (13.0, 13.6)	37.3* (28.4, 46.1)
	45 (18–71)	13.3 (10.8–15.2)	27.0 (2.0–153.0)
TE ($n=30$)	47.9 (42.8, 53.0)	13.4 (13.1, 13.7)	50.1 (33.9, 66.3)
	47 (18–71)	13.4 (11.4–15.0)	43.0 (10.0–215.0)
AA ($n=17$)	34.9 (27.5, 42.3)	13.0 (12.2, 13.7)	24.9* (17.2, 32.6)
	31 (18–69)	13.4 (9.1–14.9)	21.5 (4.0–59.0)
AU + AT ($n=7$)	53.1 (39.6, 66.6)	13.6 (13.1, 14.0)	52.3 (23.1, 81.5)
	52 (29–79)	13.6 (13.0–14.4)	43.0 (18.0–112.0)
Subjects $\leqslant 40$			
Normals ($n=6$)	36.2 (29.8, 42.5)	13.8 (11.8, 15.7)	62.3 (30.1, 94.6)
	38 (24–40)	14.0 (12.9–14.4)	55.5 (29.0–117.0)
AGA ($n=16$)	29.6 (25.3, 33.8)	13.2 (12.6, 13.8)	23.8* (15.7, 31.8)
	31 (18–40)	13.1 (10.8–15.2)	22.5 (2.0–52.0)
TE ($n=4$)	25.3 (10.4, 40.1)	12.0* (10.4, 13.6)	15.0* (0, 78.5)
	22 (18–39)	11.9 (11.4–12.7)	15.0 (10.0–20.0)
AA ($n=11$)	26.2 (21.4, 31.0)	13.0 (11.9, 14.1)	23.3* (12.0, 34.6)
	27 (18–39)	13.4 (9.1–14.9)	18.5 (4.0–59.0)

Hemoglobin levels are listed as g per dL and ferritin levels are given as μg per L. CI, confidence intervals;
*$p<0.05$ *vs* normals.

earlier studies included both men and women as patients (White *et al*, 1994; Boffa *et al*, 1995). Although the sample size of the normal group was relatively small, the mean serum ferritin level for this group (59.5 μg per L) closely approximates the mean ferritin level in normal women (54.9 μg per L) as described in a recently published large-population-based study of more than 10,000 people (Beutler *et al*, 2000). Furthermore, we evaluated the control patients for hemochromatosis through clinical and genetic testing; thus we ruled out the possibility that the ferritin level in the controls was elevated because of this common disorder. HFE-1 mutations are found in approximately 5%–10% of the population (Merryweather-Clarke *et al*, 1997; Steinberg *et al*, 2001), and heterozygotes and homozygotes have elevated ferritin levels (Beutler *et al*, 2002).

We discovered that, although both hemoglobin and ferritin levels were decreased in many women with alopecia, these levels generally still fell within the "normal range". Thus, so-called "normal values" for ferritin and hemoglobin may include women who are physiologically depleted of iron (Rushton *et al*, 2002). Because of the study design, we could only demonstrate an association between low ferritin levels and specific types of alopecia. Causality between low iron stores and alopecia was not demonstrated *per se*. As ferritin levels accurately reflect body iron stores, however (Walters *et al*, 1973; Jacobs, 1977), our study clearly demonstrates an association between low iron stores and AA or AGA.

The lack of lower ferritin levels in patients with TE may be due to its multifactorial nature. Medications, fevers, rapid weight loss, and numerous other factors may cause TE (Headington, 1993; Harrison and Sinclair, 2002). As we included all patients with TE, including chronic TE, it is possible that we may not have detected a subset of women with TE that was triggered by low iron body stores. For example, although limited by low patient numbers, our data do suggest that iron deficiency may play a role in triggering TE in women less than 40 y old. More detailed studies will be necessary to evaluate the role of iron in TE, especially in women less than 40 y old.

The normal ferritin and hemoglobin levels found in AAT/U support the notion that patients with this severe form of alopecia are genetically distinct from patients with AA (Colombe *et al*, 1995; 1999). These patients may be highly predisposed to develop AAT/U, and may not require exogenous triggering factors. Alternatively, our findings can be interpreted to mean that low body iron levels play a greater role in triggering AA rather than maintaining the condition. Future studies, however, especially into the genetics of AA and AAT/U (McDonagh and Messenger, 2001; Tazi-Ahnini *et al*, 2002), will be necessary to address this speculation.

Given the etiologically distinct nature of AA and AGA, it is surprising that they share a relatively low serum ferritin level. To explain this, we propose a "threshold hypothesis", which states that decreased iron stores lower the threshold for developing different types of alopecia (**Fig 1**). For example, in individuals with a very strong genetic predisposition to developing AA or AGA (hypothetical patient 1, **Fig 1**), it is possible that low body iron stores are not important for 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 (hypothetical patient 2, **Fig 1**). One would predict that these patients would be the most likely to benefit from iron therapy. This is particularly significant to consider in patients with AA, as the triggering factors in this disorder are not known. Lastly, in those individuals without a hereditary predisposition or without other triggering factors, low iron stores would not cause alopecia (hypothetical patient 3, **Fig 1**).

From the perspective of clinical trial design, our results suggest that correcting iron deficiency prior to the start of a clinical trial may aid in accurately assessing the efficacy of therapies for alopecia in women. Earlier evidence of differential responses to therapy in women with and without decreased ferritin levels (Rushton and Ramsay, 1992) also suggests that normalizing ferritin levels should be accomplished during the run-in period of clinical trials in order to avoid type II error (i.e., concluding that a therapy is not helpful when in reality it is efficacious). Our findings suggest that treatment of women with low ferritin levels still within the normal range may be indicated, although ideally a clinical trial evaluating the efficacy of iron supplementation in these women should be performed.

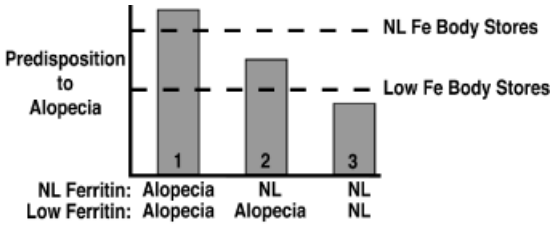

Figure 1. Alopecia threshold hypothesis. Illustrated are three hypothetical patients (1, 2, and 3). The height of the bars indicates the predisposition of each patient to developing alopecia. The *dashed line* indicates the threshold at which alopecia develops. In this model, low body iron (Fe) stores decrease the threshold for developing different types of alopecia. NL, normal.

From a biologic point of view, hair follicle matrix cells are some of the most rapidly proliferating cells in the body. At the cellular level, ferritin levels are increased in nondividing cells, such as stem cells and terminally differentiated cells, whereas rapidly proliferating cells appear to have lower levels of ferritin and higher levels of free iron (Larsson *et al*, 1988; Beaumont *et al*, 1989; Liau *et al*, 1991; Vet *et al*, 1997; Wu *et al*, 1999). This balance of ferritin and iron is at least partially controlled by the transcription factor c-myc (Wu *et al*, 1999). Overexpression of c-myc in the cutaneous epithelium results in loss of follicular differentiation and a decrease in stem cells (Waikel *et al*, 2001), but whether this phenotype is related to abnormal iron metabolism remains to be determined. Another likely mechanism for iron's possible effect on hair growth stems from its requirement as a cofactor for ribonucleotide reductase, the rate-limiting enzyme for DNA synthesis. The depletion of iron could prevent proper functioning of this enzyme resulting in inhibition of proliferation (Elledge *et al*, 1992). Inhibition of other iron-dependent enzymes, such as stearyl CoA desaturase, which when mutated causes hair loss in mice (Zheng *et al*, 1999) and is also present in the human hair follicle (Zheng *et al*, 2001), could contribute to hair loss as well.

There are several limitations to this study, including the relatively modest sample size. This remains the largest sample size of all iron status and female hair loss studies in the literature, however. *A priori* sample size calculations suggested that 10 patients per group would be needed to demonstrate a clinically significant difference in ferritin levels, and clearly we exceeded this goal. Moreover, as noted above, the similarity of the mean ferritin in normals and that from a large-population-based study (Beutler *et al*, 2000) also bolsters our findings. Other limitations of our study are similar to those seen in any study of association—selection bias, confounding, and the role of chance. We attempted to control for all of these in this study. We drew our patients with hair loss and normals from clinics in the same health care system. This technique is often used in order to minimize the differences in the populations of patients being compared, but of course it remains imperfect, and a randomized controlled trial remains the gold standard. We compared the mean ages of normals and patients with hair loss in order to control in some measure for confounding. There are other potential sources of confounding, but we addressed the only one that has been discussed in previous reports. Finally, we used the *t* test with an α correction in order to control for chance; what this means is that there is less than a 5% chance that our findings are due to chance. Because we compared multiple means to a single mean, the *t* test with correction

(allowing a maximum of 5% chance association over *all* comparisons) is the appropriate statistical technique.

Our findings should serve as an epidemiologic stepping stone from which further research, including clinical trials of iron therapy and an evaluation of the role of iron in alopecia in males, can be launched. We propose a threshold hypothesis for explaining the ecumenical effect of decreased iron stores on a variety of etiologically distinct forms of hair loss. Appreciating the importance of iron as a factor in hair loss may be important both in designing new therapies and in generating hypotheses to better elucidate the biochemical underpinnings of these disorders. Future recommended assessments for AA should include an evaluation of ferritin levels (Olsen *et al*, 1999).

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