Editorial

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No Association between Serum Ferritin Levels >10 μg/l and Hair Loss Activity in Women

Amadé Bregy Ralph M. Trüeb

Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland

Hair loss is a common complaint in women and affects over 25% of women in developed countries [1]. Female pattern hair loss (FPHL) and diffuse telogen effluvium (TE) account for the majority of cases [2–7]. In both conditions, low iron stores have been considered a possible contributing factor. Therefore, assessment of serum ferritin levels is generally recommended as part of the routine investigation, and dermatologists commonly prescribe iron supplementation in women under the assumption that low iron stores may cause hair loss. Contradictory observational data have so far failed to support this practice, however. Although nonanemic iron deficiency as an etiologic factor for diffuse hair loss in women was first postulated by Hard in 1963 [8], it is not until recently that the significance of iron stores as assessed by serum ferritin levels in women with hair loss has been systematically studied [9]. Various observational studies have evaluated the association between decreased ferritin levels and hair loss and resulted in opposing conclusions [10–16]. The controversy starts with a debate over what is the normal serum ferritin level for women [17], and is further complicated by the use of different reference ranges by different laboratories, based on individual interpretations of the literature on this subject. A cutoff point of 10–15 μg/l is considered to yield a sensitivity of 59% and a specificity of 99% for diagnosing iron deficiency [18] and is used by many laboratories as the lower limits of normal based on reference sample groups. In women of childbearing age, using a cutoff of 10–15 μg/l yields a sensitivity of 75% and specificity of 98% [19]. A cutoff of 30 μg/l yields a sensitivity of 92% and a specificity of 98% [18]. The reference laboratory cited in this study uses 10 μg/l as lower limit of normal for menstruating women, and 30 μg/l for children, men and nonmenstruating women.

Increased shedding of telogen hair results either from synchronous transition of hair follicles from the growing (anagen) to the resting (telogen) stage of the hair cycle, or from progressive shortening of duration of anagen [20, 21]. The former mechanism underlies TE, the latter FPHL. Different methods have been adapted for quantification of hair loss. Of these, the trichogram is the first technique standardized for this purpose, and has probably been the most widely used in dermatologic practice. Initially developed in 1957 by van Scott's group, subsequently other authors modified and standardized the technique defining uniform and strict criteria for reliably assessing the different morphological hair root structures to ensure comparable results [22, 23]. A telogen rate of >15% in scalp hair is considered pathologic in women. In TE, the telogen rate is elevated in all regions of the scalp, including the occipital area; in FPHL, the telogen rate is elevated in the frontal and centroparietal scalp region and spares the occipital scalp.

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Ralph M. Trüeb, MD
Department of Dermatology, University Hospital of Zurich
Gloriastrasse 31
CH–8091 Zurich (Switzerland)
Tel. +41 44 255 30 79, Fax +41 44 255 44 31, E-Mail ralph.trueeb@usz.ch

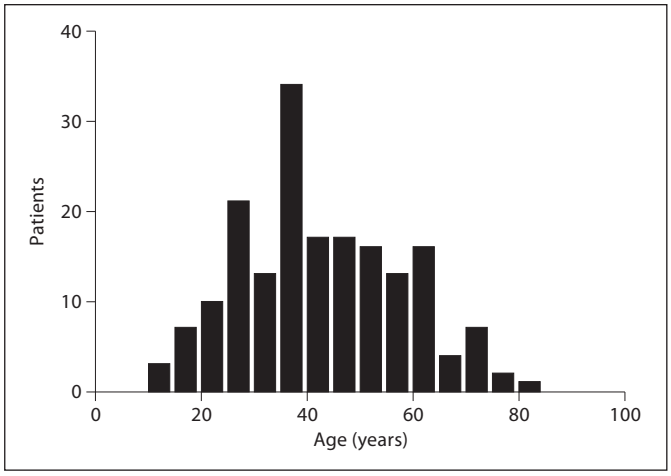

Fig. 1. Histogram showing distribution of patients and their age.

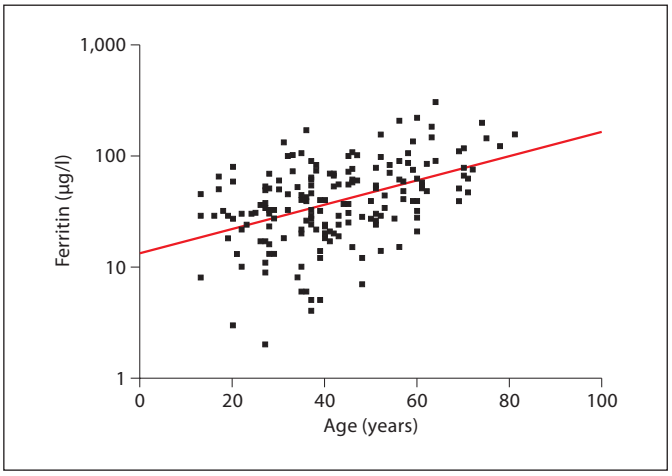

Fig. 2. Diagram showing correlation between patients' age and their serum ferritin values.

The goal of this study was to determine a relationship between serum ferritin levels and hair loss activity, as determined by trichogram, in otherwise healthy women with FPHL or TE.

Patients and Methods

Between 2002 and 2005, 418 consecutive women who presented at the Department of Dermatology, University Hospital of Zurich hair clinic, for assessment of hair loss underwent biochemical screening, including serum ferritin, and trichogram.

For the trichogram, all patients had at least fifty hairs plucked from two sampling sites on the frontal and occipital scalp, using a tightly closing epilation forceps. Uniformly, patients were instructed to leave the hair unwashed and untreated with any cosmetics for five days prior to the plucking of the hair for the trichogram. Immediately after epilation, the hair roots were embedded in Histokitt™ mounting medium which had previously been spread onto a glass slide for light microscopy. The hair roots were arranged neatly in a juxtaposition and covered with a coverslip. Quantification of the different hair roots on the basis of their morphological characteristics relating to the hair cycle was performed by the same investigator.

Biochemical investigations included thyroid function tests, C-reactive protein, and serum ferritin levels in all patients, renal and liver function tests, and hormonal studies in selected cases, as indicated. Patients with a history of disease, abnormal laboratory studies (except ferritin levels), or on drugs, including hormones, known to cause hair loss, were excluded from this study.

Statistical Analysis

Prior to statistical analyses, patients were coded as having FPHL or TE. FPHL was diagnosed either clinically (FPHL Ludwig patterns I–III with or without pathologic trichogram) or on the basis of a pathologic trichogram (frontal telogen rate >15%, occipital telogen rate normal). TE was diagnosed on the basis of a pathologic trichogram (occipital telogen rate >15%). Patients were subdivided into 3 subclasses: A: serum ferritin ≤10 µg/l, B: between 10 and 30 µg/l, C: ferritin >30 µg/l. For all subjects, subjects with FPHL, and subjects with TE and each group, the Pearson's product-moment correlation coefficient was calculated to determine a possible correlation between serum ferritin levels and telogen rates.

Results

After exclusion of patients with a history of disease, abnormal laboratory studies (except ferritin levels), or on drugs known to cause hair loss, 181 otherwise healthy women with FPHL and/or TE remained.

The mean age of these 181 women was 42.39 years (range: 13–81; fig. 1), and the mean ferritin level was 53.14 µg/l (range: 2–304). The total number of women with FPHL was 159 (87.8%), with a mean age of 42.82 years (range: 13–81). The mean ferritin level in this group was 54.95 µg/l (range: 3–304). This group was further subdivided into: women with clinical FPHL (Ludwig I–III) and normal trichogram, women with frontal telogen rate >15% with or without clinical FPHL ('active' FPHL), and women with clinical FPHL and occipital telogen rate >15% (combined FPHL and TE). The number of women with clinical FPHL and normal trichogram was 29 (16.0%) with a mean age of 38.72 years (range: 13–78) and a mean ferritin level of 47.62 µg/l (range: 5–146). The number of women with 'active' FPHL was 17 (9.4%) with a mean age of 42.94 years (range: 27–81) and a mean ferritin level of

Table 1. Mean age and ferritin values with 95% confidence intervals for all patients and subgroups

	Age, years				Ferritin, μg/l			
	mean	95% CI	median	range	mean	95% CI	median	range
All subjects (n = 181)	42.39	40.18–44.60	40	13–81	53.14	46.60–59.68	40	2–304
Total FPHL (n = 159)	42.82	40.43–45.22	40	13–81	54.95	47.96–61.93	41	3–304
Total TE (n = 135)	43.10	40.62–45.59	41	13–75	55.30	47.24–63.36	40	2–304
Subgroups								
FPHL with normal TG (n = 29)	38.72	32.38–45.07	35	13–78	47.62	35.37–59.87	40	5–146
'Active' FPHL (n = 17)	42.94	35.98–49.90	41	27–81	45.41	27.44–63.39	37	9–156
FPHL without TE (n = 46)	40.28	35.54–45.02	38	13–81	46.80	36.73–56.88	39	5–156
FPHL with TE (n = 113)	43.86	41.10–46.62	42	13–75	58.26	49.37–67.15	46	3–304
Exclusive TE (n = 22)	39.23	33.76–44.69	39	13–60	40.09	21.95–58.23	30	2–209

45.41 μg/l (range: 9–156). The number of women with combined FPHL and TE was 113 (62.4%) with a mean age of 43.86 years (range: 13–75) and a mean serum level of 58.26 μg/l (range: 3–304). The total number of women with TE (with or without clinical FPHL) was 135 (75.6%) with a mean age of 43.10 years (range: 13–75). The mean ferritin level in this group was 55.30 μg/l (range: 2–304). The number of women with exclusive TE was 22 (12.2%) with a mean age of 39.23 years (range: 13–60) and a mean ferritin level of 40.09 μg/l (range: 2–209). The mean age and serum ferritin values for all the subjects, subjects with FPHL, with TE, and subgroups are summarized in table 1.

There were 112 (61.9%) women with a serum ferritin level >30 μg/l, 55 (30.4%) between 10 and 30 μg/l, and 14 (7.7%) ferritin ≤10 μg/l. While there was a significant correlation ($p < 0.001$) between age of women and serum ferritin levels (fig. 2), with younger (menstruating) women having lower ferritin levels, no correlation was found between ferritin levels >10 μg/l and telogen rates, whether in total subjects, patients with FPHL, or patients with TE (table 2; fig. 3).

Table 2. Correlation of serum ferritin levels and telogen rates by ferritin ranges

Ferritin range	Frontal telogen rate, %	Occipital telogen rate, %	Mean ferritin value, μg/l	Correlation ($p < 0.05$)
A (≤10 μg/l)				
All (n = 14)	21.93	21.08	6.64	n.s.
FPHL (n = 10)	21.96	19.70	7.30	n.s.
TE (n = 12)	21.40	22.55	6.58	n.s.
B (>10 to ≤30 μg/l)				
All (n = 55)	20.05	22.17	22.16	n.s.
FPHL (n = 47)	19.49	19.68	22.44	n.s.
TE (n = 38)	23.01	28.50	22.23	n.s.
C (>30 μg/l)				
All (n = 112)	20.14	24.66	74.17	n.s.
FPHL (n = 102)	19.59	23.32	74.59	n.s.
TE (n = 85)	22.21	29.81	76.96	n.s.
Total				
All (n = 181)	20.25	23.63	53.14	n.s.
FPHL (n = 159)	19.71	22.02	54.95	n.s.
TE (n = 135)	22.36	28.79	55.30	n.s.

Discussion

Iron deficiency represents the most common nutritional deficiency with a prevalence of 12–16% in adolescent girls and women of childbearing age (16–49 years of age) and 6–9% in women 50 years of age and older in the USA [24]. The most common causes of iron deficiency in premenopausal women are menstrual blood loss, pregnancy and lactation, in postmenopausal women decreased absorption and gastrointestinal loss. Risk factors for iron deficiency include heavy menstrual bleeding (≥80 ml per month), use of an intrauterine device, history of iron deficiency anemia, and insufficient iron intake.

Total body iron is distributed among storage iron, transport iron, and functional iron. Storage iron is the body's iron reserves that are tissue bound and measured by serum ferritin concentration; transport iron is trans-

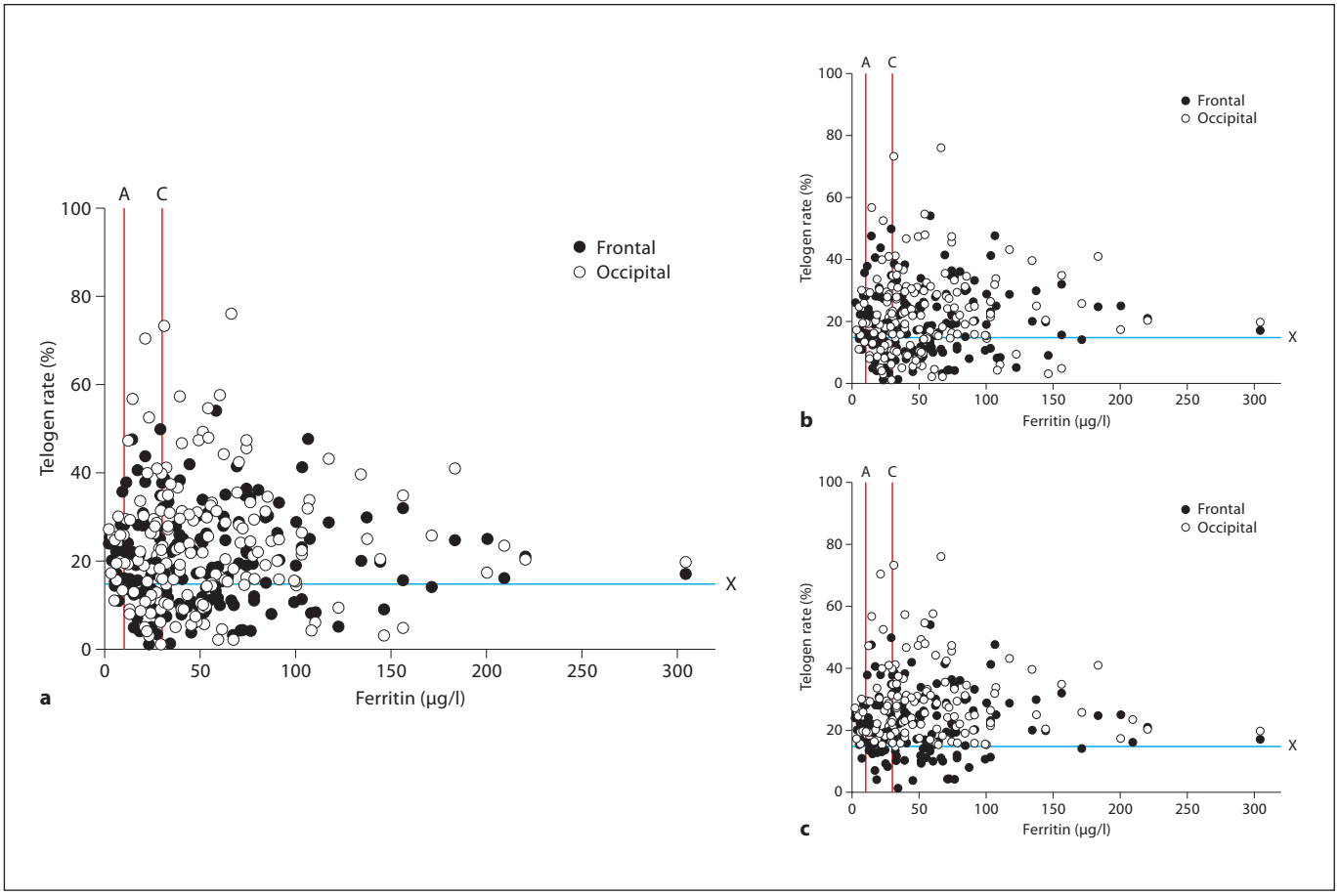

Fig. 3. Diagram showing ferritin values and corresponding telogen rates of the frontal and occipital scalp of all patients (n = 181; **a**), subjects with FPHL (n = 159; **b**) and subjects with TE (n = 135; **c**) in a linear scale. Vertical line A represents the lower reference limit of normal with 75% sensitivity and 98% specificity for diagnosing iron deficiency in women of childbearing age. Vertical line C represents the cutoff point with sensitivity of 92% and specificity of 98% for diagnosing iron deficiency. Horizontal line X represents the cutoff point for pathologic telogen rate (>15%).

ported to the tissues and measured by transferrin concentration and saturation, and functional iron consists of iron that is bound to hemoglobin, myoglobin and diverse enzymes. It is measured by hemoglobin concentration.

Iron deficiency is viewed as a continuum ranging from iron depletion to iron deficiency anemia. In the former, body iron stores are reduced, but functional and transport iron remain normal, leaving little reserves if the body requires more iron, in the latter, storage, transport, and functional iron are severely decreased and can lead to impaired function of multiple organ sites. The symptoms of iron deficiency include fatigue and decreased exercise tolerance, signs of severe anemia include skin and conjunctival pallor, tachycardia, and low blood pressure, dermatologic findings include hair loss (basically TE), cheilosis, and koilonychia. It must be noted however that some patients with iron deficiency and even anemia may remain completely asymptomatic.

Several studies have evaluated the relationship between iron deficiency and hair loss. Almost all of these studies have focused exclusively on women, and some suggest that iron deficiency even in the absence of iron deficiency anemia may cause hair loss [10, 11, 13, 14, 16], though others have challenged this view [12, 15]. Nevertheless, it is common practice for dermatologists to prescribe iron supplementation in women under the assumption that low iron stores may cause hair loss, although this practice is not evidence based per se.

We evaluated the relationship between serum ferritin levels and hair loss activity, as determined by trichogram, in otherwise healthy women with FPHL and/or TE. Of 418 women, 181 women who did not have any other factor responsible for TE, except for the variations of ferritin levels in question, were included in the study. Of the 181 women diagnosed with FPHL and/or TE on the basis of clinical FPHL and/or a pathologic trichogram, a total of 159 women suffered from FPHL, diagnosed either clinically on the basis of Ludwig pattern hair loss I–III or a frontal telogen rate >15% in the absence of clinical FPHL, and 135 women suffered from TE, diagnosed on the basis of an occipital telogen rate >15%. Of these, 113 women suffered from a combination of FPHL and TE, diagnosed on the basis of Ludwig pattern hair loss I–III and an occipital telogen rate >15%. With reference to serum ferritin levels, patients were subdivided into 3 subclasses: A, serum ferritin ≤10 μg/l (lower reference limit of normal with a sensitivity of 75% and a specificity of 98% for diagnosing iron deficiency in women of childbearing age); B, ferritin between 10 and 30 μg/l; C, ferritin >30 μg/l (lower reference limit of normal for children, men and nonmenstruating women with a sensitivity of 92% and a specificity of 98% for diagnosing iron deficiency). 112 (61.9%) women were found to have a serum ferritin >30 μg/l, 55 (30.4%) between 10 and 30 μg/l, and 14 (7.7%) ≤10 μg/l. For each of the subclasses A–C and total subjects, the Pearson's product-moment correlation coefficient was calculated to determine a possible correlation between serum ferritin levels and telogen rates in all subjects, patients with FPHL, and patients with TE (fig. 3). While there was a significant correlation between age of women and ferritin levels, with younger (menstruating) women having lower ferritin levels (fig. 2), no correlation was found between ferritin levels >10 μg/l and telogen rates, whether in the groups B and C, or in total subjects. The number of patients in group A (serum ferritin ≤10 μg/l) was too small (n = 14) to draw any significant conclusions. Moreover, there were no significant differences in mean ferritin levels between women with clinical FPHL and normal trichogram (47.62 μg/l), women with 'active' FPHL (45.41 μg/l), and women with combined FPHL and TE (58.26 μg/l), while women with exclusive TE had a mean serum ferritin level of 40.09 μg/l (table 1).

We conclude that the role of tissue iron status in female hair loss has probably been overestimated since we found that a majority (61.9%) of women with hair loss due to FPHL, TE, or a combination of both have serum ferritin levels above the cutoff point with 92% sensitivity and 98% specificity for diagnosing iron deficiency (>30 μg/l). In previous studies, Sinclair [15] also found that only 12/194 (6.2%) of women with alopecia had serum ferritin levels ≤20 μg/l, and Aydingoz et al. [12] found no significant difference in the prevalence of depleted iron stores found in total subjects with diffuse or female pattern alopecia versus controls (32.5 vs. 45.6%). More importantly, we found no association between hair loss activity assessed with the trichogram technique and serum ferritin levels >10 μg/l either in all subjects, patients with FPHL or patients with TE. A ferritin concentration of 10–15 μg/l is generally considered to yield a sensitivity of 59% and a specificity of 99% for diagnosing iron deficiency [18]. In women of childbearing age, it yields a sensitivity of 75% and a specificity of 98% [19], and is therefore cited as the lower limit of normal for menstruating women also by the reference laboratory of this study. Of the most recent authors claiming an association of decreased serum ferritin with alopecia in women, the levels were all within the stipulated ranges of normal. Kantor et al. [16] found in their androgenetic alopecia (or FPHL) and TE groups mean serum ferritin concentrations of 37.3 and 50.1 μg/l, respectively, versus 59.5 μg/l in controls. In patients with FPHL or TE who were ≤40 years of age, mean serum ferritin concentrations were 15.0 and 23.8 μg/l, respectively, versus 62.3 μg/l in controls. The values for patients with FPHL or TE are in accordance with our finding of a significant correlation between the age of women (with hair loss) and serum ferritin levels, with younger (menstruating) women having the lower ferritin levels (fig. 2).

The data presented herein show no correlation between hair loss activity and serum ferritin levels >10 μg/l in otherwise healthy women with FPHL, TE, or a combination of both. Therefore, it remains debatable whether therapeutic iron supplementation in these women is useful. Nevertheless, the final proof, if iron is beneficial in these patients or not, will depend on the results of iron supplementation therapy performed in a double-blind controlled manner in otherwise healthy women with hair loss due to FPHL or TE and serum ferritin levels >10 μg/l.

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