Original article

Treatment of low serum ferritin in females with alopecia by oral iron.

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ABSTRACT

Background: Hair loss affects over 25% of women in developed countries. Three hair disorders, androgenetic alopecia, telogen effluvium and alopecia areata which account for most cases of nonscarring alopecia in women. Iron deficiency has been reported in the majority of women presenting with diffuse hair loss. Iron has important function in oxidation-reduction reactions, collagen synthesis, and as a co-factor for enzymes.

Objectives: To assess the percentage of the low serum ferritin hair loss females and their response to oral iron replacement therapy.

Materials and methods: a prospective cohort study conducted in at Marjan teaching hospital from August 2013 to January 2015. It included 72 female complained from diffuse hair loss were enrolled in this study. Full history was taken from all patients and physical examinations were done both general examination and local examination of the scalp including pull test. Patients were sent to complete blood examinations, serum ferritin. Patients divided in to three groups according to their response to treatment. Before the treatment the severity of hair loss was assess by VAS.

Results: Fifty two patients met criteria of inclusion. Their serum ferritin levels range between (1.4-14.4) with mean 6.16±3.30 their hemoglobin levels were (8.3-13.4) with mean ±SD 11.98±1.22. Group **I** patients included 27 patients (51.9%), their severity of hair loss before treatment was assess by VAS which was 9.18±0.84, after two week of treatment the score become 7.33±1.03, P value is < 0.0001; confidence interval 95% = (1.477 to 2.277). in group **II** patients which included 12 patients (23%), their severity of hair loss before treatment was assess by VAS which was 9.33±0.49, after two week of treatment the score become 9.08±0.66, P value is 0.081 considered not significant; confidence interval 95% = (-0.037 to 0.537). The other thirteen patients (25%) represented the third group. All the patients in this group didn't show any response to treatment

Conclusion: Measurement of serum ferritin level should be done to all patients with chronic telogen effluvium before starting other anti-hair loss modalities. Iron replacement is a safe drug with a few side effects and indicated to all females with low serum ferritin level.

Keywords: ferritin, female, hair loss

Introduction

Hair loss affects over 25% of women in developed countries [1]. Three hair disorders, androgenetic alopecia, telogen effluvium and alopecia areata account for most cases of nonscarring alopecia in women ([1, 2]. Diffuse hair shedding is distressing. In many cases, the patient notes an increase in hair on the pillow, or when brushing, or in the shower drain. [3] It is usually recognized more readily by women than men. [4] Few dermatologic complaints carry as much anxiety and emotional distress as hair loss. Equally, evaluation and management of hair loss are challenging. [5]

Kligman's hypothesis was that whatever the cause of the hair loss, the follicle tends to behave in a similar way, the premature termination of anagen. The follicle is precipitated into catagen and transforms into a resting stage that mimics telogen. [6] Acute telogen effluvium presents as a diffuse, non-patterned hair loss from the scalp that occurs around 3 months after a triggering event, and is usually self-limiting within 6 months. A host of different triggers have been implicated and identify the cause, e.g., post-febrile, postpartum, accidental trauma or surgical operations with large blood loss, a crash diet, or severe emotional distress are among the most common causes [7]. While chronic telogen effluvium is diffuse shedding of telogen hairs that persists more than 6 months either represents a primary disorder and is then a diagnosis by exclusion[8], It can also be secondary to prolonged, sequential, or repeated triggers, such as a nutritional deficiency or underlying systemic disorder, and shedding can be less pronounced than in acute telogen effluvium.[9] Apart from iron deficiency as a cause of chronic diffuse hair loss, all others are less common, although the literature concerning iron deficiency remains controversial. Iron deficiency has been reported in the majority of women presenting with diffuse hair loss [10, 11].

The total iron content of an adult man is 4–5 g [12]. The major role of iron in mammals is to carry oxygen as part of the heme protein that, in turn, is part of hemoglobin. Oxygen is also bound by a heme protein in muscle, myoglobin [13].

Also it has important function in oxidation-reduction reactions, collagen synthesis, and as a co-factor for enzymes (such as succinic dehydrogenase, monoamine oxidase, and glycerophosphate oxidase [14], also including in the cytochrome system in mitochondria. Without iron, cells lose their capacity for electron transport and energy metabolism. [13]

Iron deficiency is a major risk factor for disability and disease worldwide, affecting about two billion people. General symptoms include fatigue, palpitations on exertion, sore tongue with atrophic filiform papillae, angular cheilitis, dysphagia and

koilonychias. Generalized itch may occur and hair loss with or without morphological changes of the hair shaft may be seen [12]. Free iron is toxic to cells, and the body has established an elaborate set of protective mechanisms to bind iron in various tissue compartments. Within cells, iron is stored complexed to protein as ferritin or hemosiderin. [13] The Aim of study was to assess the percentage of the low serum ferritin hair loss females and their response to oral iron replacement therapy.

Materials and Methods

A prospective cohort study included 72 female complained from diffuse hair loss were enrolled in this study. The study conducted in Marjan teaching hospital in Hilla / Babylon from Their age ranged 15-45 years. All patients were complaining from diffuse hair loss for more than 6 months. Full history was taken from all patients and physical examinations were done both general examination and local examination of the scalp including pull test. Telogen shed may be estimated by the pull test: grasping 40 hairs firmly between thumb and forefinger, followed by a slow pull that causes minimal discomfort to the patient. A count of more than 4–6 club hairs is abnormal, but the result is influenced by recent shampooing (a count of 2–3 hairs being abnormal in a freshly shampooed scalp), combing. Patient were send to complete blood examinations, serum ferritin, patients with identifiable causes of hair loss were excluded from the study e,g thyroid disease was measured by thyroid function test, or hyperandrogenism was measured by serum testosterone, deydroepiandrosterone levels. Twenty patients (27.7%) were excluded as their serum ferritin level was within the normal range (40-134) with a mean ±SD of 83.75±28.19 and their hemoglobin levels within normal range (12-15.5) with mean ±SD 13.36±0.98.Our patients divided in to three groups according to their response to treatment. Group **I** good response included those patients with more and or equal to 50% reduction in their hair loss. Group **II** mild response included those patients with less than 50% reduction in their hair loss. Group **III** none response included those patients without response.

Before the treatment the severity of hair loss was assess by VAS. The scale consisted of a 10 cm horizontal line marked from 0 (denoting absent of hair loss) to 10 (denoting worst symptoms). Serum ferritin was measured before treatment, after one month and thereafter three months (after finish course of treatment). Patients were assigned to receive 4 weeks of ferrous sulfate tab 200 mg three times daily for one month for those patients whose their serum ferritin less than 15 ng/mL, their after 200mg once daily for two months. A reduction in scores of ≥ 50% was considered as the desired improvement in symptoms during treatment.

Results

Fifty two patients were their serum ferritin levels range between (1.4-14.4) with mean 6.16±3.30 their hemoglobin levels were (8.3-13.4) with mean ±SD 11.98±1.22. Twenty one (40.3%) patients were their hemoglobin levels within normal range (12-14.9).

Group **I** patients include 27 patients (51.9%), their severity of hair loss before treatment was assess by VAS which was 9.18±0.84, after two week of treatment the score become 7.33±1.03, P value is < 0.0001; confidence interval 95% = (1.477 to 2.277). This score continued to decrease reaching to 4.63±1.36 by the end of first month; P value is < 0.0001 confidence interval 95% = (3.922 to 5.189). At the end of 2nd month the score become 2.92±1.03; P value is < 0.0001; confidence interval 95% = (5.693 to 6.825). The score continued to decrease reaching to 2.11 ±1.08 in the end of 3rd month; P value is < 0.0001; confidence interval 95% = (6.526 to 7.622), considered extremely significant as showed in table (1), figure (1).

While in group **II** patients include 12 patients (23%), their severity of hair loss before treatment was assess by VAS which was 9.33±0.49, after two week of treatment the score become 9.08±0.66, P value is 0.081 considered not significant; confidence interval 95% = (-0.037 to 0.537). This score continued to decrease reaching to 8.5±0.0.52 by the end of first month; P value is <0.0001; confidence interval 95% = (0.586 to 1.08). At the end of 2nd month the score become 8.33±0.49; confidence interval 95% = (0.729 to 1.27). The score continued to decrease reaching to 8.16 ±0.38 at the end of 3rd month. P value is < 0.0001; confidence interval 95% = (0.919 to 1.414). As showed in table (2), figure (2)

The other thirteen patients (25%) represented the third group. All the patients in this group didn't show any response to treatment, and their severity of hair loss was 9.23±0.72 and remains constant during all period of treatment. No side effect was reported except in seven patients (13.4%) develop mild gastric upset which controlled by taken the drug with food.

Discussion

Hair loss has been associated with iron deficiency. [15, 16] However, the role of iron deficiency in hair loss continues to be a controversial topic. [17, 18]

In our study twenty patients (27.7%) were excluded as their serum ferritin level was within the normal range (30-134) with a mean ±SD of 83.75±28.19 and their hemoglobin levels within normal range (12-15.5) with mean ±SD 13.36±0.98.

Other fifty two patients were their serum ferritin levels range between (1.4-14.4) with mean 6.16±3.30 their hemoglobin levels were (8.3-13.4) with mean ±SD 11.98±1.22. Twenty one (40%) patients were their hemoglobin levels within normal range (12-14.9). So we should keep in our mind that one of the important investigations to assess anemia is serum ferritin and not depend on the hemoglobin level only. Iron deficiency anemia is the condition in which there is anemia and clear evidence of iron deficiency. However, iron deficiency can be divided into three stages. [13] The first stage is *negative iron balance*, in which the demands for (or losses of) iron exceed the body's ability to absorb iron from the diet. This stage can result from a number of physiologic mechanisms including blood loss, pregnancy, rapid growth spurts in the adolescent, or inadequate dietary iron intake. Under these circumstances the iron deficit must be made up by mobilization of iron from reticuloendothelial storage sites. During this period measurements of iron stores such as the serum ferritin level or the appearance of stainable iron on bone marrow aspirations will decrease. As long as iron stores are present and can be mobilized, the serum iron, total iron-binding capacity (TIBC), levels remain within normal limits. As long as the serum iron remains within the normal range, hemoglobin synthesis is unaffected despite the dwindling iron stores. The 2nd stage when iron stores become depleted, the serum iron begins to fall, TIBC increases, transferrin saturation falls to 15 to 20%, so hemoglobin synthesis becomes impaired. This is a period of *iron deficient erythropoiesis*. Careful evaluation of the peripheral blood smear reveals the first appearance of microcytic cells later gradually hemoglobin and hematocrit begin to fall, reflecting *iron deficiency anemia*. [13] So from the above the normal hemoglobin and hematocrit not exclude iron deficiency. In our study there are twenty one (40%) patients with normal range hemoglobin levels (12-14.9) in spite of low serum ferritin.

The serum or plasma ferritin concentration is an excellent indicator of iron stores in otherwise healthy adults and has replaced assessment of bone marrow iron stores as the gold standard for the diagnosis of iron deficiency in most patients .[12,19-22]

The ferritin concentration ranges from 40 to 200 ng/mL (mcg/L) in normal subjects, and is markedly elevated in states of iron overload, due to stimulation of hepatic ferritin synthesis and release by iron. [23]

There is no clinical situation other than iron deficiency in which extremely low values of serum ferritin are seen.[20,22] By definition, marrow iron stores are absent when the serum ferritin level is <15 mcg /L.[13]

In our study the 1st patients include 27 patients (51.9%), their severity of hair loss before treatment was assess by VAS which was 9.18±0.84, after one month of treatment the score become 4.63±1.36, P value is < 0.0001 confidence interval 95% = (3.922 to 5.189). At the end of 2nd month the score become 2.92±1.03; P value is < 0.0001; confidence interval 95% = (5.693 to 6.825). The score continued to decrease reaching to 2.11 ±1.08 in the end of 3rd month; P value is < 0.0001; confidence interval 95% = (6.526 to 7.622), considered extremely significant. while the 2nd group patients include 12 patients (23%), their severity of hair loss before treatment was assess by VAS which was 9.33±0.49, after one month of treatment the score become 8.5±0.52 by the end of first month; P value is <0.0001; confidence interval 95% = (0.586 to 1.08). The score continued to decrease reaching to 8.16 ±0.38 at the end of 3rd month. P value is < 0.0001; confidence interval 95% = (0.919 to 1.414).

The other thirteen patients (25%) represented the third group. All the patients in this group didn't show any response to treatment, and their severities of hair loss were 9.23±0.72 and remain constant during all period of treatment.

Hair follicle matrix cells are one of the most rapidly proliferating cells in the body. Ferritin levels are increased in non-dividing 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 [24-28]. This balance of ferritin and iron is at least partially controlled by the transcription factor c-myc [28]. C-myc is one the proto-oncogenes associated with apoptosis, change immediately prior to or coincident with the onset of catagen. [29] The apoptosis-inhibitory proto-oncogene bcl-2 is expressed in cycling follicular epithelium during anagen, disappears during catagen and is absent in telogen.[30] Over expression of c-myc in the cutaneous epithelium results in loss of follicular differentiation and a decrease in stem cells [31], but whether this phenotype is related to abnormal iron metabolism remains to be determined.

Iron has an important function as co-factor for enzymes (such as succinic dehydrogenase, monoamine oxidase, glycerophosphate oxidase [14] and ribonucleotide reductase, the rate-limiting enzyme for DNA synthesis which has an important function in the hair growth stem cell.

The depletion of iron could prevent proper functioning of this enzyme resulting in inhibition of proliferation [32]. Inhibition of other iron-dependent enzymes, such as stearoyl-CoA desaturase activity in mammals would be expected to affect a variety of key physiological variables, including cellular differentiation, insulin sensitivity, and metabolic rate. [33]

In spite of our patients were complained from chronic telogen effluvium, certain study demonstrate iron supplementation has been recommended as an enabler of response to other treatments in patients androgenic alopecia with low serum ferritin. [34]

In this study more than 50% of the patients with chronic telogen effluvium showed dramatic improvement in severity of their hair loss after three months of therapy with iron, while only 23% of the patients showed mild improvement.

Conclusion

Measurement of serum ferritin level (as a marker of iron state) should be done to all patients with chronic telogen effluvium before starting other anti-hair loss modalities.Iron replacement is a safe drug with a few side effects and indicated to all females with low serum ferritin level.

Table (1) showed the response to treatment in group I patients

	Time	No.	Mean of hair loss severity	SD	P	95% Confidence Interval
Pair I	Before	27	9.25	0.81	P<0.001	1.150-2.554
	2nd week	27	7.40	1.07		
Pair 2	2nd week	27	7.40	1.07	P<0.001	2.039-3.443
	One month	27	4.66	1.38		
Pair 3	One month	27	4.66	1.38	P<0.001	1.150-2.554
	2nd month	27	2.81	0.96		
Pair 4	2nd month	27	2.81	0.96	P<0.05	0.0385-1.443
	3rd month	27	2.07	1.07		
Pair 5	Before	27	9.25	0.81	P<0.001	6.483-7.887
	3rd month	27	2.07	1.07		

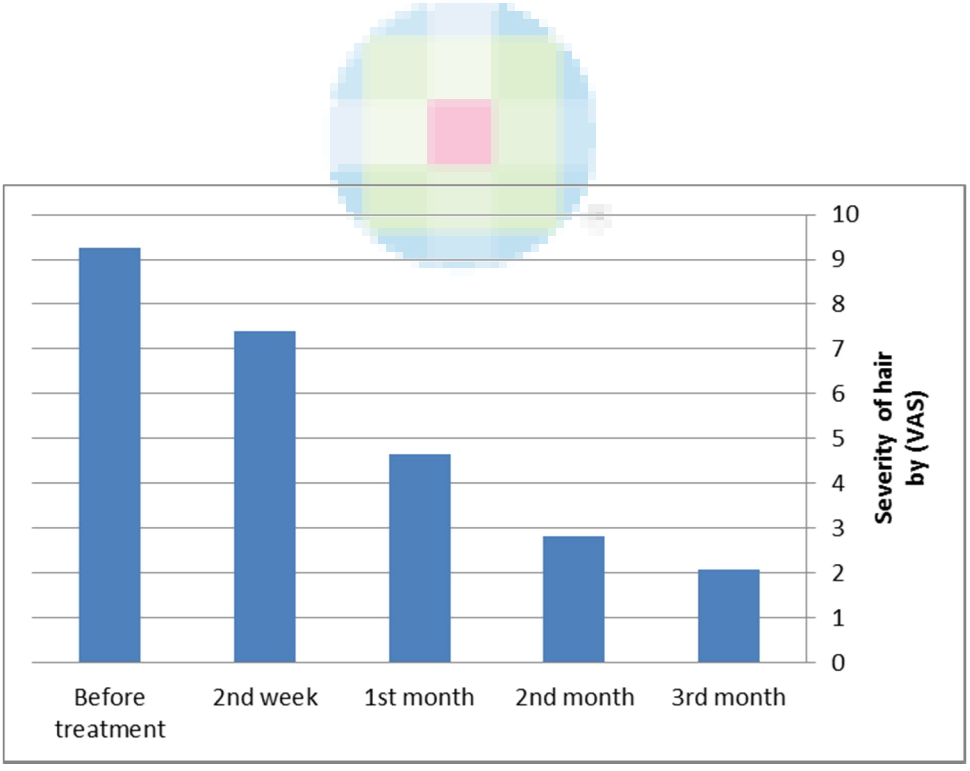

Figure (1) showed the response to treatment in group I patients

Table (2) showed the response to treatment in group II patients

	Time	No.	Mean of hair loss severity	SD	P	95% Confidence Interval
Pair I	Before	27	9.25	0.45	P<0.05	0.0367-0.7966
	2nd week	27	8.83	0.57		
Pair 2	2nd week	27	8.83	0.57	P<0.01	0.1201-0.8799
	One month	27	8.33	0.49		
Pair 3	One month	27	8.33	0.49	P>0.05	-0.2966-0.4632
	2nd month	27	8.25	0.45		
Pair 4	2nd month	27	8.25	0.45	P>0.05	-0.1299-0.6299
	3rd month	27	8	0.42		
Pair 5	Before	27	9.25	0.45	P<0.001	0.8701-1.630
	3rd month	27	8	0.42		

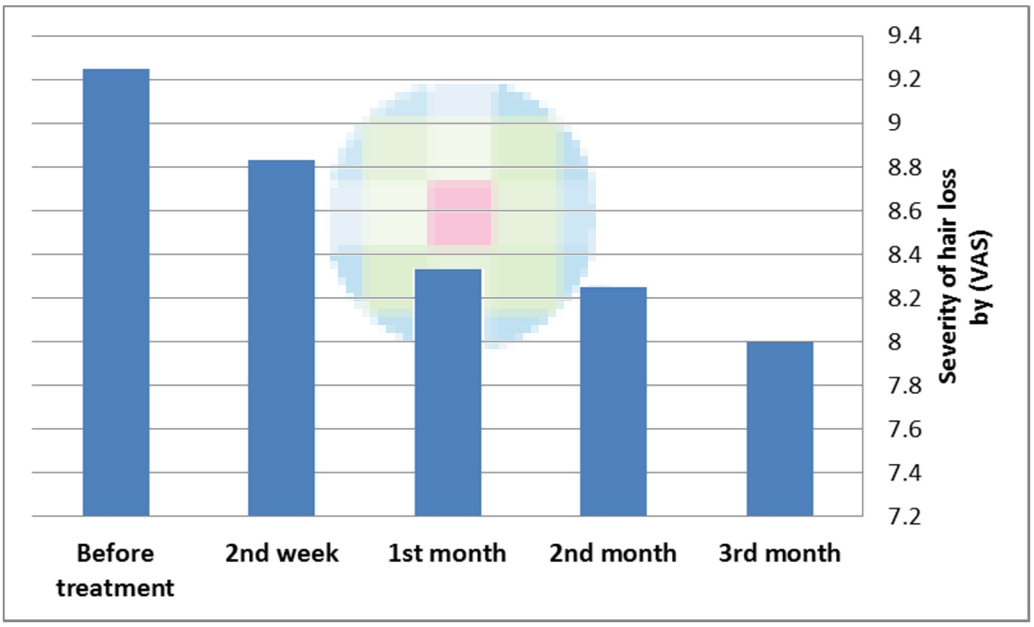

Figure (2) showed the response to treatment in group II patients

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