Review Article

Iron Deficiency and Hair Loss: Ferritin Cutoffs, Diagnostic Controversies, and Treatment Outcomes-An Updated Evidence Synthesis-Comprehensive Review

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Abstract

Clinical management for suspected iron associated non-scarring hair loss should be structured, context-sensitive, and not based solely on ferritin levels. The first step is proper phenotype determination (telogen effluvium/female pattern hair loss) based on history and physical examination of the scalp, including dermoscopy (if available). Laboratory evaluation is the most informative to look at ferritin but, it should be paired with hemoglobin indices, functional iron markers (ferritin, transferrin saturation) and with checking the inflammatory state (CRP). This combined approach results in the suppression of misclassification, particularly for patients in whom ferritin can be falsely normal or high because of inflammation. Treatment decisions should be individualized. Iron repletion is most defensible if it in telogen effluvium in which ferritin clearly is low and inflammation not distorting the biomarker. In ambiguous circumstances (non-anemia), then the choice should take into account shedding severity and duration, reproductive status and menstrual losses, dietary factors, and characteristic systemic symptoms in favor of deficiency. In female pattern hair loss, iron therapy should be reserved for the proven deficient, as the main causes of this type of hair loss are follicular miniaturization and genetic-androgenic, and there is no evidence to always pursue normality goals of ferritin. Follow-up should be on both biochemical responses, as well as in realistic timelines for improvement of hair. Ferritin and transferrin saturation may be rechecked after about 8-12 weeks in order to confirm trends of repletion when clinical improvement in shedding is usually delayed by the length of time taken for hair cycling to occur. Treatment usually needs to be ongoing beyond having the first laboratory improvement to increase the iron reserves, but prolonged therapy in the absence of actual deficiency should be avoided. Shedding scores used as consistent clinical tracking (and objective measures where this is possible) helps us to interpret response. Non-response to better iron markers gives reason for reassessment not escalation of iron. Common explanations are incorrect initial diagnosis (female pattern hair loss misdiagnosed as telogen effluvium), persistent inflammatory or endocrine disease occurrence, thyroid dysfunction or coexisting nutrition (D3, zinc, inadequate protein intake). In the case of female pattern hair loss, treatments (e.g., topical minoxidil, and other treatment specific to hair phenotype) grounded in evidence studies may be indicated irrespective of the iron status; one exception may be chronic telogen effluvium that may have multifactorial causes, and a broader workup may be indicated.

Keyword: Iron Deficiency, Ferritin Cutoffs, Hair Loss.

Introduction

Hair loss is a frequent dermatologic complaint that has significant psychosocial effects especially in reproductive-aged women. Non-scarring alopecias, in particular telogen effluvium (TE) and female pattern hair loss (FPHL), make up the majority of alopecias that one encounters in the outpatient practice [1,2]. Telogen effluvium is defined by generalized hair shedding after exposure to a physiological or

psychological stressor, which interferes with the normal hair cycle and FPHL is characterized by generalized hair thinning due to follicular miniaturization from genetic and hormonal factors [2,3]. While these conditions have distinct pathophysiological mechanisms, nutritional factors, most importantly iron deficiency has been suggested as a potential contributor on several occasions [4]. Iron has a fundamental role in cellular proliferation, DNA synthesis, mitochondrial respiration and enzymatic reactions that are essential in tissues with rapid cell turnover such as the hair follicle matrix [5]. Hair follicles are one of the most metabolically active organs in our body during the anagen phase, and therefore, subclinical disturbance of iron availability may affect follicular cycling even resulting in premature transition to telogen [6]. Experimental and clinical observations point to the possibility that low iron stores compromise the cell proliferation of keratinocytes and/or affect hair growth dynamics that are thought to contribute to hair shedding [5,7], Supporting a biologically plausible link between iron deficiency and hair shedding. Serum ferritin is commonly used as a surrogate indicator of body total iron stores, and is commonly measured in patients presenting with diffuse hair loss [8]. Normally ferritin concentrations less than 15 ng/mL have been applied to define iron deficiency in hematologic practice [9]. However, a number of dermatologic investigations have prompted either an increase of the ferritin thresholds, ranging between 30 and 70 ng/mL, which may be more relevant within the context of hair loss, especially among women without overt anemia [10,11]. This discrepancy has resulted in a great deal of controversy and raised questions for what the best ferritin cutoff value is to clinically significant iron deficiency in patients with alopecia should be. Interpretation of ferritin levels is further complicated by its role as an acute phase reactant. Inflammatory states, chronic diseases, obesity and infections may increase ferritin independently of iron stores so that there may be obscuring underlying functional iron deficiency [12]. In these conditions, the single test of ferritin may lead to an incorrect classification and it is being suggested that the transferrin saturation (TSAT) or the soluble transferrin receptor (sTfR) are supplementary indices for better diagnosis [13]. The appreciation of the role of non-anemic iron deficiency has also increased confusion, as it is possible to have patients with normal hemoglobin levels in the context of depleted iron stores with enough effect on high-turnover tissues [14]. Despite common clinical testing and empirical supplementation, the quality of evidence of an association between iron deficiency and different hair loss phenotypes is of variable quality. While results of some case-control studies show lower level of ferritin in women with TE compared to controls [10,15], results in FPHL have been less consistent and may reflect multifactorial pathogenesis other than iron availability [3,11]. Furthermore, outcomes of treatment after iron repletion differ between studies and there is heterogeneity in baseline ferritin levels, iron supplementation regimens, duration of supplementation, and outcome assessment methods [16]. Given these uncertainties in diagnosis and inconsistency in therapy, it is necessary that the current evidence will be evaluated in detail. Clarification of thresholds of ferritin, identification of major confounding factors for ferritin interpretation and critical evaluation of treatment outcomes may help improve clinical decision-making and proportion research to standardize and craft phenotype specific approaches to iron assessment in hair loss.

2. Clinical Importance of the Status of Iron to Scarring Alopecia

Iron deficiency is the most common micron-trient deficiency globally and affects a surplus of women of reproductive age and is a demographic in which diffuse hair shedding is also a common complaint [17]. In dermatologic practice, assessment of the status of iron has therefore become a matter of routine in patients with non-scarring alopecia, especially telogen effluvium (TE). This manner of clinical approach has been supported by several epidemiologic observations that showed the decreased iron stores may accompany diffuse hair loss even without overt anemia [18]. Telogen effluvium is marked by premature termination of anagen phase and synchrony in entry of follicles in telogen. Iron is extremely important in the synthesis of DNA and cell division in the hair matrix; hence, depletion of iron stores may cause dysfunctional maintenance of the anagen phase and promote rapid transition to telogen [19]. Several observational studies have shown a significantly lower mean ferritin concentration in women with TE compared with women in the control group, which reinforces clinical practice of assessment of iron parameters for women with TEs [20,21]. Although the effect can't be definitively established with any of these studies, the repetition makes the laboratories a good argument for screening ferritin. Whereas the correlation between iron status and female pattern hair loss (FPHL) is rather variable. FPHL is largely a genetic predisposition and sensitivity to androgens but some studies have indicated that the presence of concomitant iron deficiency may increase hair thinning or worsen response to therapeutic treatment [22]. Other studies, however, have not been able to demonstrate statistically significant difference in ferritin levels between women with FPHL and controls, further suggestive of the role of iron deficiency as a modifying, rather than primary pathogenic factor [23]. These discrepancies highlight the importance of interpretation of biomarkers of iron to occur in the context of the general clinical problems. Beyond classical Iron Deficiency Anemia growing interest has been focused on absence of Anemia due to lack of Iron stores (NAID) which is described as depletion of Iron stores, but without decreased haemoglobin levels. NAID can result in the development of discrete yet clinically relevant symptoms of the higher turnover tissues, such as the hair follicles [24]. The recognition of NAID is of special importance in dermatology where there is a tendency to rely only on measurement of hemoglobin and so not uncover depleted iron reserves. Ferritin thresholds to define a deficiency applied in general medicine may not be useful to define the iron demands of proliferative epithelial tissues [25]. Another aspect that is clinically relevant to the misinterpretation of ferritin is the influence of inflammation and metabolic factors on ferritin interpretation. Ferritin is also elevated in the case of systemic inflammation, something like acute phase response and may conceal a deficiency [26]. Conditions such as obesity, presence of chronic infection, autoimmune disease, so on may therefore have normal or elevated levels of ferritin with inadequate bioavailable iron. In such cases, evaluation of transferrin saturation or soluble transferrin receptor level may lead to more diagnostic clarity towards the patient [27]. Therapeutically the clinical relevance of iron status in terms of taking action go to management decision. Empirical iron supplem-entation is often initiated in patients with TE associated with low or marginal ferritin and in some cases, it is related to reduction of shedding and subjective improvement in the density of the hair after repletion [28]. However, the variability between groups in terms of baseline ferritin and supplementation regimens and duration of the therapy as well as assessment of outcomes

makes it challenging to interpret the efficacy of the therapy [29]. These inconsistencies, the need for clinical definition of meaningful ferritin levels and standardized endpoints are perhaps necessary in future research. the clinical importance in hair loss, in which it is not only of great importance to establish the diagnosis of iron deficiency anemia but also the existence of subtle iron status SHH that can affect hair follicle cycling A subtle approach, incorporating interpretation of ferritin, inflammatory and for phenotype matters, integration of the latter, is vital to proper diagnosis and rational management.

3. Biological Rationale: Metabolism of Iron and Hair Follicle Cyclical

Hair follicles are highly dynamic mini-organs that undergo a cyclical process that goes through anagen (growth), catagen (regression) and telogen (resting) phases. The anagen phase is characterized by the vigorous proliferation of keratinocytes at the hair matrix and by active melanogenesis activities and at the same time, strong mitochondrial activities. These processes include a constant requirement for energy production from the cell and a tight control of the function of enzymes in a way that is dependent on the availability of adequate iron [30]. Given the high turnover rate and metabolic requirement of matrix keratinocytes, even low levels of depletion of bioavailable iron may have an impact on follicle homeostasis. Systemically, iron metabolism is dictated by coordinated regulation of reactions of absorption, transport, storage and recycling. Hepcidin, the main iron regulatory hormone, regulates egress of iron from enterocytes and macrophages by regulating ferroportin function [31]. Inflammatory stimuli lead to increased hepcidin expression and hence sequestration of iron and low circulating iron levels in spite of normal or increased ferritin levels; This functional iron restriction may reduce the supply of iron to peripheral tissues such as the hair follicle and this affects hair follicle cycling independent of total body iron stores [32]. Experimental data suggest that proliferative tissues are particularly sensitive to changes in iron availability, because iron is a cofactor for ribonucleotide reductase, an enzyme that is critical for DNA synthesis [33]. In the hair follicle, cells of the matrix quickly divide to produce the shaft of the hair; if their DNA replication or the product of the mitochondria-producing respiration due to lack of iron affair, maintenance of anagen can be affected. Moreover, iron-dependent enzymes take part in oxidative metabolism and redox balance, which are essential to maintain follicular stem cell activity and differentiation [34].

3.1 Iron Dependent Cellular Processes in the Follicle

On the cellular level, iron is part of a number of biochemical pathways that are fundamental to hair growth. Iron is a component of cytochromes present in the mitochondrial electron transport chain which contributes to making the main polymer known as ATP which is necessary for keratinocyte proliferation and protein synthesis [35]. Deficiency in intracellular iron may decrease mitochondrial efficiency resulting in decreased matrix function and early follicular regression. Iron is also involved in the metabolism of nucleotides; its participation in the ribonucleotide reductase enzyme is involved in the reduction of ribonucleotides to deoxyribonucleotides of DNA during its replication [33]. Given the fast rate of mitotic activity of matrix keratinocytes during the anagen phase, impairment of this pathway may cause impaired shaft elongation. Furthermore, iron-dependent enzymes are involved in collagen production and remodeling of the extracellular

matrix and this process affects dermal papilla microenvironment and the integrity of the follicle [36]. Recent insights into follicular biology The importance of iron in regulating oxidative stress. Reactive oxygen species (ROS) are formed in the period of active growth phases and enzymes which contain iron help to maintain a redox balance. Both iron deficiency and iron overload can upset this balance and may lead to triggering the stress response of the cells within the follicle [37]. Such forms of oxidative perturbations could therefore impact on the stability of the stem cell niche, as well as in the signalling pathways influencing the hair cycle.

3.2. Suggested Relationships between Iron Restriction and Telogen Shift

The medical production of telogen effluvium is noted by an increased percentage of follicles that go into telogen prematurely. One postulated mechanism that connects iron deficiency to telogen shift has to do with impaired energy production in the matrix cells and the lack of this energy to sustain the activation of anagen activity [38]. When proliferative demands cannot be met, follicles may enter earlier into catagen and then telogen. Another possible pathway is associated with iron regulated signaling cascades. Iron availability affects cell hypoxia pathways and may also interact with hypoxia-inducible factors (HIFs) which have been implicated in hair growth regulation [39]. Altered iron status may modulate these pathways which have an indirect effect on the cycling of the follicles. In addition, there are subtle endocrine or metabolic changes that may be induced by systemic iron deficiency affecting anagen: telogen ratio. The functional iron deficiency secondary to inflammation may contribute further in telogen shift. Elevated levels of hepcidin during inflammatory states limits iron exports and tissue availability which may result in insufficient iron supply to follicles despite adequate ferritin levels [32]. This phenomenon could explain some of the clinical scenarios where the patients present with a thin diffuse shedding with apparently normal iron stores. All things considered, the mechanistic evidence provides evidence for a biologically plausible link between restriction of iron and interference with normal hair cycling. However, the molecular thresholds at which the iron induced by depletion results in clinically visible telogen effluvium are not yet well defined the need for integrative studies combining systemic iron biomarkers with those conducted on a follicle (local, i.e., regional) level.

4. Hair Loss Phenotypes Most Applicable for Iron Deficiency

Non-scarring alopecias form a heterogeneous group of disorders in which there is preservation of the follicular ostia and none of the permanent destruction of follicles is present. Among these, telogen effluvium (TE) and female pattern hair loss (FPHL) are the most assessed phenotypes in relation to deficiency of iron. Although both conditions could have increased shedding or visible thinning, the pathophysiologic drivers of both are now substantially different. Iron status may be the primary precipitating factor in some cases of TE, whereas it may be the potential modifying or exacerbating variable rather than an actual precipitating factor in FPHL [40]. Distinguishing between these entities is clinically important given the differences in the strength of evidence available to date for the clinical association between iron deficiency and hair loss through different phenotypes. The associations of acute and chronic forms of TE with the decreased levels of ferritin are more consistent, but the associations of FPHL with ferritin behavior variably across populations [41]. Moreover, presentations may overlap and

this may make the diagnosis unclear, especially in women with both patterned thinning and episodic shedding.

4.1. Telogen Effluvium (Acute and Chronic)

Patients with telogen effluvium typically present with diffuse shedding that results from an increase in the percentage of follicles entering prematurely the telogen phase. Acute TE is usually preceded by a triggering event (eg, systemic illness, surgery, childbirth, psychological stress, nutritional deficiency) occurring an average of 2-3 mo before the start of the shedding [42]. Chronic TE, to the contrary, lasts for more than 6 month and may not have a clearly identifiable precipitating factor. Iron deficiency is long recognized as one of the possible systemic precipitating factors of TE. Observational studies have reported a decrease in ferritin levels in women with and without diffuse shedding, who term the ferritin level lower than control, especially women in the premenopausal age [43]. The biological plausibility of this association is user-friendly on the excessive proliferative needs of the anagen follicles, which possibly are exceedingly delicate to diminished iron availability. In clinical practice therefore, TE is the most common phenotype for evaluation for iron status. However, not all patients with TE have biochemical iron deficiency and not all people with low ferritin develop shedding. This is variable and indicates that the iron depletion may reduce the threshold for telogen shift in predisposed individuals instead of acting as a common cause factor [44]. Furthermore, chronic TE often demands ruling out other systemic elements contributing to it, such as dysfunctions of the thyroid gland, and possible other micronutrients imbalances, before the inhibiting quotation of the shedding as an "iron-stremedness.

4.2. Female Pattern Hair Loss (FPHL)

Female pattern hair loss is actuarial, patterned hair loss of the central scalp due to the main cause being follicular miniaturization. Unlike TE, FPHL represents a chronic change in follicular cycling that is caused by genetic predisposition and sensitivity to androgens [45]. Clinically, it manifests itself with a widening of the midline part associated with the loss of hair density over the vertex with preservation of the frontal part of the hairline. The correlation with iron status is less clear-cut than in TE with regard to FPHL. Some studies have suggested that low iron stores may occur concurrently with FPHL and may potentially worsen hair thinning by reducing maximal anagen duration [46]. Others however, report no statistically significant difference in ferritin levels between women with FPHL and healthy controls suggesting that iron deficiency may not be a primary aetiologic factor in this phenotype [47]. It has been suggested that lack of iron in FPHL may play a role in the hair quality or hair shedding superimposed upon patterned miniaturization rather than being the cause of the miniaturization process itself. As a result correction of iron deficiency may improve the symptoms of diffuse shedding without reversing the androgen-mediated follicular changes characteristic of FPHL [48]. This distinction is of clinical importance when adjustment of patient to treatment expectation is contemplated.

4.3. Differential Diagnosis and Co-morbidities

Diffuse hair shedding is a nonspecific clinical manifestation and could be a sign of many underlying processes. Iron deficiency therefore has to be put in the context of a larger diagnosis. Thyroid dysfunction, vitamin D deficiency, zinc deficiency, chronic systemic disease and medicine from induced shift of teleogena can all manifest themselves with similar patterns in the

way of the diffuse loss [49]. Failure to take these conditions into account may result in over attribution of hair loss only to the iron status. Alopecia areata in its diffuse form can be indistinguishable from TE particularly in early stages but is an autoimmune disorder which has some unique pathophysiology [50]. Also, patients with FPHL will often describe episodic increases in the amount of shedding consistent with superimposed TE, which further adds to lack of diagnostic clarity. In such cases, even if the hair thinning can often be related to a lack of iron, it should not be considered as the primary factor responsible for the thinning of hair. Comprehensive clinical evaluation (including history, scalp examination, dermoscopy, and directed laboratory evaluation) is a key to the distinction of these three non-checking clinical overview lies. Iron deficiency should be taken in account as one part of a multifactorial assessment as opposed to an isolated determinant of non-scarring alopecia.

5. Laboratory Assessment of Iron Status.

There is no doubt that accurate evaluation of iron status is important in the evaluation of patients with non-scarring hair loss especially in cases where there is reason to suspect iron deficiency in the absence of anemia. Iron metabolism is a complex one, and in the lab, there is no single biomarker provides a complete assessment that presents us with a complete picture on the availability of iron. Instead, a combination of biomarkers, that reflect storage iron, circulating iron, functional iron supply and inflammatory activity, is often needed in order not to misclassify [51]. Interpretation may be especially difficult in dermatologic practice in which subtle deficiencies can occur in high-turnover tissues such as hair follicles before hematologic abnormalities expressed themselves.

5.1. Serum Ferritin: Helpful and Harmful

Serum ferritin is currently the most commonly used laboratory marker for the estimation of total body iron stores. Under physiologic conditions, the concentrations of ferritin are correlated with the storage of iron in the liver, spleen, and bone marrow [52]. The low ferritin is very specific to iron deficiency and generally considered as the first sign in the laboratory of depleted iron reserves. However, ferritin is also an acute phase response. Inflammatory cytokines upregulate the synthesis of ferritin in an iron-independent manner which may confound the absence of iron [53]. Conditions such as chronic inflammatory disorders, infection, obesity and metabolic syndrome may therefore produce a normal or high ferritin level despite lower bioavailability of iron. Furthermore, issues with inter-assay variation and variation in the laboratory reference ranges in universal interpretation thresholds [54]. These limitations make this especially relevant in a disease such as dermatology in which borderline levels of ferritin may be clinically relevant even without the presence of any anemia.

5.2. Hemoglobin Indices (Hb, MCV and RDW)

Hemoglobin concentration (Hb) has traditionally been used to define the state of anaemia but is a late marker of iron deficiency. Many people with low stores of iron - particularly women of child-bearing age - have near-normal Hb concentrations even though iron stores are depleted [55]. Therefore, dependence on Hb alone may not be sensitive to non-anemic iron deficiency. Mean corpuscular volume (MCV) is an average erythrocyte size and is low in advanced iron deficiency with development of microcytosis. However, MCV can stay within normal limit values at early stages of the depletion [56]. Red cell distribution width

(RDW) can be increased in the case of anisocytosis and can be increased even before overt microcytosis occurs (these values are more sensitive in the course of forming deficiency). [57] Nevertheless, hematologic indices are mostly a reflection of erythropoiesis conseq-uences on blood rather than iron availability on tissues and are thus inadequate as individual markers in the evaluation of hair loss.

5.3. Transferrin Saturation (TSAT), TIBC and Serum Iron.

Transferrin saturation (TSAT) is the percent of binding sites on transferrin that are occupied by iron and gives some idea of the amount of circulating iron available for use by the tissues. Reduced TSAT may be an indicator of limited iron supply despite normal or increased ferritin [58]. The total iron-binding capacity (TIBC) usually will be increased in the presence of iron deficiency as production of transferrin is increased in order to meet the low circulating iron [59]. Serum iron levels vary throughout the day and are affected by recent dietary intake, so are not very useful, in isolation, for diagnosis [60]. Consequently, TSAT which combines the serum iron and TIBC, promises a more stable functional measurement. In the case of suspected functional iron deficiency, especially in inflammatory condition, low TSAT associated with normal or increased ferritin may indicate limited bioavailability of iron [61].

5.4. Soluble Transferrin Receptor (sTfR) and Iron Deficiency, Functional

Soluble transferrin receptor (sTfR) is an indicator of cellular iron requirements and erythropoiesis. Unlike ferritin, sTfR is little affected by inflammation, making the molecule useful in differentiating the presence of true iron deficiency from anemia of chronic disease [62]. Elevated levels of sTfR reflect higher cell efforts to absorb iron in line with a deficient intrace-llular supply of iron. The sTfR/log ferritin index has been suggested as a composite marker to better discriminate cases where the diagnosis is in question [63]. Although this is not routinely ordered for clinical use in dermatologists because of cost and availability factors, sTfR may be especially useful when the interpretation of ferritin is in question. Its role in assessing iron status in patients with diffuse hair loss needs to be studied more, and this should especially be explored in populations with high inflammatory burden.

5.5. Hepcidin and Iron Sequestration by Inflammation

Hepcidin is the major regulator of whole-body iron homeostasis. Produced by the liver, it regulates intestinal absorption of iron and macrophage iron release by leading to degradation of the iron exporter ferroportin [64]. "Inflammatory cytokines, especially interleukin-6, promote the synthesis of hepcidin, which can result in the reduction of serum iron and functional iron sequestration in spite of being able to promote preservation or enhancement of ferritin levels [65]." This hepcidin-mediated response contributes to the phenomenon of functional iron deficiency, in which quantitative iron stores are apparently adequate, but delivery of iron to the tissues is impaired. In the context of hair loss, such mechanisms could be useful in explaining cases of diffuse shedding in people with seemingly normal concentrations of ferritin. Although hepcidin assays are as yet not standardized for routine clinical use, they do give important mechanistic insight into interactions between iron and inflammation [66].

5.6. Role of CRP and Inflammatory markers-interpretation.

C-reactive protein (CRP) and other inflammatory markers are very important adjuncts for the interpretation of iron biomarkers. Elevated CRP may mean that the ferritin levels have been falsely elevated by acute-phase reactions rather than reflects the true iron sufficiency [67]. In such settings, other indices of iron status (TSAT or sTfR) should be considered to elucidate iron status. Clinical guidelines are now urging the need to evaluate inflammatory markers in addition to ferritin where iron deficiency is likely in chronic inflammatory states [68]. For dermatologic patients presenting with diffuse hair loss and especially those with obesity, autoimmune disease, or recent infection, concomitant serum CRP measurement may improve diagnostic accuracy of the condition and preclude under-recognition of the diagnosis of iron deficiency by masking of inflammation.

6. Cutoff for Ferritin in Hair loss Definitions, Variation and Rationale

Determining the best ferritin threshold for diagnosis of clinically meaningful iron deficiency in patients with hair loss is one of the most controversial issues in dermatologic practice. Whereas hematology traditionally defines the level of iron deficiency at relatively low concentrations of ferritin, in dermatologic literature there are often higher cutoffs proposed based on the hypothesis that hair follicles as the highly proliferative tissue may require a greater availability of iron than erythropoenteric tissue in isolation [69]. This dichotomy has led to screening practices being vague and in the variability in the treatment decision. Ferritin interpretation is complicated by biological variability, as well as inflammation modulation and variation in the calibration of the laboratory. As a consequence not all ranges and populations and phenotypes of hair loss are suitable for using a one-size-fits-all-threshold. Instead, cutoffs for ferritin should be thought of in a context which combines clinical presentation, inflammatory status and demographic context.

6.1. Hematologic Threshold compared to Dermatologic Threshold

In hematologic usage, ferritin concentrations levels below 15–30 ng/mL are typically considered indicative of iron deficiency [70]. These thresholds are such that they identify iron deficiency of sufficient magnitude to impair the erythropoiesis. However, based on several dermatologic studies, higher ferritin concentrations often between 30 and 70 ng/mL have been suggested to be more appropriate while evaluating patients who present with diffuse hair shedding [71]. That the rationale for higher levels of dermatologic threshold is premised on the concept of tissue specific iron requirements. Hair matrix keratinocytes have a high rate of proliferation during anagen which may require iron stores higher than the minimal amounts necessary to maintain hemoglobin synthesis [72]. Consequently, ferritin levels which are "normal" on hematology may not be optimum for follicular function. Nevertheless, there is still heterogeneous evidence for whether or not a universal dermatologic cutoff exists and some studies do not demonstrate a clear dose response relationship between the concentration of ferritin and the hair density [73].

6.2. Assay / Platform Specificity and Range of Variation/ Reference Range Issues

Ferritin measurement is prone to inter-assay variability owing to difference in immunoassay platforms, use of calibration standards and analytical sensitivity [74]. Harmonization efforts have increased the degree of comparability between laboratories, but clinically significant differences do exist especially at low ferritin levels for which diagnostic decisions tend to be

made [75]. Reference ranges also change based on laboratory, population and manufacturer limitations. These differences may cause the interpretation of a given ferritin value as deficient or adequate to differ. Within a research context, variants in reporting assays and a lack of standardization also make comparisons at a cross-study level more difficult [76]. For clinicians evaluating hair loss it is critical that an awareness is in place of local laboratory reference intervals and assay methodology to assist against misclassification.

6.3. Populations Differences (Sex, Age, Menstrual Status)

Ferritin levels differ greatly based on one's sex, age and reproduction. In premenopausal women, higher prevalence of non-anemic iron deficit exists in contrast with men and postmenopausal women attributable to the menstrual blood loss [77]. Adolescents and young adults may also exhibit a fluctuating iron status as related to growth demand and patterns and frequencies of eating. Age-related changes are hazards for ferritin interpretation also. Older persons may show increased levels of ferritin because of chronic low-grade inflammation with no iron overload [78]. Obesity is another modifier, as adiposity is associated with elevations of inflammatory markers as well as elevation in ferritin independent of iron sufficiency [79]. Therefore, use of the same ferritin values to determine iron deficiency in different demographic groups may result in under- or over-diagnosis of iron deficiency in hair-loss populations.

6.4. Suggested Thresholds based upon Hair-Loss Phenotype (TE vs FPHL)

Telogen effluvium (TE) has been shown to have a more consistent link with decreased ferritin levels than have other types of non-scarring alopecias. Several studies have suggested ferritin levels above the traditional hematologic levels of ferritin (usually >40 ng/mL) as potential levels to optimise hair growth in TE, although there is not solid evidence from randomised studies [80]. In such cases, restoration of ferritin to moderate levels has been related to subjective diminution of shedding. That is, female pattern hair loss (FPHL) shows less robust and less consistent correlations with the levels of ferritin. Some analysis reports no significant difference between iron stores of women with FPHL and controls, which again suggest that iron deficiency may be a comorbid rather than causative factor [81]. As a result of this, ferritin targets in FPHL are often individualized and treatment is considered more on a basis of clearly established deficiency rather than empirically elevated targets. variability in the proposed ferritin cutoffs mirrors differences in the study design, choice of populations, assay methodology and clinical endpoints; Establishing phenotype-specific, inflammation-adjusted thresholds is still a primary research priority in the standardization of care of patients with non-scarring hair loss.

7. Controversies & Confounders in the Diagnosis

Interpretation of biomarkers of iron deficiency in patients having non-scarring hair loss is complicated by individual variation in biology, inflammation modulation and inconsistency in clinical definitions of deficiency. Although currently the serum ferritin is used as a main sign of iron stores, singling out any one of these parameters could lead to misclassification, esp-ecially among people with chronic inflammatory states, metabolic disorders or subclinical disease. These diagnostic controversies make a signi-ficant contribution to the lack of consistency of

research findings in the evaluation of iron status in hair loss.

7.1. Ferritin as Acute Phase Reactant: Inflammation and Undiagnosed Misclassification

Ferritin is also not only an intracellular iron storage protein, but it is an acute-phase reactant. During systemic inflammation, the synthesis of ferritin is increased independent of total body iron stores which results in elevated circulating concentrations even when iron availability is reduced [82]. Pro-inflammatory cytokines, in particular interleukin-6, lead to stimulation of hepatic ferritin synthesis and enhancement of the expression of hepcidin that stimulates the sequestration of iron in the macrophage [83]. This inflammatory response may produce a camouflaging effect of underlying iron deficiency by having ferritin levels within the range, or as high as ferritin precipitates with iron deficiency by producing sufficient ferritin for it to be within range or above normal ranges. Consequently, patients who present with diffuse hair shedding may be apparently iron-replete and subsequently the diseases may be underdiagnosed when ferritin alone is used. Failure to consider the inflammatory status (by simultaneously measuring C-reactive protein (CRP) or other markers) may thus compromise a correct clinical interpretation [84].

7.2. Chronic Disease, Obesity, Infection, and Distortion of Iron Biomarker

Chronic inflammatory conditions such as autoimmune disease, metabolic syndrome and persistent infection make the interpretation of ferritin even more difficult. Obesity in particular has been linked to low-grade systemic inflammation and high concentrations of ferritin that are not related to low iron sufficiency [85]. Adipose tissue-derived cytokines are involved in the increased production of hepcidin that limits intestinal iron absorption and decreases iron mobilization in the presence of normal or increased ferritin levels [86]. Similarly, anemia of chronic disease (also termed anemia of inflammation) is characterized by decreased circuits of iron with better or take ferritin due to deposition of iron in reticuloendothelial stores [87]. In this type of configuration, the normal cutoffs for ferritin will not reflect the amount of iron that is truly available to underlying tissues. For chronic disease hair loss patients with coexisting chronic disease assessment of transferrin saturation or soluble transferrin receptor may be of further clarification.

7.3. Non-Anemic Iron Deficiency: What is important and why there is disagreement?

Non-anemic iron deficiency (NAID) is the depletion of iron stores, but not the concentration of hemoglobin. Recognition of the presence of NAID has raised the clinical expression of iron deficiency from overt anemia [88]. Symptoms tiredness and lower level of exercise capacity or possibly hair loss may become apparent before alteration of hematologic indices. However, disagreement continues as to the clinical significance of NAID to dermatologic practice. Some authors put forward the argument that suboptimal iron stores may affect proliferative tissues such as hair follicles even when no anemia is present [89]. Others believe that the evidence for reducing mild ferritin levels to clinically relevant levels of hair loss is lacking and that overtreatment may put patients at risk of unnecessary supplementation [90]. This divergence indicates a general lack of agreement among clinicians regarding the levels at which the ferritin may be referred to a functional impairment in the non-hematologic tissues.

7.4. When Ferritin Doesn't Offer an Alternative Solution: Multi-Step Solution

Given these difficulties in diagnosis, utilisation of a multi-marker approach for assessments of iron status in hair losing patients may increase the precision in evaluation. Ferritin level and level of transferrin saturation (TSAT) combined with soluble transferrin receptor (sTfR) and inflammatory parameters can possibly be used to distinguish absolute iron deficiency from functional iron restriction [91]. For example, low TSAT levels and normal or high ferritin levels could be a sign of sub-optimal iron mobilisation that is a result of a process of inflammation rather than an adequate iron store. The sTfR/log ferritin index has also been suggested to be a useful tool in distinguishing iron deficiency from an anaemia of chronic disease, particularly when there are signs of inflammation [92]. Although this is not conventionally followed in dermato-logical settings such composite approaches may lead to a lower misclassification in complicated cases. Diagnostic controversies when interpret-ting ferritin happened in the area of Ferritin diagnosis It goes to show that the answer to interpreting ferritin is making the assessment possible in context rather than following set rules. In non-scarring forms of hair loss, judicious use of integrating clinical features, inflammatory status and balancing with biomarkers plays a very important role in the process of hair loss diagnosis and treatment which otherwise can lead to underdiagnosis or overtreatment.

8. Evidence of a Link between Iron Deficiency and Hair Loss

The relationship between iron deficiency and non-scarring hair loss has been investigated in a variety of study methods, such as case - control, cross sectional, cohort and longitudinal studies. Although the biological plausible mechanisms for the possible relationship exist and are sound, there has been a heterogeneous clinical graph. Differences in study groups, ferritin cut-off, inflammatory adjustment, and classification of phenotype are responsible for incoherent conclusions. A systematic review of available evidence by study design and phenotype gives more clarity to the strength and limitations of current data.

8.1. Case- Control and Cross- Sectional

Case - control and cross-sectional studies provide the majority of published studies of iron status in populations with hair loss. Several reports have shown significantly reduced mean ferritin concentrations in women with diffuse telogen effluvium compared with healthy controls, especially with women, when premenstrual [93,94]. In these studies, low ferritin was seen often even without overt anemia which supports the theory that a non-anemic iron deficiency could be a contributing factor. However, findings have not been consistent. Some cross-sectional studies failed to find statistically significant differences between patients with hair loss and neutralized controls in ferritin, especially with the use of traditional values for deficiency [95]. Variability in lab assays, lack of evaluation of inflammatory markers and the lack of consistent criteria to diagnose the hair loss phenotypes are likely contributing factors in these discrepancies. Furthermore, many case-control studies have limitations of small sample size and possibility of selection bias, which limits generalization.

8.2. Evidence of Cohort and Longitudinal

Prospective cohort and longitudinal studies have greater inferential value but are less numerous. A small study of the treatment of patients with chronic telogen effluvium with oral iron supplements in women found that smaller baseline levels of ferritin may predict refractory shedding over time [96]. In some longitudinal

analyses, the restoration of ferritin levels of moderate intensity was correlated with the subjective improvement of the intensity of shedding, although for the most part, there was a lack of standardized objective hair metrics. Population-based cohort data looking at iron status and incident hair loss are limited though. Large epidemiologic data sets are usually related to anemia-related outcomes rather than dermatological endpoints [97]. As a result, causality is still difficult to make. Reverse causation - or the fact that systemic illness causing hair shedding also causes changes in iron biomarkers - cannot be ruled out in many of the longitudinal studies.

8.3. Associations to Severity, Chronicity, Recurrence

Beyond hair loss presence or absence, some researches have worked on ferritin levels correlation to the severity or chronicity of hair shedding. A negative correlation between lower ferritin concentrations and numbers of hair per day (nor the duration of shedding) has been found in selected TE populations [98]. However, the size of the correlation is often small and the dose--response relationships have not necessarily been demonstrated. Recurrent telogen effluvium also has been studied with reference to variable stores of iron. Some research indicates that women who have recurrent episodes of widespread shedding have a persistently low ferritin compared with women who have single episodes of acute shedding [99]. Nevertheless, confounding variables, such as psychosocial stressors, hormonal changes and thyroid dysfunction make interpretation complicated. Longitudinal controlled trials which are robust and available are needed to determine whether or not iron deficiency is found to be an independent predictor of recurrence.

8.4. Strength of Evidence per Phenotype (TE vsFPHL)

However, stratified by phenotype, the association of iron deficiency with telogen effluvium appears to be stronger than that of female pattern hair loss (FPHL). TE studies have reported more often of low ferritin in affected people and partial clinical improvement with iron repletion [100]. This consistency supports the pathophysiologic concept that TE is a reactive process which may be stimulated by stressors in the body including nutritional deficiencies. In comparison, the evidence of a relationship between iron deficiency and FPHL is more tenuous as well as more variable. Although lower ferritin is seen in subsets of women with patterned thinning according to selected observational data, no significant differences compared with controls have been found by other investigators after adjustments for age and menstrual status [101]. Given this androgen-driven and genetically mediated nature of FPHL, iron deficiency may be a secondary aggravating factor instead of a primary drug precipitating factor. The cumulative evidence is supportive of a plausible relationship between decreased stores of iron and telogen effluvium in comparison to the relationship in FPHL; and Heterogeneity in study design, inconsistent levels of ferritin and limited adjustment for inflammation limits the confidence of conclusion Standardized, phenotype-specific, prospective investigations would be needed to refine the level of evidence between the subclasses of hair loss.

9. Treatment Outcomes: Completion of Iron & Hair Restoration

Therapeutic correction of iron deficiency in patients with non-scarring hair loss is a common but controversial method of correction. While the biological plausibility is behind reinstating such iron stores at maximizing a good follicular mass,

clinical success depends on the starting ferritin status, phenotype, regimen of supplementation and duration of therapy and other concomitant systemic factors. Evidence based on results of an interventional study found response to be more predictable in telogen effluvium (TE) with a confirmed iron deficiency than in female pattern hair loss (FPHL), in which the miniaturization caused by androgens more predominates [102].

9.1. Oral Iron Therapy: Regimen, Duration and Patterns of Response

Oral iron supplementation is an example of first-line therapy of iron deficiency because it is accessible, cost effective and has proven efficacy in replenishing iron stores [103]. Commonly used formulations are ferrous sulfate, ferrous gluconate, ferrous fumarate and usually 60-100 mg of elemental iron per day. Emerging pharmacokinetic evidence points towards alternate day dosing, which could be more effective, because hepcidin-mediated suppression is minimized [104]. Clinical response in hair shedding is usually late compared to the correction of hematology. In observational dermatologic cohorts, peace in day-to-day hair drop has been reported after 3-6 months of uniform therapy in patient with low dub baseline ferritin [105]. However, improvements in hair density that are objective are less consistently earmarked, and hair density improvement outcome measure heterogeneity prevents direct comparison between studies.

9.2. Intravenous Iron: When, How and Is It Safe?

Intravenous (IV) form of iron is usually reserved for patients having intolerance to oral therapy, malabsorption syndromes, and inflammatory bowel disease or having a severe deficiency needing rapid correction [106]. Modern IV preparations such as ferric carboxymaltose and iron sucrose are now better in terms of safety profile, compared to previous high molecular weight dextran preparations [107]. Whilst dermatology-specific randomised trials are rare, use of IV iron has been demonstrated to be superior in their ability to result in faster ferritin restoration and symptomatic benefit in non-anemic iron deficiency populations [108]. In the case of distress of chronic telogen effluvium with markedly depleted iron stores however, administration of the body ecologically intravenously is theoretically possible in order to shorten the latency time to the biochemical repletion. However, good controlled data assessing the hair specific endpoints after IV therapy are sparse.

9.3. Baseline Ferritin as a Predictor of Response

Baseline ferritin appears to be important in terms of the response to therapy. Several analyses have postulated that those with significantly low ferritin are more likely to experience subjective improvement in shedding with supplementation of iron [109]. In vulnerability, patients with borderline or normal serum ferritin may obtain a limited value; especially the hair loss may be caused mostly by androgenetic or genetic factors and not systemic lack. Dose-Response Relationships Achieved ferritin levels have not been definitively established as being linked to hair regrowth. Some clinicians target ferritin concentrations more than 40-70 ng/mL in patients with TE, although consensus levels are not defined [110]. Prospective trial on the predictive value of baseline ferritin (which may be used to stratify patients) are required.

9.4. Time Course of Hair Improvement compares to feel Biochemical Recovery

Biochemical recovery of stores of iron often precedes hair improvement which can be seen.

Hemoglobin normalization may take place within 4-8 weeks but ferritin repletion may take 2-4 months depending on dose and adherence [111]. However, in the light of the inherent length of time of the hair cycle, manifest reduction in shedding may not be visible until later anagen phases are re-established. Hair follicles entering telogen from previous restriction of iron may learn to shed continued restriction of iron because of the physiological deference in between correction of deficiency and re-old by follicular cycling [112]. As a result, assessment of treatment efficacy should take this difference in time periods of clinical evaluation into consideration.

9.5. Compliance, Gastrointestinal Tolerability & Ways to Improve Compliance

Gastrointestinal adverse effects, including nausea, abdominal discomfort, constipation and diarrhea are common with oral iron therapy and are one of the main barriers to adherence [113]. Poor compliance may impinge on ferritin restoration and creation of confusion in the interpretation of therapeutic response in hair loss patients. Strategies to enhance tolerability include alternate-day dosing, administration in combination with vitamin C to enhance the absorption and utilization of lower-dose formulations and tailor-made titration [104,114]. Avoidance of intake with calcium rich foods/proton pump inhibitors may be further optimization in absorption. Patient education about timelines of what they can expect in terms of improvement, is vital to keeping adherence.

9.6. Adverse Events, Monitoring and Mitigation of Risks

Although in most cases will be safe to use appropriately and as prescribed there are some potential risks associated with iron supplementation. Excessive supplementation is potentially giving rise to intolerance (gastrointestinal symptoms), oxidative stress and, in rare cases, iron overload in susceptible people [115]. Monitoring of ferritin and transferrin saturation if they are to be allowed continued therapy is therefore suggested to prevent supra-physiologic accumulation. Infusions of intravenous preparations of IV iron may produce infusion reactions, but serious hypersensitivity reactions are uncommon with modern-day preparations [107]. Monitoring protocols usually involve observing during and following infusion especially of individuals with a previous allergic history. Current evidence suggests that iron repletion may lessen shedding in deficient patients, including for those with definite deficiency with particular respect to TE. However, here the therapeutic benefit is more uncertain in FPHL and where there is no demonstrable iron depletion. Standardized trials using validated endpoints of hair growth are still required to define optimal regimens as well as treatment goals.

10. Implications for Mental DSM Disorders & Practice

10.1. Proposed Diagnostic Workbook of Hair Loss with Suspected Iron Deficiency

A pleasing workflow process should initially begin with the triage of the problem at a phenotypic level, subsequent to the focused approach of testing iron and finding the cause where iron deficiency is confirmed or seriously suspected. Define the phenotype/ timeline of hair loss. Acute or chronic telogen effluvium (TE), which is characterized by a predominance of shedding, also often with some lag time after forces (febrile illness, surgery, childbirth, rapid weight reduction) of 2-3 months. Female pattern hair loss also known as FPHL, is in the form of progressive patterned thinning and may accompany TE. Should the phenotype raise

suspicion for scarring alopecia, a dermatologic diagnosis and biopsy for confirmation would be preferred over a work up for iron levels. Focused history for iron loss, intake, and absorption main domains are menstrual bleeding burthen, pregnancy/postpartum, dietary iron adequacy, blood donation, gastrointestinal (GI) symptoms, bariatric surgery history, proton pump inhibitor use, and inflammatory disease. In men and postmenopausal women, a positive diagnostic evaluation for IR should prompt structured evaluation for GI blood loss based on major gastroenterology recommendations [116,118]. Minimum set baseline laboratory panel. A minimum interpreting panel for the suspicion of hair loss due to iron is CBC with indices (Hb, MCV, RDW) and Serum ferritin. Chemical reactions - including: - CRP (or its equivalent biological marker of inflammation). Ferritin and TSAT should be considered in context especially if inflammation is likely (clinical context or elevated CRP) because ferritin may be elevated as an acute-phase reactor and conceal iron-limited erythropoiesis. [116, 117]. Add-on tests in case that interpretation is unclear Where ferritin is borderline or there is inflammation an approach of multi-marker combinations (addition sTfR +/- sTfR/log ferritin index, or hepcidin where available) based strategy can be used to ensure reduced misclassification. This is most useful when levels of ferritin are "normal" but TSAT is low, or symptoms/signs are still discordant with the lab picture. [116,118] Cause-finding and parallel managing. When the diagnosis of iron deficiency has been made, investigation and repletion should be conducted in parallel. Gastroenterology advice in favour of not deferring replacement of iron only is pending investigations other than colonoscopy. Gastroenterology guidance to support not deferring replacement of iron only is pending investigation other than colonoscopy. [116]

10.2. When to Treat the Contextualized Thresholds and Clinical Judgment

Treatment decisions should be based on (i) phenotype, (ii) selection of iron biomarker pattern, (iii) inflammation status and (iv) competing etiology. High confidence of iron deficiency (treat). Very low ferritin (commonly <15-30 ug/L) is highly consistent with depleted iron stores in most contexts and generally favours treatment; however, the presence of hair shedding appears to be a key component for justification and will be discussed below (73), also because other etiologies may not be important enough to accommodate the presenting symptoms. [124]. Ferritin borderline (personalize; do not take decisions regarding only ferritin) In dermatology practice, "borderline" ferritin is often in the low-normal range and causes the great controversy. Controversy in Approach to Evaluation and Treatment The best pragmatic approach is to treat if pattern is consistent with iron deficiency: Low/low normal ferritin + Low TSAT and/or compatible history, CRP not elevated (or if elevated, TSAT/sTfR consistent with iron restriction). [116,118,124]. Ferritin cutoffs vary according to a clinical setting. Gastroenterology guidance for iron deficiency anemia (IDA) has put in a higher ferritin diagnostic cutoff in anemia (e.g., 45 ng/mL instead of 15 ng/mL) because lower cutoffs have the potential to miss detection of iron deficiency. This does not necessarily constitute an evidence-based definition of an evidence-based threshold for hair loss, but is consistent with the values of "normal range ferritin" does not rule out iron deficiency in symptomatic contexts [118,119]. FPHL-specific caution. In FPHL, iron repletion may be reasonable if there is iron deficiency, but expectations should be conservative as patterned thinning is often caused by androgen sensitive follicle miniaturization and may need to be

treated phenotypically. Endocrine evaluation is indicated in the presence of a suspicion of hyperandrogenism (hirsutism, acne, irregular menses, rapid progression) [122]. Menstrual blood loss - common drive (treat iron + deal with bleeding). In populations with menstruation, and particularly heavy menstrual bleeding, it is often necessary to address the issue of bleeding burden, so as to avoid recurrent deficiency and "non-response. [120]

10.3. Follow-Up Testing and Treatment Objectives

Follow-up should disassociate biochemical response from response of hair cycle, because it takes follicles time to come out of telogen and back into anagen. Early Response Monitoring (Hematologic Signal). For oral iron, in IDA, according to the major guidelines it is recommended to check for the early response of hemoglobin in early weeks and modifying the strategy if the response is inadequate. A trivial threshold is a measurable Hb increase in a period of ~2-4 weeks (this time varies with the regimen used and severity) [116]. Following normalize-ation of Hb (if anemia is present); advice to continue oral iron for approximately 3 months for repletion of iron stores. Although non-anemic hair-loss patients are common, a similar principle holds: biochemical repletion will often follow behind the perception of symptoms and premature termination can dispose the patient to relapse. [116]. Pragmatic lab schedule (common clinical pattern). 8-12 weeks' time: CBC + ferritin + TSAT (and CRP if there is a risk of inflammation) - to confirm the courses leading in the right direction. Every 3-6 months after this until stability has been demonstrated especially when ongoing losses or absorption issues are present [116]. Timing of Hair Recovery (clinical counseling). TE improvement usually takes several months as shedding is representative of past shifts in the cycle. Biochemical correction might happen before visible improvement therefore outcome assistance is better grounded on decreased shedding, later changes in density/coverage. Avoid overtreatment. Monitoring should also be done to prevent excessive amounts of iron from accumulating, especially with prolonged unsup-ervised supplementation or consecutive IV dosing [116,126].

10.4. Non-Responders: Other Types of Diagnostics - Co-Deficiencies

Non-response is to be addressed as structured differential and not escalating reflexively the dose of iron.

1. Confirm Adherence and Administration Factors GI intolerance and poor adherence are common factors that act as barriers. Best-practice guidance is to help with once-a-day dosing at most with every other dosing being a tolerability strategy. Vitamin C co-administration can enhance the absorption in some situations. [117,116]. Evidence of alternate-day regimens to prevent adverse gastrointestinal side effects from daily dosing therapy using data from randomized iron-depleted women shows comparable ferritin outcomes provided equal total dosing conditions (so far supporting using alternate-day dosing strategies, if tolerability is limiting). [125]
2. Re-evaluate the continuing losses and malabsorption. Persistent heavy menstrual bleeding, occult GI bleeding, bariatric surgical related malabsorption, inflamma-tory bowel disease, celiac disease can prevent biochemical recovery. GI evaluation pathways are especially highlighted for men and postmenopausal

women with a deficiency of Fe. [116,118, 119].

3. Consider phenotype mismatch or the mixed disease If normalizing of iron indices and hair loss continues, reassessment should be: FPHL progression (often requires antiandrogenic/minoxidil treatment) [122]. Alopecia areata or some other inflammatory Alopecias. Scarring alopecia (this is where dermatologic diagnosis is required as soon as possible).
4. Screen for guilty co-deficiencies (non "shotgun"). Trace element and vitamin abnormalities (folate/trace elements) are reported in chronic TE cohorts but there is ongoing debate regarding the routine use of broad panels for more targeted tests are defensible where there is an element of suggestive history/filtered diet/malabsorption risk/clinically apparent putative deficiencies. [121,123].
5. Escalate route in cases of failure of oral iron. When oral iron is not tolerated, or the ferritin fail to improve despite a sufficient trial, then expert advice is in favour of switching to intravenous iron (particularly so when there are likely not to be any problems with absorption) [117,116].

Conclusion

Iron status still has clinical relevance in non-scarring hair loss; however, ferritin guiding has to be interpreted with caution. The current evidence favors ferritin as a practical biomarker for low levels of iron stores, but it has been suggested to have somewhat limited diagnostic application because of its acute-phase profile, inter-assay reproducibility and wide heterogeneity in regard to proposed thresholds for cutoff values in publications from various studies and clinical settings. As a result, a single cutoff values for ferritin are likely to not be suitable for all patients or all phenotypes of baldness. The relation between low iron stores across phenotypes and telogen effluvium is more consistent if compared to female pattern hair loss. Iron repletion is most defensible if iron deficiency is clearly documented - especially in both diffuse shedding from telogen effluvium - but treatment expectations should remain conservative in female pattern hair loss with its centrality of androgen-mediated follicular miniaturization, and the waiting snack cord uplift capacity of such patients. A pragmatic clinical approach should focus on classifying the phenotype and making contextual interpretation of biomarkers. Ferritin evaluation is best when combined with transferin saturation and inflammatory level to check (eg CRP) and when necessary soluble TRR testing to lower the misclassification associated with inflammatory or metabolically complex states. Follow-up should take into account the time between biochemical recovery and recovery of hair cycle using steady clinical endpoints to measure response.

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