Iron Deficiency and Nonscarring Alopecia in Women: Systematic Review and Meta-Analysis

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Abstract

Background: There is no clear-cut evidence in the existing medical literature of an association between iron deficiency and nonscarring alopecia. ***Objective:*** The objective of the study was to conduct a systematic review of the medical literature on the prevalence of iron deficiency in women with nonscarring alopecia and compare their ferritin levels with those of women without this condition. ***Methods:*** The electronic databases PubMed, Scopus, and Web of Science were searched between June 15, 2019, and July 24, 2019. Studies that evaluated the prevalence of iron deficiency in women with nonscarring alopecia and/or compared ferritin levels in women with and without this condition were entered into the meta-analysis. Thirty-six of 928 identified studies entered the systematic meta-analysis. The meta-analysis was performed using the random-effects method. ***Results:*** The overall number of participants was 10,029. The prevalence of ferritin levels from 10 to 15 ng/dL and below was 21% (12; 29). Women with nonscarring alopecia had lower ferritin values at MD = −18.51 ng/dL (−25.85; −11.16, $p < 0.01$). ***Conclusion:*** Women with hair loss can benefit from higher ferritin levels.

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Published by S. Karger AG, Basel

Introduction

Scalp hair has psychological and social effects on women. Loss of hair leads to impaired quality of life and social functioning [1, 2]. There are many causes of hair loss, but a small number comprises the majority of relevant diagnoses [3] and the focus of the clinical work-up. All types of hair loss are categorized into 2 large groups: scarring and nonscarring alopecia. The most prevalent disorders of hair loss belong to the nonscarring group including telogen effluvium (acute and chronic TE), androgenetic alopecia, which is usually female pattern hair loss, and the less prevalent alopecia areata. The diagnosis of type of hair loss disorder is reached by history taking, physical examination, and tests such as the pull test and the trichogram. Opinions differ as to an association between iron deficiency/iron-deficiency anemia and hair loss in all 3 prevalent types. Some studies found significantly low ferritin levels in patients with nonscarring alopecia, while others did not [2, 4, 5]. In any event, it is a common practice among dermatologists and family doctors to conduct blood tests for patients with nonscarring alopecia including a complete blood count and ferritin level [5, 6]. The aim of this study was to conduct a systematic search of the medical literature on a potential association between iron deficiency and nonscarring alopecia in women, and to base a meta-analysis on the identified studies that met the inclusion and exclusion criteria.

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Search Strategy for Identification of Studies

The electronic databases PubMed, Scopus, and Web of Science were searched between January 15, 2020, and February 18, 2020, for studies on the association between iron deficiency and nonscarring alopecia in women. The search was not limited by date or language of publication. Two investigators (Y.T.G. and R.P.) conducted the search for relevant studies. The search was conducted in 2 steps with the keywords: alopecia and iron deficiency, hair loss and iron deficiency, and telogen effluvium and iron deficiency.

The inclusion criteria were as follows: (a) original research, (b) the study assessed either the prevalence of iron deficiency/iron-deficiency anemia or compared ferritin levels between women with and without hair loss, and (c) the study population was comprised of women. The exclusion criteria were as follows: (a) the study population was men, children, or mixed, (b) the terms iron deficiency and iron-deficiency anemia were not defined in the paper, (c) the study reported low hemoglobin levels without ferritin levels, and (d) the study participants were recruited from a population suffering from specific conditions or diseases such as patients after bariatric surgery or cancer patients.

In the first phase, the investigators reviewed the abstracts, and in the second selected full articles and bibliographic lists. If a full paper could not be obtained through the electronic database system, the authors communicated with the authors or requested the full article through ResearchGate. All papers were reviewed independently by the 2 investigators who determined whether to include the paper. In case of disagreement, the final decision was reached by consensus.

Data Collection

The data collected were as follows: authors and year of publication, type of study, sample size for statistical analyses, number of women in case-control studies (if relevant), the mean age and ethnic origin of the women, the type of hair loss, the method of diagnosis, and the measures of iron deficiency.

Risk of Bias for the Included Studies

The Newcastle-Ottawa scale is a simple, convenient tool for the quality assessment of nonrandomized studies. It uses a star system and is based on 4 domains: selection, comparability, exposure, and outcome. There are adapted versions for case-control and cohort studies [7]. We further adapted the Newcastle-Ottawa scale for our specific study purpose. The risk of bias assessment was conducted by 2 investigators in a blinded process, and in cases of disagreement, a consensus-reaching process was used.

Data Synthesis and Analysis

Meta-analyses were performed using the Metafor, Meta, and Demtar [8, 9] packages for R software (version 3.6.1) [10]. The prevalence rates for ferritin deficiency and iron-deficiency anemia were calculated from cohort and case-control studies using the inverse-variance weighting method.

Ferritin level below the range of 10–15 ng/dL was considered as ferritin deficiency [5, 11]. Several studies have found that ferritin levels below 30–40 ng/dL are more sensitive and as specific for the diagnosis of iron deficiency [5]. A separate meta-analysis was performed on studies that used this cutoff level. The mean difference in ferritin levels between patients and controls was calculated in case-control studies using the inverse-variance method. The mean difference in ferritin levels was calculated separately for studies, in which participants were of childbearing age or premenopausal women. A p value <0.05 was considered statistically significant.

In studies where the results were given in median (range), they were converted to mean (SD) by the method described by Hozo et al. [12]. In studies where the results were presented in mean and 95% confidence intervals, they were converted to mean (SD) using the Cochrane Handbook for Systematic Reviews of Interventions [13]. The meta-analysis was performed using the random-effects model because a significant heterogeneity of the included studies was expected. The inconsistency index (I^2) test and Cochran's Q were used to assess heterogeneity across studies. A value above 50%, or $p < 0.05$, indicated statistically significant heterogeneity. Additional meta-analyses were performed, excluding outliers. When significant heterogeneity was detected, funnel plots, Egger linear regression tests, and trim-and-fill methods were used to explore for publication bias. Influence analyses using the leave-one-out method were performed to identify if 1 specific study overly distorted the pooled effect size or overall heterogeneity.
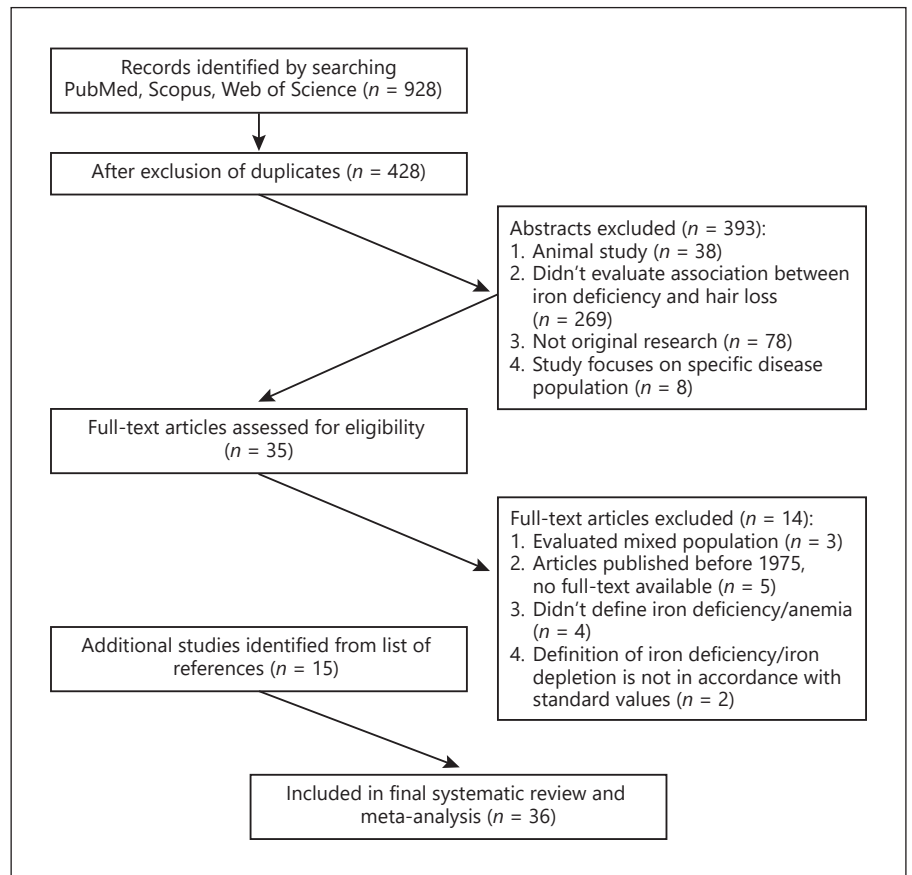
Fig. 1. Flowchart of the review process.

Results

We identified 928 studies in the electronic databases using all the search terms (see Search Strategy section). Of these, 500 were duplicates. Four hundred and twenty-eight abstracts and names of articles were reviewed in phase 1 of the selection process. In phase 2, we evaluated 35 full-text articles. The articles were obtained through the electronic library of Ben-Gurion University of the Negev. One article was received by request through ResearchGate. Two articles were received directly from the authors by email request. At the end of the process, 36 studies were entered into the systematic review and meta-analysis. The selection process is shown in the flowchart (shown in Fig. 1).

Study Characteristics

The characteristics of the studies that were included in the meta-analysis are described in Table 1. Twenty-one were case-control studies, and 15 were cohort studies. The year of publication ranged from 1988 to 2019. One

study was published in German [14], 2 in Turkish [15, 16], and the rest in English. Articles published in languages other than English were addressed using language translation agency.

The variance in sample size was large. The total number of participants was 10,029. Of these, 6,641 suffered from alopecia and 3,388 were in the control group.

The mean age of the participants ranged between 23 and 44.4 years. The countries included 7 each from India and Turkey, 4 from Egypt, 3 from the UK, 2 each from Iran and the USA, and 1 each from Switzerland, China, France, Saudi Arabia, Australia, Germany, Korea, Bangladesh, Jordan, and Nepal.

Fifteen studies evaluated the prevalence of ferritin deficiency with the accepted threshold of 10–15 ng/dL, 24 the prevalence of ferritin levels below 30–40 ng/dL, and 5 the prevalence of iron-deficiency anemia. Eighteen studies compared mean ferritin levels between patient and control groups, and 16 involved premenopausal women/women of childbearing age or included a subgroup of these women, which was clearly defined in the article.

Table 1. Characteristics of the studies included in meta-analysis

| Study	Type of study	P/C country	Mean age P/C	Type of alopecia	Diagnosis	DD Data collected
Aydingoz et al. [45]	Case-control	43/46, Turkey	25.9/age matched	TE, AnA/FPHL	Not described	Prevalence of iron deficiency, iron-deficiency anemia in cases
Bregy and Trueb [26]	Cohort	181, Switzerland	42.39	TE, AnA/FPHL	History, pull test, trichogram	Prevalence of iron deficiency
Chisti et al. [46]	Case-control	100/100, India	26.6/26.8	TE, AnA/FPHL, AA	History, physical examination	Mean ferritin level among cases and controls
Deloche et al. [18]	Cohort	2,910/2,200, France	Range 35–60	Presumably TE, AnA/FPHL	History	Prevalence of iron deficiency, iron-deficiency anemia
Deo et al. [47]	Cohort	134, India	30.96	TE, AA, AnA/FPHL	History, physical examination, pull test	Prevalence of iron deficiency
Elethawi and Jabbar [31]	Case-control	38/25, Iraq	31.15/29.1	TE	History, physical examination, pull test	Mean ferritin level among cases and controls
Ertug and Yilmaz [23]	Case-control	455/196, Turkey	29/31.3	TE	History, physical examination + pull test	Mean ferritin level among cases and controls
Fatani et al. [48]	Cohort	279, Saudi Arabia	29.8	TE	History + physical examination, pull test	Prevalence of iron deficiency
Gangaiah et al. [28]	Case-control	40/40, India	27/32.2	TE, AnA/FPHL	History, physical examination	Prevalence of iron deficiency, iron-deficiency anemia
Gurel et al. [15]	Case-control	80/80, Turkey	26.41/25.79	TE	History, physical examination	Mean ferritin level among cases and controls
Hamad et al. [19]	Case-control	34/26, Egypt	23/19.1	TE	History, physical examination, pull test, trichogram	Mean ferritin level among cases and controls
Hodeib et al. [20]	Case-control	40/20, Egypt	28.1/27.4	TE	History, physical examination, pull test, trichogram	Mean ferritin level among cases and controls
Ibrahem et al. [30]	Case-control	80/20, Egypt	25/23.2	TE	History, physical examination, pull test	Mean ferritin level among cases and controls
Islamoglu and Sari [16]	Case-control	103/125, Turkey	25.7/26.2	TE	Not described	Prevalence of iron deficiency in cases
Kantor et al. [32]	Case-control	106/11, USA	44.4/41.9 (28/36 in premenopausal subgroup)	TE, AnA/FPHL, AA	History, physical examination	Mean ferritin level among cases and controls
Karadag et al. [49]	Case-control	63/50, Turkey	29/28.4	TE	History, physical examination, dermoscopy	Mean ferritin level among cases and controls
Karim et al. [21]	Case-control	30/30, Bangladesh	25.4/24.8	TE	History, physical examination, pull test	Mean ferritin level and iron deficiency among cases and controls
Malkud [50]	Cohort	180, India	27.27	TE + AnA/FPHL	History, physical examination, trichogram	Prevalence of iron deficiency
Moeinvaziri et al. [22]	Case-control	30/30, Iran	28.1/29.4	TE	History, physical examination, trichogram	Mean ferritin level among cases and controls, prevalence of iron deficiency

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Table 1 (continued)

Study	Type of study	P/C country	Mean age P/C	Type of alopecia	Diagnosis	DD Data collected
Moltz [14]	Cohort	125, Germany	35.4	AnA/FPHL	History, physical examination	Prevalence of iron deficiency
Nazik and Bengu [51]	Case-control	39/30, Turkey	26.3/24.7	TE	History, physical examination, pull test, dermoscopy	Mean ferritin level among cases and controls
O'baidat et al. [52]	Case-control	72/30, Jordan	26/32	TE	History, physical examination, pull test	Mean ferritin level among cases and controls, prevalence of iron deficiency
Olsen et al. [29]	Case-control	381/76, USA	44.5/39.9 (37/30 in premenopausal subgroup)	TE, AnA/FPHL	History, physical examination	Mean ferritin level among cases and controls, prevalence of iron deficiency, iron-deficiency anemia
Ozden et al. [53]	Cohort	100, Turkey	32	TE + AnA/FPHL	History, physical examination	Prevalence of iron deficiency
Park et al. [54]	Case-control	113/113, Korea	42.9/40.1	AnA/FPHL	History, physical examination	Mean ferritin level among cases and controls, prevalence of iron deficiency
Poonia et al. [55]	Cohort	100, India	30.1	TE, AnA/FPHL	History, physical examination, pull test, trichogram	Prevalence of iron deficiency
Pradhan et al. [33]	Case-control	60/60, Nepal	33.9/35	TE, AnA/FPHL, AA	History + physical examination	Mean ferritin level among cases and controls
Raichur et al. [25]	Cohort	40, India	25.18	TE, AnA/FPHL	History, physical examination, pull test	Prevalence of iron deficiency
Rasheed et al. [42]	Case-control	80/40, Egypt	29.8/30.8	TE, AnA/FPHL	History, physical examination, pull test, trichogram, dermoscopy	Mean ferritin level among cases and controls
Rushton et al. (1) [43]	Cohort	50, UK	32 (subgroup)	TE, AnA/FPHL	History, physical examination, trichogram	Prevalence of iron deficiency
Rushton (2) [56]	Cohort	200, UK	No data	TE	History, physical examination, trichogram	Prevalence of iron deficiency
Sarkar et al. [57]	Case-control	40/40, India	24.3/23.1	TE	History, physical examination, pull test, trichogram	Mean ferritin level among cases and controls
Sinclair [24]	Cohort	194, Australia	Range 11–72	TE, AnA/FPHL	History, physical examination, scalp biopsy, trichogram	Prevalence of iron deficiency and iron-deficiency anemia
White et al. [17]	Cohort	20, UK	38.25	AA	Not described	Prevalence of iron deficiency
Zabolinejad et al. [58]	Cohort	41, Iran	28.1	TE, AnA/FPHL, AA	History, physical examination, pull test	Prevalence of iron deficiency
Zhang et al. [27]	Cohort	60, China	34.4	AnA/FPHL	History, physical examination, trichogram	Prevalence of iron deficiency

P/C, patients/control; AnA, androgenetic alopecia; AA, alopecia areata.
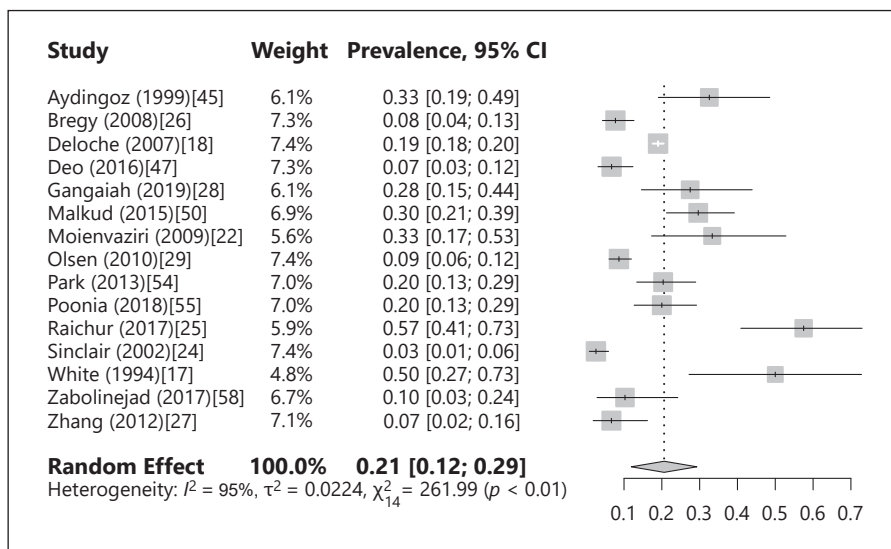
Fig. 2. Forest plot of the prevalence of iron deficiency.
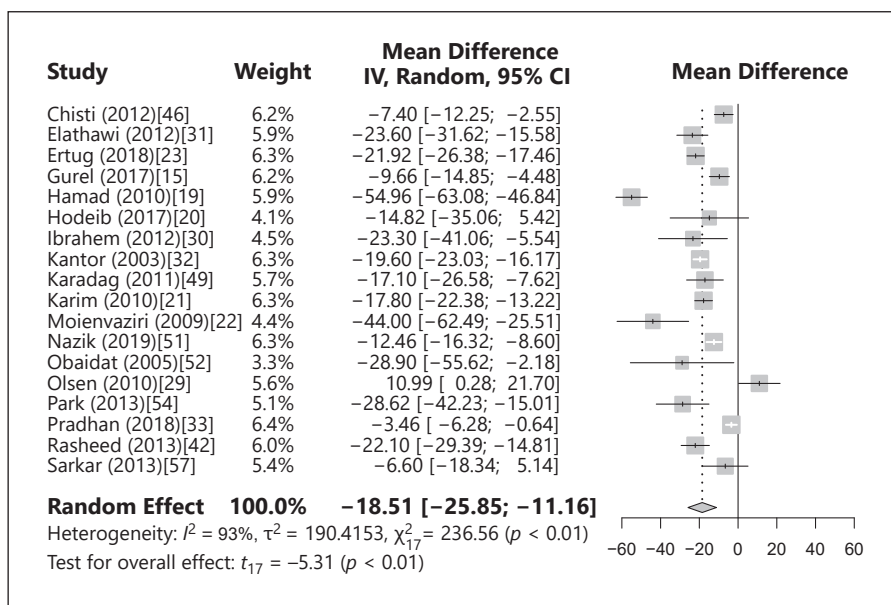
Fig. 3. Forest plot of the difference in mean ferritin values between patients and controls.

Outcomes
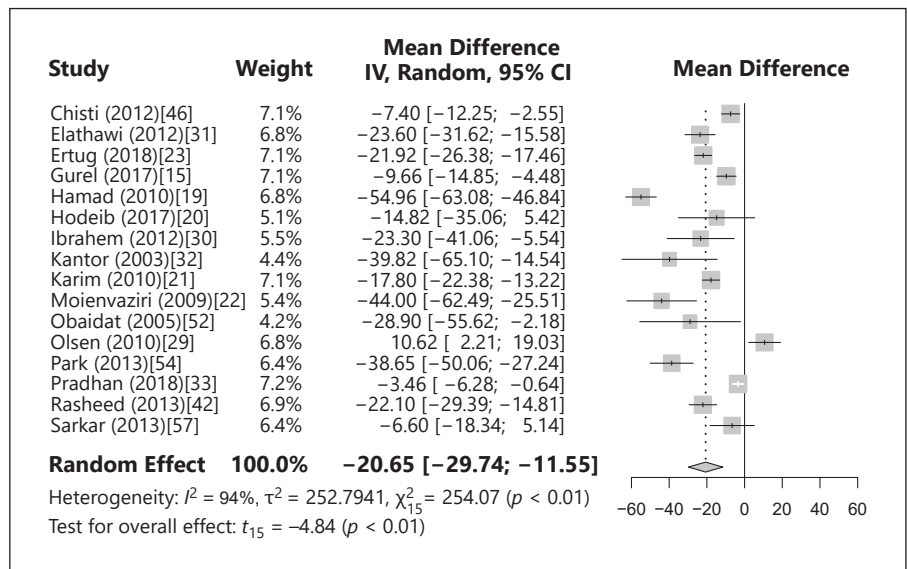
Prevalence of Ferritin Deficiency

The prevalence of ferritin deficiency was 21% (12; 29), with significant heterogeneity among the studies (I^2 = 95%, $p < 0.01$). A forest plot of the prevalence of iron deficiency is shown in Figure 2. When outliers were excluded from analysis from the subgroups, the prevalence of iron deficiency changed to 19% (12; 26). An "influence analysis" was carried out, omitting each of the studies individually without any significant effect on the prevalence of iron deficiency. A funnel plot showed no evidence for publication bias by Egger's regression test, in the studies

that examined the prevalence of ferritin levels of 10–15 ng/dL and below ($p = 0.42$).

Online supplementary Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000519952) shows a forest plot of the prevalence of ferritin levels below the cutoff of 30–40 ng/dL among women with alopecia. It demonstrates the overall prevalence of ferritin levels below the cutoff of 59% (49; 69, I^2 = 98%, $p < 0.01$). Similarly, the outlier exclusion and influence analyses did not change the results of meta-analysis significantly.

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Fig. 4. Forest plot of the difference in mean ferritin values between patients and controls among premenopausal women.

Prevalence of Iron-Deficiency Anemia (Hb < 12 g/dL, Ferritin <15 ng/dL)

Five studies examined the prevalence of iron-deficiency anemia. The overall prevalence of iron-deficiency anemia in the meta-analysis was 8% (0; 21), with significant heterogeneity among the studies ($I^2 = 97$, $p < 0.01$) (shown in online suppl. Fig. 2). In the influence analysis, the prevalence varied from 5% to 11%. There was no evidence for publication bias ($p = 0.37$) with either the funnel plot or Egger's regression test.

Difference in Mean Ferritin Values between Patients and Controls

Eighteen studies compared mean ferritin values between patients with nonscarring alopecia and controls. A forest plot of the meta-analysis is shown in Figure 3. When the studies were pooled, a statistically significant difference was seen, with the mean ferritin values lower in patients with alopecia at MD = −18.51 ng/dL (−25.85; −11.16; $p < 0.01$) with significant heterogeneity among the studies ($I^2 = 93\%$, $p < 0.01$). When outliers [19, 29, 33] were excluded from the meta-analysis, a statistically significant difference in ferritin levels was still seen between the patients and controls at MD = −18.23 ng/dL (−22.93; −13.53; $p < 0.01$, $I^2 = 74\%$, $p < 0.01$). When the studies were omitted one at a time in the influence analyses, the difference in pooled MD between patients and controls was still statistically significant. Publication bias was not the source of heterogeneity ($p = 0.15$) as measured by funnel plot and Egger's test.

Difference in Mean Ferritin Levels between Patients and Controls of Childbearing Age/Premenopause

Sixteen studies dealt with premenopausal women/women of childbearing age or included them as a subgroup. A forest plot of the meta-analysis is shown in Figure 4. When the studies were pooled in the meta-analysis, a statistically significant difference was seen with lower mean ferritin levels in patients with alopecia (MD = −20.65 ng/dL [−29.74; −11.55; $p < 0.01$]) with significant heterogeneity among the studies ($I^2 = 94\%$, $p < 0.01$). A statistically significant difference in ferritin levels between the patients and controls was still found when outlier papers [19, 29, 33] were omitted from the meta-analysis (MD = −21.11 ng/dL [−28.14; −14.08; $p < 0.01$, $I^2 = 80\%$, $p < 0.01$]). Omitting study by study in influence analyses still resulted in a statistically significant difference in pooled MD between patients and controls. The funnel plot and Egger's test did not indicate that the source of heterogeneity was publication bias ($p = 0.07$).

Risk of Study Bias

The results of an adapted Newcastle-Ottawa scale for the risk of bias assessment of the included studies are shown in online supplementary Table 1 and 2. Of 21 case-control studies, 14 were of good quality (7–8/9), 7 were of fair quality (5–6/9), and none was of poor quality. All 15 cohort studies were of good quality (2/3). The main drawback in all but one of the studies was that they focused on populations from referral centers and tertiary care hospitals.

Discussion

This meta-analysis that evaluated associations between iron deficiency and hair loss of the nonscarring type included studies from a broad range of countries from Europe, Asia, Africa, and the USA. The prevalence of iron deficiency, defined as a ferritin level between 10 and 15 ng/dL or below, was 21%. This result is comparable with the prevalence of iron depletion in the general population. In Europe, the reported rates are from 3 to 8% in Poland and Italy to 22–23% in Norway, Belgium, and France [34, 35]. The reported rate of iron deficiency in the USA and Canada is 10–12% [36]. The reported prevalence rate for iron deficiency from Asian countries is 20–26% and in different regions of Ethiopia 18–50% [37–41]. Based on these data, it would appear that ferritin deficiency in women with nonscarring alopecia is not higher than in the general population. Several studies suggested higher cutoff levels of below 30–40 ng/dL as the definition of iron deficiency [5, 29, 42–44]. This threshold of 30–41 ng/dL yields sensitivity and specificity rates of 92–98% each for iron deficiency [29]. The prevalence of iron deficiency among women with hair loss increased with this threshold to 59%. It would appear that the prevalence of reduced ferritin levels (below 30–40 ng/dL) is higher among women with diffuse hair loss than among women in the general population. Ferritin levels below 30 ng/dL were found in 40–50% of the women in Denmark and Norway [34], 32% of the women in Portugal [35], and 47% of the women in Cambodia [38].

The heterogeneity in the frequency of iron deficiency of varying degrees of severity can be explained easily by the different frequencies of iron deficiency in developing and developed countries and the difference in the ages of the participating women since the prevalence of iron deficiency decreases significantly in postmenopausal women. The overall prevalence of iron-deficiency anemia in our study was 8%. The reported prevalence rates in Europe were lower at 2–6% [34] than in 6–18% in Nepal, Pakistan, and Ethiopia [37, 39, 40]. A comparison of the individual studies with the overall meta-analysis results shows that the rate of iron-deficiency anemia among women with hair loss is not higher than in the general population of women.

The main meta-analysis in the present study summarized case-control studies and compared ferritin levels between women with nonscarring alopecia and matched population controls. It demonstrated a statistically significant difference between the groups, which was even more striking when the analysis included only premenopausal women.

Conclusion

There is a significant difference in ferritin levels between women with nonscarring alopecia and healthy women. Iron-deficiency anemia is not more common among women with nonscarring alopecia. Thus, it would appear that women who complain of hair loss can benefit from higher ferritin levels.

Author Contributions

Yulia Treister-Gotzman contributed to the conception of the research. Yulia Treister-Goltzman, Roni Peleg, and Shaked Yarza equally contributed to the design of the research. Yulia Treister-Goltzman and Roni Peleg equally contributed to the acquisition of the data. Yulia Treister-Goltzman and Shaked Yarza equally contributed to the analysis of the data. All authors contributed to the interpretation of the data. Yulia Treister-Goltzman and Shaked Yarza drafted the manuscript. All the authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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