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Iron Status in Adolescents with Eating Disorder: A Systematic Review

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ABSTRACT
Introduction: Eating disorders are major mental disorders that affect all aspects of life, including quality of life at home or workplace, personal functions, and social life. Malnutrition, particularly iron deficiency, can result from a lack of food intake caused by eating disorders.
Aim: This study aimed to determine the impact of eating disorders in adolescents on hematological alterations and iron serum indexes.
Method: The study was conducted by doing online database searches systematically using relevant search terms and appropriate criteria. Sources of literature that were traced were those published until 2022. The online searches were conducted on the following databases: MEDLINE, PubMed, PsycINFO, ScienceDirect, Scielo, and DynaMed Plus.
Results: Searching by keyword yielded 55 titles and abstracts. When they were screened, a total of 41 publications were saved for further analysis. However, only 8 publications met the inclusion criteria and were continued for review (two studies that used a cross-sectional design, one case-control study, and five cohort studies).
Conclusion: Iron deficiency and anemia were uncommon in young women who had eating disorders and weight loss. However, there was a rise in serum ferritin and serum hepcidin, as well as a decrease in transferrin, based on evaluations using biomarkers that were more sensitive for the detection of adolescent anorexia nervosa. In participants who gained weight after receiving nutritional therapy, transferrin levels increased whereas ferritin and hepcidin levels declined (rapid depletion).

KEYWORDS: Adolescence, Eating disorder, Hematology, Iron serum indexes

INTRODUCTION

Eating disorders are serious mental disorders that affect all aspects of life including quality of life at home and work, personal functioning, and social life. Eating disorders are relatively rare with an estimated lifetime prevalence of 0.9% for anorexia nervosa (AN) and 1.5% for bulimia nervosa (BN) in American women [1]. AN is one type of eating disorder and has the highest mortality rate of all mental illnesses. Eating disorders are often chronic and difficult to treat. Most of these disorders are reversible with nutrient recovery, at least in adults. However, the consequences of AN, especially for changes in growth, pubertal development, and bone mass, will be different if it occurs in adolescent girls.

In addition to the peculiarities of eating patterns, eating disorders are life-threatening and produce a wide range of public health problems because of their potential for long-term burden on overall health and reproductive health. Matters related to the health effects and other effects of eating disorders include low body mass index (BMI), poor mental health, substance abuse, changes in menstrual function, infertility, unplanned pregnancy, pregnancy complications such as low birth weight (LBW), gestational diabetes, and nausea and vomiting [1–3].

Eating disorders are very common among teenagers and have serious long-term consequences. Patients with AN are characterized by low body weight, excessive fear of gaining weight, faulty body image, denial of the seriousness of the disease, and amenorrhea. The patient with BN usually has an average weight like a normal teenager and binge eats and then forces themselves to vomit the food up. Only 1/3 of adolescents who meet the criteria for AN actually receive treatment in a mental health setting and only 6% of those receive treatment [4]. Both AN and BN can affect social relationships, school activities, and relationships with family, which are important in young patients.

Lack of food intake due to eating disorders can cause malnutrition. Malnutrition associated with eating disorders affects most of the organ systems with effects on metabolism and physiological function, depending on the severity and duration of the disease. Measurement of malnutrition is a bit difficult to do because it relies on clinical, anthropometric, and laboratory parameters to

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determine clinical risk. Traditional laboratory markers of nutritional status are normally used in children and adolescents up to the late stages of malnutrition [5].

Iron deficiency is common in malnourished children and adolescents. Iron deficiency usually occurs because of conditions of food insecurity, inadequate nutritional intake, and impaired absorption of the gastrointestinal tract [6]. Hematological changes and serum iron index changes occur in AN adolescents. Serum iron decreases (still in the normal category), but on the other hand, ferritin status may increase in adolescents with AN and affect anthropometric measurements [5,7]. Recently, it has been reported that the increase in ferritin in AN corresponds to the level of hepcidin, a substance that plays a role in maintaining iron levels in the body [8]. However, until now, the relationship between ferritin and the physiological changes that accompany malnutrition is still not well understood. This is because there are still few studies that discuss iron status in people with eating disorders such as AN, especially in cohort studies. This paper aims to identify the impact of eating disorders in adolescents on hematological changes and serum iron index.

METHODS

Data Sources and Search Strategy

This study was conducted by systematic online database searches using relevant search terms and appropriate criteria. The literature search was conducted on publications published until 2022. The search was conducted using the following online databases: MEDLINE, PubMed, PsycINFO, ScienceDirect, Scielo, and DynaMed plus. The search strategy used Boolean operators AND and OR to refine or expand the search of titles and abstracts. The keywords used were *(eating disorders OR anorexia OR bulimia OR disordered eating OR binge eating disorder)* AND *(iron status, serum ferritin)* AND *(adolescent, youth, teenagers).*

Selection of Studies

The inclusion criteria of this study included: 1). Publications with male or female adolescent respondents based on WHO criteria (10-19 years), 2). Publications with adolescent respondents of all ethnicities, socioeconomic status, or pregnancy status, 3). Publications reporting the nutritional status of iron in adolescents who experience various forms of eating disorders, 4). Publications published in peer-reviewed journals or edited academic books, 5). Publications in English. The exclusion criteria were dissertations and reports that have not been published in order to prevent the inclusion of research that is not properly reviewed and the results that are not a duplication of other studies and to ensure quality. In addition, conference abstracts and protocols were excluded, but were used to search for full-text and relevant articles. The publication selection process started from the title and abstract screening stage, then journals that are suitable or suspected to meet the eligibility criteria were downloaded to be continued with the next selection until the journals that would be reviewed were complete. The summary process of the flow of the systematic review stages is presented in Figure 1.

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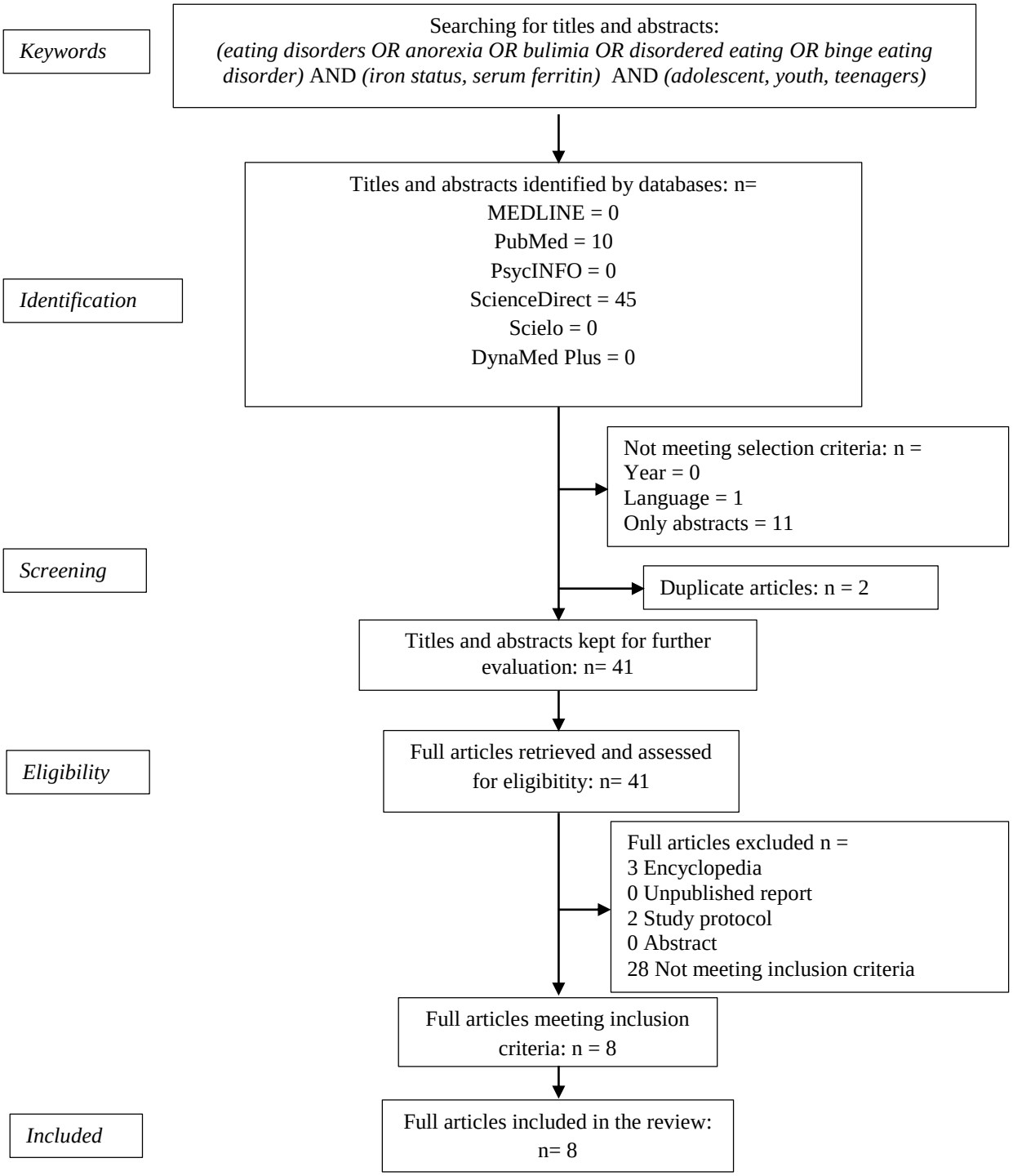

Figure 1: Search Strategy of Articles

RESULTS

Searching by keyword yielded 55 titles and abstracts. When the titles and abstracts were screened, a total of 41 publications were saved for further analysis. However, only 8 publications met the inclusion criteria and were continued for review (Table I).

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Table I: Articles Included in This Review

Author	Objective	Study Design	Characteristics of Participants	Main Findings About Iron Status
[9]	Investigating body image, weight, eating attitude, food intake, and nutritional status related to eating disorder in school adolescents in Taiwan	*Cross sectional*	Sample: 1,605 Gender: girls Age: 15-18 year Country: Taiwan	The percentage of respondents with total iron-binding capacity (TIBC) and serum iron values was significantly higher in adolescents with eating disorders than in those without eating disorders.
[10]	Verifying the relationship between body composition, biochemical parameters, and food intake in adolescent swimmers with and without eating disorders	*Cross sectional*	Sample: 77 Gender: girls Age: 11-19 year Country: Brazil	A total of 4 athletes tested positive for eating disorders, anemia, or iron deficiency. There was no significant difference in the value of hematological and biochemical parameters between the positive group with eating disorders and those without eating disorders.
[7]	1. To identify the incidence of iron deficiency in female adolescent patients who have menstruated with AN in the hospital 2. To observe changes in iron status during refeeding	Cohort	Sample: 12 Gender: girls Usia: 14-19 year Country: Australia	The patient had an increase in ferritin levels at admission and a decrease after admission. There was no significant difference in hemoglobin levels when the results at admission and after improvement were compared.
[11]	Observing the determinants of pica habits in a high-risk population (pregnant women) and their possible association with iron status	*Logitudinal cohort study*	Sample: 158 Gender: girls Age: $\leq$ 18 year Country: USA	The mean values of serum iron, TBI, and hepcidin concentrations were significantly lower in the group with pica habit.
[12]	Determining the relationship between serum ferritin and malnutrition in patients who are new to the pediatric eating disorder clinic	*Clinical cohort study*	Sample: 121 Gender: girls Usia: 9.5-17.6 tahun Negara: Australia	Serum ferritin is inversely related to BMI and serum IGF-1 (a protein produced by the liver for longitudinal growth) and is positively related to alanine aminotransferase
[13]	Evaluating the role of hepcidin in hyperferritinemia in adolescent with AN	*Case control*	Sample: 27 (cases) 11 (control) Gender: boys and girls Age: 12-16 year Country: France	Serum ferritin and hepdicin were higher in the case group (AN) than they were in the control group. There was an association between ferritinemia and hepcidin concentration ($p<0.0001$)
[14]	Analyzing hematological changes and iron stores in adolescent girls with eating disorders and weight loss	Cohort	Sample: 446 Gender: girls Age: 6-18 year Country: Sweden	Hemoglobin concentration, leukocyte count, and platelets are related to body weight and rate of weight loss. Menstruating women have low serum ferritin

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Table I: Articles Included in This Review *(cont…)*

Author	Objective	Study Design	Characteristics of Participants	Main Findings About Iron Status
				concentrations and iron stores depletion.
[5]	Analyzing the evolution of several biochemical indicators of nutritional status during the one-year follow-up of AN patients	Cohort (1 year)	Sample: 14 Gender: girls Age: 15 year Country: Spanish	Changes in transferrin, C3, and C4 during the patient's convalescent therapy may explain the increased risk of relapse after 1 year of admission to hospital. Ferritin and zinc levels appear to be affected by nutritional requirements for anabolic processes during recovery.

Population

Respondents who were included were generally young women, except for in one study which also involved young men. Respondents' age ranged from 9.5 years to 19 years. The studies reviewed were conducted in various continents, namely Europe, America, and Asia, and only one study was conducted in a developing country, namely Brazil.

Study Design

The sample size ranged from 12 to 1,605 respondents and two studies involved fewer than 20 respondents. Out of 8 total studies, about two studies used a cross-sectional design, one study is case-control study, and 5 studies are cohort studies.

Study Duration

Only one cohort study revealed the duration of the study, which was 1 year with 4 divided review time points (t0: at hospital admission, t1: 1 month after enrollment, t6: 6 months after enrollment, and t12: 12 months after enrollment) [5]. The other cohort studies did not mention the time needed to see changes after being given healing therapy in the hospital.

Variable Measurement

The studies reviewed were studies that discuss iron status in adolescents with eating disorders or discuss eating disorders, although this discussion is not the main goal of the study. Thus, the variables measured by each study varied greatly. However, for the preparation of this paper, the reviewer focused more on variables related to the iron status, namely hematology and serum iron index. The blood biochemical values reviewed included hemoglobin, hematocrit, serum iron, total iron binding protein (TIBC), transferrin, transferrin saturation, serum ferritin, MCV, and hepcidin. The reviewer also added information related to menstruation from the studies obtained.

Main Outcomes

TIBC and serum iron were significantly higher in adolescents with eating disorders than in adolescents without these disorders [9]. Patients experienced an increase in ferritin levels or AN condition at admission, but ferritin levels then decreased after the patients were given healing therapy accompanied by an increase in BMI [7,13], as well as due to menstruation which led to the depletion of iron stores [14]. The results of these parameters are different from those proposed by the other study [11], which revealed that serum iron, TBI, and hepcidin values were lower in the group with pica habits.

The concentration of several hematologic parameters such as hemoglobin, leukocyte count, and platelets is associated with a decrease and the rate of weight loss [14]. However, according to [10] through a cross-sectional study, although 4 athletes who tested positive for eating disorders were also anemic, there were no significant differences in hematological values and biochemical parameters between the groups with eating disorders and those without ones.

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DISCUSSION

The Gap That Happened

It has long been known that patients with eating disorders such as AN can develop nutritional deficiencies, especially iron deficiency, when they enter the stage of severe malnutrition. Clinically, AN patients usually have anemia with decreased platelet and white blood cell counts. Pale face in anorexic patients reinforces the notion that anemia occurs in patients with AN. Previous biochemical examinations still prioritized hematological biomarkers not based on serum iron index. However, a recent statement from the American Dietetic Association (ADA) explains that nutritional deficiencies including iron deficiency due to inadequate food intake are rare.

Another study is consistent with the recent ADA statement that patients with AN have a lower incidence of iron deficiency and a less frequent incidence of iron deficiency anemia in clinical samples [7]. There was only one patient with low serum iron but without anemia, and serum returned to normal on treatment without the use of supplements. This increase in serum iron coincides with a significant decrease in iron stores (ferritin) that is indicated by a decrease in serum ferritin levels at the time of improvement.

Eating disorders often occur in adolescents, including adolescent athletes and adolescents who are experiencing pregnancy. Eating disorder that is common among pregnant adolescents is pica (habits of consuming non-food items such as lime, sand, clay, etc). The prevalence of eating disorders in adolescent athletes is higher than that in non-athlete adolescents, presumably because sports are more focused on body mass, thus supporting eating behavior disorders. Female athletes tend to be iron deficient which is generally caused by inadequate iron intake, especially due to eating disorders. It was found that female-athlete respondents experienced anemia and iron deficiency, but there was no relationship between iron intake and serum ferritin concentration [10]. However, low iron intake does not play an important role in the occurrence of anemia, but in the long term, will result in damage to muscle metabolism and cognitive function [15].

Data on the prevalence of pica behavior in adolescents or pregnant women are very limited. Study [11] found the prevalence of pica behavior in pregnant adolescents was 46%, which was still within the range of previous survey data from pregnant adolescents and adults in North America. Adolescents with pica behavior had significantly lower iron status than those without pica behavior. Pregnant adolescents with pica behavior had significantly lower serum ferritin, TBI, and hepcidin values compared to adolescents who did not exhibit pica behavior. Although iron status is significantly associated with pica behavior, a causal relationship between iron status and pica has yet to be determined.

Hematological Changes in Adolescents with Eating Disorders

Malnutrition secondary to AN causes a contraction of circulating blood volume and decreases the hemodynamic load. Thus, patients with AN generally have low hematocrit levels, which indicate a decrease in red blood cell mass. This process involves the breakdown of red blood cells and the iron that is removed from the red blood cells is stored as ferritin, which is consistent with the increase in ferritin levels (early AN) observed at hospital admission. Blood volume is then restored with an increase in body weight that may also be due to an increase in red blood cells. Hemoglobin and MCV concentrations are normal in patients with AN. It indicates that the reduction in blood volume in malnourished and amenorrheal patients at the onset of AN can help maintain the hematocrit in the normal range by reducing red blood cell mass [14].

In general, the strength of the association between hematological changes and weight parameters and changes in body weight is weak in patients with AN. A strong relationship between hematological changes and body weight occurs in adolescent girls who have never experienced menstruation (premenarche). Adolescent girls in this condition (with younger age) who still have the potential to grow and develop are more vulnerable to the effects of starvation from AN and require additional strong nutritional improvements.

Changes in Serum Iron Index in Adolescents with Eating Disorders

Iron Serum Change

Changes in serum iron occurred in the study of [7], which showed that at the time of treatment of AN with supplements containing 10 mg/L iron or the equivalent of 5-15 mg/day of elemental iron (RDI of iron 10-13 mg/day) and a balanced diet containing iron, the levels of iron serum could increase. These results also explain why the numbers of patients who were anemic at hospital

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admission and after AN treatment were not significantly different. Frequent changes in hemoglobin and hematocrit in patients with AN result from changes in intravascular volume rather than anemia.

According to [9], there was no significant difference between blood biochemical values in respondents who were positive for eating disorders and respondents who were negative and all data, except the TIBC value, were within the range according to the reference. When the TIBC value is greater than the reference value, it may indicate an iron deficiency condition. The percentage of respondents with abnormal TIBC and serum iron was higher among respondents who were positive for eating disorders than among those who were negative. This is presumably due to inadequate protein intake, especially animal protein (food that is rich in heme iron) in respondents with eating disorder.

Ferritin Change

Ferritin is a water-soluble, iron storage protein that functions to maintain the toxicity of intracellular iron ions to a level that is safe for the body. In healthy respondents, ferritin increased as a marker of total body iron (TBI). According to [14], when serum ferritin concentration is used as an indicator of iron stores in growing adolescents, it reflects a balance between iron intake, normal weight gain, and menstruation.

Ferritin is a reactant in the acute phase. The increase in serum ferritin can also be influenced by inflammation (free ion scavenging during oxidative stress) [14,16]. However, in adolescent patients with AN, none of the adolescents showed signs or symptoms of infection and the erythrocyte sedimentation rate was usually low, indicating that there was no inflammation in adolescents with AN [14]. Ferritin levels at hospital admission were measured using normal inflammatory markers (CRP and ESR). Liver disease can also affect ferritin levels, but liver function was normal in all respondents [7]. Thus, it can be concluded that the increase in ferritin in respondents with AN was not caused by an inflammatory process or inflammation-associated disease.

Normal or high serum ferritin concentrations should not be used as an indication of normal iron status [14]. Normal serum iron and transferrin indicate that this condition is not caused by excess iron in the body. According to [12], serum ferritin is inversely related to BMI and serum IGF-1, and is positively related to ALT. Severe energy deficiency due to AN can lead to decreased IGF-1 production accompanied by decreased BMI and loss of anabolic function by liver cells. An increase in ferritin occurs in adolescent girls with AN and a decrease in ferritin occurs during nutritional recovery during therapy or treatment.

Increased ferritin was also found in malnourished patients with AN compared to controls [5]. At the time of the development of AN (t0-t1,), the ferritin levels of respondents were high in the adaptation stage to low food intake, but when body weight began to increase, ferritin levels decreased. The decrease in ferritin levels was also noticeable in the control group. Respondents from both the group with AN and the control groups experienced a very significant decrease in ferritin at the end of the treatment time point (t12). Thus, ferritin should be used as a general basis for monitoring the evolution of patients with AN.

The relationship between serum ferritin concentration and weight loss and rate of weight loss indicates that AN-induced starvation and muscle catabolism release iron from muscle myoglobin, thereby increasing the availability of stored iron in the form of ferritin [17]. It should also be noted that the mandatory exercise for adolescents with eating disorders will also be accompanied by an increase in serum ferritin [18]. The increase in serum ferritin concentration in amenorrheal female adolescents may reflect the occurrence of muscle catabolism in the absence of iron loss due to menstruation.

Adolescent girls who continue to menstruate have lower serum ferritin concentrations and almost 40% have depletion of iron stores [14]. This is more common than the results of other studies which state that as many as 15-25% of adolescent girls had low serum ferritin concentrations, which were below 16 g/L [19]. Thus, low serum ferritin in menstruating adolescent girls that is accompanied by weight loss occurs because it indicates low iron intake combined with regular iron loss. This condition can result in a negative iron balance with a depletion of iron stores (decreased serum ferritin). It occurs even though serum ferritin concentration is independent of the rate of weight loss. For example, the catabolism that occurs in weight loss can be assumed to replenish iron stores and increase serum ferritin concentrations [20].

Low serum ferritin concentrations in adolescent girls who menstruate do not reflect subnormal blood hemoglobin concentrations [14]. This is thought to occur because of dehydration and fluid loss during starvation. Another possibility is that the iron for

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hematopoiesis has been provided through muscle catabolism. This mechanism explains why anemia is rare in adolescent girls with eating disorders.

There is a complex relationship between ferritin and malnutrition, namely the relationship between ferritin and ALT (liver enzyme) and IGF-1 [12]. Ferritin is positively related to the ALT enzyme. Although serum ALT was within the normal range, ALT showed a strong positive association with ferritin. The liver enzymes appear normal although there is a severe nutritional disturbance in patients with eating disorders. The association between ALT and ferritin that was discoved in this cohort study suggests that malnutrition is caused by liver dysfunction. The levels of IGF-1 were lower in malnourished patients and negatively associated with ferritin. This is presumably because IGF-1 functions to maintain energy and improve nutritional recovery.

Ferritin is useful for the clinical measurement of malnourished children and adolescents, especially in the absence of other diseases. Therefore, ferritin is recommended to be a nutritional measurement parameter in children and adolescents with low energy intake, especially in functional and psychological problems, and can be a confirmatory marker of nutritional improvement when medication adherence is low.

Hepcidin Changes

Iron absorption is regulated by hepcidin, a liver protein product consisting of 25 amino acids and binding to ferroportin so as to inhibit iron absorption. Low hepcidin will lead to the accumulation of iron in the body, while high hepcidin will inhibit iron absorption [16]. Malnutrition contributes to low ferroportin levels and can progress to hepatic steatosis [21].

Hepcidin synthesis can be influenced by several factors including inflammation, vitamin A deficiency, leptin hormone, and increased adipose tissue. Hepcidin synthesis by inflammation is stimulated by IL-6, resulting in high serum hepcidin concentrations and also affecting macrophage iron retention and intracellular ferritin stimulation. Hepcidin synthesis and secretion by liver cells are also stimulated by iron overload by activating the bone morphogenic protein or hemojuvelin pathway [21] and through post-transcriptional iron-mediated regulation [22], which parallels increased serum ferritin concentrations. However, the increase in hepcidin levels in patients with AN was not influenced by these factors because these pathological conditions were not found in patients with AN. The increase in hepcidin in patients with AN was also not affected by liver damage.

A study of 27 French adolescents with AN reported an inversely proportional increase in hepcidin and ferritin levels with body weight, without any inflammatory response [13]. Ferritin and hepcidin levels decreased with improvement in nutritional status. Researchers suspect that malnutrition at the liver cellular level stimulates excessive production of ferritin and hepcidin. [13], stating that the serum hepcidin concentration was increased in patients with AN and correlated with the serum ferritin concentration. The increase in hepcidin and ferritin is not caused by inflammation because the values of inflammatory markers such as CRP, orosomucoid, and glucosylated ferritin in patients with AN were normal. In addition, proinflammatory cytokines including IL-6 were not detected. The two biomarkers, hepcidin, and ferritin, returned to normal after a period of recovery.

Thus, the increase in hepcidin is thought to be due to nutritional stress due to malnutrition in liver cells, which can stimulate the expression of L-ferritin (the main determinant of serum ferritin) and hepcidin genes. According to [13], this hypothesis is also suspected because serum ferritin and hepcidin concentrations return to normal after an increase in body weight that can also indicate metabolic changes with nutrient recovery and partial anthropometric recovery. The other study [5] also hypothesized that the high ferritin value is thought to be due to the adaptation process to low-calorie intake because ferritin concentration decreases when weight gain occurs.

Transferrin

There was a moderate decrease in serum transferrin concentration and an increase in transferrin saturation in respondents with AN compared to controls. The increase in transferrin saturation can serve for better iron delivery for erythroid cell development, as evidenced by normal soluble transferrin receptor concentrations and the absence of anemia. According to [5], transferrin levels can be a good biomarker for respondent with AN. Transferrin increased after 4 weeks of treatment of AN. Other complementary factors, namely C3 and C4, can be markers of the evolution of patients in severe disease conditions. Synthesis of C3 and transferrin in patients can affect the outcome of changes in fat tissue deposits. During the period of treatment of AN, including with iron-rich foods, the elevated levels of transferrin, C3, and C4 indicated a relapse after 1 year of admission to the hospital. The relationship of

serum ferritin and transferrin to changes in basic anthropometric parameters is a sensitive biomarker for changes in metabolism during nutritional rehabilitation and physical recovery.

Menstrual Conditions in Adolescents with Eating Disorders

Patients with AN were also found to have amenorrhea or no menstruation that had been occurring for 6 to 12 months at the time of admission to the hospital. Blood loss due to menstruation can lead to iron deficiency anemia, so an inadequate intake of iron in this situation can be detrimental. However, the condition of irregular menstruation in patients AN is a protection against the development of iron deficiency. These results break the hypothesis of the other study [7], which stated that the breakdown of red blood cells from contraction of circulating blood volume and low blood loss due to irregular menstruation before treatment makes this population relatively unlikely to be iron deficient.

CONCLUSION

Iron deficiency and anemia are rare in adolescent girls with eating disorders and weight loss. However, based on examination with more sensitive biomarkers in adolescents with AN, there was an increase in serum ferritin and serum hepcidin and a decrease in transferrin, which further indicated the effect of AN on iron nutritional status. Transferrin levels increased, while ferritin and hepcidin levels decreased (depleted rapidly) in respondents who experienced weight gain after a period of treatment of AN, including with the provision of a balanced diet rich in iron. In amenorrheal adolescent girls, muscle catabolism increases serum ferritin concentrations, which may give a false impression of adequate iron status. However, this is not the case for young women who continue to menstruate.

RECOMMENDATION

Further studies regarding the effects of eating disorders in adolescents on iron status, especially through preclinical trials to further ascertain the mechanism of iron nutrition in the body, are needed. Studies related to iron nutrition interventions or efforts to recover from eating disorders, including AN, also need to be done in order to determine the amount of balanced iron-rich foods or iron supplements needed and to determine the time needed to normalize the iron status index in patients with AN.

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