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THE RELATIONSHIP BETWEEN FERRITIN LEVELS AND INDICATORS OF NUTRITIONAL STATUS IN CHILDREN AND ADOLESCENTS WITH ANOREXIA NERVOSA

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Summary

Anorexia nervosa (*AN*) is a complex and potentially life-threatening eating disorder characterized by intense fear of weight gain and severe weight loss. This retrospective study included 58 patients treated at the Pediatric Department & Center for Eating Disorders, Sestre milosrdnice University Hospital Center. The objective was to assess the concentration of ferritin in relation to indicators of nutritional status and clinical characteristics in children and adolescents with *AN*. Only 2% of patients were diagnosed with the bulimic-purgative *AN* (*BP-AN*), while 5% had Eating Disorder Not Otherwise Specified (*EDNOS*), not otherwise categorized as atypical *AN* (*AAN*). Approximately 46% presented with a combination of restrictive-type *AN* and *EDNOS*. The average percentage of body weight loss was 20.46%, with the maximum recorded weight loss of 23 kg. In contrast, one patient lost no weight. The duration of illness prior to the diagnosis was longer in patients with classic *AN* compared to those with *AAN*, although the rate of weight loss was higher in the *AAN* group. This study also explored ferritin as a potential biomarker in *AN*, aiming to contribute to a better understanding of its pathophysiology and to identify novel diagnostic and therapeutic approaches.

Keywords: Anorexia nervosa, ferritin, weight loss, nutritional status

Introduction

In recent years, *AN* has increasingly taken hold in our society, particularly among young people. This eating disorder is characterized by severe body weight (*BW*) loss resulting from intentional and extreme restriction of food intake, without any known organic cause. Its prevalence continues to rise, representing a serious public health concern. Due to a distorted perception of their own body image, individuals affected by *AN* often conceal the problem and refuse to seek help, which makes the disorder especially complex and hinders both early detection and the treatment process itself (Žaja, 2014). Unfortunately, *AN* is frequently misunderstood as a lifestyle choice rather than a serious medical condition requiring professional intervention. The development of the disorder is generally associated with the family environment, media exposure, and engagement in rapid dieting practices.

Headlines such as "Battle with Fat," "One-Day Super Diet," "Lose 5 kg in Three Days," and many others like them that scream from the covers of highly popular fashion magazines, along with the well-known phrase "You can never be too rich or too thin," highlight today's priorities, especially among women. *BW* regulation is increasingly common among young people, but unfortunately not as a result of health concerns, rather as a reaction to the omnipresent cult of thinness, which has been largely perpetuated through the media (Banjari et al., 2011).

Somatic and metabolic complications are extremely serious and, at times, life-threatening. Therefore, it is not surprising that there is a growing interest in identifying biomarkers that could facilitate the early detection of *AN*. Ferritin is increasingly mentioned in this context, as a significant number of studies point to the presence of hyperferritinemia in the restrictive type of *AN*. However, the reason behind such high ferritin levels in affected individuals remains unclear. Ferritin levels tend to return to the reference range as patients begin to gain *BW*, leading to the so-called spontaneous remission of ferritin levels in the body (Wanby et al., 2016; Teixeira et al., 2023). This study examined the potential role of ferritin as a biomarker of *AN*. The aim was to investigate the concentration of ferritin in relation to nutritional status and the clinical presentation of children and adolescents diagnosed with *AN*. The research was conducted in collaboration with the Pediatric Department & Center for Eating Disorders, Sestre milosrdnice University Hospital Center.

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Participants and methods

Aim of the Study

The aim of this study was to examine the concentration of ferritin in relation to the nutritional status and clinical presentation of children and adolescents diagnosed with *AN*.

Participants

The study included 58 children and adolescents aged 9 to 18 years who were hospitalized at the Department of Gastroenterology, Pediatric Clinic, University Hospital Center "Sestre milosrdnice" in Zagreb with a diagnosis of *AN*. Study includes ethical approval from the ethics committee and official authorization for the use of medical records. The diagnosis of the eating disorder was made according to the current criteria for the given time period, specifically the *DSM-IV* criteria – *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013). The research was designed as a retrospective observational study, without a control group.

Methods

Treatment data were collected from the medical records of children and adolescents available for all 58 patients treated at the Center over the past 10 years. Anthropometric measurements and the results of biochemical blood sample analyses were collected at the time of hospitalization at the Center. Among the blood parameters, iron status was assessed with a special focus on ferritin concentration in relation to *BW*, percentage of weight loss, application of nutritional support, and the presence of metabolic complications. All biochemical analyses were performed at the Clinical Institute of Chemistry of the Pediatric Department & Center for Eating Disorders, Sestre milosrdnice University Hospital Center as part of the clinical assessment of the patients.

The data were obtained through physical examination and anthropometric measurements of *BW*, measured using a mechanical beam scale (Seca, UK), and body height (*BH*), measured with an anthropometer while barefoot.

The year of disease onset and its duration in months were monitored, as well as *BW* before the illness. Weight loss from the onset of illness (% loss) was calculated using the following formula:

$$\% \text{ loss} = [(\text{BW before anorexia} - \text{BW}) / \text{BW before anorexia}] \times 100$$

Body Mass Index (*BMI*) was determined using the NHANES percentile curves for body weight by age (NCHS, 2002).

Statistical Analysis

Frequencies were reported for nominal variables. The Shapiro-Wilk test was used to analyze the normal distribution of variables. If the distribution of continuous variables did not deviate from normal, the arithmetic mean and standard deviation were used to present central tendency and dispersion, and parametric tests were used for comparisons. If the distribution of continuous variables was not normal, the median and range were used for presentation, and non-parametric tests were used for comparison Statistical analysis and graphical presentation of data were performed using the software system R Core Team (2023) and Microsoft Excel for Microsoft 365 MSO (Version 2111. Microsoft Corporation, Redmond, WA, USA).

Results and discussion

Out of all 58 patients included in the analysis, 56 were female and 2 were male. As a limitation of this study, we can state the gender imbalance considering that we have a higher percentage of female participants (96.6%). Since certain data for some patients were unavailable, missing values for numerical variables were replaced with the average value, and missing values for categorical variables were replaced with the most frequent category.

The sample under investigation predominantly consisted of female patients, which is consistent with other studies (Petranović et al., 2014) and with the higher prevalence of *AN* among adolescent girls.

In addition to sex, numerical values were recorded for the patients, including age (years), duration of illness since diagnosis (months), % loss, *BMI* (kg/m²), and ferritin levels in the blood (μg/L). For all variables, the basic descriptive indicators are provided using the following notations: *M* – mean value, *C* – median value, *SD* – standard deviation, *Min* – minimum value, *Max* – maximum value, *A* – skewness coefficient, *S* – kurtosis coefficient, *S-W* – Shapiro-Wilk test, and are presented in Table 1.

Table 1. Basic Descriptive Indicators of Numerical Variables in the Study

	M	C	SD	Min	Max	A	S	S-W	p
Age (years)	14.36	14.50	2.16	9.50	18.00	-0.25	2.56	0.97	0.10
Duration of illness prior to admission (months)	8.54	7.00	7.63	1.00	40.00	2.28	9.01	0.76	0.00
Body weight loss (%)	20.46	20.46	9.62	-0.24	65.67	1.69	10.36	0.85	0.00
BMI (kg/m^2)	16.28	16.05	2.57	12.30	24.70	0.79	3.66	0.95	0.02
Ferritin level (µg/L)	133.65	126.50	95.71	14.50	641.00	2.57	14.68	0.79	0.00

It is clearly evident from the previous table that most of the numerical variables deviated from a normal distribution, with the exception of patients' age. It is also important to highlight the substantial variability observed in the variables related to duration of illness prior to admission, percentage of loss (%), and ferritin levels.

Patient age ranged from 9.5 to 18 years. Most patients were between the ages of 13 and 16. These results are also consistent with the available literature, which indicates that *AN* is most commonly diagnosed at the age of 13, that is, during adolescence (Peterson et al., 2019).

Distribution of patients according to the percentage of loss (%) approximately 20% of *BW* was lost by the majority of patients, while two patients experienced a loss (%) exceeding 40%. The greatest loss (%) was observed in a 15-year-old female patient, where the percentage reached 65.67%, and the illness was diagnosed slightly over a year after its onset.

The majority of patients had elevated serum ferritin levels. No patient showed ferritin levels below the minimum reference value. The highest ferritin level was recorded in a 15-year-old female patient, who also had the highest recorded loss (%).

In addition to the above values, other biochemical parameters were recorded in patients, such as: C-reactive protein (*CRP*), Leukocytes (*L*), Aspartate aminotransferase (*AST*), Alanine aminotransferase (*ALT*), Lactate dehydrogenase (*LDH*), Hemoglobin (*Hgb*), Iron (*Fe*), Unsaturated Iron Binding Capacity (*UIBC*), and Total Iron Binding Capacity (*TIBC*). These values were categorized into three groups: 0 for results within the reference values, 1 for results below the minimum reference value, and 2 for results above the reference values. Their distribution is shown in Table 2.

Table 2. Frequency of blood parameter levels in patients

Parametar	1 – below reference values n (%)	0 – within reference values n (%)	2 – above reference values n (%)	χ2	df	p
CRP	1 (1.72%)	57 (98.28%)	-	54.07	1	< 0.001
L	-	43 (74.14%)	15 (25.86%)	13.52	1	< 0.001
AST	6 (10.34%)	51 (87.93%)	1 (1.72%)	78.45	2	< 0.001
ALT	7 (12.07%)	50 (80.21%)	1 (1.72%)	73.9	2	< 0.001
LDH	-	58 (100.00%)	-	-	-	-
Hgb	1 (1.72%)	56 (96.55%)	1 (1.72%)	104.31	2	< 0.001
Fe	-	55 (94.83%)	3 (5.17%)	46.62	1	< 0.001
UIBC	-	34 (58.62%)	24 (41.38%)	1.72	1	0.19
TIBC	-	27 (46.55%)	31 (53.45%)	0.28	1	0.60

Across all observed parameters, the majority of patients had values within the reference range. Only for the parameters *UIBC* and *TIBC* the number of patients with elevated values was equal to those with values within the reference range. The data clearly indicate that elevated ferritin levels cannot be explained by inflammatory processes in the body (*CRP* levels), impaired liver function (*AST* and *ALT*), or iron metabolism (*Hgb*, *Fe*, *UIBC*, *TIBC*), and were therefore not influenced by other factors.

The results of this study are consistent with those reported by Tran et al. (2013), who also observed elevated ferritin levels in the absence of inflammation or liver dysfunction. The authors noted that this is a frequent yet still insufficiently explained biochemical phenomenon. Similar conclusions were drawn in a more recent research by Teixeira et al. (2023), which further confirmed that high ferritin concentrations may be present in patients with AN without being associated with inflammatory markers or liver function disorders.

Although these findings indicate a statistically significant association between ferritin levels and the percentage of *BW* loss, the absence of a control group limits the possibility of drawing causal inferences. Thus, while ferritin may reflect aspects of nutritional status in patients with *AN*, it should not be interpreted as a causal biomarker. Further prospective studies with appropriate

controls are needed to establish whether ferritin can serve as a valid and reliable diagnostic tool in this context. Until such validation is achieved, its use in clinical diagnostics of *AN* should be approached with caution.

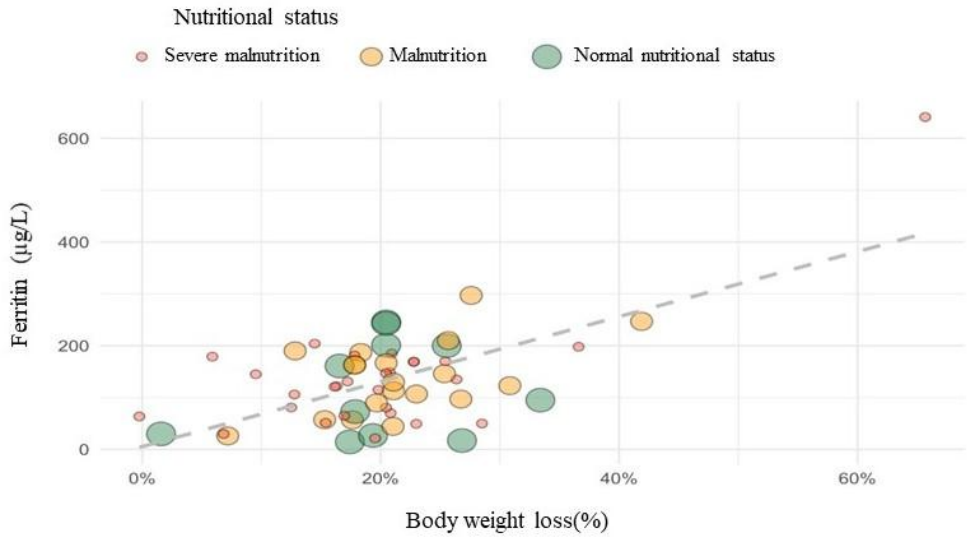

Figure 1. Graphical representation of the relationship between two variables of interest

Additionally, Figure 1 emphasizes the level of nutritional status, *BW* % loss and ferritin levels in patients with *AN*. What is particularly noteworthy is that nutritional status appears to correlate less strongly with ferritin levels than the percentage of loss (%). This is clearly evident in the distribution of each nutritional status group on the left and right sides of the graph. A similar result was reported in the study by Wanby et al. (2016), where no correlation was found between *BMI* and plasma ferritin concentration—neither in the entire patient group, nor in the subgroup of patients with *AN*, nor in the group with eating disorders without *AN*.

To examine the previously proposed hypothesis regarding the correlation between ferritin levels and the percentage of loss (%), a correlation test was conducted. Spearman's rank correlation coefficient between ferritin and loss (%) was 0.30 and it was statistically significant at a significance level of less than 5%. The correlation between ferritin and percentage of loss (%) was positive. In other words, patients with higher blood ferritin levels also had a higher percentage of loss (%).

Based on *BMI*, patients were categorized according to degree of malnutrition. Patients with a *BMI* below 16 kg/m² were classified as severely malnourished, those with a *BMI* between 16 and 18.4 kg/m² were categorized as malnourished, and those with a *BMI* between 18.4 and 24.9 kg/m² were considered to have a normal nutritional status. Figure 2 shows ferritin values within each of the three mentioned groups.

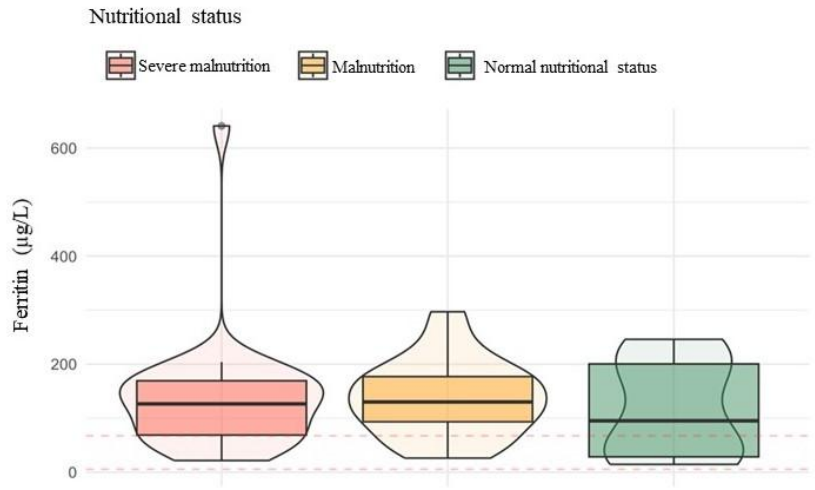

Figure 2. Blood Ferritin Levels According to the Degree of Malnutrition

Among the group of severely malnourished patients, a total of 7 out of 28 (25.00%) patients had ferritin levels within the reference range. A similar percentage was observed in the malnourished group, where 4 out of 19 (21.05%) patients had ferritin levels within the reference range. In the final group, those with normal nutritional status, 4 out of 11 (36.36%) patients had ferritin levels within the reference range.

Given that the ferritin distribution in the severely malnourished patient group markedly deviated from normality, differences were assessed non-parametrically using the Kruskal–Wallis test (Table 3).

Table 3. Results of the Kruskal–Wallis test for differences in ferritin levels among patients according to the degree of malnutrition

	C	(Min - Max)	χ2	df	p
			0.49	2	0.78
Severe malnutrition	126.5	(21.6 - 641)			
Malnutrition	130	(26.1 - 297)			
Normal nutritional status	95.1	(14.5 - 246)			

Although ferritin levels were higher in malnourished and severely malnourished patients compared to those with normal nutritional status, no statistically significant differences in ferritin levels were observed among the groups based on the degree of malnutrition.

Conclusion

This study showed that the majority of patients with *AN* have elevated ferritin levels in their blood. It is particularly noteworthy that no patient had ferritin levels below the minimum reference value. A 15-year-old female patient, who had the highest recorded ferritin levels, also experienced the greatest weight loss. Therefore, restoring ferritin to reference intervals is an important goal in the treatment of *AN* in children and adolescents, not only because it is an indicator of adequate *BW* but also because it is one of the main indicators that the body is recovering. This research makes a significant contribution to the growing body of evidence supporting ferritin as a reliable indicator of nutritional status in children and adolescents with *AN*. The results of this study confirm the hypothesis that ferritin levels correlate with nutritional status in this population, highlighting its importance in clinical assessment and monitoring of patients. Although further research is needed to fully understand the complexity of the relationship between ferritin and nutritional status in *AN*, these results represent a step forward in that direction. Overall, focusing on potential biomarkers in the future, such as ferritin, could have a significant clinical implications for early detection and monitoring of *AN*.

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