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LIPOSOMAL IRON SUPPLEMENTATION IN WOMEN OF REPRODUCTIVE AGE: ANALYSIS OF BIOCHEMICAL PARAMETERS AND SYMPTOMS

SUPLEMENTAÇÃO DE FERRO LIPOSSOMAL EM MULHERES NA IDADE REPRODUTIVA: ANÁLISE DE PARÂMETROS BIOQUÍMICOS E SINTOMAS

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ABSTRACT: This study investigates the effects of liposomal iron supplementation in women of reproductive age, focusing on biochemical parameters and clinical symptoms. This interventional study, conducted in Belo Horizonte, Brazil, included 20 women of reproductive age with regular menstrual cycles who received a daily supplementation of 30 mg of liposomal iron for 60 days. Clinical symptoms, dietary intake, and laboratory tests (transferrin saturation, ferritin, hemoglobin, and C-reactive protein) were evaluated at baseline and at the end of the study. Liposomal iron supplementation increased hemoglobin (p=0.002) and ferritin (p=0.031) but had no effect on transferrin saturation (p=0.541). Symptoms such as fatigue, weakness, hair loss, nausea, and constipation improved. Thus, the present study demonstrates that liposomal iron supplementation improved iron metabolism markers and clinical symptoms in women of reproductive age.

KEYWORDS: Dietary supplements. Iron. Iron deficiency. Women.

RESUMO: O objetivo foi avaliar os efeitos da suplementação de ferro lipossomal em mulheres na idade reprodutiva com foco em parâmetros bioquímicos e sintomas clínicos. Trata-se de um estudo intervencional, realizado em Belo Horizonte (Brasil), no qual 20 mulheres em idade reprodutiva, com ciclo menstrual regular, foram submetidas à suplementação diária de 30mg de ferro lipossomal durante 60 dias. Foram avaliados sintomas clínicos, ingestão alimentar e exames laboratoriais (saturação de transferrina, ferritina, hemoglobina e proteína C reativa) no início e ao final do estudo. A suplementação de ferro lipossomal promoveu aumento da hemoglobina (p=0,002) e ferritina (p=0,031), sem efeitos na saturação da transferrina (p=0,541). Dentre os sintomas, houve melhora de fadiga, fraqueza, queda de cabelo, náuseas e constipação. Assim, o presente estudo demonstrou que a suplementação de ferro lipossomal promoveu melhora de marcadores do metabolismo do ferro em mulheres na idade reprodutiva, além de promover melhoras de sintomas clínicos.

PALAVRAS-CHAVE: Deficiência de ferro. Ferro. Mulheres. Suplementação nutricional.

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INTRODUCTION

Iron is one of the most essential micronutrients for human health, playing a key role in fundamental biological processes such as red blood cell production, DNA synthesis, cellular respiration, and immune response. The primary consequence of iron deficiency is iron deficiency anemia, which affects a large portion of the world's population and significantly impacts their quality of life[1,2]. According to the World Health Organization (WHO), anemia is a major global public health issue, affecting nearly a quarter of the world's population, particularly children under four years old and women of reproductive age[1,2,3]. It is estimated that approximately 29% of women aged between 15 and 49 worldwide are anemic[1,4].

Anemia significantly impairs the quality of life and health. The main consequences of this clinical condition include reduced learning capacity and productivity, growth retardation, low birth weight, and perinatal mortality[2,5]. Symptoms can range from mild fatigue to reproductive problems in the most severe cases. In general, the symptoms associated with anemia depend on the severity of the iron deficiency. In mild anemia, the most common symptoms are fatigue, weakness, apathy, and paleness. In many cases, concentration and learning ability may be impaired. More severe cases may include shortness of breath, dizziness, increased heart rate, and interruption of menstruation[5].

The most common causes of iron deficiency anemia include blood loss from menstruation, hemorrhage (hemorrhagic ulcer), chronic bleeding due to colon cancer, malabsorption problems like celiac disease, meat-free diets (vegan and vegetarian), or even pregnancy due to high demand for iron for fetal development[5,6].

Dietary iron deficiency is one of the main determinants of anemia, and iron deficiency may also be associated with socioeconomic factors[7,8]. Evidence suggests that social factors, including education, employment status, income, and gender, influence a person's health and access to food, thereby increasing the risk of iron deficiency anemia and causing health inequities, which require attention from the public and government policies[7,8].

The main sources of iron are animal-based foods, such as red meat. Although iron is also present in plant-based sources, such as spinach, peas, and beets, its bioavailability is considered low due to the presence of phytate, tannins, and fiber[9]. Therefore, when dietary iron intake is insufficient, and the bioavailability of the different sources of this mineral is not met, supplementation becomes crucial to meet such needs and mitigate issues related to the deficiency of this nutrient, especially in women, whose iron needs are higher compared to men[1,5,6].

Inorganic iron sources, such as ferrous sulfate, have low absorption and often cause side effects like diarrhea, constipation, nausea, vomiting, and a metallic taste, thus influencing the effectiveness of supplementation[5,10]. In contrast, organic iron sources, such as iron polymaltose and iron chelated with amino acids, for example, iron bisglycinate, provide better absorption and reduced side effects, leading to improved adherence to supplementation. In particular, the chelated form binds iron to two glycine amino acid molecules, enhancing absorption in the jejunum[5,10,11].

Although chelated forms represent an advance in the treatment of anemia, there are still reports of side effects and, therefore, the need to further improve iron absorption and patient adherence to supplementation[10]. As a result, the industry seeks to develop new technologies that guarantee greater bioavailability of supplementation. Developing liposomal forms of iron represents a promising strategy, aiming at more effective and safer supplementation with greater adherence to treatment. Scientific evidence shows that the use of supplements with liposomal forms of iron provides a significant increase in hemoglobin and serum iron levels, increased transferrin saturation and ferritin levels, reduced

markers of iron-induced oxidative stress, and reduced common side effects of iron supplementation, as previously mentioned[12,13,14].

Clinical studies on liposomal iron supplementation in women of reproductive age are scarce, which highlights the importance of the present study. Most studies with this type of supplementation are conducted with different populations, such as pregnant women or men and women in the sample[15,16,17]. Thus, the present study aims to evaluate the effect of liposomal iron supplementation in women of reproductive age with regular menstrual cycles by analyzing biochemical parameters and clinical symptoms.

METHODOLOGY

STUDY DESIGN

This interventional, longitudinal, and prospective study conducted between June and September 2024 in Belo Horizonte, Minas Gerais, Brazil, included women of reproductive age to evaluate the effects of liposomal iron supplementation for 60 days on biochemical parameters and clinical symptoms. This study was named the FLAME Study.

ETHICAL ASPECTS

The study protocol was approved by the Institutional Research Ethics Committee (CAAE 78847124.7.0000.5105). All participants who agreed to participate signed the Free and Informed Consent Form (FICF) after receiving detailed explanations regarding the research objectives and methodology.

PARTICIPANTS

A convenience sample consisted of women who agreed to participate in the research, signed the FICF, and met the inclusion criteria. The volunteers were recruited either in person by the researchers or through invitations via phone or chat applications, such as WhatsApp® or social networks. The researchers also contacted nutritionists and other health professionals asking them to refer potential volunteers with a history of iron deficiency who could meet the inclusion criteria. The volunteers were evaluated at the Nutrition School Clinic of the School of Minas FAMINAS-BH, in Belo Horizonte, Minas Gerais, Brazil.

INCLUSION CRITERIA

This study included adult women (>18 years) with a regular menstrual cycle, ferritin levels below 50 ng/mL, and hemoglobin levels below 14 g/dL who were not taking iron supplements at the beginning of the study[18]. Information on the frequency of the menstrual cycle was self-reported by the volunteers during the anamnesis. Ferritin and hemoglobin levels were measured at the beginning of the study. Ferritin levels <50 ng/mL were selected as they indicate a possible depletion of iron stores or nutrient deficiency, indicating a need for attention to iron metabolism[18,19]. Women with hemoglobin levels >14

g/dL were excluded since higher hemoglobin levels may not respond in the same way to iron supplementation, which should focus on individuals who require the supplement[18].

EXCLUSION CRITERIA

Women who did not complete all stages of the study, including laboratory tests on the scheduled dates (0 and 60 days), were excluded. Women who did not follow the supplementation regimen during the study were also excluded. Good adherence to the supplement was considered when they consumed at least 70% of the expected doses during the study[18]. Since ferritin can increase in cases of acute inflammation, women with C-reactive protein levels above 10 mg/L were also excluded[20]. Women who presented changes in their dietary iron intake, assessed by 24-hour recalls at each assessment, and those who underwent bariatric surgery were also excluded.

PROCEDURES

BIOCHEMICAL PARAMETERS

The laboratory tests for the study were performed at the outsourced Hermes Pardini laboratory, following the same standardization of collection and analysis of the tests, in compliance with the accreditation criteria of Good Practices for Clinical Analysis Laboratories. The laboratory tests performed at the beginning of the study and after 60 days of supplementation included complete blood count, serum ferritin, transferrin saturation index, and high-sensitivity C-reactive protein.

LIPOSOMAL IRON SUPPLEMENTATION

Volunteers who met the inclusion criteria received a liposomal iron supplement for 60 days. They were instructed to take a daily dose of 30 mg of iron in the morning, following the recommendations of studies on iron supplementation, which recommend ingestion preferably in the morning, when hepcidin levels are lower[21]. The 30 mg dose of iron through supplementation is consistent with findings from other studies[17,18,22,23].

For this study, Ferro Ydrosolv® from the Yosen® brand, which presents a liposomal form of iron, was used. This product employs Ydrosolv® technology, which consists of a lipid release system in the form of liposomes to provide better absorption and fewer side effects associated with iron supplementation. The product is liquid packaged in 30 mL bottles, containing a dose of 1 mg of elemental iron per drop. Therefore, each volunteer was instructed to take 30 drops daily, diluted in a small amount of water, in the morning. This supplement is registered with the National Health Surveillance Agency (ANVISA) in Brazil and complies with all regulatory requirements for dietary supplements.

ANAMNESIS, ANTHROPOMETRY, AND 24-HOUR RECALL

The volunteers were assessed in person at the beginning of the study (T0) and after 30 (T30) and 60 (T60) days. Laboratory tests were performed at T0 and T60. Halfway through the study (T30), an in-person assessment was also performed to monitor adherence and provide supplementation for the remaining period. In each of these meetings, a nutritional care protocol prepared for this research was completed, which addressed demographic (age), socioeconomic (marital status, education), and health

(diseases, smoking, physical activity, use of medications, and dietary supplements) data. Self-reported weight and height were used to calculate the body mass index (BMI), following the standardization proposed by the WHO[24].

In addition, the volunteers responded about signs and symptoms suggestive of iron deficiency anemia, classifying them as none (not present), mild, moderate, or severe, according to each volunteer's self-perception of the severity of each symptom. This classification of symptoms, developed by the authors as a Likert-type scale, also received a score of 0 to 3, respectively, to calculate the total sum of symptoms reported. In the second and third evaluations, carried out after 30 and 60 days, respectively, the volunteers were also asked about their adherence to supplementation over the past 30 days, verifying difficulties, undesirable effects, discomfort, or perception of improvement in symptoms.

All participants were instructed to maintain their usual diet. To ensure there were no significant changes in food intake, especially in iron intake, a 24-hour recall was administered in each of the three meetings with the volunteers for comparison. This recall was administered and completed by the same researcher during the assessment, with volunteers reporting on their food and beverage consumption on the day before the interview. Participants were also asked about food preparation, such as the use of added sugar, oil, salt, and ready-made seasonings. For those who did not know how to provide the correct amount of these foods during the interview, the information was obtained from the person responsible for preparing the meals[25,26]. The consumption of dietary supplements, when present, was also included in the calculations of food intake[25]. Nutrient calculations were performed using the Webdiet® software. Energy, carbohydrates, proteins, lipids, and iron were assessed.

STATISTICAL ANALYSIS

The database was created using Microsoft Excel (Office 2013®) and analyzed with the Statistical Package for Social Sciences (SPSS®), version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was employed to assess normality and determine the statistical test to be used. Qualitative (categorical) variables were described using absolute and relative frequencies (percentages). Quantitative variables with normal distribution were presented as mean ± standard deviation and compared using the paired Student's t-test for dependent samples or Student's t-test for independent samples. Quantitative variables without normal distribution were expressed as median and minimum and maximum values (min-max), and compared using the nonparametric Wilcoxon test, or Mann-Whitney test for independent samples. A Pearson correlation analysis was also performed to verify associations between weight, BMI, height, age, marital status, and education with symptoms and with the variable ferritin and hemoglobin. Results with a significance level of 95% (p-value ≤ 0.05) were considered statistically significant.

RESULTS

Initially, 26 women were evaluated and underwent the initial assessment. After analyzing the exclusion criteria, 20 women were included in the study. Among the study participants, the median age was 32.5 years, ranging from 21 to 48 years. Table 1 presents the general, health, and anthropometric characteristics of the research volunteers.

Table 1. General, health, and anthropometric characteristics of the research volunteers. Belo Horizonte, Brazil, 2024.

Characteristics	TOTAL (n=20)
Age (years)	
Median (minimum-maximum)	32.5 (21-48)
Education – n (%)	
High School	8 (40%)
Undergraduate	2 (10%)
Graduate (Master's or Doctorate)	10 (50%)
Marital status – n (%)	
Single	11 (55%)
Married or in a stable relationship	9 (45%)
Physical activity – n (%) – at least 30 minutes of daily physical exercise	
Sedentary	8 (40%)
Once or twice a week	4 (20%)
Three to five times a week	4 (20%)
More than five times a week	4 (20%)
Height (m)	
Mean ± SD	1.62 ± 0.05
Weight (kg)	
Mean ± SD	60.8 ± 14.6
BMI (kg/m^2)	
Mean ± SD	23.0 ± 5.1
BMI Categories – n (%)	
Underweight (BMI < 18.5 kg/m^2)	2 (10%)
Eutrophic (18.5 < BMI < 25.0 kg/m^2)	14 (70%)
Overweight (BMI ≥ 25.0 kg/m^2)	4 (20%)
How do you consider your diet? – n (%)	
Healthy	10 (50%)
Good, but needs improvement	10 (50%)
Unhealthy, I eat poorly	0
Are you receiving nutritional guidance? (at the time of data collection) – n (%)	
Yes	5 (25%)
No	15 (75%)
How would you describe your menstrual cycle like? – n(%)	
Regular	20 (100%)
Irregular	0
Do you use oral contraceptives? – n (%)	
Yes	3 (15%)
No	17 (85%)
How do you consider your health in general? – n (%)	
Bad, very bad	1 (5%)
Regular	10 (50%)
Excellent	9 (45%)

Legend: BMI: body mass index; SD: standard deviation; kg: kilogram; m: meter.

When asked about comorbidities, 12 volunteers (60%) reported having none. However, 2 volunteers (10%) reported anxiety, 1 (5%) depression, 1 (5%) ankylosing spondylitis, and 1 (5%) chronic urticaria. Regarding the use of medications, 15 (75%) reported not taking any. Additionally, 3 (15%) volunteers used contraceptives, 1 (5%) antidepressants, 1 (5%) hypoglycemic medication, and 1 (5%) antihistamines. In the analysis of dietary characteristics, 10 volunteers (50%) classified their diet as good, but with areas for improvement. Only 5 (25%) volunteers were receiving nutritional monitoring upon data collection.

In the assessment of food intake, no significant changes were observed over the 60 days in the intake of calories, carbohydrates, proteins, lipids, and iron, as described in Table 2.

Table 2. Nutrient intake by research volunteers. Belo Horizonte, Brazil, 2024.

Characteristics	T0	T60	*p-value*[#]
Energy (kcal/day)			
Mean ± SD	1725.4 ± 481.3	2160.1 ± 2091.8	0.328
Carbohydrates (g)			
Mean ± SD	200.6 ± 61.9	201.9 ± 98.0	0.942
Proteins (g)			
Mean ± SD	93.3 ± 31.3	90.5 ± 38.0	0.798
Fat (g)			
Mean ± SD	65.3 ± 29.8	61.7 ± 28.3	0.675
Iron (mg)			
Mean ± SD	10.0 ± 6.8	8.9 ± 3.5	0.495

Legend: SD: standard deviation; T0: baseline; T60: after 60 days of supplementation; [#]: Student's t-test for paired samples with normal distribution.

Liposomal iron supplementation significantly increased ferritin (p=0.031) and hemoglobin (p=0.002) levels and reduced C-reactive protein (p=0.021), with no effect on the transferrin saturation index (p=0.541) (Figure 1). Table 3 shows the tests performed with the differences observed between baseline 0 and 60 days.

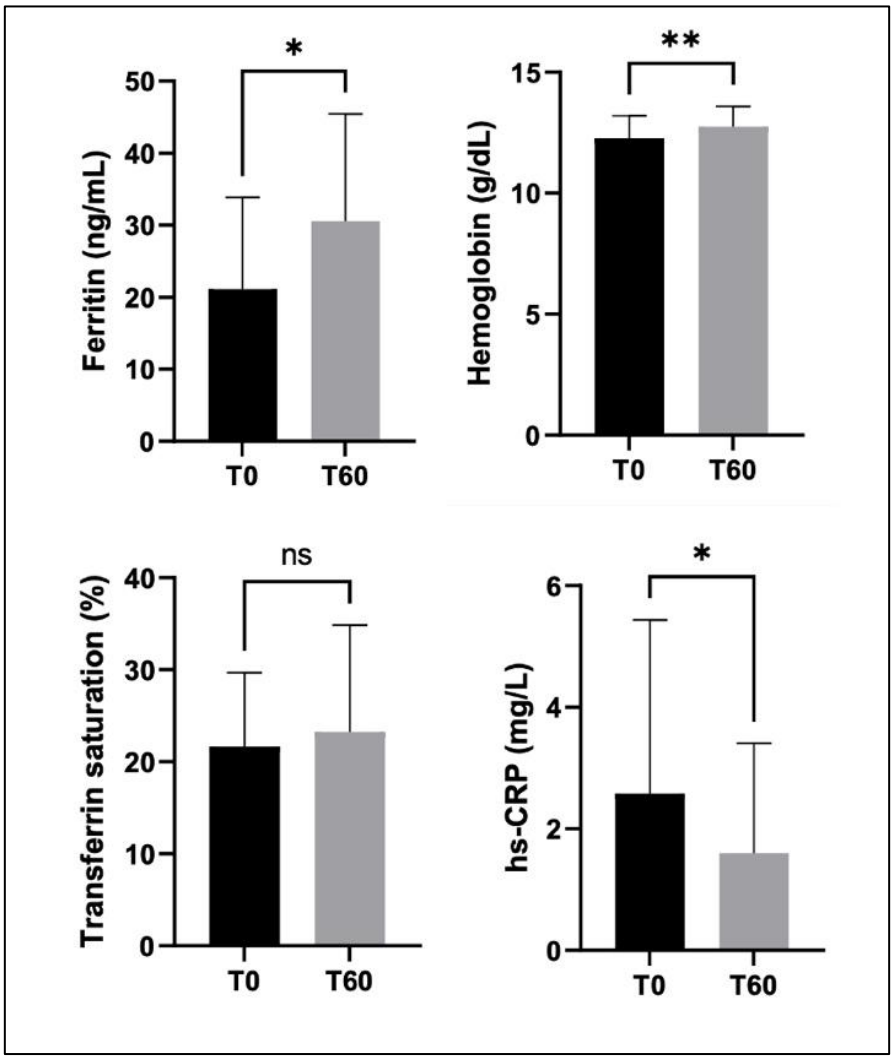

Figure 1. Biochemical parameters of the study. Belo Horizonte, Brazil, 2024.
Legend: T0: baseline; T60: after 60 days of supplementation; CRP: high-sensitivity C-reactive protein; *: p<0.05; **: p<0.01; ns: no statistical difference.

Table 3. Biochemical parameters evaluated. Belo Horizonte, Brazil, 2024.

Parameters	T0	T60	*p-value*[#]
Ferritin (ng/mL)			
Mean ± SD	21.2 ± 12.7	30.6 ± 14.9	**0.031**
Difference compared to T0	-	9.4 ± 18.1	
TIBC (mcg/dL)			
Mean ± SD	319.8 ± 33.3	315.6 ± 32.4	0.500
Difference compared to T0	-	-4.3 ± 27.6	
Serum iron (mcg/dL)			
Mean ± SD	69.4 ± 26.9	74.0 ± 39.3	0.566
Difference compared to T0	-	4.6 ± 35.6	
TSI (%)			
Mean ± SD	21.7 ± 8.0	23.3 ± 11.6	0.541
Difference compared to T0	-	1.6 ± 11.5	
Red blood cells (x10^6/mm^3)			
Mean ± SD	4.28 ± 0.30	4.36 ± 0.31	0.194
Difference compared to T0	-	0.08 ± 0.24	
Hemoglobin (g/dL)			
Mean ± SD	12.3 ± 0.9	12.7 ± 0.8	**0.002**
Difference compared to T0	-	0.5 ± 0.6	
Hematocrit (%)			
Mean ± SD	36.6 ± 2.8	37.3 ± 1.8	0.190
Difference compared to T0	-	0.7 ± 2.2	
MCV (fl)			
Mean ± SD	85.5 ± 4.1	85.7 ± 3.6	0.651
Difference compared to T0	-	0.2 ± 2.4	
MCH (pg)			
Mean ± SD	28.7 ± 1.4	28.9 ± 1.7	0.380
Difference compared to T0	-	0.2 ± 0.9	
MCHC (g/dL)			
Mean ± SD	33.6 ± 1.2	33.7 ± 1.3	0.761
Difference compared to T0	-	0.1 ± 1.4	
RDW (%)			
Mean ± SD	13.1 ± 0.9	13.4 ± 1.4	0.200
Difference compared to T0	-	0.3 ± 0.9	
High sensitivity CRP (mg/L)			
Mean ± SD	2.58 ± 2.85	1.60 ± 1.81	**0.021**
Difference compared to T0	-	-0.98 ± 1.76	

Legend: SD: standard deviation; T0: baseline; T60: after 60 days of supplementation; TIBC: total iron-binding capacity; TSI: transferrin saturation index; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: general anisocytosis index; CRP: high-sensitivity C-reactive protein; #: Student's t-test for paired samples with normal distribution.

Regarding symptoms, Table 4 shows the prevalence of each symptom at baseline and after 60 days of supplementation. There was a reduction in the prevalence, in absolute values, of symptoms commonly associated with iron deficiency, such as fatigue, weakness, and hair loss. No increase in the severity of symptoms associated with the use of iron supplements, such as metallic taste, constipation, nausea, and abdominal pain was observed. The sum assessed at T0 was 13.1 ± 5.7, with a reduction after 60 days (7.9 ± 4.6, *p*=0.001).

Table 4. Prevalence of signs and symptoms reported by volunteers. Belo Horizonte, Brazil, 2024.

Symptoms	Not at all	Mild	Moderate	Severe
Fatigue, tiredness, lack of energy				
T0	15%	20%	40%	25%
T60	25%	30%	40%	5%
Weakness				
T0	20%	20%	35%	25%
T60	45%	30%	20%	5%
Paleness of skin or mucous membrane				
T0	60%	15%	20%	5%
T60	85%	10%	0	5%
Nausea and vomiting				
T0	75%	20%	5%	0
T60	100%	0	0	0
Abdominal pain, stomach pain				
T0	90%	10%	0	0
T60	95%	0	5%	0
Reflux, heartburn				
T0	70%	25%	5%	0
T60	75%	20%	5%	0
Constipation				
T0	55%	40%	0	5%
T60	90%	5%	5%	0
Diarrhea				
T0	90%	5%	0	5%
T60	90%	5%	0	5%
Change in stool color				
T0	85%	10%	0	5%
T60	45%	15%	35%	5%
Difficulty concentrating				
T0	25%	25%	30%	20%
T60	45%	25%	25%	5%
Shortness of breath				
T0	70%	15%	10%	5%
T60	95%	0	5%	0
Tachycardia				
T0	80%	10%	5%	5%
T60	100%	0	0	0
Interruption of menstruation				
T0	95%	5%	0	0
T60	100%	0	0	0
Hair loss or dry hair				
T0	5%	30%	15%	50%
T60	45%	40%	10%	5%
Headache				
T0	55%	10%	25%	10%
T60	80%	10%	5%	5%
Irritability				
T0	25%	20%	25%	30%
T60	55%	15%	25%	5%
Metallic taste				
T0	85%	10%	5%	0
T60	90%	10%	0	0
Change in tooth color				
T0	90%	10%	0	0
T60	45%	45%	0	10%

Legend: T0: baseline; T60: after 60 days of supplementation.

In the correlation analysis, baseline ferritin levels were negatively correlated with the symptoms reported by the volunteers at baseline (r= -0.478, *p*=0.033), indicating that women with lower ferritin levels had a higher total sum of symptoms. Baseline hemoglobin levels did not correlate with the other study variables, except for age (r= -0.524, *p*=0.018). There was no association between sociodemographic and anthropometric variables (marital status, education, weight, height, and BMI) and iron metabolism variables or symptoms.

DISCUSSION

This study demonstrated that liposomal iron supplementation improved hemoglobin and ferritin levels in women of reproductive age. Furthermore, this increase occurred simultaneously with a decrease in the severity of symptoms commonly associated with iron deficiency or supplementation.

Iron deficiency is one of the most common nutritional deficiencies and is prevalent in women of reproductive age, including pregnant women, who require a higher intake of this nutrient. Likewise, iron supplementation is also common in these women[2,3,27]. The problem is that the chemical forms of this mineral commonly used in clinical practice, such as ferrous sulfate, iron gluconate, or iron bisglycinate, are associated with adverse events, including constipation, changes in tooth color, darkening of stools, stomach pain, among others. These side effects impair patient adherence to supplementation and represent a significant cause of treatment discontinuation. In addition, forms such as ferrous sulfate or iron gluconate have lower bioavailability, which impairs treatment efficiency[13,28]. Given this, the industry seeks to develop new formulations to improve iron absorption, bioavailability, and supplement stability while mitigating adverse events. One such formulation is liposomal iron, which was tested in the present study[13,29,30,31].

In the present study, 30 mg/day of iron is considered a nutritional dose and has been used in other studies, including those using liposomal iron[17,23]. Although some studies test higher doses, choosing a dose that does not exceed the maximum limits recommended in the DRIs (Dietary Reference Intake) allows for safer use of the supplement. It can also be prescribed by different health professionals, including Brazilian nutritionists, who cannot exceed 45 mg/day according to their supplementation legislation[32]. Furthermore, it is also important to understand that one of the proposals for using technologies in supplementation, such as the application of liposomes, is to increase the bioavailability of the nutrient, allowing smaller doses to be effective since they exhibit higher absorption[13,29]. However, in this specific case, studies of dose equivalence compared to doses of the most common forms are necessary and may be the subject of future investigations.

Ferritin and the hemoglobin tests were the main variables of this study, as they are normally responsive to iron supplementation[33]. In the present study, liposomal iron supplementation promoted a statistical increase in serum ferritin levels, with an average increase of 9.4 ng/mL in 60 days, representing an increase of 44.3%. This result was similar to that observed in the study by Blanco-Rojo et al.[34], who supplemented 18 mg of liposomal iron in 122 women of menstrual age for 16 weeks. In 8 weeks, the authors observed an increase of 8.7 ng/mL, rising from 25.4 to 34.1 ng/mL. On the other hand, the studies by Abbati et al.[23] and Bastida et al.[17] supplemented 30 mg of liposomal iron for 12 weeks and did not observe an increase in serum ferritin levels.

Regarding hemoglobin, the mean increase of 0.5 g/dL observed in the present study is similar to that reported by Bastida et al.[17], who supplemented 30 mg of liposomal iron in men and women and observed this same increase in 12 weeks, differing from the present study, in which the increase was

observed in 8 weeks. A similar increase was also reported by Abbati et al.[23], who tested the same dose of liposomal iron as in the present study but in a sample of men and women with inflammatory bowel diseases. The mean increase in hemoglobin was greater, in absolute values, in the study by Plesea-Condratovici et al.[35], who used a patented supplement containing 14 mg of liposomal iron combined with vitamin C, B12, and folic acid. Hussain et al.[36] tested a different supplementation containing 14 mg of liposomal iron combined with vitamin C, B12, and B9 in 437 women of reproductive age with iron deficiency anemia and observed an average increase of 1.76 g/dL in hemoglobin after 12 weeks. It is noteworthy that most studies performed supplementation for a period of 3 months, whereas the results observed in the present study were similar, in some cases within 2 months.

The increase in transferrin saturation appears to require a longer supplementation period for changes to occur. In the present study, supplementation with 30 mg of liposomal iron for 60 days did not promote changes in this marker. This was also observed by Blanco-Rojo et al.[34], who found no change in the transferrin saturation index after 8 and 16 weeks of liposomal iron use. The transferrin saturation index reflects the nutrient transport and, in cases of iron deficiency or excess, may present altered parameters. The hypothesis is that in a deficiency state, the priority is to meet the cellular demand for the nutrient and, therefore, the saturation of the transporter may require more time to be observed[33]. The same may apply to other parameters of the blood count or iron metabolism that did not change in the present study. Future research may investigate the effects of this supplementation for longer periods to determine whether the duration of treatment may influence the results.

Since ferritin, in addition to representing the body's iron stores, is also considered a marker of acute inflammatory response, it was decided to evaluate the high-sensitivity CRP test, also classified as an inflammatory marker in scientific studies. In inflammatory conditions, ferritin may increase, and this would be more related to inflammation[20]. However, in the present study, CRP values were decreased, demonstrating that the statistical increase in ferritin is not associated with an increase in the inflammatory process. Additionally, high CRP values were part of the exclusion criteria to prevent this effect of inflammation in the analysis of the results. Similarly, in the study by Bastida et al.[17] CRP values also decreased after 12 weeks of supplementation with 30 mg of liposomal iron.

One of the objectives of liposomal iron supplementation is to mitigate side effects commonly associated with iron supplements and improve symptoms of iron deficiency or anemia. In this sense, the supplement tested in the present study seems to achieve this purpose. Iron deficiency usually causes symptoms such as fatigue, weakness, pale mucous membranes, difficulty concentrating, menstruation interruption, and hair loss, among others. When taking iron supplements, gastrointestinal symptoms are common, such as changes in stool color, constipation, diarrhea, abdominal pain, reflux, metallic taste in the mouth, and changes in tooth color[13,29,30]. In the present study, a reduction in the severity of these symptoms was observed, except for stool color changes, which is expected, and a small number of reports of changes in tooth color, which is also common with liquid iron supplements. In the study by Bastida et al.[17] with the same dose used in the present study, the volunteers also showed an improvement in the severity of gastrointestinal symptoms and in quality of life. The authors further demonstrated that the tolerability of the supplement also improved, including metallic taste, abdominal pain, and constipation. Other studies have similarly demonstrated improvement in symptoms related to iron deficiency and/or supplementation, particularly gastrointestinal symptoms[12,13,23,27,35].

It is worth noting that iron deficiency anemia and iron deficiency may be influenced by socioeconomic and demographic factors. Family income, gender, and education impact access to food and increase the risk of anemia, which highlights the need for public health policies[7,8,37]. Rocha et al.[37], for instance, found that the risk of anemia increases in regions of social vulnerability. The present study

did not assess the per capita income of the volunteers, which could be an interesting issue for future studies. Regarding education, most volunteers (60%) completed higher education or graduate studies, master's or doctorate degrees. However, correlation analysis demonstrated no association between education, marital status, and anthropometry variables and ferritin and hemoglobin levels, which can be partly explained by the sample size, as the studies that demonstrate this association are epidemiological studies in most cases[7,8].

As a practical implication, this study demonstrates that supplementation with new forms of iron, such as liposomal iron, can contribute to improving parameters associated with the metabolism of this mineral. This provides health professionals with an alternative to correct nutritional deficiencies at a lower dosage, with fewer symptoms or adverse effects, thereby improving the health and quality of life of women with iron deficiency.

This research has some limitations. One is the absence of a control group composed of individuals receiving another common form of iron supplementation or placebos, which could be done in future studies. Another limitation is the non-randomized sample composed of women who agreed to participate in the research. This fact may mean that volunteers with more severe cases of deficiency could volunteer. However, despite the limitations, this research is valuable because it demonstrates in humans the effect of supplementation with a newer and more advanced chemical form of iron, whose use has been increasing, combined with an improvement in symptoms, confirming what liposome technology proposes. Furthermore, a lower dose was used compared to the usual dose in many studies with other more common forms of iron supplementation, and the results were observed in a shorter period, which makes this research interesting from the perspective of assisting patients with iron deficiency in routine clinical care.

CONCLUSION

This study demonstrated that liposomal iron supplementation effectively increased ferritin and hemoglobin levels in women of reproductive age and reduced the severity of clinical symptoms common in iron deficiency and symptoms associated with other chemical forms of iron. Future research could compare the effects of this form of liposomal iron in humans with traditional forms used in clinical practice and investigate the bioequivalence of liposomal iron compared to other types of iron available for supplementation to determine the most appropriate dose since the absorption and bioavailability of this type of iron are higher.

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