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Association of Metabolic Syndrome and Hyperferritinemia in Patients at Cardiovascular Risk

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Ricardo José Tofano[1,2]
Leticia Maria Pescinni-Salzedas[1]
Eduardo Federighi Baisi Chagas[2]
Claudia Rucco Penteado Detregiachi[2]
Elen Landgraf Guiguer[1–3]
Adriano Cressoni Araujo[1,2]
Marcelo Dib Bechara[1]
Claudio José Rubira[1]
Sandra Maria Barbalho[1–3]

[1]Department of Biochemistry and Pharmacology, School of Medicine, University of Marília (UNIMAR), Marília, São Paulo, Brazil; [2]Postgraduate Program in Structural and Functional Interactions in Rehabilitation, UNIMAR, Marília, São Paulo, Brazil; [3]School of Food and Technology of Marilia (FATEC), Marilia, São Paulo, Brazil

Aim: To evaluate the association between parameters of hyperferritinemia (HF) and metabolic syndrome (MS) in patients at cardiovascular risk.

Patients and Methods: This is a cross-sectional analytical observational study that included 269 patients who attended a cardiology unit. Biochemical and anthropometric parameters were evaluated to identify the presence of HF and MS. The presence of MS was evaluated according to NCEP ATP III. Biochemical parameters (glycemia, triglycerides, HDL-c) were assessed according to the manufacturer's protocols. Anthropometric measurements and blood pressure measurements were made by a trained professional. The chi-square (X^2) test, odds ratio, normality distribution (verified by the Kolmogorov–Smirnov test), and Levene's test were used to analyze the variables. To evaluate the effect of MS, HF, and the interaction between MS and HF, two-way analysis of variance (ANOVA) was performed based on the homogeneity of the variances, followed by Bonferroni's post hoc comparisons. Spearman correlation analysis was performed to evaluate the relationship between quantitative variables. A multiple linear regression model was used to analyze the effect of covariables. A logistic regression model was built to analyze the variables that contribute significantly to predict the outcome (HF) using the backward method.

Results: Our results showed that 57% of men and 49.5% of women presented with MS; 44% of men and 11% of women presented with HF. The presence of MS and hypertriglyceridemia increase the probability of having HF by up to 2.1 and 1.88 times, respectively, while for male sex it is increased by 6.2 times. Patients with HF have higher values of C-reactive protein, ferritin, and transferrin saturation, regardless of the presence of MS. The linear regression analysis model indicated that the variables considered in this study explain less than 30% of the variation in ferritin and that the presence of MS in men is responsible for 22% of the variation in the probability of the occurrence of HF.

Conclusion: Our results show that hyperferritinemia is closely associated with the components of MS (positive correlation with glycemia, triglycerides levels, blood pressure, and waist circumference, and negative correlation with HDL-c values) in the studied population.

Keywords: cardiovascular disease, hyperferritinemia, iron overload syndrome, metabolic syndrome

Correspondence: Sandra Maria Barbalho
Department of Biochemistry and Pharmacology, School of Medicine, University of Marília (UNIMAR), Av. Higino Muzzi Filho 1001, Marília 15525-902, São Paulo, Brazil
Tel +55 14 99655-3190
Email smbarbalho@gmail.com

Introduction

Metabolic syndrome (MS) is currently a major public health problem in both men and women worldwide, reaching rates of 30% in some populations. Several definitions of MS have emerged over the years, showing, however, some variations

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concerning the criteria and reference values of the metabolic parameters involved.[1–4]

There are several diagnostic consensuses for MS, but most include cardiometabolic risk factors, such as obesity, dyslipidemia, high blood pressure, insulin resistance, and pro-inflammatory state. The National Cholesterol Education Program ATP III criteria (NCEP ATP III) require the presence of any three of the following five conditions: abdominal obesity, hyperglycemia, low levels of HDL-c, high levels of serum triglycerides, and high blood pressure.[1,5,6]

Hyperferritinemia is a condition in which excessively high levels of ferritin are observed, which may indicate iron overload, and which can be related to damage to the myocardium, liver, and several other tissues. However, four causes are responsible for more than 90% of cases of hyperferritinemia: inflammatory conditions, cytolysis, alcoholism, and MS. Ferritin is a protein with ubiquitous distribution and is essential for the maintenance of iron homeostasis. Its concentration in the blood represents the level of iron storage in the body but can be augmented under different conditions, such as inflammatory processes and injury. The literature has shown a positive correlation between ferritin levels and hypertension, hyperglycemia, abdominal fat, dyslipidemia, peripheral insulin resistance, and metabolic syndrome. However, the pathophysiological mechanism of this association and the direct consequences of the development of hyperferritinemia (HF) with peripheral insulin such as resistance, to the author's knowledge, are not known.[7–10]

Previous studies have shown a relationship between MS and insulin resistance (IR) and ferritin levels. Iron overload is verified when transferrin saturation is above 45–50%, when there is an accumulation of iron in the liver, as determined by biopsy or magnetic resonance, because 90% of the body's iron is deposited in the liver, or by quantitative phlebotomy (absence of anemia after 16 weekly bleeds, which is equivalent to the removal of at least 4 g of iron). As liver iron overload syndrome and MS have been frequently observed in association with other pathologies that are, globally, a significant cause of morbidity and mortality, studies are needed to show the relationships between these pathologies. Therefore, it is crucial to evaluate the relationship between the indicators of iron storage, MS, and its components to obtain full understanding of the role of iron and development of these diseases.[7,11,12] For these reasons, this study aimed to evaluate the association between HF and MS parameters in patients at cardiovascular risk.

Methods

Study Design

The experimental protocols followed in our study were approved by the Institutional Ethics Committee of the University of Marilia, Marilia, São Paulo, Brazil, and were initiated only after the subjects signed a free and informed consent form (according to Resolutions 466/2012 and 510/2016 of the National Health Council). All procedures followed the ethical standards of the Institutional Ethics Committee and the Helsinki Declaration of 1975 (revised in 2008).

This cross-sectional analytical observational study included 269 patients who attended the University Hospital (University of Marilia, Marilia, São Paulo, Brazil). Patients who came to the cardiology unit with cardiovascular symptoms or for routine consultations were included in the study.

Anthropometric and Biochemical Analysis

The following parameters were investigated: weight and height (to calculate the body mass index (BMI), as weight/height^2), waist circumference (WC), neck circumference (NC), blood pressure (BP), fasting blood glucose, glycated hemoglobin (HbA1c), fasting insulin, triglycerides, total cholesterol (TC), high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), vitamin D, ferritin, and ultrasensitive C-reactive protein (CRP). Biochemical parameters followed the São Francisco Laboratory protocol at the University Hospital (University of Marilia, Marilia, São Paulo, Brazil), which uses the reference values for the results given by the test manufacturer in the analyses. These results, as well as anthropometric parameters, are in accordance with those used by Ter Horst et al.[1] The serum ferritin levels were evaluated using the chemiluminescence method (Cobas e411, Roche Diagnostic Ltd., Switzerland); the minimum concentration that could be detected was 0.5 ng/mL. We followed the manufacturer's reference levels for ferritin: < 150 ng/mL in women and < 400 ng/mL in men. The Castelli Indexes I and II were calculated, using TC/HDL-c and LDL-c/HDL-c ratios, respectively.[13]

The presence of MS was evaluated according to NCEP ATP III, which requires the presence of any three of the following five conditions: abdominal obesity (WC ≥ 102 cm in men and ≥ 88 cm in women); hyperglycemia

(fasting plasma glucose ≥ 100 mg/dL); serum HDL-c ≤ 50 mg/dL in women and ≤ 40 mg in men; serum triglycerides (TG) ≥ 150 mg/dL (1.7 mmol/L); and BP ≥ 130/85 mmHg).[1] Other parameters were also evaluated, such as smoking and alcohol consumption.

Statistical Analysis

Qualitative variables are described by the distribution of absolute (*f*) and relative (%) frequency. To analyze the association between qualitative variables, the chi-square (X^2) association test was used. The odds ratio was calculated, and its significance was determined when its 95% confidence interval (95% CI) did not include the value 1. The quantitative variables were described by the mean and standard deviation. The normality distribution was verified using the Kolmogorov–Smirnov test and the homogeneity of variances by Levene's test. The effects of MS and HF, and the interaction between MS and HF were evaluated using two-way analysis of variance (ANOVA) based on the homogeneity of the variances, followed by Bonferroni's post hoc comparisons. Spearman correlation analysis was used to evaluate the relationship between quantitative variables. The multiple linear regression model was used to analyze the effect of covariables (criterion for MS) on ferritin values by the backward method. The coefficient of determination of the percentage of variation explained by the model was verified using R^2. A logistic regression model was built to analyze the variables that contributed significantly to predict the outcome (hyperferritinemia) using the backward method. The X^2 statistic was used to determine whether the variables inserted in the logistic regression model are significant to predict the outcome, and Nagelkerke's R^2 was used to determine the percentage of variation in the outcome variable explained by the model. The SPSS software version 19.0 for Windows was used for all analyses, with a significance level of 5%.

Results

The sample included 269 participants, aged 56.39 ± 13.73 years (minimum = 20 years, maximum = 87 years, median = 57 years). Of these, 57.24% (n = 154) were men. In all, 133 participants (49.44%) had a diagnosis of MS, of which 39% (n = 52) were women, and 60.9% (n = 81) were men, with no statistical difference, as determined using the X^2 test (p = 0.2310). Among men with HF (44%), the ferritin concentration was 572.2 ± 297.1 ng/mL (minimum = 323.7 ng/mL, maximum = 2000 ng/mL, median = 486.5 ng/mL).

Among women with HF (11%) the ferritin concentration was 379.5 ± 92.8 ng/mL (minimum = 202.0 ng/mL, maximum = 584.0 ng/mL, median = 354.0 ng/mL). These values are significantly (p <0.0001) greater than those of people who do not show such clinical change (89%) (range = 123.9 ± 74.3 ng/mL, minimum = 6.7 ng/mL, maximum = 283.0 ng/mL, median = 119.6 ng/mL).

Table 1 shows a significant association between MS, hypertriglyceridemia (TG_MS), and sex with HF. Patients with MS showed 2.1 greater probability of having HF, while TG_MS increases the probability of having HF by 1.88 times. Being male increases the probability of having HF by 6.2 times. The other variables were not significantly associated with HF.

In Table 2, two-way ANOVA did not show any significant interaction between HF and MS for the quantitative variables. However, the main effect of HF and MS was seen. A significant effect of HF was observed for the values of NC, insulin, aspartate transaminase (AST), alanine transaminase (ALT), iron, and ferritin. Higher values were observed in the HF group of CRP, and ferritin regardless of the presence of MS. Insulin, AST, and ALT values were significantly higher in HF, but only among subjects with MS.

Table 2 also showed a significant effect of diabetes mellitus (DM) for the values of BMI, NC, glycemia, TG, diastolic blood pressure (DBP), HDL-c, WC, HbA1c, insulin, vitamin D, AST, and ALT. In the MS group, higher values of BMI, NC, glycemia, TG, WC, HbA1c, insulin, AST, and ALT, and lower values of HDL-c were observed, regardless of the presence of HF. Higher bronchopulmonary dysplasia (BPD) and lower vitamin D values in the MS group were observed only in subjects without HF. Lower CRP values and higher AST and ALT values in the MS group were observed only in subjects with HF.

Table 3 presents the quantitative variables that showed a significant correlation with ferritin values. The increase in ferritin correlated positively with increases in BMI, CRP, glycemia, TG, SBP, DBP, WC, insulin, AST, and ALT. However, for HDL-c values, the ferritin was negatively correlated.

Regression analysis (Table 4) indicated that the set of quantitative variables used for the diagnosis of MS (model 1) has a significant effect on the variation of ferritin values. However, these variables together explain only 10.1% (using Nagelkerke's R^2) of the ferritin values. In model 2 of the linear regression analysis, only variables with significant effects (TG and WC) were maintained. Model 2 also had

Table 1 Distribution of Absolute (N) and Relative (%) Frequency of Sex, Age Group, Smoking, Drinking, Diagnostic Criteria for Metabolic Syndrome (MS) and MS Among Subjects with and without Hyperferritinemia

		Hyperferritinemia N (%)		X^2	Odds	IC 95% (Odds)	
		Present (n=81)	Absent (n=188)	p-value		Inf	Sup
MS	Present Absent	51 (63.0) 30 (37.0)	84 (44.7) 104 (55.3)	0.006*	2.10†	1.23	3.59
SBP_MS	Present Absent	25 (31.3) 55 (68.8)	56 (30.1) 130 (69.9)	0.853	1.05	0.59	1.86
DBP_MS	Present Absent	27 (33.8) 53 (66.3)	46 (24.7) 140 (75.3)	0.131	1.55	0.87	2.74
BP_MS	Present Absent	31 (38.8) 49 (61.3)	65 (34.9) 121 (65.1)	0.554	1.17	0.68	2.02
Glycemia_MS	Present Absent	20 (25.0) 60 (75.0)	41 (21.8) 147 (78.2)	0.569	1.19	0.64	2.20
TG_MS	Present Absent	45 (55.6) 36 (44.4)	75 (39.9) 113 (60.1)	0.018*	1.88†	1.11	3.18
HDL-C_MS	Present Absent	35 (43.2) 46 (56.8)	86 (45.7) 102 (54.3)	0.702	0.90	0.53	1.52
WC_MS	Present Absent	49 (60.5) 32 (39.5)	119 (63.3) 69 (36.7)	0.664	0.88	0.52	1.51
Gender	Male Female	68 (84.0) 13 (16.0)	86 (45.7) 102 (54.3)	0.001*	6.20†	3.21	11.90
Age group	>60 y <60 y	36 (44.4) 45 (55.6)	85 (45.2) 103 (54.8)	0.908	0.96	0.57	1.63
Smoking	Present Absent	11 (13.8) 69 (86.3)	20 (10.9) 164 (89.1)	0.505	1.30	0.59	2.87
Alcohol consumption	Present Absent	33 (41.3) 47 (58.8)	66 (36.1) 117 (63.9)	0.426	1.24	0.72	2.13

Notes: *p≤0.05 significant association by the Chi-Square test (X^2); Odds ratio odds; CI 95% confidence interval; †Odds significant when CI does not include value 1.
Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein; MS, metabolic syndrome; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

a significant effect on the variation of significant values but, like model 1, the variables TG and WC explain only 9.2% (R^2) of the variation in ferritin values. In model 3, quantitative variables that showed a significant correlation (Table 3) with ferritin values, TG, and WC values were included in the linear regression analysis. An improvement in the percentage of explanation of the variation in the ferritin values (R^2) of 19.3% was observed in model 3; however, many independent variables did not show a significant effect. In model 4, after removing the nonsignificant variables using the backward method, a significant effect of TG, NC, AST, and ALT on the variation of ferritin was observed, explaining 28.3% (R^2) of its variation. Although the values of TG, NC, AST, and ALT represent the best model to explain the variations of ferritin, these variables explain less than 30% of the variation of ferritin; more than 70% of the variation of its values is related to other factors not considered in this study.

In Table 5, logistic regression analysis was used to verify the qualitative variables that have a significant effect on the probability of hyperferritinemia occurring. In model 1, only qualitative variables related to the presence of MS and its diagnostic criteria were included. Although model 1 had a significant effect on the probability of occurrence of HF, these variables together explain only 8.2% (R^2) of the variation in the probability of HF. Furthermore, in the model, only the presence of MS had a significant effect. In model 2, it was observed that the presence of MS and WC_MS has a significant effect in increasing the probability of HF;

Table 2 Comparison of the Mean and Standard Deviation (SD) of the Quantitative Variables Between the Groups for Hyperferritinemia and Metabolic Syndrome

	With Hyperferritinemia						Without Hyperferritinemia						ANOVA-Two-Way		
	MS (Yes)			MS (No)			MS (Yes)			MS (No)			p-value		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	HF	MS	Interaction
Age (year)	51	57.0	12.8	30	53,8	14,2	84	58,2	12,2	104	55,4	15,2	0,470	0,112	0,917
BMI (kg/m2)	51	32.5	5.9	30	28,0‡	4,8	84	31,0	6,1	104	27,3‡	5,1	0,161	<0,001†	0,581
NC (cm)	51	41.6	4.2	30	39,2‡	4,0	84	39,6ϕ	4,0	104	36,5‡,ϕ	3,7	<0,001*	<0,001†	0,428
Glycemia (mg/dL)	49	121.9	41.6	30	96,0‡	9,5	84	113,4	28,6	103	94,0‡	13,0	0,135	<0,001†	0,353
TG (mg/dL)	51	210.6	92.4	30	129,5‡	76,1	84	187,7	98,7	104	115,8‡	55,1	0,097	<0,001†	0,678
SBP (mmHg)	50	133.2	18.5	30	125,6	17,2	83	281,1	1317,1	103	122,1	13,1	0,475	0,410	0,454
DBP (mmHg)	50	84.5	11.2	30	80,5	8,8	83	85,0	10,8	103	78,8‡	9,5	0,702	<0,001†	0,439
HDL-c (mg/dL)	51	39.3	8.0	30	52,4‡	14,9	84	41,1	11,1	104	56,9‡	41,1	0,392	<0,001†	0,701
WC (cm)	51	110.6	13.3	30	95,3‡	9,8	84	106,6	12,6	104	93,5‡	13,3	0,095	<0,001†	0,549
TC (mg/dL)	51	189.5	45.1	30	198,4	43,5	84	190,4	49,1	104	192,3	41,5	0,674	0,379	0,574
LDL-c (mg/dL)	50	107.8	39.9	30	120,2	40,0	83	115,0	43,4	104	117,4	37,6	0,686	0,178	0,360
CRP (mg/dL)	50	5.7	7.9	30	5,2	6,3	84	5,9	11,4	103	4,0	3,9	0,617	0,270	0,523
HbA1C (%)	51	6.2	1.2	30	5,3‡	0,4	84	6,4	1,5	103	5,5‡	0,6	0,218	<0,001†	0,917
Insulin (mU/L)	51	18.1	9.8	30	11,7‡	7,9	84	15,4ϕ	10,4	103	9,7‡	6,1	0,046*	<0,001†	0,756
Vit D (ng/mL)	51	27.9	8.9	30	30,1	9,2	83	28,1	11,4	103	31,8‡	9,3	0,470	0,028†	0,556
ALT (U/L)	37	43.0	29.7	21	32,4‡	21,3	59	28,6ϕ	13,8	70	24,1	10,6	<0,001*	0,011†	0,305
AST (U/L)	37	33.2	20.1	21	26,0‡	8,3	59	24,2ϕ	10,9	69	22,2	6,7	0,001*	0,019†	0,182
Iron (mmol/L)	35	122.1	38.1	18	115,3	32,5	56	96,3ϕ	32,8	66	95,1ϕ	34,2	<0,001*	0,497	0,639
Ferritin (ng/mL)	51	563.3	337.2	30	512,9	156,1	84	159,6ϕ	77,9	104	139,7ϕ	84,2	<0,001*	0,130	0,512

Notes: *Significant effect of HF by the ANOVA-one-way test for p-value ≤ 0.05; †Significant effect of MS by the ANOVA-one-way test for p-value ≤ 0.05; ‡Indicates significant difference in relation to the group with MS within the groups with and without HF by the Bonferroni Post hoc test for p-value ≤ 0.05; ϕIndicates a significant difference in relation to the group with HF within the groups with and without MS by the Bonferroni Post hoc test for p-value ≤ 0.05.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BP, blood pressure; CRP, C reactive protein; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein; LDL-c, low-density lipoprotein; MS, metabolic syndrome; NC, neck circumference; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; Vit D, vitamin D; WC, waist circumference.

Table 3 Analysis of the Correlation for Quantitative Variables That Showed a Significant Correlation with the Ferritin Values

	Ferritin (ng/mL)	
	r	p-value
BMI (kg/m^2)	0.131	0.031*
NC (cm)	0.310	<0.001*
Glycemia (mg/dL)	0.151	0.013*
TG (mg/dL)	0.221	<0.001*
SBP (mmHg)	0.127	0.039*
DBP (mmHg)	0.138	0.025*
HDL-c (mg/dL)	−0.176	0.004*
WC (cm)	0.147	0.016*
Insulin (mU/L)	0.158	0.010*
ALT (U/L)	0.288	<0.001*
AST (U/L)	0.185	<0.001*

Notes: *p≤0.05 significant correlation coefficient by Spearman's nonparametric test; r, Spearman correlation coefficient.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BP, blood pressure; CRP, C reactive protein; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein; LDL-c, low-density lipoprotein; NC, neck circumference; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

however, in isolation, only the presence of MS showed a significant effect. Other parameters were also evaluated, such as smoking and alcohol consumption. were considered, together with MS and WC_MS. The variables included in model 3 increased the percentage of variation in the probability of having HF, but only MS and sex had a significant isolated effect. In model 4, it was observed that the presence of MS and being of the male sex increase the probability of having HF, and these variables together are responsible for 22% (Nagelkerke's R^2) in the variation in the probability of HF occurring.

Discussion

In summary, our results show that 57% of men and 49% of women presented with MS; while 44% of men and 11% of women presented HF. The presence of MS and hypertriglyceridemia increase the probability of having HF by up to 2.1 and 1.88 times, respectively, while being of the male sex increases the likelihood by 6.2 times. Patients with HF

Table 4 Linear Regression Analysis of the Effect of Quantitative Variables for the Diagnosis of MS on Ferritin Values

Variables		B	IC 95% (B)		p-value	Model	
Dependent	Independent		Inf	Sup		p-value	R^2
Ferritin (model 1)	(Constant)	−201.45	−495.01	92.11	0.178	<0.001†	0.101
	Glycemia (mg/dL)	0.31	−0.79	1.42	0.578		
	TG (mg/dL)	0.55	0.21	0.89	0.001*		
	SBP (mmHg)	0.01	−0.03	0.04	0.788		
	DBP (mmHg)	0.98	−1.94	3.90	0.509		
	HDL-c (mg/dL)	−0.56	−1.61	0.49	0.294		
	WC (cm)	2.91	0.82	5.01	0.006*		
Ferritin (model 2)	(Constant)	−164.01	−367.00	38.98	0.113	<0.001†	0.092
	TG (mg/dL)	0.59	0.25	0.92	<0.001*		
	WC (cm)	3.35	1.36	5.34	<0.001*		
Ferritin (model 3)	(Constant)	−316.28	−623.60	−8.97	0.044	<0.001†	0.285
	TG (mg/dL)	0.33	−0.05	0.71	0.089		
	WC (cm)	−0.34	−4.65	3.97	0.877		
	BMI (kg/m2)	−1.32	−10.42	7.77	0.774		
	NC (cm)	9.58	−1.42	20.58	0.088		
	Insulin	1.28	−3.57	6.13	0.604		
	ALT	2.99	0.60	5.37	0.014*		
	AST	5.33	1.65	9.01	0.004*		
Ferritin (model 4)	(Constant)	−330.96	−631.53	−30.40	0.031	<0.001†	0.283
	TG (mg/dL)	0.35	−0.01	0.72	0.059		
	NC (cm)	8.33	0.14	16.52	0.046*		
	ALT	2.97	0.62	5.33	0.013*		
	AST	5.44	1.84	9.04	0.003*		

Notes: B regression coefficient; 95% CI 95% confidence interval for B; *p-value ≤0.05 significant effect of the independent variable; †p-value ≤0.05 model is significant to predict the dependent variable; R^2 linear percentage of variation of the dependent variable explained by the model.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BP, blood pressure; CRP, C reactive protein; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein; LDL-c, low-density lipoprotein; MS, metabolic syndrome; NC, neck circumference; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

have higher values of CRP and transferrin saturation, regardless of the presence of MS. A linear regression analysis model indicated that the variables considered in this study explain less than 30% of the variation in ferritin and that the presence of MS in men is responsible for 22% of the variation in the probability of the occurrence of HF.

Different results are found in the literature. Honda et al[14] did not find an association of ferritin levels or abdominal circumference in a study that included 2322 patients with chronic kidney disease in a cohort study in Japan. Coimbra et al[15] found a positive correlation between ferritin and BMI in obese children. Other studies, in Korea,[16] Switzerland,[17] and China,[12,18] also investigate the association of ferritin and obesity and concluded that BMI influenced the ferritin–MS association, and was considered as a confounding factor.

In a trial with women with polycystic ovary syndrome, increased serum ferritin levels were associated with IR, visceral adipose tissue (measured by dual-energy X-ray absorptiometry, trunk, and android fat mass). The authors of this trial also found a positive correlation with triglycerides, insulin, and homeostatic model assessment, but not with BMI and WC.[19]

Boemeck et al[20] found increased levels of ferritin (>322 ng/mL) in 80% of men and 8.7% of women in a study of patients with nonalcoholic fatty liver disease (NAFLD) but did not find significant differences between ferritin levels and adequate or inadequate NC. Neck circumference is a rapid and low-cost evaluation and may work as an anthropometric indicator that is not influenced by variations in some conditions, such as abdominal distension.

In a study with 905 women and 225 men,[21] Choma et al showed that BMI is negatively associated with ferritin concentration, and WC is positively but not significantly associated. The authors of this study suggested that in women, BMI is associated with low ferritin concentrations, while WC is related to increased ferritin levels.[21]

Table 5 Analysis of Logistic Regression on the Effect of the Presence of Criteria for Metabolic Syndrome and Covariates on the Probability of Hyperferritinemia (HF) Occurring

Variables		B	Odds	IC 95% (Odds)			Model	
Dependent	Independent			Inferior	Superior	p-value	p-value	R^2
HF (model 1)	MS	1.22	3.39	1.33	8.61	0.010*	0.045†	0.082
	SBP_MS	−0.28	0.75	0.22	2.62	0.657		
	DBP_MS	0.80	2.21	0.64	7.61	0.207		
	BP_MS	−0.64	0.53	0.10	2.86	0.460		
	Glycemia_MS	−0.16	0.85	0.42	1.73	0.657		
	TG_MS	0.19	1.21	0.63	2.32	0.559		
	HDL-c_MS	−0.45	0.64	0.34	1.18	0.154		
	WC_MS	−0.56	0.57	0.28	1.17	0.124		
	Constant	0.68	1.98			0.500		
HF (model 2)	MS	1.04	2.83	1.45	5.53	0.002*	0.007†	0.053
	WC_MS	−0.62	0.54	0.27	1.06	0.073		
	Constant	0.19	1.21			0.682		
HF (model 3)	MS	0.89	2.44	1.20	4.95	0.013*	<0.001†	0.231
	WC_MS	−0.10	0.91	0.44	1.88	0.789		
	Gender	1.99	7.34	3.53	15.24	<0.001*		
	Age range	−0.02	0.98	0.53	1.80	0.938		
	Smoke	0.09	1.10	0.46	2.60	0.836		
	Alcohol consumption	−0.50	0.61	0.32	1.17	0.137		
	Constant	−2.36	0.09			0.056		
HF (model 4)	MS	0.77	2.17	1.21	3.86	0.009*	<0.001†	0.220
	Gender	1.85	6.38	3.27	12.48	<0.001*		
	Constant	−2.80	0.06			<0.001*		

Notes: B regression coefficient; odds ratio (Odds); 95% CI 95% confidence interval for Odds; *p-value ≤0.05 significant effect of the independent variable; †p-value ≤0.05 model is significant to predict the dependent variable; Nagelkerke's R^2 indicates the percentage of variation of the dependent variable explained by the model.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BP, blood pressure; CRP, C reactive protein; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein; HF, hyperferritinemia; LDL-c, low-density lipoprotein; MS, metabolic syndrome; NC, neck circumference; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

Shim et al[22] investigated 15,963 Korean men and women between 2005 and 2011 and found that both IR and abdominal obesity were augmented across the ferritin levels quartiles after adjustment for sex. Furthermore, they found that the risk of MS was augmented across the ferritin quartiles in men and women. Shim et al[22] also showed that the highest serum ferritin quartile resulted in a 1.62-fold increased risk of MS in men and 1.36-fold increased risk in women. Other studies showed a correlation between ferritin and MS and cardiovascular disease (CVD) risk.[23,24] Olesnevich et al[25] found that serum levels of ferritin, independent of elevated CRP, is related to increased 10-year CVD risk in a population of African American women.

Our results did not show a positive correlation between hyperferritinemia and glycemic levels, HbA1c, or insulin levels. According to Sachinids et al,[26] the serum levels of ferritin increase proportionally according to the increase in IR and the number of components of MS. In addition, Sachinids et al[26] postulate that the dysregulation of iron metabolism is linked to a multifactorial process triggered by an unhealthy diet, genetic factors, and increased fat deposition in visceral adipose tissue. Dragovic et al[27] also found an association between glycemia and levels of ferritin in a group of patients with HIV. Increased ferritin levels were also associated with HbA1c in modulating its association with glycemia. In a cohort study of 2225 Chinese subjects, Chen et al[28] found higher levels of ferritin in patients with type 2 diabetes than in patients without type 2 diabetes. Other authors found similar results.[29–31]

Zhang et al[12] investigated the correlation of markers of iron storage (ferritin, iron, and total body iron) with MS and its components in children from China and found that the relationship of the evaluated three iron indexes, MS, and its components is not entirely consistent, suggesting that the underlying pathways are complex and require further investigation.

Pitchika et al[32] studied the role of ferritin with prevalent and incident DM (type 2 diabetes) and MS in 3232 participants from Germany over a follow-up period of about 10 years. They found that ferritin level is associated with a higher prevalence of both diabetes and MS.

In another interesting study, Suárez-Ortegón et al[33] investigated ferritin levels with MS components in a sample of 725 adults (19–93 years) from Croatia and found that ferritin levels are significantly associated with MS both in men and postmenopausal women. Nevertheless, the authors did not find associations of ferritin with HbA1c. Moreover, they observed that the level of ferritin was significantly associated with a higher probability of exhibiting MS components (with an exception for BP in men).

Tang et al[34] also investigated the levels of ferritin in a longitudinal study with 857 men, and a cross-sectional study including 2417 men in China, and found that the level of this parameter is related to the independent components of MS, and is thus an independent risk factor for MS in this population.

In a 6.5 year follow-up study, Hämäläinen et al investigated the association between modifications in serum ferritin levels and the development of MS in Finnish adults. Their results showed that ferritin level was significantly increased in both men and women with incident MS when compared with subjects without the syndrome. Moreover, the increase in ferritin levels was significantly less in women in whom MS compounds were resolved during the study period (glycemia and WC). Conversely, the levels of ferritin were higher in those with increased WC. In men, ferritin levels reduced significantly more in those for whom the triglyceride and glucose levels reduced during the follow-up period. These results showed a significant correlation between ferritin levels and change in WC in both sexes. Also, in men and women, there was a negative correlation between ferritin and HDL-c.[35]

It is also worth mentioning the dysmetabolic iron overload syndrome that is related to mild increases in liver and body iron stores linked with the components of the MS and absence of identifiable causes of iron excess. The dysmetabolic iron overload syndrome is characterized by the presence of HF with regular or moderately increased transferrin saturation, and metabolic abnormalities, such as increased BMI and WC, IR, high BP, dyslipidemia, and steatohepatitis.[36,37]

Another important cause of hyperferritinemia that must be seen separately is genetic hemochromatosis. These conditions can be differentiated through a clinical history associated with laboratory tests. In recent years, there has been an increase in the diagnosis of iron overload unrelated to hereditary hemochromatosis, associated with several manifestations of MS, mainly with hepatic steatosis. Its incidence has increased significantly in Western countries, and population studies of more than 10,000 patients attest to the positive correlation of hyperferritinemia with changes in glucose profile.[38]

Iron contributes to liver damage by being a potent catalyst for oxidative events leading to increased oxidative stress, which in turn causes lipid peroxidation. As a result, there is an activation of stellate liver cells (HSCs), leading to fibrogenesis in patients with NAFLD, which is considered to be a hepatic manifestation of MS and is estimated to affect one billion individuals worldwide. It is estimated that 3 to 12% of the American population is affected by an evolution of NAFLD, which is known as nonalcoholic steatohepatitis (NASH). Although patients with NASH are at an increased risk of progression, it should be noted that some patients may progress directly from NAFLD to fibrosis. This condition can progress to cirrhosis, and in about 2 to 3% of patients, hepatocellular carcinoma may occur.[39–44] For all these reasons, it is crucial to investigate the ferritin concentration and the MS parameters in patients.

Our results hardly corroborate the studies that have proposed that iron overload is closely associated with the components of MS; however, our sample is not large, and this may have limited possible associations. Moreover, it is relevant to mention that HF and MS have been frequently associated with other pathologies that are a significant cause of morbidity and mortality in the world, and more studies are needed to show the relationships of these pathologies for the adequate therapeutic approach of the patient.

Author Contributions

All authors participated in data collection and analysis, drafting or revising the manuscript, approved the final version of the manuscript, and agree to be responsible for all the aspects of this work.

Disclosure

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