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Association Between Serum Ferritin Levels and Insulin Resistance in Nondiabetic Brazilians

ORIGINAL

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Abstract

Background: Previous studies have pointed to a relation between high serum levels of ferritin and insulin resistance.

Objective: To analyze the association between the serum concentrations of ferritin and resistance to insulin, and metabolism of glucose, in nondiabetic persons.

Method: A transversal study was undertaken with 151 nondiabetic persons in São Luís, Brazil, in 2013. The following biochemical variables were analyzed: glycated hemoglobin, fasting glycemia, fasting insulin, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, serum ferritin and high-sensitivity C reactive proteins (hs-CRP).

Results: Among the participants with high levels of ferritin, approximately 20% and 40%, respectively, also had raised LDL-C (p=0.040) and hs-CRP (p=0.021). Prediabetes (p=0.016) and insulin resistance (p=0.026) had a statistically significant association with high levels of ferritin. The participants with raised ferritin also had double the probability of having raised hs-CRP (odds ratio = 2.29/p=0.036).

Conclusion: There was a statistically significant association between prediabetes and insulin resistance and raised levels of ferritin.

Keywords
Ferritin; Insulin Resistance, Metabolic Syndrome.

Introduction

Authors have observed that carriers of hemochromatosis have an accumulation of iron in the hepatocytes and altered insulin metabolism [1]. The mechanism which links overload of iron to the develop-

ment of diabetes is not yet completely established. However, publications have presented evidence of the influence of iron status on the metabolism of glucose, even in the absence of significant overload of iron [2-4].

In the general population, iron stocks have been associated positively with a greater area of subcutaneous visceral fat, with the development of intolerance to glucose, with type 2 diabetes (DM2) and with gestational diabetes. Previous studies have also pointed to a relation between high serum levels of ferritin and glycated hemoglobin in persons with metabolic syndrome (MetS), termed prediabetes by some authors [5-9].

As a result, it is possible to assert that the rise in the concentrations of serum ferritin in non-pathological conditions reflects a subclinical iron overload. On the other hand, it has been observed that frequent blood donation and specific diets result simultaneously in the reduction of the iron reserves, improvement of insulin sensitivity, and protection against developing DM2 [10-11].

It is important to highlight that iron is an essential mineral for human health, found in foods such as eggs, spinach and red meats, and that it must always be consumed. As a result of this, researchers emphasize that further studies must be undertaken on this issue prior to promoting an antidiabetic diet based on the control of ingestion of iron in nondiabetic persons. In the case of those with prediabetes, it is recommended that they should reduce the quantity of iron in their diet, under the guidance of a health professional [11].

To the best of our knowledge, there are no records of scientific publications on this issue with diabetic or healthy patients in Brazil. On the other hand, Brazilian health authorities recommend the undertaking of studies, debates and interventions with the aim of preventing new cases of diabetes. Approximately 12 million people in Brazil have this disease, which increases their chances of death by 6.4 times [12].

As a result, this study aimed to ascertain the association between the serum concentrations of ferritin and insulin resistance (IR) and metabolism of glucose in nondiabetic persons.

Method

This is a quantitative study of the transversal and analytic type, undertaken with persons of São Luís, Maranhão, Brazil, in 2013.

The present study was approved by the Research Ethics Committee of the Teaching Hospital of the Federal University of Maranhão. All the patients received explanations regarding the objectives and methodology of the study prior to signing the terms of free and informed consent.

The study population was made up of patients of a public hospital in the above-mentioned place and period. The study participants were nondiabetic persons aged ≥ 18 years old, of both sexes, and for whom medical staff had requested the following examinations: Glycated Hemoglobin (HBA1c), Fasting Blood Glucose (FBG), Insulin (FI), total Cholesterol (T-Chol), Triglycerides, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), Serum ferritin and high-sensitivity C-reactive protein (hs-CRP). The following were excluded from the study: persons with iron deficiency or who were using medications with iron present in their composition; persons with cardiac diseases (declared in the patient's medical records) and pregnant women.

In the comparative analysis of the above-mentioned metabolic and inflammatory parameters, the recommendations of the Brazilian Diabetes Society and of the Brazilian Guidelines on Dyslipidemias and Guidelines on Prevention of Atherosclerosis of the Brazilian Society of Cardiology for healthy persons were used as reference values [12-13].

Another variable analyzed was the homeostatic model assessment insulin resistance (HOMA-IR) level. Values ≤ 3.4 were considered normal[14].

Bartlett's test was used for evaluating the homogeneity of the variables. In the inferential item, tests of association were undertaken between the categorical variables, using the Chi-squared test or Fisher's Exact test when applicable. In the comparison of the means, the Student t-test and Mann-Whitney test were used according to the homogeneity of the variables. In order to evaluate the predictive capacity, an association was made between the levels of ferritin and each one of the glycemic markers studied, through calculations of the weighted odds ratio using the Mantel-Haenszel Chi-squared test. A confidence interval of 95% was adopted in all the analyses.

Results

The sample was made up of 151 eligible persons, 56 men (37%) and 95 women (63%) based on a population of approximately 300 nondiabetic subjects. The group's mean age was 54.9 (SD±14.0) years old. In a substantial proportion of the participants, the parameters referent to the normal stratification were predominant in the parameters referent to the glycidic profile: fasting blood glucose (86%), HOMA level (76.2%) and insulin (96.7%). Only in the evaluation of the Hb A1c was predominance of those classified as prediabetics observed (60.3%).

Similarly, in the evaluation of the lipid profile, was observed of subjects with normal classification in the items of HDL-C (69.5%) and triglycerides (80%), while in the item of LDL-C, there was a predominance of persons with high levels (63.6%). In the evaluation of the item of hs-CRP (74.8%) there was also of the normal strata among the participants.

Only 26.5% of the study's participants presented raised levels of ferritin. This protein's mean concentration was 187.6 SD (±179.9) ng/mL. No statistically significant association was identified between the glycidic profile and that of ferritin. On the other hand, approximately 20% of the sample simultaneously presented raised LDL-C and ferritin (p=0.040). Furthermore, approximately 40% of the subjects with raised hs-CRP also had a statistically significant rise in ferritin (p=0.021) **(Table 1)**.

Table 1. Distribution of the participants according to association between the glycidic/lipid profile and ferritin. São Luís, Brazil. 2013..

Parameter	Ferritin		p value
	FBG	Raised	
FBG			
Normal	96(73.8%)	34(26.2%)	0.401*
Prediabetes	15(71.4%)	6(28.6%)	
Hb A1c			
Normal	46(76.7%)	14(23.3%)	0.242*
Prediabetes	65(71.4%)	26(28.6%)	
Insulin			
Normal	109(74.7%)	37(25.3%)	0.116**
Raised	2(40%)	3(60%)	
HOMA			
Normal	86(74.8%)	29(25.2%)	0.264*
Insulin resistance	25(69.4%)	11(30.6%)	
HDL-C			
Normal	78(74.3%)	27(25.7%)	0.370*
Low	33(71.7%)	13(28.3%)	
LDL-C			
Normal	45(68.7%)	10(31.3%)	0.040*
Raised	66(81.8%)	30(18.2%)	
Total Cholesterol			
Normal	58(75.3%)	19(24.7%)	0.306*
Raised	53(71.6%)	21(28.4%)	
Triglycerides			
Normal	91(66.7%)	30(33.3%)	0.176*
Raised	20(75.2%)	10(24.8%)	
hs-CRP			
Normal	88(77.9%)	25(22.1%)	0.021*
Raised	23(60.5%)	15(39.5%)	

*: corrected Yates' Chi-squared test. **: Fisher's Exact test.

The subjects classified with prediabetes (p=0.016) and with insulin resistance (p=0.026) had higher and statistically significant serum concentrations of ferritin in relation to those with normal parameters. Similarly, the participants with raised LDL-C had nearly doubled levels of ferritin in relation to patients with raised levels of cholesterol (p<0.001) **(Table 2)**.

In sequence, it may be observed that the persons with raised ferritin had double the probabilities of presenting raised hs-CRP (odds ratio = 2.29/ p= 0.036).

Table 2. Distribution of the participants, according to the glycemic, lipid and ferritin parameters. São Luís, Brazil. 2013.

Parameter	Ferritin			Bartlett test	p value
	Mean (ng/mL)	Median (ng/mL)	Standard Deviation (±) (ng/mL)		
FBG					
Normal	173.5	132.7	169.5	0.109	0.016*
Prediabetes	274.8	191.9	219.5		
Hb A1c					
Normal	189.3	134.9	187.8	0.568	0.922*
Prediabetes	186.4	142	175.6		
Insulin					
Normal	183	134.9	178.6	0.932	0.088*
Raised	322.3	266.1	184.3		
HOMA					
Normal	169.5	118.1	170.9	0.274	0.026*
Insulin resistance	245.3	153.1	197.8		
HDL-C					
Normal	202.2	138	193.7	0.014	0.304**
Low	154.2	134.3	139.8		
LDL-C					
Normal	121.3	103.7	103.5	<0.001	<0.001**
Raised	225.5	151.6	202.5		
Total cholesterol					
Normal	172.2	141	152.5	0.012	0.827**
Raised	203.5	126	204.5		
Triglycerides					
Normal	189.7	136.6	177.2	0.543	0.768*
Raised	178.9	136	193.5		
hs-CRP					
Normal	177.9	134.4	172	0.229	0.255*
Raised	216.4	149.5	201.4		

*: Student t-test. **: Mann-Whitney test.

The correlations established between the variables of the glycidic and lipid profiles and that of ferritin, based on the Pearson coefficient, were weak. The variables of FBG (r=0.269/p< 0.001) and LDL-C (r=0.274/p< 0.001) presented a positive and statistically significant correlation with the variable of ferritin. In the case of the item of HDL-C (r=-0.242/p=0.003), there was a negative and statistically significant correlation. In the other variables, such as HbA1c (r=0.125/p=0.126), insulin (r=0.134/p=0.100), the HOMA level (r=0.160/p=0.050), total cholesterol (r=0.077/p=0.349), triglycerides (r=0.011/p=0.398) and hs-CRP (r= 0.007/p=0.930) there was no statistically significant evidence in the correlations made with ferritin.

Discussion

This study identified an association between LDL-C and ferritin levels. Studies undertaken with European and Asian patients reached the same conclusion in samples with both men and women [15-20]. However, it is important to emphasize that a considerable number of the subjects had prediabetes. We cannot, therefore, totally disregard the influence of this issue on the association identified.

Statistically significant associations were identified in this study between the serum levels of ferritin and the prediabetes and IR.

Indeed, one meta-analysis concluded that greater ingestion of heme iron and an increase of stocks of iron in the body are associated with a greater risk of DM2. However, the total iron in the diet, of non-heme iron, or use of supplements of this product, are not correlated with the appearance of DM2 [21]. In addition to iron levels, alterations in the transferrin receptor are also determinants for increasing the chances of developing DM2 [16].

Data from a randomized double-blind study with persons with MetS, termed prediabetes by some researchers, presented divergent data. In that study, the reduction of status iron was induced through phlebotomy (the removal of approximately 300 mL of blood) on two occasions, separated by four weeks, over a six-week period. At the end, there was a significant improvement in glycemic and lipid parameters in the intervention group [22].

The role of the metabolism of iron in the risk for DM is not totally clear, although some explanations have been put forward. The excessive depositing of iron in the liver can increase the production of local glucose or even favor a situation of nonalcoholic steatosis (an independent risk factor for DM2). Another possible explanation is the oxidative stress in pancreatic cells triggered by the excess of the concentration of iron. The chronic inflammation could be responsible for IR and the development of new cases of MetS [23].

In relation to the chronic inflammation, it is important to highlight that in this study, the probabilities of having raised hs-CRP were doubled in those with raised levels of ferritin. Raised levels of hs-CRP have been considered as one of the principal focuses for studies on the risk for diabetes; in addition to this, they are mentioned as predictors for obesity, unstable angina, MetS and IR. However, in relation to diabetes, this association has not been not totally established and clarified, as there are divergent data [24-25].

As it is a protein, a marker of systemic inflammation, in which a rise occurs in response to various types of injury, particularly in bacterial infections, this finding should be observed with caution. Independently of this, it is recommended that levels of us-CRP should be monitored in the primary and secondary prevention of diabetes in the health services, given that the role of chronic low intensity inflammation in the pathogenesis and progression of DM2 and arteriosclerosis is known.

Broadly speaking, it is necessary to be cautious in generalizing from this study's data, as there may be differences in the serum levels of ferritin according to the study sample's ethnicity [23]. Furthermore, this study presents some limitations in its underta-

king, namely: it is a study with a small sample size; and sleep quality, eating habits and kidney and liver functions were not evaluated simultaneously. All are possible triggers of interference in the metabolism of iron. As a result, it is suggested that further studies be undertaken on this issue with young nondiabetic persons, and over a longer period of monitoring.

In Brazil, the monitoring of levels of ferritin, iron or hs-CRP are not part of the guidelines of the Brazilian Diabetes Society or of the official manuals used in the primary care services.

Establishing correlations between markers for IR and ferritin levels may be important in the tracking of persons who are vulnerable in relation to diabetes.

Conclusions

Among the participants with raised levels of ferritin, approximately 20% and 40%, respectively, concomitantly had raised LDL-C and hs-CRP. Prediabetes and insulin resistance presented statistically significant association with raised levels of ferritin. The participants with raised ferritin levels also presented double the chances of presenting raised hs-CRP.

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References

1. Huang J, Jones D, Luo B, Sanderson M, Soto J, Cooksey RC, et al. Iron overload and diabetes risk: a shift from glucose to Fatty Acid oxidation and increased hepatic glucose production in a mouse model of hereditary hemochromatosis. Diabetes 2011; 60(1):80-7.
2. Utzschenneider, KM, Kowdley KV. Hereditary hemochromatosis and diabetes mellitus: implications for clinical practice. Nat Rev Endocrinol. 2010; 6(1):26-33.
3. Gillum RF. Association of serum ferritin and indices of body fat distribution and obesity in Mexican American men-the Third National Health and Nutrition Examination Survey. Int J Obes Relat Metab Disord 2001; 25:639-645.
4. Vari IS, Balkau B, Kettaneh A, Andre P, Tichet J, Fumeron F, et al. Ferritin and transferrin are associated with metabolic syndrome abnormalities and their change over time in a general population: data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Diabetes Care 2007; 30:1795-1801.
5. Salonen JT, Tuomainen TP, Nyyssönen K, Lakka HM, Punnonen K. Relation between iron stores and non-insulin-dependent diabetes in men: case-control study. Br Med J 1999; 317:727-730.
6. Barbieri M, Ragno E, Benvenutti E, Zito GA, Corsi A, Ferrucci L. New aspects of the insulin resistance syndrome: impact on haematological parameters. Diabetologia 2001; 44:1232-1237.
7. Lao TTCP, Tam KF: Gestational diabetes mellitus in the last trimester: a feature of maternal iron excess? Diabet Med 2001; 18:218-223.
8. Iwasaki T, Nakajima A, Yoneda M, Yamada Y, Mukasa K, Fujita K, et al. Serum ferritin is associated with visceral fat area and subcutaneous fat area. Diabetes Care 2005; 28:2486-91.
9. Fernandez-Real JM, Lopez-Bermejo A, Ricart W. Iron stores, blood donation, and insulin sensitivity and secretion. Clin Chem 2005; 51:1201-5.
10. Ascherio A, Rimm EB, Giovannucci E, Willett WC, Stampfer MJ. Blood donations and risk of coronary heart disease in men. Circulation 2001; 103:52-7.
11. Ellervik C, Mandrup-Poulsen T, Andersen HU, Tybjærg-Hansen A, Frandsen M, et al. Elevated transferrin saturation and risk of diabetes: three population-based studies. Diabetes Care 2011; 34(10): 2256-8.
12. Sociedade Brasileira de Diabetes. Diretrizes da Sociedade Brasileira de Diabetes 2014-2015. São Paulo: AC Farmacêutica; 2015.
13. Sociedade Brasileira de Cardiologia. IV Diretriz Brasileira sobre Dislipidemias e Prevenção da Aterosclerose. Departamento de Aterosclerose da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2007; 88 Suppl I:2-19.

14. Oliveira EP, Souza MLA, Lima MDA. Índice HOMA (homeostasis model assessment) na prática clínica: uma revisão. J. Bras. Patol. Med. Lab. 2005; 41(4): 237-243.
15. Hämäläinen P, Saltevo J, Kautiainen H, Mäntyselkä P, Vanhala M. Erythropoietin, ferritin, haptoglobin, hemoglobin and transferrin receptor in metabolic syndrome: a case control study. Cardiovascular Diabetology, 2012; 11:116.
16. Park SK, Ryoo JH, Kim MG, Shin JY. Association of Serum Ferritin and the Development of Metabolic Syndrome in Middle-Aged Korean Men A 5-year follow-up study. Diabetes Care 2012; 35(12): 2521-2526.
17. Kang HT, Linton JA, Shim JY. Serum ferritin level is associated with the prevalence of metabolic syndrome in Korean adults: the 2007-2008 Korean National Health and Nutrition Examination Survey. Clin Chim Acta 2012, 413(5-6):636-641.
18. Lecube A, Hernandez C, Pelegri D, Simo R. Factors accounting for high ferritin levels in obesity. Int J Obes (Lond) 2008, 32(11):1665-1669.
19. Sun L, Franco OH, Hu FB, Cai L, Yu Z, Li H, et al. Ferritin concentrations, metabolic syndrome, and type 2 diabetes in middle-aged and elderly chinese. J Clin Endocrinol Metab 2008, 93(12): 4690-4696.
20. Bozzini C, Girelli D, Olivieri O, Martinelli N, Bassi A, De Matteis G, et al.. Prevalence of body iron excess in the metabolic syndrome. Diabetes Care 2005, 28(8):2061-2063.
21. Bao W, Rong Y, Rong S, Liu L. Dietary iron intake, body iron stores, and the risk of type 2 diabetes: a systematic review and meta-analysis. BMC Med.2012; 10:119.
22. Houschyar KS, Lüdtke R, Dobos GJ, Kalus U, Broecker-Preuss M, Rampp T, et al. Effects of phlebotomy-induced reduction of body iron stores on metabolic syndrome: results from a randomized clinical trial. BMC Med. 2012; 10:54.
23. Jung CH, Lee MJ, Hwang JY, Jang JE, Leem J, et al. Elevated serum ferritin level is associated with the incident type 2 diabetes in healthy Korean men: a 4 year longitudinal study. PLoS One 2013; 8:75250.
24. Gelaye B, Revilla L, Lopez T, Suarez L, Sanchez SE, Hevner K. Association between insulin resistance and C-reactive protein among Peruvian adults. Diabetol. Metab. Syndr. 2010; 2:30.
25. Shankar A, Li J. Positive association between high-sensitivity C-reactive protein level and diabetes mellitus among US non-Hispanic black adults. Exp. Clin. Endocrinol. Diabetes 2008; 116:455-460.