Association Between Serum Ferritin Levels and Insulin Resistance in Nondiabetic Brazilians

Sally Cristina Moutinho Monteiro¹, Ilka Kassandra Pereira Belfort¹, Maurício Avelar Fernandes¹, Wandson Rodrigues Sousa¹, Márcio Flávio Moura de Araújo ²

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.

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 over-
load of iron [2-4].

In the general population, iron stocks have been associated positively with a greater area of subcu-

taneous visceral fat, with the development of into-

tolerance 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-patholo-

gical conditions reflects a subclinical iron overload.

On the other hand, it has been observed that fre-

quent blood donation and specific diets result si-

multaneously 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 essen-

tial 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 nondia-

betic persons. In the case of those with prediabe-

tes, 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 re-
cords 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 as-

sociation between the serum concentrations of fe-
rerin 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 Luis,

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 nondia-

betic 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 cho-

lesterol (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 com-

position; persons with cardiac diseases (declared

in the patient’s medical records) and pregnant

women.

In the comparative analysis of the above-men
tioned 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) le-

tel. 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 glycemic 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 glycemic 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.**

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

*: 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.

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

*: 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.

Acknowledgments
Study design: SCM Monteiro, IKP Belfort, MFM Araújo
Data collection and analysis: SCM Monteiro, IKP Belfort, Fernandes MA, Sousa WR
Manuscript preparation: SCM Monteiro, MFM Araújo

Funding
The research received financial support of the Foundation support research and scientific and technological development from Maranhão (FAPEMA).

References


Publish in International Archives of Medicine

International Archives of Medicine is an open access journal publishing articles encompassing all aspects of medical science and clinical practice. IAM is considered a megajournal with independent sections on all areas of medicine. IAM is a really international journal with authors and board members from all around the world. The journal is widely indexed and classified Q1 in category Medicine.