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Original Article

Serum Ferritin: An Early Marker of Insulin Resistance in Metabolic Syndrome

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Abstract

Background: Metabolic syndrome (MetS) is a combination of conditions that include hyperinsulinemia, obesity, dyslipidemia, and hypertension. Increased body iron stores are associated with the development of glucose intolerance, type 2 diabetes mellitus, and insulin resistance (IR) syndrome. Ferritin, being an acute phase reactant, has a tendency to increase in inflammatory conditions. Although the etiopathogenesis of MetS have been linked to iron overload and IR, controversy exists about the levels of ferritin in MetS. Hence, we aimed to estimate the levels of ferritin in cases of MetS and to correlate their levels with the individual components of MetS.

Materials and Methods: This Case–control study included a total of 140 participants with 70 cases and 70 controls. Cases were selected on the basis of modified the National Cholesterol Education Program Adult Treatment Panel III Criteria. Their fasting blood samples were collected to estimate blood sugar, iron, ferritin, and insulin. IR was calculated using homeostasis model assessment IR (HOMA-IR) formula. Statistical analysis was performed by independent *t*-test, Mann–Whitney *U*-test, Pearson's correlation test, and Spearman's correlation test.

Results: Serum ferritin, iron, insulin, and HOMA-IR were significantly high ($P < 0.001$) in cases when compared to controls. We found a significant positive correlation between iron levels and HOMA-IR ([$r = 0.846$, $P < 0.001$] and [$r = 0.432$, $P = 0.010$]) in males and females, respectively. Similarly, we found a significant positive correlation between ferritin levels and HOMA-IR ([$r = 0.705$, $P < 0.001$] and [$r = 0.509$, $P = 0.002$]) in males and females respectively.

Conclusion: Serum ferritin plays a key role in the pathogenesis of MetS and could be used as a marker for early diagnosis of MetS.

Key words: Ferritin, Homeostasis model assessment-insulin resistance, Insulin resistance, Metabolic syndrome

INTRODUCTION

Metabolic syndrome (MetS) or syndrome X is a cluster of conditions which includes hyperinsulinemia, obesity, dyslipidemia, and hypertension.[1] It is prevalent in 20-25% of the world's adult population.[2] There lies a 5-fold increase in the risk of developing type 2 diabetes mellitus (T2DM), a 2-fold increased risk of developing cardiovascular disease, a 2-4 fold increased risk of developing stroke, and a 3-4 fold increased risk of developing myocardial infarction.[3]

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The pathophysiology that lies behind the development of MetS is insulin resistance (IR). Insulin, secreted by the β cells of pancreatic islets of Langerhans, not only plays an important role in the maintenance of blood glucose levels by facilitating cellular glucose uptake but also has mitogenic effects promoting cell division and growth. Hence, dysregulation of this hormone in the form of IR results in various metabolic and endocrine disorders.[4]

IR is characterized by a decrease in tissue sensitivity to the action of insulin, leading to a compensatory increase in insulin secretion.[5] Various research articles suggest that moderately elevated iron and ferritin levels are associated with an increased prevalence of MetS and markers of IR.[6,7]

Iron, an essential trace element, has an important role in oxygen transport and enzymes of mitochondrial respiration. The liver plays an important role in the regulation of

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body iron stores in iron overload situations.[8] Increased body iron stores are associated with the development of glucose intolerance, T2DM, and IR syndrome (IRS).[9] Iron overload induces oxidative damage to pancreatic beta cells. It causes impairment of hepatic insulin extraction and interferes with insulin's ability to suppress hepatic glucose production.[10]

Serum ferritin is a key protein in the regulation of iron homeostasis. It protects the iron from oxidative damage as iron is taken up in the ferrous form by ferritin.[11] However, in certain conditions such as inflammation, malignancy, infection, liver or kidney disease, ferritin acts as an acute phase reactant. In these conditions, though ferritin levels are high, transferrin saturation will be low or normal. Hence, it does not reflect iron status.[12] Many studies concluded that serum ferritin levels could be used as a marker of IR.[6,13-15]

However, there are some studies that found no correlation between serum ferritin and MetS.[16,17] Although the etiopathogenesis of MetS has been linked to iron overload and IR, controversy exists about the levels of ferritin in the cases of MetS. Moreover, only limited studies on serum ferritin levels in MetS have been done in India. Hence, this study is designed to estimate the levels of serum ferritin and serum iron in MetS and to correlate their levels with IR.

MATERIALS AND METHODS

This was a case–control study conducted in Pondicherry Institute of Medical Sciences, India, with a total of 140 participants, with 70 in each group. Cases were selected in the age group of 40-65 years, based on the modified the National Cholesterol Education Program Adult Treatment Panel-III (NCEP ATP-III) criteria: ≥3 criteria:[18]

1. Waist circumference (WC) of ≥90 cm in men and ≥80 cm in women,
2. Systolic blood pressure (SBP) ≥130 mmHg or diastolic BP (DBP) ≥85 mmHg or current use of antihypertensive drugs,
3. Fasting blood glucose ≥100 mg/dl or current use of oral hypoglycemic agents,
4. High density lipoprotein (HDL) <40 mg/dl for men and <50 mg/dl in women,
5. Triglycerides (TG) ≥150 mg/dl or current use of lipid-lowering drugs.

We compared the cases with age and gender-matched healthy controls. We excluded patients with acute and chronic inflammatory condition - infections, autoimmune disorders, chronic liver disease, chronic blood transfusions for thalassemia syndromes, chronic anemia, and chronic kidney disease. After an overnight fast, blood samples were collected from the study population, centrifuged and serum was used for the following analysis: Glucose was estimated spectrophotometrically by hexokinase method (Roche Integra 400 plus). Iron levels were measured by ferrozine colorimetric method. Insulin and ferritin levels were measured by Sandwich Electrochemiluminescence immunoassay method (Roche Cobas e411). IR is measured using the formula based on homeostasis model assessment (HOMA) method.[19] It is the product of fasting glucose and insulin levels divided by a constant 405. The study was approved by Institute Ethics Committee.

Statistical Analysis

Data were entered in MS Excel 2007 and analyzed by SPSS 20.0 version. Descriptive statistics with numbers, mean and standard deviation (SD) were used. As the reference values of the biochemical parameters vary with gender, the study group was divided into two groups based on gender. Independent *t*-test and Mann–Whitney *U*-test were used to compare the biochemical parameters between cases and controls. The differential distribution of ferritin and iron levels among these groups was analyzed. For correlating these biochemical parameters, Pearson's correlation test and Spearman rank correlation test were used. A $P < 0.05$ was considered significant.

RESULTS

The study was conducted on 140 subjects, of which 70 were cases who fulfilled the (NCEP ATP-III) criteria and 70 were controls. There were an equal number of males and females among cases and controls. Among the 140 participants, 76 (54.2%) participants were in the age group of 40-50 years, 40 (28.5%) participants were in the age group of 50-60 years, and 24 (17%) participants in the age group of >60.

Table 1 compares the diagnostic characteristics of the cases and controls. The diagnostic characteristics include WC, SBP, DBP, fasting blood sugar, HDL, and TG. There is no significant difference in the age between the two groups. There is a significant difference in the diagnostic characteristics between cases and controls with a $P < 0.001$.

Table 2 compares the insulin and HOMA-IR levels between cases and controls. Mann–Whitney *U*-test was applied. Insulin levels were expressed as μIU/mL. The insulin and HOMA-IR levels are significantly higher in cases when compared to controls with a $P < 0.001$**.

Table 3 compares the iron levels between the cases and controls. All the values were expressed as mean ± SD. Student's *t*-test was applied to compare the mean of iron

levels between cases and controls. The iron levels are significantly higher in cases when compared to controls with a $P < 0.001$**.

Mann–Whitney *U*-test was applied to compare the ferritin levels between the cases and controls. The ferritin levels are significantly higher in cases when compared to controls with a $P < 0.001$** (Table 4).

Table 5 compares the iron levels between cases and controls on the basis of gender. Iron levels were expressed in μg/dL. All the values were expressed as mean±SD. Student's *t*-test was applied. There is a significant difference in the iron levels among males and females between cases and controls with a $P < 0.001$**.

Table 6 compares the ferritin levels between cases and controls on the basis of gender. Mann–Whitney *U*-test was applied. There is a significant difference in the ferritin levels among males and females between cases and controls with a $P < 0.001$**.

Figure 1 shows the correlation of iron levels with HOMA-IR in males. Pearson's correlation test was applied. There is a significant positive correlation with HOMA-IR ($r = 0.846$, $P < 0.001$).

Figure 2 shows the correlation of iron levels with HOMA-IR in females. Pearson's correlation test was applied. There is a significant positive correlation with HOMA-IR ($r = 0.432$, $P = 0.010$).

Figure 3 shows the correlation of ferritin levels with HOMA-IR in males. Spearman rank correlation test was applied. There is a significant positive correlation with HOMA-IR ($r = 0.705$, $P < 0.001$).

Figure 4 shows the correlation of ferritin levels with HOMA-IR in females. Spearman rank correlation test was applied. There is a significant positive correlation with HOMA-IR ($r = 0.509$, $P = 0.002$).

DISCUSSION

This study involves 70 cases and 70 controls, in which males and females were equally distributed. The majority of the patients (54.2%) were in the age group of 40-50 years. This indicates that IR begins to develop in the fourth decade itself along with the development of risk factors such as hypertension, dyslipidemia, and obesity. In our study, we found that all the MetS patients have elevated insulin levels

Table 1: Comparison of the diagnostic characteristics of cases and controls

Baseline parameters	Cases (*n*=70)	Controls (*n*=70)	*P* value
Age (years)	50.9±7.2	50.6±7.1	0.795
WC (cm)	95.6±5.2	73.3±3.5	<0.001**
SBP (mm/Hg)	135±11	115±7	<0.001**
DBP (mm/Hg)	88±7	75±5.6	<0.001**
FBS (mg/dL)	178.2±66.1	80.1±8.2	<0.001**
HDL (mg/dL)	34±5.6	57.7±5.1	<0.001**
TG (mg/dL)	152.7±39	106±10.3	<0.001**

**P<0.01 highly significant. Student's *t*-test all the values were expressed as mean±SD. SD: Standard deviation, DBP: Diastolic blood pressure, FBS: Fasting blood sugar, HDL: High density lipoprotein, SBP: Systolic blood pressure, TG: Triglycerides, WC: Waist circumference

Table 2: Comparison of insulin and HOMA-IR levels in cases and controls

Parameters	Cases		Controls		*P* value
	Mean±SD	Median	Mean±SD	Median	
Insulin	23.6±11.1	20.5	10.1±1.7	10.0	<0.001**
HOMA-IR	10.7±6.4	8.9	1.7±0.34	1.8	<0.001**

**P<0.01 highly significant. SD: Standard deviation, HOMA-IR: Homeostasis model assessment insulin resistance

Table 3: Comparison of iron levels in cases and controls

Parameters	Cases	Controls	*P* value
Iron (μg/dL) Mean±SD	106.99±28.39	59.75±16.89	<0.001**

**P<0.01 highly significant. SD: Standard deviation

Table 4: Comparison of ferritin levels in cases and controls

Parameter	Cases	Controls	*P* value
Ferritin (ng/mL)			
Mean±SD	106.99±28.39	59.75±16.89	<0.001**
Median	166.5	65.0	

**P<0.01 highly significant. SD: Standard deviation

Table 5: Comparison of iron levels in cases and controls on the basis of gender**

Parameters	Cases	Controls	*P* value
Iron (μg/dL)			
Males	109.9±28.7	68.7±3.9	<0.001**
Females	100.8±24.7	46.3±4.1	

**P<0.01 highly significant

Table 6: Comparison of ferritin levels in cases and controls on the basis of gender**

Parameter	Males		Females	
	Cases	Controls	Cases	Controls
Ferritin (ng/mL)				
Mean±SD	204.8±84.1	72.0±21.3	169.5±64.2	58.4±15.3
Median	191.2	73	152.9	56
P value	<0.001**		<0.001**	

**P<0.01 highly significant, SD: Standard deviation

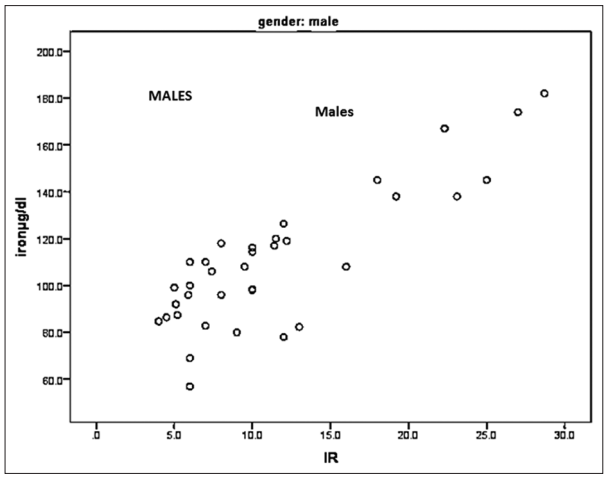

Figure 1: Correlation of iron levels with homeostasis model assessment insulin resistance in males. **P<0.01 highly significant

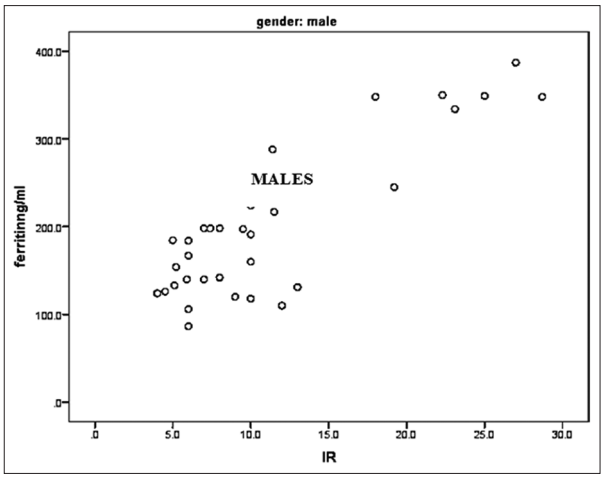

Figure 3: Correlation of ferritin levels with homeostasis model assessment insulin resistance in males. **P<0.01 highly significant

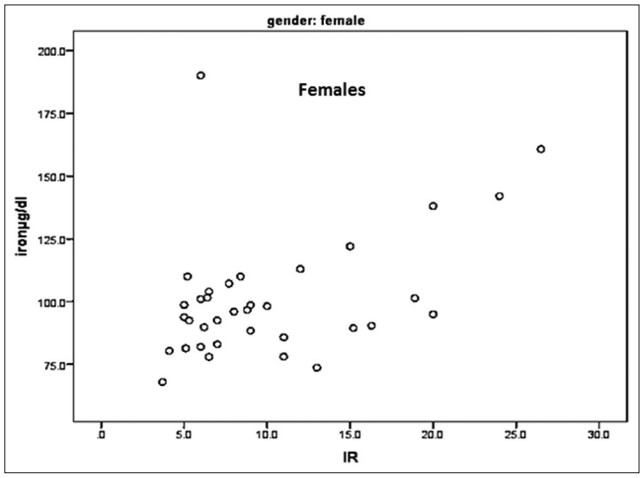

Figure 2: Correlation of iron levels with HOMA-IR in females. **P<0.05 statistically significant

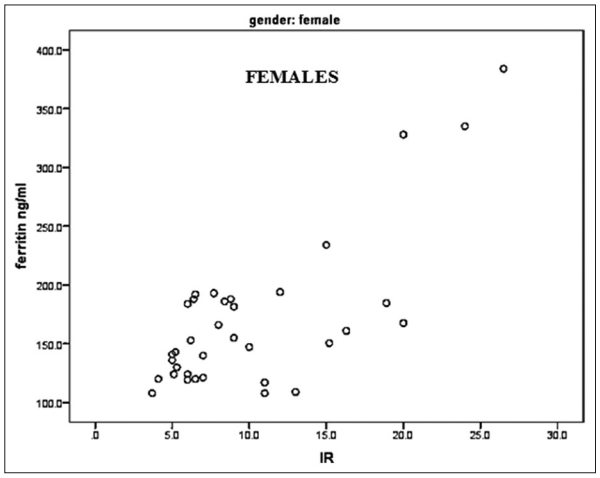

Figure 4: Correlation of ferritin levels with homeostasis model assessment IR in female. **P<0.01 highly significant

and raised HOMA-IR values (Table 2). This emphasizes the role of IR in the development of MetS. Our study is supported by the study of Regazzetti *et al.* who suggested that in obesity, adipose tissue hypoxia resulted in IR state which explained the pathogenesis of metabolic changes in MetS.[20] Similar to our study, Leiva *et al.* also found that MetS patients had higher HOMA-IR levels.[21]

We compared the iron levels in cases and controls. The mean concentrations of iron are significantly elevated in patients when compared to controls (Table 3). As the reference interval varies with gender, we also compared iron levels with respect to gender between the cases and controls. This shows increased levels of iron in patients when compared to controls, and the difference is statistically significant (Table 5). Our findings are supported by various studies. Bozzini *et al.* found that the prevalence of excessive body iron is high in MetS patients who satisfied the ATP-III criteria.[22] The mechanism that lies behind the development of IR as explained by Winterbourn was iron-induced oxidative damage to the pancreatic beta cells resulting in defective insulin secretion.[23]

Fernández-Real *et al.* concluded that iron removal done by phlebotomy improved insulin sensitivity in diabetic patients.[24] These studies confirmed the role of iron overload in MetS as seen in our study.

We compared the ferritin levels in cases and controls. The ferritin levels are significantly higher in cases when compared to controls (Table 4). As the reference interval varies with gender, we also did the comparison of ferritin levels between cases and controls with respect to the gender and found that ferritin levels are significantly elevated in patients when compared to controls, and the difference is statistically significant (Table 6).

Our findings are in accordance with those reported by other authors. Moirand *et al.* also concluded that the prevalence of metabolic disorders was high in patients with elevated ferritin and normal transferrin saturation.[25] Waeber *et al.* suggested that increased iron intake or elevated ferritin are individual risk factors for diabetes, MetS or gestational diabetes.[26] Contrary to our study, Xiao *et al.* concluded that serum ferritin and serum iron levels was lower in MetS patients when compared to controls.[27]

We did the correlation of iron and ferritin levels with HOMA-IR in cases of MetS with respect to gender. There is a significant positive correlation between iron levels with HOMA-IR ([r = 0.846; P < 0.001] and [r = 0.432; P = 0.010]) in males and females, respectively (Figures 1 and 2). Similarly, we found a significant positive correlation between ferritin levels and HOMA-IR ([r = 0.705; P < 0.001] and [r = 0.509; P = 0.002]) in males and females, respectively (Figures 3 and 4). Our study was supported by Abril-Ulloa *et al.* in their meta-analysis which found an independent positive association of ferritin levels with MetS after adjusting for inflammatory markers.[2] Similarly, Wrede *et al.* in their study in a German population found that there was a significant association of raised serum ferritin with IRS criteria and its severity emphasizing a causal relationship.[28]

In obese individuals, the adipose tissue synthesizes more hepcidin. Hence, when there is an increase in central adiposity, hepcidin expression also increases resulting in altered iron homeostasis.[29] Apart from the stimulus from iron, inflammation can also cause hepcidin secretion. Hepcidin excess results in the decreased expression of ferroportin. As a result, iron is retained in the liver cells. In iron overload state, there occurs hepatic erythrophagocytosis of iron resulting in hepatic iron deposition, subsequent inflammation, and oxidative stress follows.[30] When the body iron stores increase, there is a decrease in pancreatic insulin secretion resulting in hepatic and peripheral IR. When there is hepatic iron overload, it results in peripheral hyperinsulinemia and IR and muscle iron overload results in decreased glucose utilization.[31] Iron in excess results in the generation of reactive oxygen species which causes augmentation of oxidative stress by attacking cell membrane, increasing lipid peroxidation resulting in DNA fragmentation and tissue damage. Apart from that, obesity and T2DM *per se* increase oxidative stress and increase IR.[32] Hence, iron overload aggravates IR by affecting the insulin receptor signaling, and as a result, there is impaired utilization of carbohydrates in the liver and the muscle.

Limitations

Our study also had limitations. We did not measure other iron specific markers such as transferrin and iron binding capacity. Dietary factors which could influence iron markers were not dealt with.

CONCLUSION

Our study found that IR has an important role in the development of MetS. This was the first study to correlate iron and ferritin levels with insulin and HOMA-IR on the basis of gender. We found a significant positive correlation of these levels with HOMA-IR. Hence, it could be used as a marker for early diagnosis of MetS. Still further studies are needed to explore the role of ferritin as a valid biomarker in MetS.

REFERENCES

1. Sacks DB. Diabetes mellitus. In: Burtis CA, Ashwood ER, Bruns DE, editors. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed. New Delhi: Elsevier; 2012. p. 1415-50.
2. Abril-Ulloa V, Flores-Mateo G, Solà-Alberich R, Manuel-y-Keenoy B, Arija V. Ferritin levels and risk of metabolic syndrome: Meta-analysis of observational studies. BMC Public Health 2014;14:483.
3. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome - A new worldwide definition. Lancet 2005;366:1059-62.
4. Eckel RH. The metabolic syndrome. In: Jameson LJ, editor. Harrison's Endocrinology. 3rd ed. New York: McGraw-Hill; 2013. p. 253-60.
5. Bentley DP, Williams P. Serum ferritin concentration as an index of storage iron in rheumatoid arthritis. J Clin Pathol 1974;27:786-8.
6. Jehn M, Clark JM, Guallar E. Serum ferritin and risk of the metabolic syndrome in U.S. Adults. Diabetes Care 2004;27:2422-8.
7. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of Type 2 diabetes in apparently healthy women. JAMA 2004;291:711-7.
8. Ganz T. Molecular control of iron transport. J Am Soc Nephrol 2007;18:394-400.
9. Fernández-Real JM, López-Bermejo A, Ricart W. Cross-talk between iron metabolism and diabetes. Diabetes 2002;51:2348-54.
10. Kaye TB, Guay AT, Simonson DC. Non-insulin-dependent diabetes mellitus and elevated serum ferritin level. J Diabetes Complications 1993;7:246-9.
11. Higgins T, Eckfeldt JH, Barton JC, Doumas DT. Hemoglobin, iron and bilirubin. In: Burtis CA, Ashwood ER, Bruns DE, editors. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed. New Delhi: Elsevier; 2012. p. 985-1024.
12. Camaschella C, Poggiali E. Towards explaining "unexplained hyperferritinemia". Haematologica 2009;94:307-9.
13. Kim G, Shin JY. Association of serum ferritin and the development of metabolic syndrome in middle-aged Korean men. Diabetes Care 2012;35:2521-6.
14. Lee JY, Park JM, Hong JA, Lee DC, Im JA, Lee JW. Serum ferritin is differentially associated with anti-oxidative status and insulin resistance in healthy obese and non-obese women. Korean J Fam Med 2012;33:205-10.
15. Smotra S, Kudyar RP. Relationship between serum ferritin and Type-2 diabetes mellitus. JK Sci 2008;10:170-4.
16. Raj S, Rajan GV. Correlation between elevated serum ferritin and HbA1c in Type 2 diabetes mellitus. Int J Res Med Sci 2013;1:12-5.
17. Zafar U, Qureshi HJ, Karim A. Insulin resistance and serum parameters of iron status in Type 2 diabetics. Pak J Physiol 2011;7:28-31.
18. Grundy SM, Cleeman JI, Smith SC, Lenfant D. Definition of metabolic syndrome: Report of the National, Heart, Lung, and Blood Institute/ American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433-8.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell

function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
20. Regazzetti C, Peraldi P, Grémeaux T, Najem-Lendom R, Ben-Sahra I, Cormont M, *et al.* Hypoxia decreases insulin signaling pathways in adipocytes. Diabetes 2009;58:95-103.
21. Leiva E, Mujica V, Sepulveda P, Guzman L, Nunez S, Orrego R, *et al*. High levels of iron status and oxidative stress in patients with metabolic syndrome. World J Gastroenterol 2012;18:3782-6.
22. 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;28:2061-3.
23. Winterbourn CC. Toxicity of iron and hydrogen peroxide: The Fenton reaction. Toxicol Lett 1995;82-83:969-74.
24. Fernández-Real JM, Peñarroja G, Castro A, García-Bragado F, Hernández-Aguado I, Ricart W. Blood letting in high-ferritin Type 2 diabetes: Effects on insulin sensitivity and beta-cell function. Diabetes 2002;51:1000-4.
25. Moirand R, Mortaji AM, Loréal O, Paillard F, Brissot P, Deugnier Y. A new syndrome of liver iron overload with normal transferrin saturation. Lancet 1997;349:95-7.
26. Waeber G, Vollenweider P, Marques-Vidal PM. Dysmetabolic hyperferritinemia: A new target for treatment? Rev Med Suisse 2013;9:2002, 2004-7.
27. Xiao X, Liu J, Luo B, Feng X, Su Y. Relationship of dietary iron intake, body iron overload and the risk of metabolic syndrome. Biol Trace Elem Res 2011;143:625-36.
28. Wrede CE, Buettner R, Bollheimer LC, Schölmerich J, Palitzsch KD, Hellerbrand C. Association between serum ferritin and the insulin resistance syndrome in a representative population. Eur J Endocrinol 2006;154:333-40.
29. Bekri S, Gual P, Anty R, Luciani N, Dahman M, Ramesh B, *et al.* Increased adipose tissue expression of hepcidin in severe obesity is independent from diabetes and NASH. Gastroenterology 2006;131:788-96.
30. Aigner E, Theurl I, Theurl M, Lederer D, Haufe H, Dietze O, *et al.* Pathways underlying iron accumulation in human nonalcoholic fatty liver disease. Am J Clin Nutr 2008;87:1374-83.
31. Dongiovanni P, Valenti L, Ludovica Fracanzani A, Gatti S, Cairo G, Fargion S. Iron depletion by deferoxamine up-regulates glucose uptake and insulin signaling in hepatoma cells and in rat liver. Am J Pathol 2008;172:738-47.
32. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, *et al.* Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004;114:1752-61.

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