SERUM FERRITIN CONCENTRATIONS IN AN IMPAIRED FASTING GLUCOSE POPULATION AND THEIR NORMAL CONTROL GROUP

F. Sharifi*, H. Jazebi-Zadeh, N. Mousavi-Nasab and H. Amirmoghadami

Metabolic Diseases Research Center, Vali-e-Asr Hospital, Zanjan University of Medical Sciences, Zanjan, Iran

Abstract- Some recent studies have revealed the relationship among excess ferritin, coronary heart disease, and insulin resistance. This study was designed to assess the association between serum ferritin concentration and impaired fasting glucose (IFG). A total of 187 people including 91 IFG subjects and 96 normal glucose subjects were enrolled. The cohorts were well matched for age, sex and body mass index (BMI). BMI and blood pressure of the participants were measured and serum cholesterol, triglyceride and ferritin were evaluated. All the data were analyzed by *t* test, x^2 test and analysis of variance. Serum ferritin was higher in the IFG cohort (85.5 ± 6.6 µg/l vs. 49.4 ± 3.7 µg/l; *P*, 0.001). A positive correlation was found between fasting plasma glucose (FPG) and serum ferritin in this study (r, 0.29; *P*, 0.001). Using multiple regression analysis, we found an association between serum ferritin and BMI (0.06; *P*, 0.4), blood pressure (0.15; *P*, 0.01), FPG (0.29; *P*, 0.001), triglyceride (0.08; *P*, 0.01) and cholesterol (0.07; *P*, 0.03). The odd's ratio for the association of IFG in male subjects with the high serum ferritin level was 8.3 (CI 95%, 1.211.9; *P*, 0.01) and for females was 3.06 (C.I 95%, 0.58-15; *P*, 0.1). Our study implying that hyperferritinemia occurs before elevation of plasma glucose concentration more than 126 mg/dl. If prospective and interventional studies confirm an etiologic role of iron overload in the pathogenesis of insulin resistance, reduced dietary iron intake would appear to be a logical consequence.

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Key words: Ferritin, Glucose tolerance, Impaired fasting glucose, Prediabetes stage, Diabetes mellitus, Fasting plasma glucose

INTRODUCTION

Two large epidemiological studies have recently reported a strong association between elevated serum ferritin concentration and increased risk for diabetes (1, 2). Moreover, other studies have revealed the relationship among excess ferritin, coronary heart disease, and insulin resistance and have therefore renewed interest in ferritin as a risk factor for diabetes. In our previous study in Iran we revealed a positive correlation between type 2 diabetes mellitus and serum ferritin concentration (3). If ferritin can be considered as a risk factor for diabetes type 2, then it should be elevated in prediabetes stages such as subjects with impaired fasting glucose (IFG) who are prone to develop overt hyperglycemia.

This study was designed to investigate the association between serum ferritin concentration and IFG in Zanjan, a city about 300 Km in the west of Tehran, in 2004.

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*** Corresponding Author:**
Faranak Sharifi, Metabolic Diseases Research Center, Vali-e-Asr Hospital, Zanjan University of Medical Sciences, Zanjan, Iran
Tel: +98 241 4262486,
Fax: +98 241 4262730
E-mail: faranaksharifi@hotmail.com

MATERIALS AND METHODS

This study was carried out in a group of subjects more than 20 years of age with IFG who had been recognized in a large epidemiological study in Zanjan, one of the provinces of Iran, in 2001.

From 2200 people who had been randomly entered in the original study, 110 were recognized to have IFG with two different fasting blood samples. They were recalled to reevaluate their fasting plasma glucose (FPG) concentrations in 2004 and all the people with FPG more than 110 mg/dl and less than 126 mg/dl were enrolled.

After excluding all the subjects with hemoglobin concentration less than 12 mg/dl and those with acute or chronic inflammatory or infective disease, 91 subjects were entered in the study. The subjects were not on medications affecting blood glucose concentration. The control group consisted of individuals who had been recognized normal in the same epidemiological study in Zanjan in 2001 and their FPG was normal (less than 100 mg/dl) in the reevaluation in 2004. These normal participants were matched with the cases in terms of their sex and age. We obtained informed consent from all participants.

Weight and height were measured by a standard measurement and body mass index (BMI) was calculated based on weight/(height)² formula. Blood pressure was measured in all the subjects in a sitting position and with a standard manometer in two different visits, and the mean of them was considered as the blood pressure of the subject. Serum cholesterol and triglyceride of all the participants were measured after 14 hours of fasting and serum ferritin was measured by radioimmunoassay in the same laboratory centre. Ferritin concentrations more than 295 µg/l for men and 155µg/l for women was defined elevated (4).

Results were analyzed with SPSS version 11.5. *t* test for quantitative and x^2 test for qualitative variables was used. Pearson regression and analysis of variance was used and odd's ratio was calculated for IFG in high ferritin concentration. This study was approved by Ethics Committee of Zanjan Medical University.

RESULTS

A total of 187 people including 91 IFG subjects and 96 normal glucose subjects were studied. Table 1 show the anthropometric and laboratory characteristics of the case and control subjects included in this study. The cohorts were well matched for age, sex and BMI.

Serum ferritin was higher in the IFG cohort (85.5 ± 6.6 µg/l vs. 49.4 ± 3.7 µg/l; *P*, 0.001). Levels of fasting plasma glucose in the IFG group were remarkably higher than in the healthy control subjects. Table 2 compares male and females for the laboratory findings in the case and control cohorts. In general, concentrations of ferritin in men were higher than in women ($P < 0.05$).

A positive correlation was found between fasting plasma glucose and serum ferritin in this study (r, 0.29; *P*, 0.001). Using multiple regression analysis, we found an association between serum ferritin and BMI, blood pressure, FPG, triglyceride and cholesterol (Table 3). The odd's ratio for the association of IFG with high serum ferritin concentration was 3.3 (CI 95%, 1.3- 8.3; *P*, 0.01).

The odd's ratio for the association of IFG in males with the high serum ferritin level was 8.3 (CI 95%, 1.2–11.9; *P*, 0.01) and for females was 3.06 (CI 95%, 0.58-15; *P*, 0.1). Subjects with hypertension had higher ferritin concentrations (71 ± 4.9 µg/l vs. 55.6 ± 5.2 µg/l in the normotensives; *P*, 0.03). Serum ferritin concentration showed no significant difference in smokers and non smokers (76.6 ± 13 µg/l vs. 65.2 ± 4 µg/l).

Table 1. Characteristics of the case and control subjects*

Parameter	IFG (n = 91)	Normal (n = 96)	*P* value
Age (year)	47.7 ± 16	47.5 ± 16	0.9
Male (%)	40	45	0.9
Hypertension (%)	24	29	0.4
BMI(Kg/m^2)	26.4 ± 0.4	25.4 ± 0.5	0.8
Smokers (%)	17.5	13.5	0.5
FPG (mg/dl)	115 ± 4.7	92 ± 8.7	0.01
Cholesterol (mg/dl)	213 ± 6.5	196 ± 5	0.01
Triglyceride(mg/dl)	200 ± 12	154 ± 9	0.002
Ferritin (µg/l)	85.5 ± 6.6	49.4 ± 3.7	0.0001

Abbreviations: FPG, fasting plasma glucose; BMI, body mass index.
*Data for continues variables are given as mean ± SD.

Table 2. Characteristics of the two different sexes in the case and control group*

	Male (n = 84)		Female (n = 103)	
Parameter	**IFG**	**Normal**	**IFG**	**Normal**
Age (year)	45.7 ± 14.5	48.5 ± 18	49.4 ± 16	46.8 ± 15
BMI (kg/m^2)	25.5 ± 0.59	24.3 ± 0.55	27 ± 0.54	26 ± 0.7
Ferritin (µg/l)	108 ± 11	59 ± 5.5	67.7 ± 7	41.5 ± 4.8
Cholesterol (mg/dl)	205 ± 6.4	191± 6.8	222 ± 7.4	199 ± 7.2
Triglyceride (mg/dl)	198 ± 15	163 ± 14	202 ± 18	148 ± 12

Abbreviations: IFG, impaired fasting glucose; BMI, body mass index.
*Data for continues variables are given as mean ± SD.

DISCUSSION

In our study, ferritin concentration in IFG subjects, the high risk population for type 2 diabetes, was significantly higher compared with normal control subjects, implying that hyperferritinemia occurs before elevation of plasma glucose concentration more than 126 mg/dl.

In recent years, the issue of the potential pathology of serum ferritin in type 2 diabetes has gained remarkable interest (5). In the previous study in Zanjan, we found that serum ferritin concentrations were remarkably increased in type 2 diabetes (3). In the other study, subjects with higher concentrations of ferritin consequently had higher HbA_{1c}, glucose, and insulin concentrations (6). These results further proved a positive association between type 2 diabetes and high plasma ferritin concentrations.

The exact mechanism through which elevated ferritin promotes the development of type 2 diabetes is unknown. Some investigations argued that abnormalities in ferritin metabolism might be a primary cause of type 2 diabetes (7, 8). Some studies have revealed that normal glucose tolerant first-degree relatives in the type 2 diabetic pedigrees had higher ferritin concentrations than normal control subjects (4). A small intervention study provided preliminary evidence that bloodletting, which resulted in 50% reduction of serum ferritin concentrations, improved glycemia and insulin sensitivity in patients with type 2 diabetes (9). However, interpretation of mechanistic studies in patients with overt type 2 diabetes mellitus are complicated because glycemic control itself influences serum ferritin concentrations (glycosylated ferritin has a longer serum half-life) (10). The association between serum ferritin and poor glucose tolerance seems to be secondary to an association with insulin resistance but not with beta cell dysfunction. Mechanisms through which iron causes insulin resistance with ultimate impact on glucose homeostasis probably exist in the liver (10). However, muscle and fat cannot be excluded. Iron is a potent pro-oxidant, and reactive oxygen species have been shown to interfere with insulin signaling at the cellular level (11). Conversely, insulin resistance may be the cause rather than the consequence of disturbances in iron metabolism, as recently reviewed (12). Finally, although we adjusted for leukocyte count and C-reactive protein level, we cannot entirely exclude the possibility that serum ferritin level is an additional marker of subclinical inflammation, which itself may be a risk factor for type 2 diabetes mellitus (13). Nevertheless, in view of the sustained improvement in insulin sensitivity after bloodletting (9), it appears possible that iron overload is a weak but effective etiologic factor in the pathogenesis of insulin resistance.

In this study we studied patients with IFG that in some extent is equal to impaired glucose tolerance (IGT). Both of these situations are prediabetic stages with insulin resistance. Studies on patients with IGT,

Table 3. Correlations(r) between serum ferritin and other variables in all the subjects

	Ferritin concentration	
Variable	**(µg/l)**	***P* value***
BMI (Kg/m^2)	0.06	0.4
FPG (mg/dl)	0.29	0.001
TG (mg/dl)	0.08	0.01
Chol (mg/dl)	0.07	0.03

Abbreviations: FPG, fasting plasma glucose; BMI, body mass index; TG, triglyceride; Chol, cholesterol.
* *P* value less than 0.05 is significant.

diagnosed with glucose tolerance test have shown higher ferritin concentration in this group and found a positive correlation between serum ferritin and 2-hour glucose concentration (10).

It is quite plausible that the unhealthy diets contribute to diabetes risk not only through excess fat intake but also through excess iron supply (for example, in meat or in iron-supplemented food). Moreover, the iron overload hypothesis partially explains the reduced risk for diabetes in premenopausal women and vegetarian societies (14).

In conclusion, it may become advisable to routinely screen for mildly elevated or even high-normal serum ferritin concentrations in the context of glucose intolerance. If prospective and interventional studies confirm an etiologic role of iron overload in the pathogenesis of insulin resistance and type 2 diabetes, reduced dietary iron intake, especially in men and postmenopausal women (15) with additional risk factors for type 2 diabetes, would appear to be a logical consequence. In the future, actively lowering body iron stores may become a tool in preventing type 2 diabetes in selected subjects with impaired glucose metabolism.

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Conflict of interests

The authors declare that they have no competing interests.

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