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Original Article

High serum ferritin levels are associated with insulin resistance but not with impaired glucose tolerance in a healthy people population

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ABSTRACT

Aim: To assess the association between elevated serum ferritin levels and the presence of insulin resistance (IR) or impaired glucose tolerance (IGT) in a population of individuals with no endocrine or metabolic disorders background.
Methods: Analytical cross-sectional study, carried out in adults of both sexes with no medical history of type 2 diabetes mellitus (T2DM) or other metabolic or endocrine disorder, who attended the outpatient service of a private clinic in Lima-Peru during 2012–2014 period. Impaired serum ferritin levels were defined as serum ferritin values >300 μg/L in men and >200 μg/L in women. IR was defined as a Homeostasis Model Assessment (HOMA-IR) value ≥3.8 and IGT was defined as an oral glucose tolerance test (OGTT) value between 126 mg/dL and 199 mg/dL. The reported association measure was the prevalence ratio (PR) with their respective 95% confidence intervals (95% CI).
Results: We analyzed 213 participants, the average age was 35.8 ± 11.1 years and 35.7% were males. The prevalence of impaired serum ferritin levels, IR and IGT in the population was 12.7%, 33.3% and 9.9% respectively. In the adjusted Poisson regression models, the prevalence of IR was higher among the group with impaired serum ferritin levels (PR = 1.74; 95%CI:1.18–2.56); however, we found no association between impaired serum ferritin levels and IGT (PR = 1.42; 95%CI:0.47–4.30).
Conclusions: Impaired levels of serum ferritin are associated with IR, nevertheless, not with IGT in a metabolically healthy population. Serum ferritin could be considered as an early marker of IR prior to the onset of glycaemia disorders.

1. Introduction

Insulin resistance (IR) is an abnormal biological response of glucose to a normal concentration of insulin [1]. Patients with IR have an elevated risk of subsequently develop impaired glucose tolerance, metabolic syndrome and type 2 diabetes mellitus. IR has also been associated with the presence of some gynaecologic malignancies. A meta-analysis, found that there are significantly higher levels of circulating fasting insulin, Homeostasis Model Assessment values (HOMA-IR), and C-peptide, in women with endometrial cancer [2]. Additionally, another meta-analysis described the relationship between the presence of insulin-like growth factor 1 (IGF-1) and IGF-binding proteins (IGFBPs) with the development of IR and ovarian cancer [3]. Furthermore, the association between IR and the presence or progression of renal failure has been described [4]. Therefore, IR is not only a risk factor for the development of metabolic diseases.

The evolution of IR to type 2 diabetes mellitus has led to an increase in health systems costs around the world, mainly due to complications such as diabetic foot or end-stage renal disease. A study conducted in Spain, Italy and Germany found that the treatment of hypertension and metabolic syndrome in 2008 generated costs of 1900, 4887 and 24,427 million euros for each country respectively. Nevertheless, it is projected that these costs will increase by 1.5–2 times more by 2020 [5].

Previous studies have described that iron overload generates a dysfunction in the insulin action. Thus, retrospective and

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prospective studies have shown that elevated serum ferritin levels independently predict the development of glucose metabolism disorders as well as type 2 diabetes mellitus [6]. Oxidative stress from free radicals would be related to iron overload in the pancreatic beta cells and liver cells, leading to persistent cell damage and IR by the liver [7]. This condition, forces the pancreas to produce a higher secretion of insulin to keep glucose regulated; however, after exceeding their production limits, there would be an insulin deficit with the subsequent glucose impairments [8]. Then, iron overload would be a marker of IR in people with no type 2 diabetes mellitus.

Some studies carried out in populations with no type 2 diabetes mellitus, found an association between elevated serum ferritin levels and fasting hyperinsulinemia. However, there did not evaluated the association between elevated serum ferritin levels and impaired glucose tolerance [8–10]. Therefore, the aim of this study was to assess the association between elevated serum ferritin levels and the presence of IR or impaired glucose tolerance in a population of individuals with no medical background of endocrine or metabolic disorders.

2. Methods

2.1. Study design and population

Analytical cross-sectional study, carried out in adults of both sexes with no medical history of type 2 diabetes mellitus or other metabolic or endocrine disorder, who attended the outpatient service of a private clinic in Lima-Peru.

2.2. Sample type and analysis unit

A non-probabilistic sampling was performed and the sample consisted of all patients who attended the outpatient service of the private clinic during the 2012–2014 period and met the eligibility criteria of the study, thus sample size was not calculated.

2.3. Procedures

We reviewed the medical records of the patients treated during the study period and collected all the data of interest. The values of fasting glucose, oral glucose tolerance test (OGTT) and insulin levels were only collected if the patient laboratory tests were performed with a maximum of 30 days after they were attended in the outpatient service of the private clinic. Fasting plasma glucose levels were measured for all participants; then, they drank a 75-g glucose load and their plasma glucose levels were measured again 2 h later [11]. All participants had a minimum fasting period of eight hours for laboratory tests, according to the protocols established by the individual medical centre.

2.4. Eligibility criteria

Participants included were aged ≥18 with no medical background of type 2 diabetes mellitus or other metabolic diseases (polycystic ovary syndrome, hypothyroidism, subclinical hypothyroidism, hyperthyroidism or metabolic syndrome).

We excluded participants aged ≥60, patients with fasting glucose values ≥126 mg/dL, participants with OGTT ≥200 mg/dL, thyroid hormones values outside the following ranges: free triiodothyronine (FT3): 2.3–4.2 pg/mL, free thyroxine (FT4): 0.89–1.76 ng/dL, thyroid stimulation hormone (TSH): 0.35–5.5 μU/mL [12]; levels of serum ferritin <30 μg/L [13], history of chronic use of corticosteroids and pregnant women.

2.5. Variables definition

2.5.1. Exposure

Participants who met the eligibility criteria were categorized in two groups according to their serum ferritin levels: impaired serum ferritin levels (serum ferritin values >300 μg/L in men and >200 μg/L in women) and normal serum ferritin levels (serum ferritin values <300 μg/L in men and <200 μg/L in women) [14].

2.5.2. Outcomes: IR and impaired glucose tolerance

IR was defined as a Homeostasis Model Assessment (HOMA-IR) value ≥3.8 [15]. Mathews et al. proposed HOMA-IR in 1985 in a mathematical model to assess hyperinsulinemia. The gold standard to assess IR is the hyperinsulinemic euglycemic clamp, however HOMA-IR is well correlated with it. HOMA-IR was calculated using the formula: fasting glucose (mg/dL) x fasting insulin (μU/mL)/405 [16].

To assess impaired glucose tolerance, we used the OGTT. Participants were divided in two groups according to their plasma glucose levels after the glucose intake: impaired glucose tolerance (glucose levels between 126 mg/dL and 199 mg/dL) and normal glucose tolerance (glucose levels <126 mg/dL) [17].

2.5.3. Other variables

We also included in the analysis: age, sex, body mass index (BMI), fasting glucose, fasting insulin, FT3, FT4 and TSH.

2.6. Statistical analysis

We used STATA v14.0 (Statacorp, TX, USA) for our analysis. Descriptive results for numeric variables were presented as means with standard deviation (SD) or medians with interquartile range (IQR), depending on their distributions; otherwise, qualitative variables were presented as numbers with percentages. The characteristics of the participants with impaired serum ferritin values, IR or impaired glucose tolerance were compared using the Chi square test, the student T test or the Wilcoxon rank sum test as appropriate. The Pearson correlation coefficient (r) was used to assess the relationship between quantitative variables as serum ferritin levels with values of HOMA-IR or OGTT. For correlations, when the numeric variables were skewed distributions, they were transformed to a normal distribution using a logarithmic transformation.

Crude and adjusted Poisson regression models were constructed to assess the association between serum ferritin levels and IR or impaired glucose tolerance. The reported association measure was the prevalence ratio (PR) with their respective 95% confidence intervals (95% CI). The adjusted model to evaluate the association between serum ferritin levels and IR included a prior the following confounding variables: age, sex, BMI and FT3 [18]. The adjusted model to assess the association between serum ferritin levels and impaired glucose tolerance included prior the following confounding variables: age, sex and BMI.

2.7. Ethical considerations

The data was collected by an independent researcher to study epidemiological surveillance. For this study, participant information was delivered in a Microsoft Excel 2010 file with no biological identifiers, maintaining the confidentiality of the information.

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