Increased serum ferritin is associated with oxidized low-density lipoprotein in prediabetes patients: A pilot study

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ABSTRACT

Aims: This pilot study aimed to determine if increased serum ferritin (SF) is associated with cardiovascular risk factors in patients with prediabetes.

Methods: Eighteen patients with prediabetes and 36 subjects without prediabetes (control) were included. Participants had no inflammation or vascular complications. SF and metabolic markers were evaluated in both groups.

Results: SF and oxidized low-density lipoprotein (oxLDL) were increased in prediabetes subjects. Moreover, in prediabetes and control groups as a whole, ln-SF correlated with oxLDL and ln-oxLDL/LDL after adjustment for sex, ln-age, ln-fasting plasma glucose (FPG), ln-body mass index, ln-triglyceride (TG), total cholesterol (TC), and high-density lipoproteins. Finally, ln-SF was an independent contributor to ln-oxLDL/LDL ratio in control and prediabetes subjects (β = 0.2915) after the introduction of potential confounders such as FPG, TC, TG, and hypertension.

Conclusions: The results of this study indicate that hyperferritinemia is associated with oxLDL, considered one of the main cardiovascular risk factors, which allows us to suggest that an increase in SF could contribute to the progression of prediabetes, prior to the appearance of diabetes. Further research is required to establish a causal relationship of iron disruption metabolism in oxLDL generation under prediabetes conditions.

1. Introduction

Atherosclerosis is a major complication of diabetes [1], and the oxidative modification of low-density lipoprotein (LDL) is associated with the origin and progression of atherosclerotic lesions in diabetes [2]. Oxidized LDL (oxLDL) is implicated in the pathogenesis of endothelial dysfunction, foam cell formation, smooth muscle cell migration and proliferation, and induction of platelet adhesion and aggregation; all of them are phases of atherosclerosis [2]. Prediabetes and diabetes are at a higher risk of developing into vascular diseases through atherosclerosis than normoglycemic state [3]. Prediabetes is the intermediate state linking normoglycemia and diabetes and is defined as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or increased HbA1c [4]; this state is also at high risk for the development of not only diabetes but also its associated complications [3]. Recently, meta-analysis evidence has proposed that high-risk populations with prediabetes, emphasizing those with other cardiovascular risk factors, should be contemplated for controlled trial treatment to minimize or prevent future vascular complications [5]. There is evidence that oxLDL can appear in conditions of mild hyperglycemia, such as IGT subjects, and that this process can be implicated in atherosclerotic risk [6]. However, information about oxLDL in the IFG population remains inconsistent [7, 8].

Furthermore, at present, the oxidation of LDL is still being studied. One hypothesis is that iron disruption can guide iron overload, which can generate an ambient oxidative stress, and through oxidative species, LDL can be modified [9]. Lastly, iron overload, defined as an abnormal increment of serum ferritin, is associated with diabetes and complications such as oxidative stress generation [9, 10, 11], which are events that could begin in the prediabetes state [12]. In order to understand the...
potential role of ferritin as an acute phase reactant in a stage prior to the
development of diabetes, in this work we evaluate the potential associ-
ation of increased serum ferritin with cardiovascular risk markers in
patients with prediabetes.

2. Materials and methods

2.1. Subjects

This cross-sectional study was conducted at the Department of Med-
icine and Health Sciences of the University of Sonora in Mexico. Eighteen
subjects with prediabetes were recruited. The diagnosis of IFG was based on
the American Diabetes Association [4] criteria (≥5.6 to < 7.0
mmol/L). Another 36 normoglycemic subjects matched for male/female
ratio, age, and body mass index (BMI) were selected as controls. All
participants were non-white Hispanic, nonindigenous origin, Mexican
mestizo descent. Subjects had no type 2 diabetes (T2D), acute inflam-
mation, infection, iron deficiency anemia (<12 μg/L ferritin), extremely
high serum ferritin (>1000 μg/L), hemoglobinopathies, cancer, hyper-
thryroidism, vascular complications, hepatic disease, renal illness, auto-
immune diseases, alcoholism, pregnancy, or breastfeeding. Additionally,
none of them were on therapy using antihypertensives, iron supplements,
steroids, hormone replacement, nonsteroidal anti-inflammatory drugs, steroids,
replacement, pioglitazone, thyroglobulin,

2.2. Sample collection and laboratory tests

The subjects were asked to night fast for 10 h–12 h, avoiding stren-
uous exercise and any alcohol intake for 48 h before the evaluation.
Venous blood samples were collected with EDTA and nonanticoagulant
tubes using a standard Vacutainer method (Becton Dickinson, Franklin
Lakes, NJ, USA). Plasma and serum samples were further prepared into
smaller aliquots and were stored at -80 °C until the biochemical standard
laboratory test was performed.

The same plasma sample was used for the following measures, total
cholesterol (TC), triglyceride (TG), and high-density lipoprotein (HDL-
cholesterol (HDL-C), and was then spectrophotometrically quantified by
standardized commercially available diagnostic tests in a Hitachi
Modular P800 Analyzer (Roche Diagnostics Co., Indianapolis, IN, USA).
The LDL-cholesterol (LDL-C) concentration was calculated using the
Friedewald [13] formula. Fasting plasma glucose (FPG) was determined
using a glucose oxidase assay (Hitachi Modular P800 Analyzer). The
following analytes were measured by immunoenzymatic assay: adipone-
ctin (ab99968; Abcam, Cambridge, UK), interleukin-6 (IL-6; 900-K16;
PeproTech, Rocky Hill, NJ, USA), oxLDL (10-1143-01; Mercodia,
Uppsala, Sweden), and serum ferritin (ab108837; Abcam). Height and
weight were measured using a precalibrated wall-mounted stadiometer
(Holtain Ltd., Dyfed, UK) and an electronic balance (Defender 3000 se-
ties; Ohaus, Pine Brook, NJ, USA), respectively. BMI was calculated as
weight (kg) divided by height (m) squared. Waist circumference (WC)
was directly measured on the skin between the mean point of the iliac
peak and the inferior border of the last rib at the level of the umbilicus
while in a standing position at the end of normal expiration, making sure
that the tape was positioned perpendicular to the vertical (Y) axis of the
body and parallel to the floor. Hip circumference was measured over the
widest part of the gluteal region at the level of pubic tubercle in standing
position. Waist-to-hip ratio (WHR) was determined by WC (cm) divided
by hip circumference (cm). Blood pressure was also evaluated using a
manual sphygmomanometer after the subjects rested for 5 min in a

2.3. Statistical analysis

Data were examined for the assumptions of homogeneity of variances
using the Levene test and normality distribution using the Kolmogor-
rov-Smirnov test and expressed as mean ± standard deviation or median
(25th percentile, 75th percentile) as appropriate. To determine the sta-
tistical differences between groups, a two-tailed independent t-test was
used with previous natural logarithm (ln) transformation application in
case of nonparametric data. For percentages, Pearson’s chi-squared test
was applied. The correlation between ferritin and selected variables
was analyzed using the Pearson correlation previous ln-transformation of
variables in which skewness distribution was found. To analyze the
relation of ln-ferritin with oxLDL and ln-oxLDL/LDL-C after adjustment
for confounders, partial correlation coefficient was calculated adjusting
for sex, ln-age, ln-BMI, ln-FPG, ln-TG, TC, and HDL-C. Results were
considered significant when p < 0.05. The association of ferritin with
oxLDL/LDL-C was evaluated by multiple regression with backward
elimination strategy. Variables introduced to the analysis were as fol-
lows: ln-ferritin (μg/L), sex (male, 0; female, 1), ln-age (years), ln-BMI
(μg/m²), ln-TG (mmol/L), HDL (mmol/L), TC (mmol/L), ln-FPG
(mmol/L), ln-IL-6 (pg/L), adiponectin (IU/mL), hypertension (0 = no,
1 = yes), and WHR. p < 0.05 of β coefficient was set for the statement of
independent variable. Statistical analysis was performed using NCSS9
(NCSS LLC, Kaysville, UT, USA).

3. Results

3.1. Clinical characteristics of the study subjects

Table 1summarizes the characteristics and biomarker results of the
two groups. Control and prediabetes subjects were comparable con-
cerning age, distribution of gender (slightly higher proportion of fe-
males), and BMI. Indicators for abdominal obesity, WC as well as WHR,
were not different, neither the adipokine adiponectin, apparently
showing no differences in central adiposity. Prediabetes group had about
three times more hypertension (33.33%) than the control group
(11.11%) with statistical significance (p = 0.048), showing importance as
a possible contributor to the physiopathology of prediabetes subjects.
According to the group classification, accounting glucose and lipid
metabolism indicators, the levels of FPG were higher in prediabetes in-
dividuals than in controls (p < 0.001; Table 1). Blood lipid levels showed
differences between the groups, being notably increased in the predia-
betes group with significantly higher TC (p = 0.002) and LDL-C (p =
0.019) as well as oxLDL concentration (p = 0.028), which indicates the
presence of dyslipidemia, whereas no difference was found on TG, HDL-
C, TC/HDL-C ratio, and LDL-C/HDL-C ratio. Lastly, the prediabetes group
had significant differences in serum ferritin levels (p = 0.02; Table 1),
probably not related to inflammation, considering that no significant
differences were observed in IL-6 levels between both groups, although
no additional inflammation markers were examined.

3.2. Correlation between serum ferritin levels and metabolic markers

With the aim of determining whether serum ferritin could be related to
metabolic abnormalities in prediabetes subjects, the Pearson correla-
tion coefficients were estimated between serum ferritin and cardiovas-
cular risk factors, focusing the attention on oxLDL and oxLDL/LDL-C.
Because skewness distribution was found in serum ferritin levels and
other variable data, ln transformation was assessed. ln-serum ferritin was
also correlated with ln-FPG, TC, LDL-C, HDL-C, WHR, oxLDL, and ln-
oxLDL/LDL-C (Table 2).
As various studies have reported increased serum ferritin with alteration in lipid metabolism [12], oxidative stress, and oxLDL [9], partial correlations were undertaken between serum ferritin and oxLDL, adjusting for potential confounders (i.e., sex, ln-age, ln-FPG, ln-BMI, ln-TG, TC, and HDL-C). Across the study sample as a total, significant partial correlation was found between serum ferritin and ln-oxLDL/LDL-C (r = 0.397, p = 0.006) after adjustment for sex, ln-age, ln-FPG, ln-BMI, ln-TG, TC, and HDL-C.

### 3.4. Association between serum ferritin concentration and oxLDL/LDL-C ratio

In a multivariate regression analysis of independent determinants for oxLDL/LDL-C, it was revealed that, after using backward elimination and introducing possible predictors (ln-ferritin (μg/L), sex (male, 0; female, 1), ln-age (years), ln-BMI (kg/m2), ln-TG (mmol/L), HDL-cholesterol (mmol/L), TC (mmol/L), ln-FPG (mmol/L), ln-IL-6 (pg/L), adiponectin (IU/mL), hypertension (0 = no, 1 = yes), and WHR) [6], serum ferritin level with ln transformation was a positive independent contributor of oxLDL/LDL-C (Table 3; β (regression coefficient) = 0.2915; 95% CI [confidence interval] = 0.1444–0.4385; p < 0.001), a fact observed for the first time in subjects with prediabetes, which adds information to the relation of iron metabolism and/or inflammation (as acute-phase reactant) on the oxidation of LDL in glycemia unbalance conditions, before an established diabetes disease appears. In addition, TC (mmol/L; β = 0.5229; 95% CI = 0.1296–0.3800; p < 0.001) and ln-TG (mmol/L; β = 0.5229; 95% CI = 0.2601–0.7856; p < 0.001) were also predictive variables in the model, which are events that have been observed in healthy and prediabetic subjects [15]. Finally, hypertension was another indicator for oxLDL/LDL-C ratio seen in the present whole population (Table 3; β = 0.4188; 95% CI = 0.0560–0.7816; p = 0.02), adding information to the knowledge regarding this known risk factor for vascular complications and a component of metabolic syndrome (MetS) [16].

### 4. Discussion

Several reports have positively shown an association between oxidative stress and the development of vascular complications [2]. The measurement of oxidative species has been demonstrated to be valuable in the search for possible origins of complications, and oxidative stress has been proposed as a treatment target [9]. In the current study, we first observed that, in addition to hyperglycemia, the prediabetes state has a higher degree of dyslipidemia; actually, there are increased levels of circulating oxLDL in subjects with prediabetes compared to control subjects.
modification of lipids and proteins is involved in inflammatory diseases, including diabetes. Although increased oxidation products have been found in frank diabetes [19], the mechanisms of lipoprotein oxidative damage in the earlier stages of diabetes have not been fully understood, especially in incidents prediabetes patients, where usually there is no rigorous treatment application for glycemia and lipidemic control [5, 6].

Lipid peroxidation can be produced by highly toxic free radicals, for instance, hydroxide and superoxide anions formed by iron. The disruption of iron homeostasis can guide tissue iron overload, which has been proven to contribute to the generation of ROS and oxidative stress [9]. Body iron stores, expressed as serum ferritin, have been proposed to play an active role in the development of atherosclerosis [16], although the epidemiological association is yet to be fully understood [20, 21]. The confirmation for this hypothesis is that high serum ferritin levels are associated with oxidative stress, an event implicated in lipoprotein oxidation [9], such as oxLDL [16], Figure 2 shows a diagram that summarizes the possible relationship between oxLDL ferritin-oxidative stress. In the present study, we observed increased levels of serum ferritin in subjects with prediabetes compared to controls. In fact, in the population of the study as a whole, there was a positive correlation between serum ferritin and oxLDL as well as oxLDL/LDL after adjustment for age, sex, BMI, and FPG. This finding suggests that disbalance in iron metabolism among serum ferritin levels could be implicated in LDL modification. Tuomainen et al. [22] reported an association between serum ferritin and oxysterols (cholesterol oxidation products mostly carried by lipoprotein particles that are suggested to play an active role in the development of atherosclerosis). This study was conducted on middle-aged men with cardiovascular complications from Finland; the authors concluded that iron overload might be implicated in the increase of oxysterols. In another study, Brouwers et al. [23] observed that serum ferritin levels were significantly associated with oxLDL/LDL ratio in healthy Caucasians after adjustment for lipids, highly sensitive C-reactive protein (hsCRP), smoking, BMI, and hemochromatosis gene C282Y detection, but no information about glycaemia state was assessed. Similar results were found in the study by Aranda et al. [14]. They worked with Caucasian adults of the northeastern Mediterranean region of Spain and found that not only serum ferritin but also transferrin saturation was associated with lipid peroxidation assessed as oxLDL/LDL ratio. In our research, in multiple regression by backward elimination analysis for oxLDL/LDL-C ratio in both groups as a whole, serum ferritin levels were independent predictors after potential independent variables were introduced, including IL-6, a marker of inflammation; this supports the idea that serum ferritin and oxLDL/LDL association was not only related to ferritin acute-phase expression [24]. TC, TG, and hypertension were also oxLDL/LDL indicators, which are well-recognized risk factors for atherosclerosis [15, 17]. In a stepwise multiple regression, Ikeda et al. [16] found that serum ferritin levels are associated with oxLDL in subjects with T2D after adjustment for major predictors such as BMI, TG, and hsCRP. Furthermore, Khalili et al. [25] stated that serum ferritin and oxLDL could be good parameters for the identification of premature coronary disease, and a positive correlation was found between serum ferritin and oxLDL with coronary artery

Table 3. Multiple regression for ln-oxLDL/oxLDL-C ratio in control and prediabetes subjects.

| Variable         | \( \beta \) | 95% CI        | \( p \)       | Adjusted r model |
|------------------|-------------|---------------|---------------|------------------|
| ln-oxLDL/LDL-C   |             |               |               |                  |
| TC (mmol/L)      | 0.2548      | 0.1296-0.3800 | <0.001        | 0.3988           |
| Hypertension (0 = no, 1 = yes) | 0.4188 | 0.0560-0.7816 | 0.0246        |                  |
| ln-ferritin (μg/L) | 0.2915 | 0.1444-0.4385 | <0.001        |                  |
| ln-TG (mmol/L)   | 0.5229      | 0.2601-0.7856 | <0.001        |                  |

Multiple regression analysis by backward elimination method was performed. Parameters that were processed as probable independent variables were as follows: In-ferritin (μg/L), sex (male, 0; female, 1), ln-age (years), ln-BMI (kg/m²), ln-TG (mmol/L), HDL (mmol/L), TC (mmol/L), ln-FPG (mmol/L), ln-IL-6 (pg/L), adiponectin, hypertension (0 = no, 1 = yes), and WHR. Data are presented as \( \beta \) and 95% CI of indicators for ln-oxLDL/oxLDL-C ratio prediction. \( p < 0.05 \) was considered significant. The contribution of the model for ln-oxLDL/oxLDL-C ratio is presented as adjusted \( r \).
interpretation is that ferrous ion (Fe^{2+}) causality of iron induced-damage like lipid peroxidation. Such as methylglyoxal can lead to iron release of ferritin through reduction action (from Fe^{3+} to Fe^{2+}) and can accelerate the process of lipid oxidation [30]. However, when the antioxidant imbalance and prooxidant environment are sustained, ferritin may be a source of iron, as the superoxide anion, hydrogen peroxide, and glycation products such as methylglyoxal can lead to iron release of ferritin through reduction action (from Fe^{3+} to Fe^{2+}) and can accelerate the process of lipid oxidation [30]. The interpretation is that ferrous ion (Fe^{2+}), when providing an electron, leads to the production of hydroxyl radical from hydrogen peroxide, through the Fenton reaction [9, 31]. The Fenton and Haber–Weiss reactions drive OH radical formation and then to react in the oxidation of lipid molecules in cell membrane and lipoprotein lipids to form LPOOH [30, 32]. Other possibility discussed, is that serum ferritin is an inflammatory marker [33], that correlates but not necessary by itself is implicated in the causality of iron induced-damage like lipid peroxidation.

disease (CAD) score in patients with CAD with no history of renal disease, liver disease, or diabetes. However, to the best of our knowledge, our study is the first to exhibit a positive association between serum ferritin and oxLDL/LDL-C in NFG and prediabetes subjects.

Some reports show discrepancies regarding iron metabolism, which may be due to the fact that body iron stores vary with ethnicity [26], and previous multiethnic studies have shown how ethnicity could impact T2D prevalence and body iron stores [26]. Furthermore, most prior studies were conducted between US and European populations [8, 10, 14, 22, 23, 25]. There is little evidence in Asian populations [11, 12, 16, 21], and there is scarce information regarding iron metabolism on Mexican and South American populations [26]. Caucasians and Asians have been shown to maintain different serum ferritin levels, suggesting a possible difference in the homeostasis of ferritin between populations [26, 27]. Therefore, it is of scientific interest to examine whether serum ferritin levels could be implicated in metabolic disorders in the Mexican mestizo population.

However, there are some considerations that need to be addressed. In this observational cross-sectional study, we studied the association between ferritin levels and oxLDL/LDL among a small size but suitable statistical power sample. In addition, we adjusted for well-established diabetes metabolic disorder risk factors (including BMI, lipids, adiponectin, and hypertension). As the ferritin-oxLDL association was not permitted. However, this may suggest further investigation of the relation of body iron status and lipid oxidation in stages that precede diabetes and complications.

In conclusion, the results of this pilot study allow us to propose that the increase in serum ferritin in prediabetes could contribute to a state of low-grade chronic inflammation, favoring the oxidation of LDL in a state prior to the development of diabetes. However, considering that the group of subjects that participated in the study was small, we believe that the results obtained could be considered as the basis for future research that would allow establishing a causal relationship between serum ferritin concentration with cardiovascular risk factors and the progression of prediabetes.

Declarations

Author contribution statement

Juan Manuel Martínez-Soto: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

María del Carmen Candia-Plata: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Luis Fernando López-Soto and Jesús Adriana Soto-Guzmán: Conceived and designed the experiments; Analyzed and interpreted the data.

Alma Yolanda Camacho-Villa: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Gerardo Álvarez-Hernández: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Ana Lourdes Mata-Pineda: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.
José Manuel Galván Moroyoqui: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement
Data will be made available on request.

Declaration of interests statement
The authors declare no conflict of interest.

Additional information
No additional information is available for this paper.

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