Association of insulin resistance with serum ferritin and aminotransferases-iron hypothesis

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Abstract

AIM: To investigate the relationship of iron indices with diabetes mellitus (DM) in those without hemochromatosis.

METHODS: This cross-sectional study examined data collected during the Third National Health and Nutrition Examination Survey (NHANES III). Only those who fasted properly and were not anemic with transferrin saturation < 45% were included (n = 6849). Insulin sensitivity and beta cell function were calculated from fasting glucose and insulin concentrations. Indices of iron metabolism were examined in the presence or absence of DM. We examined the relationship of insulin sensitivity and beta cell function with serum ferritin concentration. The influence of C-reactive protein and liver enzymes was also investigated.

RESULTS: Serum ferritin concentration was significantly higher in diabetic subjects (P = 0.0001 to < 0.000001). The difference remained significant after adjustment for age, body mass index, alcohol consumption, and mineral/iron supplement (P = 0.03 to < 0.000001). In those who did not take insulin, serum ferritin concentration was negatively associated with insulin sensitivity (P = 0.05 to 0.00001), but not with beta cell function. The alanine aminotransferase was correlated with serum ferritin concentration (P = 0.02 to < 0.000001) but not with insulin sensitivity, suggesting the role of the liver in iron-associated insulin resistance.

CONCLUSION: As most of diabetes is type 2 diabetes and insulin resistance is a cardinal feature of type 2 diabetes, disordered iron metabolism could play a role in the pathogenesis of insulin resistance and type 2 diabetes through its effect on liver function.

Key words: Diabetes mellitus; Insulin sensitivity; Beta cell function; Ferritin; Liver

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Core tip: Hemochromatosis and excess iron load has been implicated to play a role in the pathogenesis of diabetes mellitus. Serum ferritin concentration was significantly higher in diabetic subjects. Serum ferritin concentration was negatively associated with insulin sensitivity, but not with beta cell function. The association of alanine aminotransferase correlated with serum ferritin concentration, but not insulin sensitivity, suggesting the role of the liver in iron-associated insulin resistance. Disordered iron metabolism could play a role in the pathogenesis of insulin resistance and type 2 diabetes mellitus through its effect on liver function.

INTRODUCTION

Diabetes mellitus (DM) is a common manifestation (53%-80%) of hereditary hemochromatosis[3], which is an autosomal recessive disorder caused by mutations in a gene designated HFE (OMIM: 235200). A mutation, C282Y, was detected in 83% of the patients, while it was only found in 3.2% of control chromosomes[2]. However, the allelic frequencies of C282Y mutation were similar between diabetic and control groups (6.3% vs 5.5%) in a large population from the United Kingdom[3]. Meta-analysis of published studies showed no evidence for over-representation of this allele in patients with type 2 diabetes[3]. Therefore, the C282Y mutation does not play a role in the pathogenesis of type 2 diabetes. Nevertheless, the role of iron metabolism in the pathogenesis of diabetes in the general population has been suggested in many cross-sectional studies[10-12]. Furthermore, a nested case-control study suggested a potential interaction between the HFE genotypes and heme iron in relation to the risk of type 2 diabetes[13].

In hereditary hemochromatosis, both insulin resistance and impaired insulin secretion have been suggested to play a role in its pathogenesis[3]. The role of insulin resistance in patients with secondary hemochromatosis from thalassemia major has been reported, while an additional defect in beta cell secretion cannot be excluded[10]. The association of serum ferritin concentration and insulin resistance has been reported in various liver diseases[11,12]. Furthermore, the underlying mechanism of iron-associated abnormal glucose homeostasis in the general population is not well understood.

To examine the role of iron in the pathogenesis of diabetes, we investigated the iron indices and the relative influence of an inflammatory marker and liver enzymes on glucose homeostasis in a nationally representative survey, third National Health and Nutrition Examination Survey (NHANES III).

MATERIALS AND METHODS

Ethics statement

The National Center for Health Statistics of the Centers for Disease Control and Prevention conducted the NHANES III in the United States from 1988 through 1994. This survey was designed to assess the health and nutrition status of a large representative sample in the United States. The survey and data collection was approved by the NHANES Institutional Review Board and documented consent was obtained from participants. Analysis of de-identified data from the survey is exempt from the federal regulations for the protection of human research participants. Only de-identified data from the survey was used in this study.
**Study design and study sample**

Detailed descriptions of the survey and the analytical methods of various assays have been published\[13\] and are also available at its website (http://www.cdc.gov/nchs/about/major/nhanes/datalink.htm#NHANESIII). Race and ethnicity were self-reported by the participants. NHANES III was designed to provide reliable information from three major racial/ethnic groups: Non-Hispanic whites (NHW), non-Hispanic blacks (NHB), and Hispanics. The 4th group was excluded from this analysis for its small sample size and for encompassing a heterogeneous racial/ethnic group. There were 15021 subjects who had serum ferritin, fasting glucose and insulin concentration measured. Proper fasting is required to define diabetes status and to calculate insulin sensitivity and beta cell function from the fasting samples\[14,15\]. Only those who fasted for ≥ 8 h and ≤ 16 h were included (n = 7701). We excluded 180 subjects with hemoglobin < 11 g/dL, which is frequently associated with iron deficiency and falsely low HbA1C. Since hemochromatosis is an established cause of diabetes, those with transferrin saturation ≥ 45 were also excluded\[16\] (n = 672), which identified 98% of iron-overloaded subjects\[17\].

**Ascertained of DM**

Diabetes was defined as a fasting glucose concentration ≥ 126 mg/dL (7.0 mmol/L) or a 2-h postchallenged glucose concentration ≥ 200 mg/dL (11.1 mmol/L)\[14\]. Without the 2-h postchallenged glucose concentration, the diagnosis of diabetes is frequently missed in those with elevated 2-h postchallenged glucose concentrations and normal fasting glucose concentrations\[18\]. However, only 3010 subjects had 2-h postchallenged glucose concentration measured. Their HbA1C was very well correlated with 2-h postchallenged glucose concentration (r = 0.7558, P < 0.000001) and 2-h postchallenged glucose concentration of 200 mg/dL (11.1 mmol/L) was equivalent to HbA1C of 6.3%. Therefore, we also defined diabetes in those with HbA1C ≥ 6.3%.

**Calculation of beta cell function and insulin sensitivity**

Beta cell function (%B) and insulin sensitivity (%S) were calculated based on the homeostasis model assessment (HOMA)\[15,19\].

\[
%B = \left( \frac{20 \times \text{fasting insulin concentration in mU/L}}{	ext{fasting glucose concentration in mmol/L - 3.5}} \right)
\]

\[
%S = 22.5 \times \frac{\text{fasting insulin concentration in mU/L}}{\text{fasting glucose concentration in mmol/L}}.
\]

Those with fasting glucose concentration < 3.5 mmol/L were excluded from analysis, since they had negative %B (n = 9). %B and %S obtained from the HOMA had been shown to correlate very well with the measured beta cell function and insulin sensitivity from various methods\[15,20-22\]. A quantitative insulin sensitivity check index (QUICKI), which had been shown to correlate with the measured insulin sensitivity by hyperinsulinemic euglycemic clamp very well\[23\], was also used.

\[
\text{QUICKI} = 1 / \left( \log_{10}(\text{fasting insulin concentration in mU/L}) + \log_{10}(\text{fasting glucose concentration in mg/dL}) \right).
\]

All of these methods have been validated in both non-diabetic subjects and diabetic subjects who did not take insulin\[21-23\]. Those who took insulin were excluded from these analyses (n = 51).

**Statistical analysis**

General descriptive variables were expressed as means ± SD. Since gender and ethnicity could potentially affect both iron metabolism and glucose homeostasis, the data were analyzed separately by gender and ethnic groups. Continuous variables were compared using two-tail Student t test between two groups or Analysis of Variance for more than two groups. Continuous data were expressed as means with 95%CI. Analysis of variance was used to examine the influence of covariates [age and body mass index (BMI)] on continuous variables between two groups. Least square regression analysis was used to investigate the relationship between two continuous variables. The influence of covariates (age, BMI, alcohol consumption, and mineral/iron intake) was also accounted for least square regression analysis. To further assess the association of serum ferritin concentration with estimated beta function and insulin sensitivity indices as well as the association of liver aminotransferases and C-reactive protein (CRP) with serum ferritin concentration and estimated insulin sensitivity indices, we also examine the trend across the quintile of serum ferritin concentration, liver aminotransferases and CRP. The comparisons were also adjusted for age, BMI, alcohol consumption, and mineral/iron intake. All the analyses were conducted in SYSTAT 11, Systat Software, Inc., Point Richmond, California, United States. A P value less than 0.05 was considered significant.

**RESULTS**

**Study populations**

The clinical features of the studied subjects were shown by gender and ethnic groups in Table 1. Based on previously published upper reference ranges\[24\], in male participants, 8.2% had elevated aspartate aminotransferase (AST > 37 U/L) and 9.6% had elevated alanine aminotransferase (ALT > 40 U/L) and in female participants, 7.7% had elevated AST (> 37 U/L) and 7.1% had elevated ALT (> 37 U/L).

**Comparison of indices of iron metabolism in the presence or absence of diabetes**

Iron, total iron binding capacity (TIBC), transferrin saturation, and serum ferritin concentration were
Table 1  Clinical features of studied subjects

|                      | Non-Hispanic whites | Non-Hispanic blacks | Hispanics |
|----------------------|----------------------|---------------------|-----------|
|                      | Male | Female | Male | Female | Male | Female |
| n                    | 1373 | 1602   | 896  | 1057   | 957  | 964    |
| Age (yr)             | 55 ± 19 | 54 ± 20 | 43 ± 17 | 42 ± 16 | 42 ± 17 | 41 ± 17 |
| Systolic blood pressure (mmHg) | 130 ± 18 | 125 ± 21 | 128 ± 18 | 122 ± 20 | 125 ± 17 | 120 ± 20 |
| Diastolic blood pressure (mmHg) | 76 ± 10 | 72 ± 9 | 79 ± 11 | 74 ± 11 | 76 ± 10 | 71 ± 10 |
| Body mass index (kg/m²) | 26.79 ± 4.63 | 26.39 ± 5.80 | 26.74 ± 5.34 | 29.07 ± 7.22 | 27.10 ± 4.64 | 28.26 ± 5.97 |
| Ferritin (mcg/L)     | 27.93 ± 8.39 | 24.58 ± 8.78 | 26.22 ± 8.11 | 21.75 ± 8.51 | 28.23 ± 8.59 | 22.95 ± 8.98 |
| Aspartate aminotransferase (U/L) | 176 ± 142 | 190 ± 111 | 215 ± 170 | 93 ± 111 | 169 ± 142 | 67 ± 95 |
| Alanine aminotransferase (U/L) | 18 ± 11 | 14 ± 10 | 19 ± 13 | 18 ± 11 | 28 ± 24 | 21 ± 23 |
| Ferritin (mcg/L)     | 35 ± 55 | 21 ± 20 | 46 ± 59 | 35 ± 55 | 46 ± 53 | 30 ± 31 |
| C-reactive protein (mg/dL) | 0.43 ± 0.76 | 0.45 ± 0.62 | 0.48 ± 0.79 | 0.53 ± 0.65 | 0.44 ± 0.84 | 0.53 ± 0.80 |

Data presented mean ± SD.

Table 2  Comparison of serum indices of iron by the presence or absence of diabetes mellitus

|                      | Non-Hispanic whites | Non-Hispanic blacks | Hispanics |
|----------------------|----------------------|---------------------|-----------|
|                      | Male | Female | Male | Female | Male | Female |
| Iron (mcg/dL)        | 166  | 1207   | 137  | 1465   | 115  | 842    |
| (95%CI)              | (89, 97) | (94, 97) | (78, 88) | (86, 89) | (84, 97) | (96, 100) |
| p                    | NS | NS | NS | NS | 0.01 | NS |
| p²                   | NS | NS | NS | NS | NS | NS |
| p³                   | 0.002 | NS | NS | NS | NS | NS |
| Total iron binding capacity (mcg/dL) | 351  | 344  | 359  | 360 | 333  | 334    |
| (95%CI)              | (343, 359) | (341, 346) | (350, 368) | (357, 363) | (322, 344) | (330, 337) |
| p                    | NS | NS | NS | NS | NS | NS |
| p²                   | NS | NS | NS | NS | NS | NS |
| p³                   | 0.002 | NS | NS | NS | NS | NS |
| Transferrin saturation (%) | 27  | 28  | 28  | 25 | 25  | 26 |
| (95%CI)              | (26, 28) | (28, 29) | (22, 25) | (24, 25) | (23, 26) | (26, 27) |
| p                    | NS | NS | NS | NS | NS | NS |
| p²                   | NS | NS | NS | NS | NS | NS |
| p³                   | 0.002 | NS | NS | NS | NS | NS |
| Ferritin (mcg/L)     | 228  | 169    | 152  | 84 | 282  | 206    |
| (95%CI)              | (200, 256) | (161, 177) | (129, 175) | (79, 89) | (195, 218) | (139, 195) |
| p                    | < 0.000001 | 0.000001 | 0.000003 | < 0.000001 | 0.000001 | < 0.000001 |
| p²                   | 0.0001 | 0.000003 | 0.02 | 0.0001 | 0.000001 | < 0.000001 |
| p³                   | 0.0002 | 0.000003 | 0.03 | 0.0001 | 0.000004 | < 0.000001 |

Data presented mean with 95%CI. To convert values for iron and total iron binding capacity to mol/L, multiply by 0.1791. *p values for unadjusted comparison; †p values for comparison after adjustment for age and body mass index; ‡p values for comparison after adjustment for age, body mass index, alcohol consumption, and mineral/iron supplement. NS: Not significant (p > 0.05); DM: Diabetes mellitus; NDM: Non-diabetic mellitus.

compared between those with or without diabetes (Table 2). No consistent results were observed for iron, TIBC, and transferrin saturation, while serum ferritin concentration was markedly higher in diabetic than in non-diabetic subjects in all six groups. The diabetic subjects were older than non-diabetic subjects by 14-16 years (p < 0.000001) and were also more obese than non-diabetic subjects per BMI by 2.40-4.81 kg/m² (p < 0.000001). The difference in ferritin concentration between diabetic and non-diabetic subjects remained significant after adjustment of age, BMI, alcohol intake, and mineral/iron supplement. Thus, diabetes was associated with elevated serum ferritin concentration.

**Association of serum ferritin concentration with beta cell function and insulin sensitivity**

Diabetes results from an imbalance between beta cell function and insulin sensitivity. Thus, serum ferritin concentration could potentially be associated with either beta cell function, insulin sensitivity, or both. No association between %B and serum ferritin concentration was found after adjustment for both age and BMI (Table 3). In contrast, serum ferritin concentration was negatively associated with %S and...
QUICKI in all six groups. This relationship persisted after adjustment for age, BMI, alcohol consumption, and mineral/iron supplement. Therefore, we concluded that ferritin concentration was negatively associated with insulin sensitivity.

Role of inflammation in association between serum ferritin concentration and insulin sensitivity

In addition to reflection of the body iron store, serum ferritin is also an acute reactant. To explore the role of inflammation on the observed correlation, we examined the relationship of these indices with a marker of inflammation, CRP. No consistent association of CRP with either %S or QUICKI was observed (Table 4). A positive association between CRP and serum ferritin concentration was observed in NHW (both males and females), non-Hispanic black females, and Hispanic females, but not in non-Hispanic black. The associations remained unchanged after adjustment for age, BMI, alcohol intake, and mineral/iron supplement. Therefore, inflammation could not provide a uniform explanation for the underlying mechanism of the observed correlation between serum ferritin concentration and insulin sensitivity.

Role of the liver in association between serum ferritin concentration and insulin sensitivity

Elevated liver enzymes could result from iron deposition in the liver. To examine the role of the liver in the association of serum ferritin concentration with insulin sensitivity, we investigated the association of liver enzymes with serum ferritin concentration and insulin sensitivity. We focused on AST or SGOT, gamma glutamyl transpeptidase (GGT), and ALT or SGPT.
Table 4  Serum ferritin concentration and estimated insulin sensitivity indices by quintile of inflammatory marker - C-reactive protein

| Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | P<sup>1</sup> | P<sup>2</sup> | P<sup>3</sup> |
|------------|------------|------------|------------|------------|-------------|-------------|-------------|
| Serum ferritin concentration (mcg/L) | | | | | | | |
| Non-Hispanic white males | 0.335 | 0.336 | 0.337 | 0.338 | 0.339 | < 0.000001 | 0.000002 | 0.000005 |
| Non-Hispanic white females | 0.327 | 0.328 | 0.329 | 0.330 | 0.331 | < 0.000001 | 0.000002 | 0.000005 |
| Non-Hispanic black males | 0.354 | 0.355 | 0.356 | 0.357 | 0.358 | < 0.000001 | 0.000002 | 0.000005 |
| Non-Hispanic black females | 0.337 | 0.338 | 0.339 | 0.340 | 0.341 | < 0.000001 | 0.000002 | 0.000005 |
| Hispanic males | 0.342 | 0.343 | 0.344 | 0.345 | 0.346 | < 0.000001 | 0.000002 | 0.000005 |
| Hispanic females | 0.336 | 0.337 | 0.338 | 0.339 | 0.340 | < 0.000001 | 0.000002 | 0.000005 |

The association of AST with %S and QUICKI was only noted in Hispanic males, but not in other 5 groups (Table 5). Adjustment for age, BMI, alcohol consumption, and mineral/iron supplement had no impact on the results. In contrast, a very close association was noted between AST and ferritin concentration in all 6 groups. Since AST is present in many tissues, including heart, skeletal muscle, kidney, and brain, we could not exclude the role of the liver based on no association between AST and insulin sensitivity in some groups.

GGT is a very sensitive indicator of hepatobiliary diseases and is found predominately throughout the hepatobiliary system, but also in other tissues. It was negatively associated with %S and QUICKI in all 6 groups (Table 6). The association remained after adjustment for age, BMI, alcohol consumption, and mineral/iron supplement. It was positively associated with serum ferritin concentration after adjustment for age and BMI. Therefore, the relationship of GGT with insulin sensitivity and serum ferritin concentration could provide a mechanistic insight of the liver in the association between insulin sensitivity and serum ferritin concentration.

The primary source of ALT is the liver. It was negatively associated with both %S and QUICKI in all six groups, and remained highly significant regardless of the adjustment for age, BMI, alcohol consumption, and mineral/iron supplement (Table 7). This relationship indicated an association of insulin resistance and liver diseases. Serum ferritin concentration was positively associated with ALT and also this association remained significant regardless of adjustment for age, BMI, alcohol consumption, and mineral/iron supplement. Since ALT is an indicator of liver diseases, a positive association between ALT and serum ferritin concentration suggests that increased iron deposition...
in the liver is associated with liver dysfunction. Furthermore, a positive association between ALT and serum ferritin concentration and a negative association between ALT and insulin sensitivity suggests a negative association of serum ferritin concentration with insulin sensitivity as we had observed.

**DISCUSSION**

To examine the role of iron metabolism in diabetes, the indices of iron metabolism were compared in patients with and without diabetes. We found that subjects with diabetes had a higher serum ferritin concentration than those without diabetes. To explore the underlying pathophysiology, we observed that serum ferritin concentration was negatively associated with insulin sensitivity (%S and QUICKI), but not with beta cell function. Therefore, a high serum ferritin concentration is associated with insulin resistance and is a risk factor for DM.

Since ferritin contains the second largest pool of iron in the body next to hemoglobin\cite{16}, serum ferritin concentration closely correlates with total body iron stores, mainly in the liver\cite{21}. In this study, serum ferritin concentration is negatively associated with insulin sensitivity, suggesting an association of insulin resistance with total body iron stores. However, it is well known that ferritin is also an acute phase reactant\cite{26}. To further explore this issue, we examined the correlation of CRP, an inflammatory marker\cite{27}, with insulin sensitivity and serum ferritin concentration. Without a consistent result across 3 ethnic/racial groups and both genders, we concluded that in this study, no consistent relationship of CRP with either insulin sensitivity or serum ferritin concentration was observed in all 6 groups. Furthermore, in this population only

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**Table 5  Serum ferritin concentration and estimated insulin sensitivity indices by quintile of aspartate aminotransferase**

| Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | P₁ | P₂ | P₃ |
|------------|------------|------------|------------|------------|-----|-----|-----|
| Serum ferritin concentration (mcg/L) | | | | | | | |
| Non-Hispanic | 148 | 154 | 180 | 170 | 228 | <0.000001 | <0.000001 | <0.000001 |
| white males | (134, 162) | (140, 167) | (165, 196) | (155, 186) | (205, 251) | | |
| Non-Hispanic | 58 | 61 | 85 | 102 | 140 | 0.004 | 0.02 | 0.02 |
| white females | (51, 65) | (55, 68) | (76, 94) | (91, 112) | (122, 158) | | |
| Non-Hispanic | 175 | 203 | 197 | 227 | 267 | 0.05 | 0.003 | 0.004 |
| black males | (155, 196) | (178, 228) | (173, 222) | (203, 251) | (236, 296) | | |
| Non-Hispanic | 84 | 84 | 77 | 95 | 127 | 0.00001 | 0.004 | 0.005 |
| black females | (71, 96) | (66, 88) | (67, 92) | (81, 109) | (106, 149) | | |
| Hispanic males | 139 | 134 | 149 | 155 | 223 | <0.000001 | <0.000001 | <0.000001 |
| Hispanic females | (124, 153) | (118, 151) | (134, 163) | (132, 177) | (194, 251) | | |
| | 47 | 49 | 59 | 79 | 101 | <0.000001 | 0.0001 | 0.00002 |
| | (39, 56) | (42, 55) | (50, 68) | (57, 101) | (86, 115) | | |
| Insulin sensitivity by the homeostasis model assessment (%S) | | | | | | | |
| Non-Hispanic | 0.491 | 0.517 | 0.497 | 0.506 | 0.478 | NS | NS | NS |
| white males | (0.457, 0.526) | (0.484, 0.559) | (0.466, 0.528) | (0.471, 0.541) | (0.441, 0.514) | | |
| Non-Hispanic | 0.575 | 0.597 | 0.591 | 0.555 | 0.506 | 0.02 | NS | NS |
| white females | (0.544, 0.607) | (0.559, 0.630) | (0.554, 0.628) | (0.521, 0.588) | (0.470, 0.543) | | |
| Non-Hispanic | 0.512 | 0.531 | 0.528 | 0.557 | 0.561 | NS | NS | NS |
| black males | (0.465, 0.559) | (0.470, 0.584) | (0.486, 0.569) | (0.508, 0.605) | (0.499, 0.623) | | |
| Non-Hispanic | 0.447 | 0.452 | 0.472 | 0.461 | 0.443 | NS | NS | NS |
| black females | (0.410, 0.484) | (0.418, 0.487) | (0.437, 0.506) | (0.424, 0.499) | (0.401, 0.485) | | |
| Hispanic males | 0.503 | 0.535 | 0.534 | 0.551 | 0.401 | <0.000001 | <0.000001 | <0.000001 |
| Hispanic females | (0.460, 0.542) | (0.495, 0.604) | (0.473, 0.574) | (0.424, 0.530) | (0.359, 0.449) | | |
| | 0.472 | 0.48 | 0.468 | 0.49 | 0.374 | 0.006 | NS | NS |
| | (0.430, 0.514) | (0.443, 0.516) | (0.430, 0.507) | (0.442, 0.539) | (0.330, 0.418) | | |
| Insulin sensitivity by the simple QUICKI | | | | | | | |
| Non-Hispanic | 0.337 | 0.34 | 0.338 | 0.338 | 0.334 | NS | NS | NS |
| white males | (0.333, 0.340) | (0.337, 0.343) | (0.335, 0.341) | (0.334, 0.342) | (0.330, 0.338) | | |
| Non-Hispanic | 0.346 | 0.347 | 0.347 | 0.347 | 0.336 | 0.009 | NS | NS |
| white females | (0.343, 0.349) | (0.344, 0.350) | (0.343, 0.350) | (0.340, 0.346) | (0.332, 0.340) | | |
| Non-Hispanic | 0.337 | 0.339 | 0.341 | 0.343 | 0.3417 | NS | NS | NS |
| black males | (0.332, 0.342) | (0.334, 0.344) | (0.337, 0.345) | (0.338, 0.348) | (0.336, 0.346) | | |
| Non-Hispanic | 0.331 | 0.332 | 0.335 | 0.333 | 0.33 | NS | NS | NS |
| black females | (0.327, 0.335) | (0.328, 0.336) | (0.332, 0.339) | (0.329, 0.337) | (0.326, 0.334) | | |
| Hispanic males | 0.337 | 0.342 | 0.338 | 0.333 | 0.325 | <0.000001 | <0.000001 | <0.000001 |
| Hispanic females | (0.333, 0.342) | (0.337, 0.346) | (0.333, 0.343) | (0.328, 0.338) | (0.320, 0.329) | | |
| | 0.334 | 0.336 | 0.334 | 0.335 | 0.32 | 0.0001 | NS | NS |
| | (0.329, 0.338) | (0.332, 0.340) | (0.330, 0.338) | (0.331, 0.340) | (0.315, 0.325) | | |

Data presented mean with 95%CI. ¹P values for trend, unadjusted; ²P values for trend, after adjustment for age and body mass index; ³P values for trend, after adjustment for age, body mass index, alcohol consumption, and mineral/iron supplement; ⁴%S = 22.5/(fasting insulin concentration in mU/L × fasting glucose concentration in mmol/L); ⁵QUICKI = 1/[log(fasting glucose concentration in mg/dL) + log(fasting insulin concentration in mU/L)]. NS: Not significant; QUICKI: Quantitative insulin sensitivity check index.
1.28% (range: 0.64% in Hispanic males to 1.95% in non-Hispanic black males) of the participants had an elevated CRP ≥ 3 mg/L, which is the 90th percentile for healthy young adults. After exclusion of those with a CRP ≥ 3 mg/L, association of CRP with insulin sensitivity was only observed in NHW females ($P = 0.006$ for %S and $P = 0.00002$ for QUICKI) and NHB females ($P = 0.03$ for %S and $P = 0.0001$ for QUICKI) and correlation of CRP with ferritin concentration was only observed in NHW females ($P = 0.005$), NHB females ($P = 0.001$), and MA females ($P = 0.01$), after adjustment for age and BMI. Therefore, it is very unlikely that inflammation is the underlying mechanism for the observed negative association between serum ferritin concentration and insulin sensitivity.

Next we examined the role of the liver on the observed association between insulin sensitivity and serum ferritin concentration. Among these three liver enzymes, AST is the least specific liver maker and ALT is the most liver specific marker. All three liver enzymes were correlated with serum ferritin concentration very well, suggesting a close association between elevated serum ferritin and liver dysfunction. However, we observed the different strengths of the correlation of insulin sensitivity across three liver enzymes. Among them, AST is the least specific for the liver diseases, the association between AST and insulin sensitivity only observed in Hispanic male group. In contrast, a negative association of ALT and GGT with insulin sensitivity was observed in all 6 groups. The negative correlation of liver enzymes with insulin sensitivity indicates the role of hepatic dysfunction in insulin resistance. Therefore, these observations imply the role of iron-associated elevated ALT and GGT in the pathogenesis of insulin resistance. The role of the liver in the pathogenesis of DM is well-established. Furthermore, the relation-
Table 7 Serum ferritin concentration and estimated insulin sensitivity indices by quintile of alanine aminotransferase

| Serum ferritin concentration (mcg/L) | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | P1 | P2 | P3 |
|-------------------------------------|------------|------------|------------|------------|------------|----|----|----|
| Non-Hispanic white males             | 147        | 169        | 168        | 177        | 220        | <0.000001 | <0.000001 | <0.000001 |
| Non-Hispanic black males             | 168        | 187        | 201        | 247        | 267        | 0.01 | 0.00005 | 0.00005 |
| Hispanic females                     | 128        | 128        | 142        | 172        | 229        | <0.000001 | <0.000001 | <0.000001 |
| Hispanic males                       | 113        | 143        | 116        | 126        | 157        | (0.343, 0.353) | (0.337, 0.345) | (0.326, 0.334) |
| Non-Hispanic white males             | 50         | 70         | 57         | 64         | 101        | <0.000001 | <0.000001 | <0.000001 |
| Non-Hispanic white females           | 42         | 70         | 57         | 64         | 101        | <0.000001 | <0.000001 | <0.000001 |

Data presented mean with 95%C.I. P1 values for trend, unadjusted; P2 values for trend, after adjustment for age and body mass index; P3 values for trend, after adjustment for age, body mass index, alcohol consumption, and mineral/iron supplement; %S = 22.5/(fasting insulin concentration in mU/L × fasting glucose concentration in mmol/L); QUICKI = 1/[log(fasting glucose concentration in mg/dL) + log(fasting insulin concentration in mU/L)]. NS: Not significant; QUICKI: Quantitative insulin sensitivity check index.

Huang J et al. Ferritin and insulin resistance

The role of serum ferritin concentration in diabetes

Elevated ferritin concentration has been reported to be associated with an increased risk of diabetes, but the role of inflammation could not be excluded[39]. Elevated serum ferritin concentration also has been reported to be associated with insulin resistance[39]. In the present study, we confirmed the association of serum ferritin concentration with DM and insulin sensitivity assessed by both %S and QUICKI. Although the association of inflammation and insulin resistance has been demonstrated in this population[39], we demonstrated that the inflammatory hypothesis is not likely the underlying mechanism of the reported associations in this study. In addition, from the observed associations of ALT and GGT with serum ferritin concentration and insulin sensitivity, we provided the evidence suggesting that the role of liver in the pathogenesis of iron-associated insulin resistance.

Iron-induced oxidant stress has proposed to play a key role in iron-mediated tissue damage[40-42]. Although the molecular events of iron-mediated tissue damage have not been fully elucidated, mitochondria are the targets of iron-mediated damage and iron may be preferentially toxic to cells with high mitochondrial activity[39], such as hepatocytes and pancreatic beta cells. Impaired mitochondrial activity has been observed in the insulin-resistant offspring of patients with type 2 diabetes.
2 diabetes and mitochondrial defect can also lead to the metabolic syndrome. Therefore, iron-induced oxidative stress with mitochondrial dysfunction could be one of the underlying mechanisms in these metabolic disorders.

Because of the cross-sectional nature of the study, a temporal relationship and the biological basis of the association between serum ferritin concentration and these metabolic disorders could not be established. However, our observations have some bearing on the plausible mechanisms. Furthermore, the caustic role of iron in these processes is suggested by interventional studies. In patients with clinical evidence of non-alcoholic fatty liver disease, quantitative phlebotomy induced iron depletion to a level of near-iron deficiency results in a 40%-55% improvement of both fasting and glucose-stimulated plasma insulin concentrations and near-normalization of ALT. Quantitative phlebotomy also leads to improvement in insulin sensitivity in a group of subjects with high-ferritin type 2 diabetes. Therefore, iron could be the culprit of these conditions.

The current sample set did provide enough information to distinguish type 1 and type 2 diabetes. However, as 95% of diabetes is type 2 diabetes and insulin resistance is a cardinal feature of type 2 diabetes, the current study is most applicable to type 2 diabetes. Our observations are consistent with the published results with some new clinical implications. In this study, even without clinical evidence of iron overload, iron could be associated with liver damage and insulin resistance. A clinical trial of quantitative phlebotomy in the subjects with elevated ferritin concentration is warranted to test this hypothesis. Once it is demonstrated, quantitative phlebotomy could be recommended for those patients with DM or insulin resistance, who also have elevated serum ferritin concentration. Although the underlying molecular mechanism of the association remains to be elucidated, our observations imply that the liver could play a role in iron-associated insulin resistance.

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