Association Of Serum Ferritin And Cardiovascular Risk Factors: A Cross-Sectional Analysis Of Data From The Third National Health And Nutrition Examination Survey

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Citation

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Abstract

Background: Few data have been published on the association of variables of the insulin resistance syndrome and serum ferritin, an indicator of body iron stores and putative risk factor for cardiovascular morbidity, in representative samples of total populations or in Hispanic Americans.

Methods: To describe the distribution of serum ferritin concentration and its association with indicators of insulin resistance, data were analyzed from a cross-sectional survey of a large national sample, the Third National Health and Nutrition Examination Survey. The analysis was restricted to Mexican American men aged 40-74 years. Measurements included glycated hemoglobin, body mass index (BMI), body fat distribution, HDL cholesterol, fasting serum insulin, serum triglycerides and serum ferritin concentrations.

Results: Distributions of serum ferritin, glycated hemoglobin, fasting serum insulin and plasma glucose changed little between ages 40 and 69. Log serum ferritin was not correlated with glycated hemoglobin percent and inconsistently correlated with HDL and blood pressure. Log serum ferritin concentration showed significant positive associations with fasting serum insulin concentration independent of age and BMI, levels being elevated in persons with ferritin in the fifth quintile. The association was strongest at age 40-49.

Conclusion: Further research is needed on the associations of serum ferritin concentration with insulin resistance and other components of the insulin resistance syndrome to elucidate the mechanisms and significance of observed associations.

INTRODUCTION

Few studies have examined the relationship of body iron stores and increased serum insulin concentration or insulin resistance, despite the relationship postulated for both variables with coronary heart disease and atherosclerosis ([1,2,3,4,5,6]). One study of Finnish men reported independent associations of serum ferritin, the best serum indicator of body iron stores, with fasting serum insulin and blood glucose ([7]). In a small study of healthy volunteers, no association of serum ferritin with fasting serum insulin was found, although serum ferritin was associated with insulin sensitivity among those in the upper half of the ferritin distribution ([8]). Well established are associations of metabolic risk factor clustering with insulin sensitivity and hyperinsulinemia, the insulin resistance syndrome ([4,5,6, 9]). In order to test the hypothesis that variables comprising the

insulin resistance syndrome are significantly associated with body iron stores as indicated by serum ferritin concentration independent of gender, ethnicity, age or maturity level, data from the Third National Health and Nutrition Examination Survey (NHANES III) were examined. Mexican Americans were selected for study because of the reported higher prevalence of obesity, diabetes, and insulin resistance compared to non-Hispanic whites or blacks ([10, 11]). Serum ferritin levels were similar in Hispanics and non-Hispanic whites in NHANES II ([12]). The study was restricted to men to eliminate confounding by gender, pregnancy, menopause, parity or hormone use and reduce possible confounding by iron deficiency and iron therapy. The study was restricted to persons older than 40 and younger than 75 years because that was the subsample, which received an oral glucose tolerance test in NHANES III.

METHODS

The Third National Health and Nutrition Examination Survey (NHANES III) was conducted in 1988-1994 on a nationwide multi stage probability sample of approximately 40,000 persons from the civilian, non-institutionalized population aged 2 months and over of the United States excluding reservation lands of American Indians. Of these, 31,311 were examined. The descriptive analyses of serum ferritin concentration and nonfasting glycated hemoglobin in this report are restricted to 860 Mexican American men aged 40-74 years examined with valid serum ferritin, and glycated hemoglobin (HbA1c) measured in the survey and not taking insulin or oral hypoglycemic agents. The analyses of serum ferritin and fasting serum insulin are further restricted to 394 men examined in the morning after fasting 9 to 24 hours with valid serum insulin data. Numbers of persons in various correlation and regression analyses that follow may vary slightly due to differing numbers with missing values on selected other variables. Details of the plan, sampling, operation and response have been published as have procedures used to obtain informed consent and to maintain confidentiality of information obtained ([13]).

Demographic, medical history, and behavioral information was collected prior to the examination by household interview. Race and Mexican American ethnicity were determined by self- report ([13]). Examinations were carried out in a mobile examination center. Blood samples were obtained at the examination center. Blood in a redtop Vacutainer tube was allowed to stand for 45 min at room temperature to allow complete clotting and clot retraction. Samples were centrifuged at 1500 x g for 30 min at 4 degrees Celsius. Samples were frozen at -20 degrees Celsius. Ferritin in serum was measured by the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, using the Bio-Rad Laboratories' Quantimmune Ferritin IRMA kit (Bio-Rad Laboratories, Hercules, CA) ([15]). This is a single-incubation, two-site immunoradiometric assay (IRMA) based on the general principles of assays as described elsewhere ([15,16,17,18]). The reference range for the overall population was considered to be 10-800 ug/L; men with levels > 400 ug/L are considered to have elevated levels ([18]). C-reactive protein concentration, a marker of inflammation, was measured at the Immunology Division of the University of Washington (Seattle, Washington) with latex-enhanced nephelometry ([15]).

Frozen serum was sent to The Missouri Diabetes Diagnostic Laboratory and stored at -70 C until analysis for serum insulin concentration. Insulin radioimmunoassay (RIA) was performed using the Pharmacia Insulin RIA kit (Pharmacia Diagnostics AB, Uppsala, Sweden) for the majority of samples. (Prior to November, 1990, RIA kits purchased from Cambridge Laboratories, Cambridge, Massachusetts and its successor Ventrex, Inc., Cambridge, Massachusetts were used. Based on simultaneous analyses using all three assays, results from these kits were converted to Pharmacia equivalence.) Quality control procedures included the reanalysis of 5% of specimens randomly selected either within-assay or between assay and the analysis of batch specimens consisting of four levels of control pools before and after all survey specimens. The internal reference range for fasting serum insulin in non-obese, nondiabetic adults (mean age 28.1 years) was 3.08-11.92 uIU/mL ([15]). The cross-reactivity of Pharmacia insulin antibody with proinsulin is approximately 40%. Concentration of C-peptide in serum was performed by RIA in a 3-day, batch, sequential-saturation method with two incubations ([15]). The internal reference range for fasting serum C-peptide was 0.266-1.079 pmol/mL. Frozen plasma was sent to the Missouri Diabetes Diagnostic Laboratory for determination of plasma glucose using a modified hexokinase enzymatic method on the Cobas Mira Chemistry System (Roche Diagnostic Systems, Inc, Montclair, New Jersey). Within and between-assay quality control procedures were used. During the 6 years of the survey the coefficient of variation of the method was 1.6-3.7% ([15]). Glycated hemoglobin (HbA1c) in whole blood was determined using a high-performance liquid chromatographic assay on the Diamat automated HPLC system, model 723 (Bio-Rad Laboratories, Hercules, CA). The upper limit of normal for HbA1c in this system has been defined as 6.1% ([19]).

Technicians measured height to the nearest 0.1 centimeter, weight to the nearest 0.01 kg, triceps, subscapular, suprailiac and mid-thigh skinfold thickness to the nearest 0.1 millimeter and waist and buttocks circumference to the nearest 0.1 centimeter as described in detail elsewhere ([13, 20, 21]). With the sample person standing at minimal respiration, waist circumference was measured in a horizontal plane at the level of the high point of the iliac crest to the nearest 0.1 cm. This method was chosen after consultation with experts in the field to maximize reproducibility. Hip circumference was measured in a horizontal plane at the maximum extension of the buttocks. The following were computed:

waist-to-hip circumference ratio (WHR), and body mass index (BMI=weight /height2, kg/m2). Extensive descriptive data on diabetes, glucose tolerance, height, weight, BMI and obesity prevalence as well as serum ferritin in the NHANES III population are being published elsewhere and will not be duplicated here ([18], [19], [21]).

STATISTICAL ANALYSIS

The plan of the present analyses was as follows. Detailed descriptive statistics and measures of association were computed initially using unweighted data using the Statistical Analysis System (SAS) ([22]). Pearson partial correlation was used to assess the association of the natural logarithm (LN) of serum ferritin concentration with other variables controlling for age or age and BMI ([22]). Correlation analysis results are presented because of their familiarity, ease of interpretation by a wide audience, and use in previous reports that may be compared to the present one. Linear multivariate regression analysis was used to develop models for controlling for confounding of the association of LN serum ferritin with fasting serum insulin ([22]). Only variables with pre-specified hypotheses were entered into the regression models. Following these preliminary analyses, weighted analyses were performed using techniques that incorporated sampling weights and design features of the survey ([23]). Population estimates for means and percentiles of variables were produced using weighted SAS or SUDAAN procedures ([24]). Pearson correlations of LN serum ferritin with other variables were performed using SAS weighted analysis and all statistical testing and variance estimation were performed using the PROC REGRESS procedure for linear regression models in the SUDAAN system ([22],[23],[24]).

RESULTS

Mean levels of serum ferritin are shown in Table 1. The distribution showed similar levels in each decade of life from the fifth through seventh decades. LN serum ferritin was not correlated with age overall or within decades with the possible exception of the sixth (Table 2). The distribution of HbA1c also varied little with age (not shown). The cumulative distribution of fasting serum insulin concentration (not shown), indicated little variation with age until the seventh decade. Mean levels are shown in Table 1, which shows means by age for all variables. Only blood pressure showed a consistent, graded change with increasing age.

Figure 1

Table 1: Mean serum ferritin concentrations and variables of the insulin resistance yndrome by age in Mexican American men aged 40-74 years: hird National Health and Nutrition Examination Survey, 1988-1994

Variable	Age, yrs				
	40-49	50-59	60-69	70-74	40-74
Ferritin (ug/L)	185.03	185.84	182.65	188.78	185.01
HG A1C (%)	5.53	5.93	5.74	5.86	5.68
HDL (mg/dL)	43.67	46.75	45.33	44.24	44.71
SBP (mm Hg)	124.17	131.13	139.20	140.18	12.905
DBP (mm Hg)	79.68	80.82	79.86	75.62	79.79
WHR	0.99	1.02	1.03	1.03	1.01
WAIST (cm)	98.98	101.22	101.14	99.45	99.85
BMI (kg/m2)	28.49	28.55	27.64	26.87	28.29
FSI (pmol/L)	78.67	80.75	72.87	62.46	77.27
FPG (mmol/L)	6.08	6.55	6.08	5.55	6.15
FSCP (nmol/L)	0.85	0.89	0.92	0.86	0.87
2HSI (pmol/L)	374.83	485.37	395.32	401.44	402.56
2HPG (mg/dL)	7.28	8.44	8.04	8.72	7.73
2HSCP (nmol/L)	3.04	3.52	3.70	4.13	3.31
TG (mmol/L)	2.12	1.92	1.78	1.78	2.00

HG A1C, glycosylated hemoglobin concentration; HDL, HDL cholesterol concentration;systolic blood pressure; DBP, diastolic blood pressure; WHR, waist-to-hip ratio; WAIST, waist circumference; BMI, body mass index FPG, fasting plasma glucose concentration; FSI, fasting serum insulin concentration;FSCP, fasting C-peptide concentration; 2HPG, 2-hour post-load plasma glucose concentration;2HSI, 2-hour post-load serum insulin concentration; 2HSCP, 2-hour post-load serum C-peptide concentration; TG, fasting serum triglyceride concentration.RFG2 JOBS 7824, 8034 04JUN99 C:\123W4R\DATA\NHANES3\FERIRS1W.WK4 6-4-99 (weighted)

Table 2 shows (weighted) correlation coefficients within strata of age and overall of LN serum ferritin concentration with variables associated with the insulin resistance syndrome. In Mexican American men not on insulin or oral hypoglycemic agents, the largest positive coefficients were seen for waist circumference and BMI at age 40-49 years, for HDL at age 70-74, and for diastolic blood pressure at each age except 50-59. Coefficients for HbA1c were consistently small.

Figure 2

Table 2: Correlations* of log serum ferritin concentration with components of the insulin resistance

Variables	Age, yrs				
	40-49	50-59	60-69	70-74	40-74
HB A1C	0.08	0.05	0.06	-0.07	0.05
HDL	-0.15	-0.06	0.01	0.08	-0.08
SBP	0.13	-0.02	0.03	-0.11	0.02
DBP	0.14	0.01	0.07	0.02	0.08
WHR	0.12	-0.10	0.07	-0.02	0.03
WAIST	0.25	0.07	0.14	0.01	0.17
BMI	0.24	0.11	0.06	-0.06	0.17
AGE	0.00	-0.16	0.00	-0.08	-0.07
N	349	150	283	78	860

HB A1C, glycated hemoglobin concentration; HDL, HDL cholesterol concentration;SBP, systolic blood pressure; DBP, diastolic blood pressure; WHR, waist-to-hip ratio; WAIST, waist circumference; BMI, body mass index *Pearson correlation coefficients RFG2 JOB 4989 07JUN99 C:\123W4R\DATA\NHANES3\FERRIRS2.WK4 6-7-99 (weighted)

Table 3 shows (weighted) correlation coefficients within strata of age and in all men for LN serum ferritin concentration with fasting blood measurements of insulin resistance and glucose tolerance. Fasting serum insulin was positively correlated with LN ferritin overall and within each decade except at age 70-74. Similar correlations were observed for C-peptide and plasma glucose. Values at two hours post glucose load showed a similar but less consistent pattern of correlations. Serum triglycerides were positively correlated with LN ferritin at each age. Figure 1 shows mean fasting serum insulin level by quintile of serum ferritin concentration, indicating a marked elevation in the fifth quintile (first quintile 65.37 pmol/L, fifth quintile 107.16 pmol/L), suggesting a threshold effect. Similar patterns were observed for fasting C-peptide and plasma glucose (not shown).

Figure 3

Table 3: Correlations* of log serum ferritin concentration with components of the insulin resistance syndrome in fasting Mexican American men aged 40-74 years: Third National Health and Nutrition Examination Survey, 1988-1994

Obesity variables	Age, yrs				
	40-49	50-59	60-69	70-74	40-74
FSI	0.34	0.18	0.15	-0.17	0.24
FPG	0.21	0.22	0.04	0.00	0.16
FSCP	0.37	0.15	0.05	0.05	0.23
2HSI	0.24	0.11	0.13	-0.23	0.15
2HPG	0.28	0.07	0.14	0.23	0.17
2HSCP	0.21	0.17	0.01	-0.07	0.11
TG	0.28	0.17	-0.01	-0.10	0.20
AGE	0.05	-0.14	-0.13	-0.20	-0.08

FPG, fasting plasma glucose concentration; FSI, fasting serum insulin concentration;FSCP, fasting C-peptide concentration; 2HPG, 2-hour post-load plasma glucose concentration;2HSI, 2-hour post-load serum insulin concentration; 2HSCP, 2-hour post-load serum C-peptide concentration; TG, fasting serum triglyceride concentration.C:\123W4R\DATA\NHANES3\FERIRS3W.WK4 6-8-99 (weighted)

Figure 4

Figure 1: Mean fasting serum insulin concentration by quintile of serum ferritin concentration in Mexican American men aged 40-69 years in the Third National Health and Nutrition Examination Survey, 1988-1994.
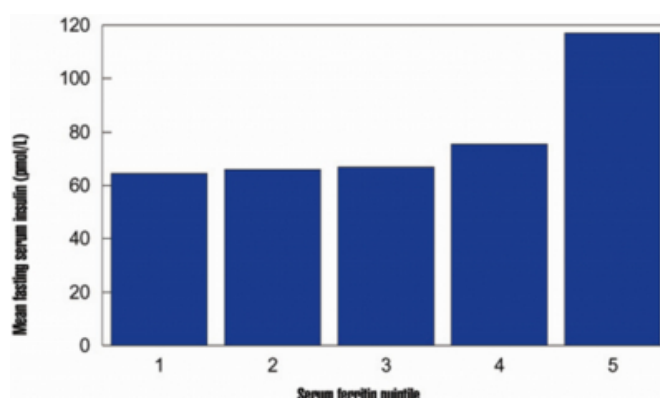
Linear regression models were fit with fasting serum insulin concentration as the dependent variable and serum ferritin > 272 ug/L (5th versus quintiles 1-4) as the exposure variable with age (y), BMI, and all interaction terms in men aged 40-69. (Men 70-74 were excluded because of the small number and suggested reversal of direction of associations in correlation analyses.) No interaction terms were statistically

significant. At ages 40-69, the difference in fasting serum insulin between the first through fourth and the fifth quintile of serum ferritin was 31.1 (SE 10.2) pmol/L after controlling for age, and BMI (p=0.004). Results were essentially the same when men with C-reactive protein greater than 1 mg/dL were excluded. When variables for smoking status (never/former/current smoker) were added to the model, the coefficient for ferritin changed little. In age-specific models controlling for age and BMI, serum insulin was significantly higher (difference 40.7, SE 14.7 pmol/L) in men in the fifth than in those in lower quintiles of serum ferritin (p=0.0001) at age 40-49 and borderline significantly higher at ages 60-69 (difference 15.5, SE 7.3, p=0.04) but not 50-59 (difference 14.7, SE 13.3, p=0.28). Thus, serum ferritin in the fifth quintile was a consistent, significant correlate of increased fasting serum insulin after controlling for age and BMI.

The association of serum ferritin concentration with history of acute myocardial infarction (AMI) and history of stroke was assessed in the non-fasting sample. There were 38 men with a history of AMI and 20 men with a history of stroke. In logistic regression analysis controlling for age, neither serum ferritin concentration nor serum ferritin in the fifth quintile versus lower quintiles was significantly associated with either prevalent AMI or stroke.

DISCUSSION

Fasting serum insulin, C-peptide, plasma glucose and triglyceride and post-load plasma glucose concentrations showed consistent positive associations with serum ferritin levels across age subgroups in a national sample of Mexican American men aged 40-69 years. A threshold effect with marked elevations of fasting serum insulin in the fifth quintile of ferritin was suggested.

Mechanisms. Ferritin is a major iron storage protein found in all cell types with isoferritin moieties identified in liver and spleen (L isoferritin), and for heart and kidneys (H isoferritin) [25, 26]. Iron-free apoferritin is a spherical protein (MW 480 kDa) with 24 subunits surrounding a central cavity, which can store over 4000 molecules of iron as ferrihydrite [26]. In mature cells, ferritin expression is regulated at translation via mRNA. Serum ferritin is iron-poor (mostly apoferritin). Serum ferritin may be synthesized and released from the liver and/or reticuloendothelial system [26]. It most resembles L isoferritin with a plasma half-life of up to 30 hours. A significant proportion is glycosylated. Most iron in plasma is bound to transferrin, with only very small amounts in ferritin, which has very high affinity for iron. Because iron directly induces synthesis of apoferritin, a representative fraction of ferritin being released into blood plasma under most metabolic circumstances, serum or plasma ferritin concentration correlates well with body iron stores [25].

The insulin resistance syndrome, also termed Syndrome X, is usually defined as associated insulin resistance or hyperinsulinemia, glucose intolerance, dyslipoproteinemia (low HDL, elevated triglycerides), and hypertension [4,5,6, 9, 27, 28]. The related metabolic syndrome or metabolic vascular syndrome also includes central obesity, hyperuricemia, hypercoagulability, atherosclerotic vascular disease and related disorders [27, 28]. Insulin resistance may be defined as "a state in which greater-than-normal amounts of insulin are required to elicit a quantitatively normal response [29]". In epidemiologic studies, fasting serum insulin concentration is used as the best measure of insulin resistance, since it is not feasible to measure it more directly using the euglycemic hyperinsulinemic clamp technique. Insulin resistance and/or hyperinsulinemia is postulated to cause the other components of the narrowly defined insulin resistance syndrome, but its role in the broader metabolic syndrome is in question.

Increased iron stores in the liver are postulated to induce liver-mediated insulin resistance, with reduced hepatic insulin extraction and hyperinsulinemia and reduced ability of insulin to suppress hepatic glucose production [8]. Increased iron stores in muscle could enhance oxidation of free fatty acids, which might interfere with glucose disposal [7]. Serum ferritin level has been found to be associated with decreased insulin sensitivity and increased fasting serum insulin and blood glucose [7, 8]. These abnormalities might lead to increased adiposity. In several studies, serum ferritin was correlated with other components of the insulin resistance syndrome [8, 28, 30, 31]. Hereditary hemochromatosis, an autosomal-recessive disorder, occurs in 2-4 per 1,000 European Americans, with a gene frequency of 7-10% [32]. Beta cell function is impaired in homozygotes with diabetes, but hyperinsulinemia has been observed prior to the development of overt diabetes, suggesting that iron overload leads to insulin resistance. Iron deposition has been observed in pancreatic islets restricted to beta cells [32]. Glucose tolerance and insulin sensitivity of heterozygotes and female homozygotes with minimal or mildly elevated iron stores have not been well studied [32]. Increased body

iron stores might be particularly deleterious in the setting of insulin resistance syndrome, which reportedly is associated with increased oxidative stress from other sources ($_{33}$). However, despite preliminary conjectures and reports and a large body of subsequent research, a relationship of serum ferritin or various other measures of body iron stores with the incidence of coronary heart disease or stroke remains controversial ($_{1}$, $_{34}$).

Comparisons with previous reports:

Only a few studies have assessed associations of insulin resistance with serum ferritin concentration, yielding inconsistent results ($_{7}$, $_{8}$). Consistent with the present findings, one study of Finnish men reported independent associations of serum ferritin with fasting serum insulin and blood glucose ($_{7}$). Fasting glucose but not insulin was higher in German men with serum ferritin >= 200 ug/L compared to < 200 ($_{35}$); a positive association with glucose was also seen in an earlier report on Finnish men ($_{36}$). In a small study of 36 healthy volunteers, no association of serum ferritin with fasting serum insulin was found, although serum ferritin was associated with insulin sensitivity among those in the upper half of the ferritin distribution ($_{8}$). A recent analysis of NHANES III data showed elevated serum ferritin in persons with newly diagnosed or previously diagnosed diabetes ($_{37}$). In all ethnic groups and age groups combined, serum ferritin was positively correlated with serum insulin and glucose. No results for Mexican Americans, C- peptide data, or data from the glucose tolerance test were shown.

Several studies are consistent with NHANES III data in finding associations of serum ferritin concentration with serum lipids and obesity indices associated with the insulin resistance syndrome ($_{7}$, $_{8}$, $_{30}$, $_{35}$, $_{36}$). For example, among over 300 male Norwegian oil workers, waist-to-thigh ratio (WTR) and BMI were significantly associated with ferritin in models including multiple cardiovascular risk factors ($_{30}$). The effect of WTR was linear and independent of BMI (also linear). In a metabolic study, the log of serum ferritin was not significantly correlated with WHR; BMI (but not WHR) was correlated with ferritin only among those in the top half of the ferritin distribution of the sample ($_{8}$). In healthy German men, serum ferritin was positively associated with serum triglycerides and negatively associated with HDL cholesterol ($_{35}$).

Limitations of the present study include possible bias arising from survey nonresponse and from missing values for some

variables. Several special studies of earlier HANES and NHANES III data have indicated little bias due to nonresponse ($_{12}$, $_{18}$, $_{23}$). Adequate reliability has been demonstrated for serum ferritin ($_{15}$). Day-to-day variability in serum ferritin would tend to bias reported associations towards the null ($_{38}$). Ferritin shows no appreciable circadian rhythm ($_{25}$). Blood collection conditions in NHANES III were standardized with regard to body position and vein constriction. Males donating blood four or more times a year may have depleted iron stores and reduced serum ferritin; however, blood donors were not excluded since serum ferritin still accurately reflects body iron stores ($_{25}$). Since serum ferritin is a positive acute-phase protein and does not accurately reflect body iron stores in the presence of inflammation ($_{25}$, $_{39}$), the regression analyses were repeated excluding men with C-reactive protein concentrations >= 1 mg/dL; findings were essentially unchanged. This was also true after excluding men with any detectable C-reactive protein (>=0.21 mg/dL). Unfortunately, no completely unbiased measure of insulin resistance is available for use in large population surveys ($_{40,41,42,43,44}$). As in the present study, serum insulin concentration both fasting and two hours post glucose load have been used as indirect measures of insulin resistance. However, traditional insulin assays such as the one used in NHANES III measure proinsulin and several split products as well as specific insulin, leading to falsely high values, especially in prediabetes ($_{41}$). This could lead to biased estimates of the association of serum ferritin and serum insulin. However, this seems unlikely because the results for C-peptide showed the same pattern of association as for insulin ($_{42}$). Regression analyses of serum ferritin as a predictor of fasting serum insulin were also repeated after exclusion of 13 men with self-reported history of doctor diagnosed diabetes without medication; results were essentially unchanged.

The lack of a single, generally accepted measurement protocol for insulin resistance or insulin resistance syndrome in epidemiologic studies remains a problem for interstudy comparisons, perhaps explaining in part inconsistencies among studies ($_{29}$, $_{40,41,42,43,44}$). Confounding by variables not controlled for cannot be excluded. However, given the uncertainty about the nature of the association, it is unclear which other variables should be controlled for as confounders. Results were essentially unchanged after controlling for smoking. The large sample size in NHANES III provided good statistical power. Since the number of tests was restricted to those of regression models and p values for

LN ferritin were <0.01, chance is an unlikely explanation of findings. The representativeness of the sample and the use of sample weights provide wide generalizability of the results to United States Mexican American men of the same ages, but not necessarily to females or persons of other ethnic groups.

Future research should include longitudinal studies of insulin resistance syndrome and serum ferritin in nonHispanic white and black and Hispanic men and women to determine temporal sequence of the relationship. Euglycemic clamp, minimal model or other techniques for accurate measurement of insulin resistance and specific insulin assays should be used to confirm whether insulin resistance, fasting specific insulin and proinsulin vary in their association with serum ferritin. Insulin resistance and serum ferritin should be assessed jointly as risk factors for development of noninvasively measured atherosclerosis (e.g. carotid intima-medial thickness) and non-insulin dependent diabetes.

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ABBREVIATIONS

Third National Health and Nutrition Examination Survey (NHANES III)

Body mass index (BMI)

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