Diabetes and Serum Ferritin Concentration Among U.S. Adults

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OBJECTIVE — We examined the association between serum ferritin concentration and the risk of diabetes.

RESEARCH DESIGN AND METHODS — We examined the cross-sectional associations among ferritin concentration, glucose tolerance status, and concentrations of insulin, glucose, and glycosylated hemoglobin in 9,486 U.S. adults aged ≥20 years from the Third National Health and Nutrition Examination Survey (1988–1994).

RESULTS — After adjusting for age, sex, ethnicity, education, BMI, alcohol consumption, alanine aminotransferase concentration, C-reactive protein concentration, and examination session attended, and after dichotomizing ferritin concentration into <300 and ≥300 μg/l for men and <150 and ≥150 μg/l for women, the odds ratios for newly diagnosed diabetes were 4.94 (95% CI 3.05–8.01) for men and 3.61 (2.01–6.48) for women. The increased risk of newly diagnosed diabetes was concentrated among participants with transferrin saturations <45%. All multiple linear regression coefficients between ferritin concentration and concentrations of insulin, glucose, and glycosylated hemoglobin were positive and significant for both men and women.

CONCLUSIONS — Elevated serum ferritin concentration was associated with an increased risk of diabetes. We were unable to eliminate conclusively the possibility that the observed association reflected inflammation rather than excess body iron stores.

Diabetes Care 22:1978–1983, 1999

In recent years, the issue of the health effects caused by iron overload has gained considerable visibility (1). Significant tissue accumulations of iron can lead to pathology in the liver, heart, endocrine organs, and musculoskeletal system (2). Excess iron deposition in the pancreas is known to cause a secondary form of diabetes, which has lead to speculation that higher concentrations of iron may increase the risk of developing diabetes. Earlier studies provided mixed evidence in support of the iron–diabetes hypothesis, and consequently the hypothesis was largely dismissed (3).

More recently, a report of 1,013 Finnish men showed a positive association between ferritin and diabetes (4). In this study, higher concentrations of serum insulin, glucose, and fructosamine were found in men in the highest quintile of ferritin concentration than in men in the lowest quintile. Shortly thereafter, the results of a nested case-control study of 53 men who developed diabetes in this same group of Finnish men were published (5). The authors reported a strong association between the ratio of transferrin receptors to ferritin and diabetes incidence. These studies have renewed interest in iron as a risk factor for diabetes.

To further investigate the association between iron status and diabetes, we examined data from the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative survey of noninstitutionalized individuals in the U.S.

RESEARCH DESIGN AND METHODS

— NHANES III began in 1988 and ended in 1994. By using a multistage stratified sampling design, 20,050 individuals aged ≥17 years were recruited into the survey. Details about the survey and its methods have been published previously (6,7). After an interview in the home, participants were invited to attend one of three examination sessions: morning, afternoon, or evening. For some participants who were unable to attend the examination because of health reasons, a blood sample was obtained during the home interview. Individuals attending the morning session were asked to fast for 12 h before the session. Subjects attending the afternoon or evening sessions were asked to fast for 6 h. Serum ferritin concentration was measured by using the Quantimmune IRMA kit (Bio-Rad, Hercules, CA). Details about the laboratory procedures and quality control have been published (7). Normal ranges for ferritin concentration are 20–250 μg/l for adult men and 10–120 μg/l for women. We defined elevated concentrations of ferritin as ≥300 μg/l for men and ≥150 μg/l for women.

Four categories of diabetes status were constructed by using the new diagnostic criteria (8): none, impaired fasting glucose, newly diagnosed diabetes, and previously diagnosed diabetes. Serum glucose concentration was measured by using an enzymatic reaction (Cobas Mira Chemistry System; Roche Diagnostic Systems, Montclair, NJ) (7). Participants who indicated that a physician had previously stated that they had diabetes were considered to have previously diagnosed diabetes. For the remaining participants who had fasted ≥8 h, subjects with a plasma glucose concentration <6.1mmol/l (<110 mg/dl) were considered to be normal, subjects with a fasting glucose concentration of 6.1 to <7.0 mmol/l (110–125 mg/dl) were considered to have impaired

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Received for publication 14 January 1999 and accepted in revised form 8 September 1999.

Abbreviations: NHANES III, Third National Health and Nutrition Examination Survey.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Unadjusted means of various demographic characteristics and cardiovascular disease risk factors by diabetes status among participants aged ≥20 years (NHANES III)*

	Diabetes status				
	None*	Impaired fasting glucose*	Newly diagnosed diabetes*	Previously diagnosed diabetes*	*P* (analysis of variance)
n	7,861	701	310	614	—
Prevalence (%)	83.2 (0.1)	5.6 (<0.1)	2.3 (0.2)	8.9 (0.4)	—
Age (years)	42.1 (0.4)	56.6 (0.9)†	59.4 (1.0)†	58.9 (0.8)†	<0.001
Sex (% men)	49.1 (0.7)	60.4 (2.3)†	52.7 (4.6)	43.7 (3.1)	0.001‡
Education (years)	12.5 (0.1)	11.3 (0.2)†	11.2 (0.3)†	10.9 (0.3)†	<0.001
Systolic blood pressure (mmHg)	117.5 (0.4)	130.8 (1.1)†	132.2 (1.5)†	129.6 (1.8)†	<0.001
HDL cholesterol (mmol/l)	1.32 (0.01)	1.22 (0.02)†	1.08 (0.03)†	1.20 (0.03)†	<0.001
Triglycerides (mmol/l)	1.42 (0.03)	1.93 (0.06)†	2.86 (0.21)†	2.57 (0.35)†	<0.001
BMI (kg/m^2)	26.0 (0.1)	29.1 (0.4)†	30.8 (0.4)†	30.3 (0.4)†	<0.001
Alcohol use (drinks/month)	8.7 (0.3)	14.1 (2.8)†	6.4 (1.8)	4.9 (0.8)	<0.001
White blood cell count (1,000/μl)	6.9 (<0.1)	7.3 (0.1)†	7.5 (0.3)†	7.3 (0.1)†	<0.001
Serum C-reactive protein (mg/l) (geometric mean)	2.8 (0.0)	3.2 (0.1)†	4.6 (0.3)†	3.9 (0.3)†	<0.001
Transferrin saturation (%)	28.9 (0.3)	26.7 (0.5)†	26.4 (0.8)†	26.4 (0.8)†	<0.001

Data are means ± SEM. *Maximum sample size; †*P* values <0.05 compared with participants with normal glucose tolerance; ‡*P* value from χ^2 test.

fasting glucose, and subjects with a fasting glucose concentration of ≥7.0 mmol/l (≥126 mg/dl) were considered to have newly diagnosed diabetes.

Other variables included in the analyses were age, sex, race or ethnicity (white, African-American, Mexican American, other), education (number of years attended), systolic blood pressure, serum HDL cholesterol concentration, serum triglyceride concentration, BMI (in kilograms per meters squared), alcohol consumption (number of drinks per month), white blood cell count, serum C-reactive protein concentration, serum alanine aminotransferase concentration, serum insulin concentration, and glycosylated hemoglobin concentration. Alcohol consumption was determined from responses to a food frequency questionnaire. C-reactive protein concentration was measured at the University of Washington Department of Laboratory Medicine by using latex-enhanced nephelometry. Alanine aminotransferase concentration was measured on a Hitachi model 737 multichannel automated analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Insulin concentration was measured by using a radioimmunoassay, and glycosylated hemoglobin concentration was measured by using ion-exchange high-performance liquid chromatography with a glycosylated hemoglobin analyzer system (DIAMAT; Bio-Rad) (7).

We limited the analyses to nonpregnant participants aged ≥20 years who attended the medical examination and who had fasted for at least 8 h. Geometric means for ferritin concentration were calculated by diabetes status. Least-squares adjusted means of log-transformed ferritin concentrations were calculated by using analysis of covariance. To test for differences in means among categories of diabetes status, we performed an analysis of variance. Sex-specific quintiles of ferritin concentration were calculated for the 9,486 participants who had both complete information to establish their diabetes status and a serum ferritin determination. To examine the significance of means or percentages of covariates by quintiles of ferritin concentration, we performed tests for linear trend. We calculated rank correlation coefficients between ferritin concentration and concentrations of insulin, glycosylated hemoglobin, and glucose by calculating Pearson correlation coefficients for the ranked data. The relationships between log-transformed ferritin concentration and concentrations of insulin, glycosylated hemoglobin, and fasting glucose were examined by using linear regression analysis. Results for untransformed and transformed ferritin concentrations were very similar; this study presents the results for transformed data only. By using multiple logistic regression analysis, we calculated adjusted odds ratios for the association between elevated ferritin concentration and newly diagnosed diabetes or impaired fasting glucose. All analyses used SUDAAN (Software for the Statistical Analysis of Correlated Data) to obtain proper variance estimates because of the complex sampling design (9).

RESULTS — A total of 16,573 individuals aged ≥20 years attended the medical examination. Of these participants, 9,964 had fasted for at least 8 h. After excluding pregnant women, 9,541 participants had data on diabetes status, and 9,486 participants had complete information to establish both their diabetes status and a serum ferritin determination.

Background data for each of the diabetes categories are presented in Table 1. On average, individuals with diabetes were older; were less educated; had higher systolic blood pressure levels, triglyceride concentrations, BMI, white blood cell counts, and serum C-reactive protein concentrations; and had lower HDL cholesterol concentrations and transferrin saturation than individuals with normal glucose concentrations.

Unadjusted ferritin concentration and the percentage of individuals with elevated ferritin concentrations were lowest for individuals without diabetes, somewhat higher for individuals with impaired fasting glucose, and highest for individuals with diabetes (higher in individuals with newly diagnosed diabetes than in individuals with previously diagnosed diabetes) (Table 2). After adjusting for age, sex, race or ethnicity, education, BMI, alcohol use, examination session, and C-reactive protein concentration, the relationship between

Table 2—*Distributional information of serum ferritin concentration by selected variables among participants aged ≥20 years (NHANES III)*

Characteristic	Sample size (*n*)	Geometric mean (μg/l)	Percentage with elevated serum ferritin concentration*
Total	9,486	82.1 ± 1.4 (2–1,979)	14.2 ± 0.6
Sex			
Men	4,566	136.1 ± 3.1 (3–1,742)	14.1 ± 1.0
Women	4,920	49.8 ± 1.3 (2–1,979)	14.3 ± 0.5
Diabetes status			
Normal			
Men	3,732	131.5 ± 3.2 (3–1,698)	12.0 ± 1.1
Women	4,129	46.4 ± 1.2 (3–1,494)	11.5 ± 0.6
Impaired fasting glucose			
Men	416	142.3 ± 9.9 (3–1,742)	17.8 ± 2.9
Women	285	75.4 ± 7.7 (3–1,143)	29.7 ± 3.0
Newly diagnosed diabetes			
Men	166	214.7 ± 2.9 (18–1,137)	46.3 ± 5.1
Women	144	121.9 ± 11.0 (3–725)	51.1 ± 4.9
Previously diagnosed diabetes			
Men	252	207.6 ± 17.3 (3–1,534)	35.9 ± 5.8
Women	362	81.4 ± 7.1 (3–1,979)	34.9 ± 4.1

Data are *n*, means ± SEM (ranges), or means ± SEM. *Elevated serum ferritin concentration is defined as ≥300 μg/l for men and ≥150 μg/l for women.

serum ferritin concentration and diabetes status changed little.

With increasing ferritin concentration, age, cholesterol concentration, triglyceride concentration, BMI, C-reactive protein concentration, glucose concentration, glycosylated hemoglobin concentration, insulin concentration, and transferrin saturation increased significantly among men and women (Tables 3 and 4). Serum HDL cholesterol concentrations showed no significant linear trend as a function of ferritin concentration in either sex. Among men, systolic blood pressure appeared to be related to ferritin concentration in a nonlinear fashion, alcohol use was positively related to ferritin concentration, and means of education varied little by quintiles of ferritin concentration. Among women, education was inversely related to ferritin concentration, and systolic blood pressure was positively related to ferritin concentration. Although mean intake of alcohol tended to increase with increasing ferritin concentration, the trend was not significant.

After adjusting for age, race or ethnicity, education, BMI, alcohol intake, C-reactive protein concentration, and examination session attended, men with newly diagnosed diabetes had an odds ratio of 4.94 (95% CI 3.05–8.01) and women had an odds ratio of 3.61 (2.01–6.48) regarding having elevated ferritin concentrations as men and women with normal glucose concentrations did. The adjusted odds ratios for impaired fasting glucose were 1.35 (0.99–1.83) for all participants, 1.13 (0.69–1.85) for men, and 1.64 (1.09–2.47) for women.

Table 3—*Unadjusted means or percentages of various demographic characteristics and cardiovascular disease risk factors by quintiles of ferritin concentration among men aged ≥20 years (NHANES III)*

	Quintiles of serum ferritin concentration (μg/l)					*P* for linear trend
	≤76*	77–115*	116–171*	172–255*	256–1,742*	
n	962	831	918	840	1,015	—
Age (years)	43.7 ± 0.8	39.9 ± 0.9	41.5 ± 0.8	41.5 ± 0.8	47.6 ± 0.8	<0.001
Race or ethnicity (%)						
White	76.9 ± 2.9	79.3 ± 2.5	76.5 ± 2.4	76.4 ± 2.8	74.4 ± 1.9	<0.001†
African-American	7.5 ± 0.8	7.9 ± 0.8	10.2 ± 0.8	10.3 ± 1.1	13.2 ± 1.1	—
Mexican American	7.1 ± 1.0	6.1 ± 0.7	5.8 ± 0.6	5.5 ± 0.7	4.7 ± 0.6	—
Other	8.5 ± 2.5	6.7 ± 2.1	7.6 ± 2.1	7.9 ± 2.2	7.7 ± 1.5	—
Education (years)	12.4 ± 0.2	12.5 ± 0.2	12.6 ± 0.1	12.5 ± 0.2	12.4 ± 0.1	0.973
Systolic blood pressure (mmHg)	122.5 ± 1.0	120.4 ± 1.0	120.3 ± 0.7	121.7 ± 0.8	123.9 ± 0.8	0.094
Total cholesterol (mmol/l)	5.06 ± 0.06	5.13 ± 0.05	5.18 ± 0.05	5.37 ± 0.06	5.39 ± 0.06	<0.001
HDL cholesterol (mmol/l)	1.18 ± 0.02	1.21 ± 0.02	1.20 ± 0.02	1.20 ± 0.03	1.14 ± 0.02	0.161
Triglycerides (mmol/l)	1.45 ± 0.07	1.43 ± 0.04	1.45 ± 0.05	1.80 ± 0.07	2.06 ± 0.11	<0.001
BMI (kg/m^2)	25.7 ± 0.2	26.0 ± 0.3	26.5 ± 0.2	26.9 ± 0.3	28.1 ± 0.3	<0.001
Alcohol use (drinks/month)	8.5 ± 0.6	12.7 ± 2.1	10.5 ± 0.8	15.5 ± 1.5	15.0 ± 1.2	<0.001
Serum C-reactive protein (mg/dl) (geometric mean)	0.26 ± 0.01	0.25 ± 0.01	0.27 ± 0.01	0.27 ± 0.01	0.29 ± 0.01	0.007
Glucose (mmol/l)	5.46 ± 0.05	5.36 ± 0.04	5.48 ± 0.03	5.51 ± 0.05	6.04 ± 0.09	<0.001
Glycosylated hemoglobin (%)	5.4 ± <0.1	5.3 ± <0.1	5.3 ± <0.1	5.3 ± <0.1	5.6 ± 0.1	0.007
Insulin (pmol/l)	57.9 ± 2.1	54.7 ± 1.2	57.4 ± 1.9	62.4 ± 3.6	79.3 ± 4.1	<0.001
Transferrin saturation (%)	28.6 ± 0.7	30.8 ± 0.5	31.8 ± 0.6	31.5 ± 0.5	33.2 ± 0.7	<0.001

Data are means ± SEM. *Maximum sample size (because of missing data, sample sizes vary); †trends for white versus nonwhite.

Table 4—*Unadjusted means or percentages of various demographic characteristics and cardiovascular disease risk factors by quintiles of ferritin concentration among women aged ≥20 years (NHANES III)*

	Quintiles of serum ferritin concentration (μg/l)					*P* for linear trend
	≤21*	22–39*	40–65*	66–115*	116–1,979*	
n	1,004	906	922	954	1,134	—
Age (years)	38.4 ± 0.5	39.1 ± 0.9	42.7 ± 0.8	48.4 ± 0.9	57.9 ± 0.8	<0.001
Race or ethnicity (%)						
White	67.6 ± 2.9	75.7 ± 2.0	79.8 ± 1.6	79.7 ± 1.6	74.3 ± 1.9	<0.001†
African-American	13.6 ± 1.4	10.0 ± 0.9	9.8 ± 0.9	9.9 ± 1.1	15.4 ± 1.3	—
Mexican American	7.8 ± 0.9	5.4 ± 0.6	4.3 ± 0.5	4.1 ± 0.5	2.9 ± 0.3	—
Other	10.9 ± 2.2	8.9 ± 1.5	6.2 ± 1.3	6.3 ± 1.3	7.5 ± 1.4	—
Education (years)	12.4 ± 0.1	12.6 ± 0.1	12.2 ± 0.2	12.3 ± 0.1	11.4 ± 0.1	<0.001
Systolic blood pressure (mmHg)	112.2 ± 0.8	112.4 ± 1.0	113.7 ± 0.7	118.0 ± 1.0	126.1 ± 1.1	<0.001
Total cholesterol (mmol/l)	4.90 ± 0.05	5.01 ± 0.06	5.24 ± 0.04	5.44 ± 0.04	5.80 ± 0.06	<0.001
HDL cholesterol (mmol/l)	1.42 ± 0.02	1.43 ± 0.02	1.44 ± 0.02	1.43 ± 0.03	1.38 ± 0.02	0.270
Triglycerides (mmol/l)	1.17 ± 0.05	1.29 ± 0.10	1.36 ± 0.04	1.44 ± 0.04	1.90 ± 0.07	<0.001
BMI (kg/m^2)	25.3 ± 0.3	25.7 ± 0.3	26.1 ± 0.2	26.6 ± 0.3	28.0 ± 0.3	<0.001
Alcohol use (drinks/month)	4.4 ± 0.4	5.8 ± 0.6	5.1 ± 0.4	5.2 ± 0.6	6.0 ± 0.8	0.224
Serum C-reactive protein (mg/dl) (geometric mean)	0.27 ± 0.01	0.29 ± 0.01	0.31 ± 0.01	0.33 ± 0.01	0.37 ± 0.01	<0.001
Glucose (mmol/l)	5.09 ± 0.04	5.11 ± 0.04	5.18 ± 0.04	5.38 ± 0.05	6.04 ± 0.10	<0.001
Glycosylated hemoglobin (%)	5.1 ± <0.1	5.1 ± <0.1	5.2 ± <0.1	5.3 ± <0.1	5.7 ± 0.1	<0.001
Insulin (pmol/l)	55.2 ± 2.0	54.9 ± 1.9	57.0 ± 1.9	60.0 ± 2.4	75.9 ± 2.5	<0.001
Transferrin saturation (%)	19.7 ± 0.5	25.7 ± 0.6	27.6 ± 0.6	28.4 ± 0.6	29.0 ± 0.5	<0.001

Data are means ± SEM. *Maximum sample size (because of missing data, sample sizes vary); †trends for white versus nonwhite.

For newly diagnosed diabetes, the interaction term for sex and ferritin concentration was not significant ($P = 0.309$). The interaction term for ethnicity and ferritin was significant ($P = 0.005$) but was limited to women ($P = 0.008$) and not men ($P = 0.514$). The odds ratios were 4.29 (2.86–9.81) for European-American women, 2.73 (1.00–7.47) for African-American women, and 4.11 (1.87–9.03) for Mexican-American women.

To explore whether the associations between ferritin concentration and newly diagnosed diabetes were similar across levels of transferrin saturation, we created a new four-category variable by dichotomizing transferrin saturation as <45% and ≥45%: *1*) transferrin saturation <45%, ferritin concentration <300 μg/l for men and <150 μg/l for women (reference category); *2*) transferrin saturation <45%, ferritin concentration ≥300 μg/l for men and ≥150 μg/l for women; *3*) transferrin saturation ≥45%, ferritin concentration <300 μg/l for men and <150 μg/l for women; and *4*) transferrin saturation ≥45%, ferritin concentration ≥300 μg/l

Table 5—*Linear regressions of fasting concentrations of plasma insulin, glycosylated hemoglobin, and plasma glucose on log-transformed serum ferritin concentration among participants aged ≥20 years (NHANES III)*

Independent variables	Rank correlation coefficient	Unadjusted ln(ferritin)	R^2	*P*	Adjusted ln(ferritin)*	R^2	*P*
Men†							
Insulin (pmol/l)	0.13	0.0025 ± 0.0004	0.022	<0.001	0.0016 ± 0.0005	0.052	0.001
Glycosylated hemoglobin (%)	0.01	0.0790 ± 0.0202	0.007	<0.001	0.0483 ± 0.0234	0.048	0.044
Glucose (mmol/l)	0.11	0.0796 ± 0.0113	0.020	<0.001	0.0683 ± 0.0137	0.059	<0.001
Women‡							
Insulin (pmol/l)	0.19	0.0039 ± 0.0005	0.026	<0.001	0.0028 ± 0.0005	0.176	<0.001
Glycosylated hemoglobin (%)	0.25	0.2373 ± 0.0248	0.041	<0.001	0.0791 ± 0.0298	0.173	0.011
Glucose (mmol/l)	0.30	0.1524 ± 0.0164	0.046	<0.001	0.0767 ± 0.0155	0.177	<0.001

Data are means ± SEM. *Adjusted for age, race, education, BMI, alcohol intake, C-reactive protein concentration, and examination session attended; †sample sizes for serum insulin concentration were 4,531 and 4,424 for univariate and multivariate analyses, respectively; sample sizes for serum glycosylated hemoglobin concentration were 4,550 and 4,441 for univariate and multivariate analyses, respectively; sample sizes for serum glucose concentration were 4,566 and 4,457 for univariate and multivariate analyses, respectively; ‡sample sizes for serum insulin concentration were 4,898 and 4,796 for univariate and multivariate analyses, respectively; sample sizes for serum glycosylated hemoglobin concentration were 4,901 and 4,799 for univariate and multivariate analyses, respectively; sample sizes for serum glucose concentration were 4,920 and 4,817 for univariate and multivariate analyses, respectively. ln(ferritin), log transformation of ferritin concentration.

for men and ≥150 μg/l for women. Of 309 participants with newly diagnosed diabetes, 16 (14 men and 2 women) had a transferrin saturation ≥45%. A total of 57 participants with newly diagnosed diabetes had a transferrin saturation <45% with a ferritin concentration ≥300 μg/l. The odds ratios for the four categories were 1.00, 4.22 (2.97–5.99), 0.30 (0.09–1.02), and 1.79 (0.60–5.33), respectively.

Ferritin concentration was positively and significantly related to concentrations of insulin, glycosylated hemoglobin, and glucose among all participants (Table 5). For men, the largest correlation coefficient was for insulin. For women, the largest correlation coefficient was for glucose concentration. The magnitudes of all correlation and regression coefficients were larger for women than for men.

CONCLUSIONS — In the largest study to examine the association between ferritin concentration and diabetes to date, we found that serum ferritin concentration was strongly associated with newly diagnosed diabetes. The association was similar for men and women. Because these results are based on cross-sectional data, any causal inference is speculative. These results support similar findings from other recent studies (4,5,10). In some studies, high ferritin concentrations were found in 6–33% of patients with type 2 diabetes, which suggests that ferritin concentration may be abnormally high among individuals with diabetes (11–13). Several studies have produced mixed findings about differences in ferritin concentration between diabetic patients and control subjects (14–17). One study suggested that treating diabetic patients with desferoxamine lowered ferritin concentrations and improved the management of diabetes (18), but these findings were not confirmed in subsequent studies (12,13).

At least three possible explanations may account for the elevated ferritin concentrations in participants with diabetes. First, elevated ferritin concentrations may represent elevated iron body stores. Second, ferritin is also an acute-phase reactant, and elevated ferritin concentrations may reflect inflammation. Third, delayed clearance of glycosylated ferritin in participants with diabetes may have led to elevated ferritin concentrations (19). The finding that the increased risk of diabetes was concentrated among participants with the lowest transferrin saturation concentrations indicates that the iron overload hypothesis does not likely explain this association and instead may implicate inflammation as a more plausible mechanism. Although we tried to correct for possible inflammation by including C-reactive protein (another acute-phase reactant) in the model, we may not have adjusted fully for inflammation.

The mechanisms through which iron may promote the development of diabetes are unknown. Although the evidence supporting a role for oxidation in the pathogenesis of diabetes is not well developed, some data suggest that free radical formation may play a role by disrupting insulin action and total body glucose disposal (20,21). The facts that iron is a powerful pro-oxidant (22) and that oxidative stress is increased in glucose-intolerant states (23–30) suggest possible mechanisms for iron's action.

This study has several limitations. First, this was a cross-sectional study, and therefore the directionality of associations cannot be clearly established. Second, although ferritin is considered a good measure of body iron stores, it is not a "gold standard." Ferritin is also an acute-phase reactant and may reflect inflammatory activity.

Mean serum ferritin concentration was highest in individuals with newly diagnosed diabetes, although it was not significantly different from concentrations in individuals with previously diagnosed diabetes. Because ferritin concentration reflects the sum of body iron stores and the production of acute-phase reactants, changes in either can alter ferritin concentration. Thus, the lower mean ferritin concentration in individuals with previously diagnosed diabetes may be due to changes in body iron stores or may be due to changes in factors that affect the production of acute-phase reactants. Our data suggest that smoking cessation and weight are associated with lower ferritin concentrations. Thus, changes in these lifestyle factors occurring after the disease is diagnosed may result in decreases in ferritin concentration. If some of the hyperferritinemia among newly diagnosed individuals with diabetes is in part transient, this could have implications for the optimal timing of hemochromatosis screening in individuals with diabetes. Additional study of these possibilities is clearly necessary.

In conclusion, serum ferritin concentration was significantly associated with newly diagnosed diabetes in NHANES III, and the association was stronger in men than in women. The interpretation of these findings is complicated by the finding that all of the increased risk was concentrated in participants with the lowest transferrin saturations, which thus casts doubt on excess iron as an explanation for this association.

References

1. Franks AL, Marks JS: Introduction to supplement on iron overload, public health, and genetics. *Ann Intern Med* 129:923–924, 1998
2. Powell LW, George DK, McDonnell SM, Kowdley KV: Diagnosis of hemochromatosis. *Ann Intern Med* 129:925–931, 1998
3. Redmon JB, Robertson RP: Iron and diabetes: an attractive hypothesis, but.... *Mayo Clin Proc* 69:90–92, 1994
4. Tuomainen TP, Nyyssonen K, Salonen R, Tervahauta A, Korpela H, Lakka T, Kaplan GA, Salonen JT: Body iron stores are associated with serum insulin and blood glucose concentrations: population study in 1,013 eastern Finnish men. *Diabetes Care* 20:426–428, 1997
5. Salonen JT, Tuomainen TP, Nyyssonen K, Lakka HM, Punnonen K: Relation between iron stores and non-insulin dependent diabetes in men: case-control study. *BMJ* 317: 727, 1998
6. Centers for Disease Control and Prevention: *Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–94*. Bethesda, MD, National Center for Health Statistics, 1994 (Vital Health Stat. 1, no. 32)
7. Centers for Disease Control and Prevention: *The Third National Health and Nutrition Examination Survey (NHANES III 1988–94) Reference Manuals and Reports* (CD-ROM). Bethesda, MD, National Center for Health Statistics, 1996
8. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
9. Shah BV, Barnwell BG, Bieler GS: *SUDAAN User's Manual. Version 7.5.* Research Triangle Park, NC, Research Triangle Inst., 1997
10. Hughes K, Choo M, Kuperan P, Ong CN, Aw TC: Cardiovascular risk factors in non-insulin-dependent diabetics compared to non-diabetic controls: a population-based survey among Asians in Singapore. *Atherosclerosis* 136:25–31, 1998
11. O'Brien T, Barrett B, Murray DM, Dinneen S, O'Sullivan DJ: Usefulness of biochemical screening of diabetic patients for hemochromatosis. *Diabetes Care* 13:532–534, 1990
12. Kaye TB, Guay AT, Simonson DC: Non-insulin-dependent diabetes mellitus and

elevated serum ferritin level. *J Diabetes Complications* 7:246–249, 1993
13. Redmon JB, Pyzdrowski KL, Robertson RP: No effect of deferoxamine therapy on glucose homeostasis and insulin secretion in individuals with NIDDM and elevated serum ferritin. *Diabetes* 42:544–549, 1993
14. Touitou Y, Proust J, Carayon A, Klinger E, Nakache JP, Huard D, Sachet A: Plasma ferritin in old age: influence of biological and pathological factors in a large elderly population. *Clin Chim Acta* 149:37–45, 1985
15. Woo J, Mak YT, Law LK, Swaminathan R: Plasma ferritin in an elderly population living in the community. *J Med* 20:123–134, 1989
16. Dinneen SF, O'Mahony MS, O'Brien T, Cronin CC, Murray DM, O'Sullivan DJ: Serum ferritin in newly diagnosed and poorly controlled diabetes mellitus. *Ir J Med Sci* 161:636–638, 1992
17. Dinneen SF, Silverberg JD, Batts KP, O'Brien PC, Ballard DJ, Rizza RA: Liver iron stores in patients with non-insulin-dependent diabetes mellitus. *Mayo Clin Proc* 69:13–15, 1994
18. Cutler P: Deferoxamine therapy in high-ferritin diabetes. *Diabetes* 38:1207–1210, 1989
19. Van Oost BA, Van den Beld B, Cloin LGLM, Marx JJM: Measurement of ferritin in serum: application in diagnostic use. *Clin Biochem* 17:263–269, 1984
20. Paolisso G, D'Amore A, Di Maro G, Galzerano D, Tesauro P, Varricchio M, D'Onofrio F: Evidence for a relationship between free radicals and insulin action in the elderly. *Metabolism* 42:659–663, 1993
21. Paolisso G, D'Amore A, Gugliano D, Ceriello A, Varrichio M, D'Onofrio F: Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients. *Am J Clin Nutr* 57:650–656, 1993
22. Papas AM: Diet and antioxidant status. In *Antioxidant Status, Diet, Nutrition, and Health*. Papas AM, Ed. Boca Raton, FL, CRC, 1999, p. 21–36
23. Kitahara M, Eyre HJ, Lynch RE, Rallison ML, Hill HR: Metabolic activity of diabetics' monocytes. *Diabetes* 29:251–256, 1980
24. Oberly LW: Free radicals and diabetes. *Free Radic Biol Med* 5:113–124, 1988
25. Baynes JW: Role of oxidative stress in development of complications in diabetes. *Diabetes* 40:405–412, 1991
26. Gillery P, Monboissa JC, Mauquart FX, Borel JP: Does oxygen free radical increased formation explain long term complications of diabetes mellitus? *Med Hypotheses* 29:47–50, 1989
27. Armstrong D, Al-Awadi F: Lipid peroxidation and retinopathy in streptozocin induced diabetes. *Free Radical Biol Med* 11:433–436, 1991
28. Gopaul NK, Anggard EE, Mallet AI, Betteridge DJ, Wolff SP, Nourooz-Zadeh J: Plasma 8-epi-PGF2 alpha levels are elevated in individuals with non-insulin dependent diabetes mellitus. *FEBS Lett* 368:225–229, 1995
29. Dandona P, Thusu K, Cook S, Snyder B, Makowski J, Armstrong D, Nicotera T: Oxidative damage to DNA in diabetes mellitus. *Lancet* 347:444–445, 1996
30. Giugliano D, Ceriello A, Paolisso G: Oxidative stress and diabetic vascular complications. *Diabetes Care* 19:257–267, 1996