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Association Between High Serum Ferritin Levels and Carotid Atherosclerosis in the Study of Health in Pomerania (SHIP)

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Background and Purpose—Several studies have provided evidence for a relationship between body iron load and cardiovascular disease. We analyzed the association of serum ferritin levels with carotid atherosclerosis.

Methods—We assessed intima-media thickness and plaque prevalence in the carotid arteries by high-resolution ultrasound among 2443 participants (1200 women; age, 45 to 79 years) in the Study of Health in Pomerania (SHIP), a population-based study in northeast Germany.

Results—In multivariate analysis, serum ferritin levels were not independently associated with carotid intima-media thickness among women or men. In contrast, the relationship between serum ferritin levels and carotid plaque prevalence was significant among men (odds ratio per 1-SD increase of serum ferritin levels, 1.33; 95% confidence interval, 1.08 to 1.44) yet not among women (odds ratio, 1.29; 95% confidence interval, 0.98 to 1.75). However, both men and women showed a dose-response relation between serum ferritin levels and carotid atherosclerosis in which higher serum ferritin levels were associated with greater odds ratios for carotid plaque prevalence. Additionally, there was an interaction of serum ferritin levels with low-density lipoprotein (LDL) cholesterol ($P=0.039$) among men in which the association of serum ferritin levels with carotid plaque prevalence became stronger with increasing LDL cholesterol levels.

Conclusions—Our study identified a relationship between serum ferritin levels and carotid atherosclerosis that was potentiated by LDL cholesterol. This relationship adds support to the hypothesis of a link between iron and cardiovascular disease. (*Stroke*. 2004;35:453-457.)

Key Words: atherosclerosis ■ epidemiology ■ ferritin ■ iron ■ ultrasonography

A putative role of iron as a contributor to the development of atherosclerosis has been discussed and is assumed to account in part for the sex differences seen in cardiovascular disease.¹ The proatherogenic properties of iron are supposed to rely on its ability to generate reactive oxygen species, to oxidize lipoproteins,^{2,3} and to activate platelets.⁴ This hypothesis is in agreement with several epidemiological studies that observed an association between measures of body iron stores and myocardial infarction,^{5,6} as well as with progression of carotid atherosclerosis.⁷ Further support comes from animal studies in which increased body iron load was related to enhanced progression of atherosclerosis^{8,9} and from clinical investigations that observed a relationship between iron and endothelial dysfunction in humans.^{10,11}

However, although seemingly well substantiated and biochemically appealing, the association of iron with cardiovascular disease is currently under debate and subject to ongoing controversy. A number of epidemiological studies either produced

equivocal results¹² or found no association of different markers of body iron load with surrogate measures of atherosclerosis¹³ or coronary risk.¹⁴ Similarly, a study in a large number of blood-donating health professionals¹⁵ and a meta-analysis that reviewed 12 prospective studies¹⁶ both failed to provide convincing evidence for such a relationship. Additionally, 1 animal study even reported atheroprotective effects of iron, describing diminished atherosclerosis in iron-overloaded apolipoprotein E-deficient mice.¹⁷ We consequently undertook to further investigate the hypothesis of a link between iron and cardiovascular disease by analyzing the association of serum ferritin levels as a measure of body iron stores with carotid intima-media thickness (IMT) and plaque prevalence among participants of the Study of Health in Pomerania (SHIP), an epidemiological survey in northeast Germany.

Methods

SHIP is a cross-sectional survey in West Pomerania in northeast Germany. The design of the study has been described previously.¹⁸

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The study was approved by the ethics committee of the University of Greifswald, and all participants gave informed written consent. A random sample from the population 20 to 79 years of age was drawn, and 4310 subjects participated (68.8% of eligible subjects). Ultrasound measurements were performed in subjects ≥ 45 years of age. Study participants with known malignancies ($n=42$) and a history of chronic liver disease ($n=28$) were excluded. This resulted in a final sample of 2443 participants (1200 women, 1243 men) for analysis. Sociodemographic characteristics and medical histories were assessed by computer-aided interviews. Hypertension was defined as a systolic blood pressure (BP) of ≥ 140 mm Hg, a diastolic BP of ≥ 90 mm Hg, or self-reported use of antihypertensive medication. As for smoking status, study participants were classified as nonsmokers or current smokers. Alcohol consumption was quantified in grams per day. Diabetes was defined as self-reported physician diagnosis of diabetes or serum HbA_{1c} of $>7.0\%$. Information concerning menopause was obtained from the interview. Height and weight were measured for calculation of body mass index [BMI=weight (kg)/height² (m²)]. Nonfasting blood samples were taken and analyzed in a central laboratory. Serum ferritin levels were determined by an immunoturbidimetric assay (Cobas Micra Plus, F. Hoffmann-La Roche Ltd). Serum low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were precipitated and measured photometrically (Boehringer). HbA_{1c} was determined by high-performance liquid chromatography (Bio-Rad Diamat).

Ultrasound Measurements

The ultrasound protocol has been described previously.¹⁹ In brief, certified medical assistants examined the extracranial carotid arteries bilaterally with B-mode ultrasound using a 5-MHz linear-array transducer and a high-resolution instrument (Diasonics VST Gateway). Both the near and far walls of the common carotid, the internal carotid, and the carotid bifurcations on both sides were evaluated online for the presence of atherosclerotic plaques. Each vessel segment was visualized in multiple longitudinal and transversal planes. Atherosclerotic plaques (yes/no) were defined by the following criteria: (1) focal widening relative to adjacent segments (as evidenced by protrusion into the lumen and/or localized roughness with increased echogenicity) and (2) an area of focal increased thickness (≥ 1.3 mm) of the intima-media layer. Plaque prevalence was defined as the presence of ≥ 1 plaques. For measurement of IMT, scans through the axis of the distal straight portion (1 cm in length) of both common carotid arteries were digitized and recorded for subsequent offline analysis. Certified readers calculated the mean far-wall IMT by averaging the 10 consecutive measurement points (in 1-mm steps) from both sides. IMT was defined as the distance between the characteristic echoes from the lumen-intima and media-adventitia interfaces. Reproducibility studies for IMT measurements have been performed between paired measurements of sonographers and readers. All measurements of intrareader, intrasonographer, interreader, and intersonographer variations revealed coefficients of variation of $<2.6\%$, Spearman correlation coefficients of >0.90 , and differences in mean IMT (2 SD) of $<1.0\%$ ($<10.0\%$).

Statistical Analysis

Continuous variables were compared between groups by Student's *t* test; categorical variables, by χ^2 test. The relationship between serum ferritin levels and IMT was analyzed in several multivariate models with IMT as the dependent variable and serum ferritin levels as the independent variable. In a first step, IMT and serum ferritin levels were both entered as continuous variables into a multiple linear regression model. In a second step, IMT values in increasing sex-specific ferritin quartiles were compared by general linear model analysis of variance. Odds ratios (ORs) and 95% confidence intervals (CIs) for plaque prevalence were estimated in several binary logistic regression models into which, in a first step, serum ferritin levels were entered as a continuous variable. In further steps, ORs were compared between quartile and octile groups of serum ferritin levels. Adjustments were made for age, systolic BP, diabetes, smoking status, BMI, alcohol consumption, and LDL cholesterol. Furthermore, the interaction between serum ferritin and LDL cho-

TABLE 1. Clinical Characteristics of Study Subjects

	Women (n=1200)	Men (n=1243)
Age, y	61 \pm 10	62 \pm 9
Systolic BP, mm Hg	140 \pm 21	149 \pm 20‡
Diastolic BP, mm Hg	84 \pm 10	88 \pm 12‡
Hypertension, %	49.8	68.5‡
Current smoking, %	25.9	31.9‡
Alcohol intake, g/d	8.9 \pm 12.9	31.2 \pm 32.1‡
Diabetes, %	12.8	14.9
HbA _{1c} , %	5.7 \pm 1.0	5.8 \pm 0.9
BMI, kg/m ²	28.3 \pm 5.4	28.4 \pm 4.1
LDL cholesterol, mmol/L	3.9 \pm 1.1	3.7 \pm 1.2‡
HDL cholesterol, mmol/L	1.6 \pm 0.5	1.3 \pm 0.4‡
Ferritin, μ g/L		
Premenopausal	50.9 \pm 43.9	160 \pm 162‡
Postmenopausal	89.7 \pm 90.8	
Premenopausal, %	19.7	...
IMT (age-adjusted), mm	0.76 \pm 0.01	0.83 \pm 0.01‡
Carotid plaque, %	63.5	75.7‡

Continuous variables are mean \pm SD. Probability values are for comparison between sexes.

* $P<0.05$; † $P<0.01$; ‡ $P<0.001$.

lesterol was tested by a sequence of backward and forward stepwise regression analyses. The decision to maintain the interaction was made by use of the likelihood ratio. The model fit was measured by the adjusted R^2 . A value of $P<0.05$ was considered statistically significant. Analyses were performed with SPSS software version 11.0 (SPSS Inc).

Results

Clinical Characteristics

The clinical characteristics of all study participants included in this analysis are outlined in Table 1. Compared with women, men had higher BP values and, accordingly, a higher proportion of hypertensives. Moreover, they were more likely to be smokers, consumed more alcohol, and had lower LDL and HDL cholesterol levels.

Serum Ferritin Levels and IMT

In multiple linear regression models, there was no independent association between serum ferritin levels and IMT among women or men or in the whole study population. Similarly, if the study population was separated into sex-specific ferritin quartiles, neither age-adjusted nor fully adjusted IMT values differed between those groups (Table 2). Independent correlates of IMT in our sample were age, sex, systolic BP, diabetes, current smoking, alcohol consumption, and LDL cholesterol.

Serum Ferritin Levels and Prevalence of Atherosclerotic Plaques

Women with and without carotid plaques had serum ferritin levels of 90.8 \pm 104.6 and 67.3 \pm 59.8 μ g/L ($P<0.001$), respectively. Men with and without plaques had serum ferritin levels of 163 \pm 170 and 147 \pm 159 μ g/L ($P=0.317$), respec-

TABLE 2. Adjusted Plaque Prevalence Odds in Women and Men According to Quartiles of Serum Ferritin Levels

	Women				Men			
	Quartiles of Serum Ferritin Levels, $\mu\text{g/L}$							
	1 <38	2 38–65	3 66–101	4 >102	1 <69	2 69–118	3 119–189	4 >189
IMT (age-adjusted), mm	0.75	0.74	0.76	0.77	0.84	0.85	0.82	0.83
IMT (multivariate), mm	0.75	0.75	0.76	0.76	0.84	0.84	0.82	0.83
OR for plaques (age-adjusted)	1.00	0.71	1.02	1.14	1.00	1.22	1.08	1.21
95% CI	...	0.47–1.06	0.84–1.24	1.00–1.31*	...	0.82–1.81	0.89–1.32	1.05–1.38†
OR for Plaques (multivariate)	1.00	0.68	1.00	1.09	1.00	1.27	1.09	1.20
95% CI	...	0.45–1.04	0.82–1.22	0.95–1.25	...	0.82–1.97	0.89–1.35	1.04–1.39*

OR's and 95% CI's are derived from binary logistic regression models for comparison with the first quartile. Multivariate adjustments are made for age, systolic BP, smoking status, alcohol consumption, diabetes, BMI, and LDL cholesterol.

* $P < 0.05$; † $P < 0.01$.

tively. In a first step, the relationship between plaque prevalence and serum ferritin levels as a continuous variable was assessed. As shown in Table 3, serum ferritin levels were significantly associated with plaque prevalence among men, whereas this association failed to attain significance ($P=0.120$) among women. In a second step, ORs for plaque prevalence in ferritin quartiles were examined. Table 2 shows that men in the fourth quartile had increased ORs for plaque prevalence compared with those in the first quartile. No such pattern was observed among women. In a third step, we examined whether the link between iron and carotid atherosclerosis becomes more apparent with higher serum ferritin levels. For this purpose, the study sample was further divided into sex-specific ferritin octiles. Figure 1 indicates the presence of a dose-response relation between serum ferritin levels and carotid plaque prevalence in which ORs for carotid plaque prevalence became greater with increasing serum

ferritin levels. This association was similar for women and men. The results for the female subsample were altered only minimally if the analysis was restricted to postmenopausal women (data not shown). Further independent correlates of plaque prevalence in our sample are shown in Table 3.

Because iron has been shown to promote the formation of oxidized LDL cholesterol in vitro,^{2,3} we tested for interactions between LDL cholesterol and serum ferritin levels in our sample. No such pattern was observed among women. Among men, however, a significant interaction between LDL cholesterol and serum ferritin levels ($P=0.039$) was found in which the magnitude of the relationship between serum ferritin levels and carotid plaques became greater with increasing LDL cholesterol levels (Figure 2).

TABLE 3. Association of Carotid Plaques With Selected Cardiovascular Risk Factors

	Women		Men	
	OR	95% CI	OR	95% CI
Ferritin, per 1-SD increase	1.29	0.98–1.75	1.33	1.08–1.44†
Age, per 1-SD increase	1.88	1.71–2.04‡	1.85	1.65–1.99‡
Systolic BP, per 1-SD increase	1.19	1.08–1.35†	1.28	1.11–1.49‡
Diabetes, y/n	1.47	1.05–2.59*	2.04	1.27–3.55†
BMI, per 1-SD increase	1.37	1.20–1.58‡	1.07	0.98–1.22
Current smoking, y/n	1.17	1.02–1.66*	1.40	1.15–2.75†
LDL, per 1-SD increase	1.09	0.96–1.34	1.08	0.96–1.23
Alcohol, per 1-SD increase	0.92	0.81–1.19	1.09	0.79–1.45

OR's and 95% CI's are derived from binary logistic regression models that included all of the following: age, systolic BP, diabetes, BMI, smoking status, alcohol consumption, LDL cholesterol, and serum ferritin levels.

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

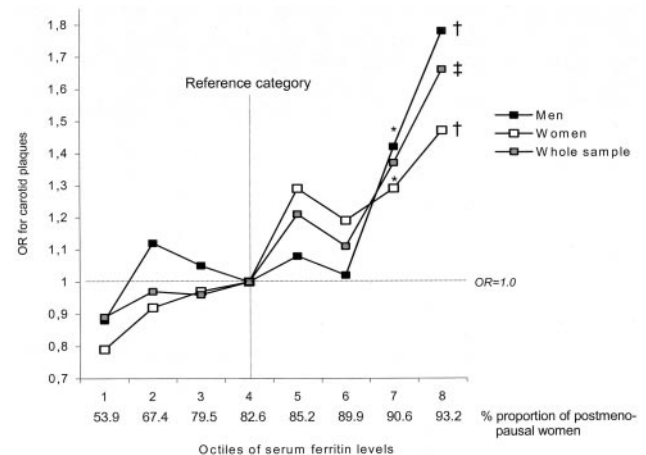


Figure 1. Association between serum ferritin levels and multivariate OR for carotid plaques according to octile groups of serum ferritin levels. Fourth octile group represents average serum ferritin levels and served as reference group. For each octile group, percentage proportion of postmenopausal women is given. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

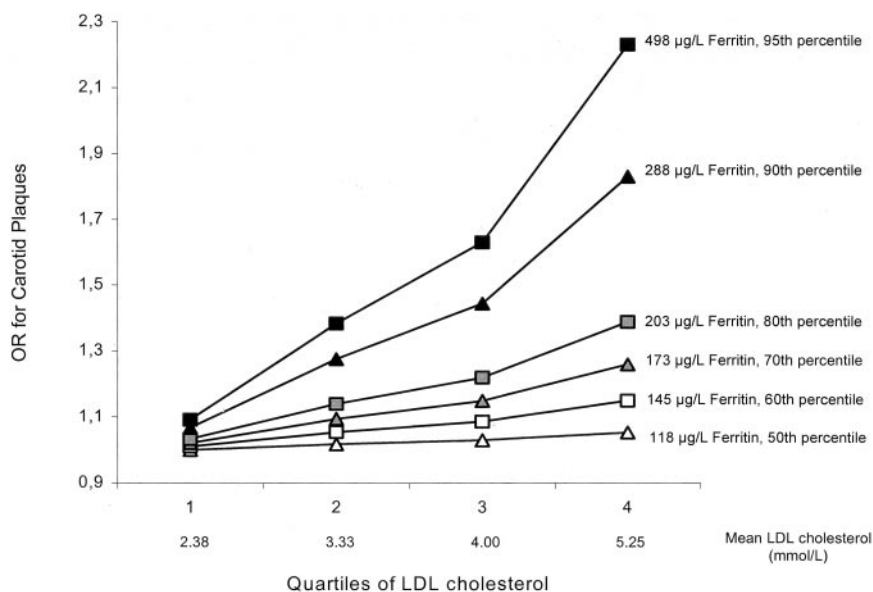


Figure 2. Synergistic relationship of serum ferritin levels with LDL cholesterol as to association with carotid plaques among men. Graphs demonstrate OR for plaque prevalence across increasing quartiles of LDL cholesterol for serum ferritin levels ranging from 118 (50th percentile) to 498 (95th percentile) $\mu\text{g/L}$.

Discussion

In this study, we investigated the relationship between serum ferritin levels and carotid atherosclerosis in a general population sample that represents both sexes and a broad age range. Men and, although less pronounced, women with higher serum ferritin levels showed increased OR for carotid plaque prevalence. Among men, this association was potentiated by an interaction between serum ferritin levels and LDL cholesterol. These 2 parameters showed a synergistic relationship in which the magnitude of the association between serum ferritin levels and carotid atherosclerosis became greater with higher LDL cholesterol levels. Among women, increasing serum ferritin levels and, hence, increasing ORs for plaque prevalence were paralleled by a rise in the proportion of postmenopausal women. This is in agreement with the hypothesis that iron depletion through menstrual bleeding might act atheroprotectively among women. This hypothesis gained support from the Bruneck study⁷ in which women with the greatest degree of postmenopausal iron accumulation demonstrated the highest incidence of carotid atherosclerosis.

Because the relationship between carotid atherosclerosis and coronary heart disease^{20,21} and stroke²² is clearly established, our results are consistent with findings from previous studies. In the Kuopio study, serum ferritin levels were found to be one of the strongest risk factors for acute myocardial infarction among Finnish men.⁵ Similar findings were reported from a Canadian study that observed an increased risk of myocardial infarction among subjects in the highest serum iron category²³ and from the Bruneck study⁷ in which serum ferritin levels were closely related to incident carotid atherosclerosis and the progression of preexisting atherosclerotic lesions.

In contrast, a prospective investigation by Ascherio et al,¹⁵ which enrolled >38 000 blood-donating health professionals, produced no evidence for a relationship between the frequency of blood donations, serum ferritin levels, and risk of myocardial infarction. However, blood donors mostly have low to normal body iron stores, and although this investigation observed no beneficial effect of iron lowering, it might have missed an impact of excess iron stores on incident myocardial infarction. In

another study, investigators found no evidence that iron deficiency is related to decreased incidence of myocardial infarction.²⁴ However, findings raised for iron deficiency do not exclude the possibility that high or even excess body iron stores exert some proatherogenic effect.

It remains to be determined how the relationship between iron and carotid atherosclerosis is mediated. However, we observed a synergistic interaction between serum ferritin levels and LDL cholesterol as to their relationship with carotid atherosclerosis. It is therefore reasonable to speculate that some interference of iron with lipid metabolism might be involved. Similar interactions have been described in the Kuopio study⁵ and the Bruneck study,⁷ and the capability of iron to contribute to the generation of free oxygen radicals and to LDL oxidation as observed in several in vitro experiments^{2,3} lends biological plausibility to such an interaction.

In our study, we established no association of serum ferritin levels with carotid IMT. However, although plaque formation and intima-media thickening are essential components of atherogenesis, they are pathologically distinct processes that act independently of each other.²⁵ Although intima-media thickening is predominated by smooth muscle cell proliferation and lipid deposition, plaque formation and growth rely more on factors that promote platelet aggregation, hypercoagulability, and attenuated fibrinolysis.²⁶ One might thus speculate that iron is more involved in the progression of preexisting wall thickening, eg, the development from fatty streaks to manifest atherosclerotic lesions. An association of serum ferritin levels with intima-media thickening was also not observed in the Atherosclerosis Risk in Communities study.¹³ However, a relationship with plaque prevalence was not assessed in this study. Another investigation that reported an association of serum ferritin levels with carotid plaque prevalence, albeit only among women, is the Perth Carotid Ultrasound Disease Study.²⁷ However, the same investigation did not show a correlation of serum ferritin levels with carotid IMT. Only 1 recent study disclosed a relationship between serum ferritin levels and carotid IMT

yet enrolled only a small sample of subjects with end-stage renal disease.²⁸ This condition may have substantially contributed to the positive finding and therefore does not allow extrapolation of these results to the general population.

Several limitations of the present study merit discussion. The present data are derived from a cross-sectional study that did not allow us to assess the time course of the relationship between serum ferritin levels and carotid atherosclerosis. Serum ferritin levels can vary over time, which may be of significance for the female subsample of our study, which included both premenopausal and postmenopausal women.

The prevalence of carotid plaques in our sample was comparatively high. However, our definition of atherosclerotic plaques constitutes an a priori definition and was not guided by the distribution of the data. Moreover, the pattern of independent risk factors for plaque prevalence strongly resembles the one that is usually found for other atherosclerotic end points. This argues in favor of our plaque prevalence as a valid marker for general atherosclerosis.

The relationship between serum ferritin levels and carotid atherosclerosis might have been confounded by inflammation and mild liver disease, especially among subjects with metabolic syndrome and diabetes, conditions that are strong correlates of atherosclerosis. Although we excluded subjects with malignancies and manifest liver disease, residual confounding by such factors cannot be ruled out.

Finally, for practical reasons, we could analyze only nonfasting blood-samples. The mostly elderly study participants were nonfasting because of the long travel times in the large rural area from which the sample was recruited and because of the duration of the cumulative examinations (4 to 6 hours in total).

In summary, we observed an independent relationship between serum ferritin levels and carotid atherosclerosis. Among men, this relationship appeared to be strengthened by a synergistic association between ferritin and LDL cholesterol that could suggest a proatherogenic interference of iron with lipid metabolism. Our findings are in agreement with previous results and hence supply further support to the hypothesis that iron is linked to cardiovascular disease.

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