

High Stored Iron Levels Are Associated With Excess Risk of Myocardial Infarction in Eastern Finnish Men

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Background. Iron can induce lipid peroxidation in vitro and in vivo in humans and has promoted ischemic myocardial injury in experimental animals. We tested the hypothesis that high serum ferritin concentration and high dietary iron intake are associated with an excess risk of acute myocardial infarction.

Methods and Results. Randomly selected men ($n=1,931$), aged 42, 48, 54, or 60 years, who had no symptomatic coronary heart disease at entry, were examined in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) in Eastern Finland between 1984 and 1989. Fifty-one of these men experienced an acute myocardial infarction during an average follow-up of 3 years. On the basis of a Cox proportional hazards model adjusting for age, examination year, cigarette pack-years, ischemic ECG in exercise test, maximal oxygen uptake, systolic blood pressure, blood glucose, serum copper, blood leukocyte count, and serum high density lipoprotein cholesterol, apolipoprotein B, and triglyceride concentrations, men with serum ferritin ≥ 200 $\mu\text{g/l}$ had a 2.2-fold (95% CI, 1.2–4.0; $p<0.01$) risk factor-adjusted risk of acute myocardial infarction compared with men with a lower serum ferritin. An elevated serum ferritin was a strong risk factor for acute myocardial infarction in all multivariate models. This association was stronger in men with serum low density lipoprotein cholesterol concentration of 5.0 mmol/l (193 mg/dl) or more than in others. Also, dietary iron intake had a significant association with the disease risk in a Cox model with the same covariates.

Conclusions. Our data suggest that a high stored iron level, as assessed by elevated serum ferritin concentration, is a risk factor for coronary heart disease. (*Circulation* 1992;86:803–811)

KEY WORDS • ferritin • hemoglobin • iron • coronary heart disease • myocardial infarction • population studies

Oxygen free radicals promote the oxidation of lipids, which has been postulated to be involved in the development of atherosclerosis.¹ This is supported by the observed association between the titer of autoantibodies against oxidatively modified low density lipoprotein (LDL) and the progression of carotid atherosclerosis in men.² Free iron catalyzes free radical production, which generates a range of potent oxidants that can induce oxidation of lipids.^{3–6} Thus, free iron might increase the risk of coronary heart disease (CHD) by promoting the oxidation of lipids and possibly of catecholamines. Free radical formation and lipid peroxidation can be prevented by the iron-chelating agent desferrioxamine.^{4–6} Iron chelators have also prevented or limited experimental myocardial ischemia

or improved recovery after reperfusion injury in isolated rat hearts and other animal models.^{3–8}

We have observed an association between high serum concentrations of copper, another potential promotor of lipid oxidation, and accelerated atherosclerosis and excess risk of acute myocardial infarction (AMI).^{9,10} We have also found accelerated atherogenesis and an increased risk of coronary and cardiovascular death in men with a low status of selenium, a cofactor of the free radical-scavenging glutathione peroxidase enzymes.^{9,11} It has been hypothesized that iron overload is a major

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cause of the higher occurrence of CHD in men than in women.^{7,12} There are, however, no previous reports concerning the relation of iron status to the risk of CHD in humans. We tested the hypothesis, formulated on the basis of chemical plausibility, that excess body iron, as estimated by serum ferritin concentration, is associated with an increased risk of AMI in middle-aged men. We also studied the association of dietary iron intake with the risk of AMI.

Methods

Subjects

The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) is a population study to investigate

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previously unestablished risk factors for AMI and carotid atherosclerosis¹³ in Eastern Finnish men, the population with the highest recorded incidence of and mortality from CHD.¹⁴ This study presents the first prospective analysis based on all participants in the KIH baseline examinations. These were carried out between March 1984 and December 1989. The study sample included 3,235 Eastern Finnish men aged 42, 48, 54, or 60 years at the baseline examination. Of these, 2,682 (82.9%) participated. Men with prevalent CHD ($n=677$) were excluded from the present analyses. Prevalent ischemic heart disease was defined as either a history of myocardial infarction or angina pectoris, positive angina pectoris on effort in the London School of Hygiene interview,¹⁵ or the use of nitroglycerin tablets once a week or more frequently. Of the remaining 2,005 men, data on both serum ferritin and blood hemoglobin concentrations were available for 1,931 men. Data on serum LDL cholesterol, serum high density lipoprotein (HDL) cholesterol, and maximal oxygen uptake were missing for 17, seven, and 191 men, respectively. For these men, the mean value of the variable in question was used; when the variable was dichotomized, they were placed in the category indicating low risk.

Laboratory Methods

The examination protocol and measurements have been described in detail earlier.^{13,16,17} Subjects gave blood specimens between 8:00 and 10:00 AM on Tuesday, Wednesday, or Thursday after having abstained from ingesting alcohol for 3 days, smoking for 12 hours, and eating for 12 hours. After the subject had rested in the supine position for 30 minutes, blood was drawn with Terumo Venoject VT-100PZ vacuum (Terumo Corp., Tokyo). No tourniquet was used.

Serum specimen for ferritin assays were kept frozen at -20°C for 1–5 years. Ferritin concentrations were measured with a radioimmunoassay (Amersham International, Amersham, UK) using a Multigamma model 1261 gamma counter (LKB Wallac, Turku, Finland). The method is based on a double antibody technique. The between-batch variation in serum ferritin was determined at three levels of Lyphochek control serum (Bio-Rad, Anaheim, Calif.). The between-batch coefficient of variation was 6.4%, 6.0%, and 10.9% for ferritin levels of 52, 172, and 490 $\mu\text{g/l}$, respectively ($n=20$).

Blood hemoglobin was measured photometrically (Gilford Stasar III, Instrument Laboratories Inc.) using the cyanmethemoglobin method¹⁸ within a few hours of blood sampling. The hemoglobin measurement was calibrated against cyanmethemoglobin standard (Finnish Red Cross, Helsinki). The day-to-day variation of hemoglobin measurement was assessed using commercially available control blood (Merz & Dade AG, Duedingen, Switzerland and 4C, Coulter Diagnostics, Hialeah, Fla.). The between-batch coefficient of variation was 1.2% at the hemoglobin level of 138 g/l and 1.7% at 123 g/l ($n=14$). The between-batch coefficient of variation for blood hematocrit was 2.4% for Merz & Dade control, 3.5% for 4C normal control, and 4.0% for 4C abnormal control. Blood cells were counted using the Coulter-Counter cell counter model DN (Coulter Counter Electronics Ltd., Luton, UK).

Plasma ferritin and blood hemoglobin concentrations were redetermined in a subsample of 447 hypercholesterolemic men in samples drawn 1–5 years after the KIH baseline examination. The Pearson's correlation between the baseline and the remeasurement values was 0.67 for ferritin and 0.71 for hemoglobin.

Copper concentrations were determined from frozen serum specimens (-20°C) 1–5 years after the baseline examination.⁹ The Perkin-Elmer (Norwalk, Conn.) 306 Atomic Absorption Spectrometer was used with flame atomization against standards made in 5% glycerol. The Seronorm control serum (Nyegaard, Oslo, Norway) was included in all daily batches. The between-batch coefficient of variation was 4.0% ($n=12$).

The main lipoprotein fractions (very low density lipoprotein [VLDL], LDL, and HDL) were separated from fresh serum samples using ultracentrifugation and precipitation as described earlier in detail.¹⁹ The HDL₂ and HDL₃ subfractions were separated during a second ultracentrifugal spin at 108,000g for 62 hours against a density of 1.125 g/cm³.¹⁹ The cholesterol contents of all lipoprotein fractions were measured enzymatically (CHOD-PAP method, Boehringer Mannheim, Mannheim, FRG) on the day after the last spin. A Seronorm lipid (Nycomed, Oslo, Norway) control serum sample was included in each daily batch of cholesterol determinations. The between-batch coefficient of variation was 2.2% for total, 5.2% for LDL, 9.2% for HDL, and 10.8% for HDL₂ cholesterol ($n=210$). Apolipoprotein B was determined by an immunoturbidimetric method of KONE Oy (Espoo, Finland). The method uses an antiserum prepared by Orion (Espoo, Finland). The between-batch coefficient of variation was 2.7% and 2.8% ($n=117$) for the control serum values of 0.75 g/l and 1.07 g/l, respectively. Blood glucose was measured by glucose dehydrogenase method (Merck, Darmstadt, FRG) after precipitation of proteins by trichloric acetic acid. The between-batch coefficient of variation was 2.4% for Seronorm and 3.6% for Pathonorm control specimens.

Assessment of Dietary Iron Intake

The consumption of foods was assessed at time of blood sampling with an instructed and interview-checked 4-day food recording by household measures.¹⁷ The intake of nutrients, including dietary iron, was estimated using the Nutrica computer program for calculation of nutrient intake. The data bank of Nutrica is compiled using mainly Finnish values for the nutrient composition of foods.²⁰ The food recording was repeated approximately 12 months after the baseline examination in a random subsample of 50 men. The intraclass correlation coefficient between the original and reassessment of iron intake was 0.52 (Pearson's coefficient, 0.51). The use of iron tablets and iron-containing nutritional supplements was assessed by a self-administered questionnaire. Only 37 men reported intake of iron-containing tablets or other prepartes in the previous 7 days.

Other Risk Factor Measurements

The number of cigarettes, cigars, and pipefuls of tobacco currently smoked daily, the duration of regular smoking in years, history of myocardial infarction, angina pectoris and other ischemic heart disease, the

presence of hypertension, and current antihypertensive medication were recorded using a self-administered questionnaire, which was checked by an interviewer. Reinterviews to obtain medical history were conducted by a physician. The family history of CHD was defined as positive if the biological father, mother, sister, or brother of the subject had CHD history. The history of hypertension in siblings was defined as positive if any sisters or brothers were reported to ever have had hypertension.

A subject was defined as a smoker if he had ever smoked on a regular basis and had smoked cigarettes, cigars, or a pipe within the past 30 days. The lifelong exposure to smoking ("cigarette pack-years") was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination. "Years smoked" were defined as the sum of years of smoking regardless of when smoking had started, whether the subject had stopped smoking, or whether it had occurred continuously or during several periods. The consumption of alcohol in the previous 12 months was assessed with the Nordic Alcohol Consumption Inventory, which contains 15 items.²¹

Resting blood pressure was measured between 8:00 and 10:00 AM on the first examination day by one nurse with a random-zero mercury sphygmomanometer. The measuring protocol included, after a supine rest of 5 minutes, three measurements in supine, one in standing, and two in sitting position with 5-minute intervals. The mean of all six systolic pressure values was used in the present analyses as the systolic blood pressure and the mean of all six diastolic measurements as diastolic blood pressure.

The respiratory gas exchange was measured breath-by-breath with an MGC 2001 system (Medical Graphics Corp., Minneapolis, Minn.) during a symptom-limited exercise test. The testing protocol comprised a linear increase of work load by 20 W/min.¹⁶ Highest oxygen uptake (average of 8 seconds) during the test was defined as $\dot{V}O_{2\max}$. Exercise ECGs were coded manually by one cardiologist. The criteria for ischemia were 1) ischemic ECG defined as horizontal or downsloping ST depression ≥ 0.5 mm or upsloping ST depression ≥ 1.0 mm; 2) typical angina pectoris pain leading to discontinuation of exercise; or 3) maximal heart rate during exercise ≤ 130 beats per minute. Diabetes was defined as previous clinical diagnosis of diabetes or fasting blood glucose ≥ 8.0 mmol/l.

Determination of Follow-up Events

As a part of the multinational MONICA project,^{22,23} an AMI registry was established in the province of Kuopio in 1982. The registry collects detailed diagnostic information of all heart attacks in the population (which also includes the present study cohort) in a prospective manner. Heart attacks were classified as definite AMI, possible AMI, no AMI, or insufficient data according to explicitly defined, uniform diagnostic criteria described earlier in detail.^{19,23} The coverage of the AMI registry was checked against the national computerized death certificate register. We obtained diagnostic information and the date of onset of all heart attacks in our study cohort by record linkage based on the uniform Finnish personal identification code (social security number). No personal identification codes were missing either in

our study cohort or in the AMI registry data. Therefore, the losses to follow-up were negligible, if any.

Between March 1984 and December 1989, a suspected fatal ($n=9$) or nonfatal ($n=42$) AMI was registered in 51 of the 1,931 men at risk. Five of these men were hospitalized due to prolonged chest pain, but during the hospitalization, the criteria (ECG and enzymes) for either definite or possible FINMONICA²³ AMI were not fulfilled. The statistical analysis was carried out in two ways: by using all 51 registered events and by using only the 46 events that were classified as either a definite or a possible AMI according to the FINMONICA algorithm.²³ These analyses gave very similar results, and for that reason only those from the former are presented here. In the case of multiple events during follow-up, the first one for each subject was taken as the end point for the present analyses. There were 28 deaths from causes other than CHD. The follow-up period for individual subjects was up to 5¾ years, and mean follow-up time was approximately 3 years.

Statistical Methods

Associations between blood hemoglobin and serum ferritin concentrations and risk factors for ischemic heart disease were estimated with the Pearson's correlation coefficients adjusted simultaneously for age and the year of the baseline examination (1985 versus other, 1986 versus other, 1987 versus other, 1988 versus other, 1989 versus other), as both covaried with serum ferritin or blood hemoglobin.

Risk factors were entered in BMDP Cox proportional hazards models uncategorized.^{24,25} Different sets of fixed covariates were entered. AMIs were defined as events and deaths from other causes as losses. The fit of the proportional hazards models was examined by analyzing changes in the proportionality of hazards with time and with risk factor levels. The results indicated that the application of the models was appropriate. All tests of significance were two-sided. Risk factor-adjusted relative hazards were estimated as antilogarithm of a coefficient for a binary (0,1) independent variable. Their confidence intervals were estimated based on the assumption of the asymptotic normality of estimates. The statistical significance of synergistic association of two risk factors with AMI risk was tested by comparing relative hazards from two separate models in subsamples according to the risk factor tested for effect modification. The standardized normal deviate of the difference of coefficients was derived by dividing the difference by the pooled standard error of the coefficients. A correction for the regression dilution bias in the relative hazard estimates was used as explained earlier in detail.¹⁹

Results

Serum ferritin concentration ranged in our subjects from 10 $\mu\text{g/l}$ to 2,270 $\mu\text{g/l}$ (mean, 166 $\mu\text{g/l}$; SD, 149 $\mu\text{g/l}$). There was no trend over time in the annual means of serum ferritin concentration. The mean daily estimated dietary intake of iron was 19 mg (range, 0.03–64 mg; SD, 6 mg).

Both serum ferritin and blood hemoglobin concentration decreased with increasing age from the age of 48 years on. The age-specific serum ferritin means were

TABLE 1. Age-Adjusted and Examination Year-Adjusted Intercorrelations Between Serum Ferritin Concentration and Selected Coronary Risk Factors

	Hb	SBP	Leuk	VO ₂ max	HDL ₂ C	TG	Apo B	Cig	Gluc	IHD
Serum ferritin	0.211	0.117	0.022	-0.139	-0.085	0.165	0.064	-0.014	0.179	0.012
Blood hemoglobin (Hb)		0.162	0.146	-0.069	-0.182	0.206	0.174	0.010	0.052	0.043
Systolic blood pressure (SBP)			0.078	-0.176	-0.019	0.108	0.077	-0.065	0.163	0.054
Blood leukocytes (Leuk)				-0.195	-0.163	0.125	0.146	0.408	0.076	0.024
Maximal oxygen uptake (VO ₂ max)					0.200	-0.214	-0.157	-0.148	-0.155	-0.167
Serum HDL ₂ cholesterol (HDL ₂ C)						-0.370	-0.329	-0.059	-0.059	-0.073
Serum triglycerides (TG)							0.377	-0.009	0.129	0.047
Serum apolipoprotein B (Apo B)								0.055	0.036	0.049
Cigarette years (Cig)									0.022	-0.012
Blood glucose (Gluc)										0.035

IHD, Ischemic exercise ECG (yes vs. no).

181.1, 187.0, 164.4, and 132.7 $\mu\text{g/l}$ ($p=0.001$ for linear trend), and the blood hemoglobin means were 145.9, 146.6, 146.4, and 143.0 g/l in the four age strata (42, 48, 54, and 60 years), respectively ($p=0.017$ for linear trend). The intake of alcohol (grams per week) correlated weakly with both serum ferritin (Pearson, $r=0.024$) and hemoglobin ($r=0.059$). Of all foodstuffs, the consumption of meat had the strongest correlation with serum ferritin concentration ($r=0.179$). Serum ferritin concentration had weak age-adjusted correlations with blood hematocrit ($r=0.157$) and blood hemoglobin concentration ($r=0.211$).

Serum ferritin concentration had a significant positive correlation with blood glucose concentration, serum triglyceride concentration, systolic blood pressure, and serum apolipoprotein B concentration and an inverse correlation with maximal oxygen uptake and serum HDL₂ cholesterol concentration (Table 1). Blood hemoglobin correlated positively with serum triglyceride and apolipoprotein B concentrations, systolic blood pressure, blood leukocyte count, blood glucose, and ischemic ECG in the exercise test and inversely with serum HDL₂ cholesterol concentration and maximal oxygen uptake. Neither serum ferritin nor blood hemoglobin concentration correlated (absolute value of $r<0.050$) with either cigarette-years, family history of ischemic heart disease, serum copper, serum selenium, or plasma fibrinogen concentrations (data not shown). The association of serum ferritin and blood hemoglobin concentrations with serum C-reactive protein and ceruloplasmin concentration was studied in a subsample of 88 men. None of these correlations was statistically significant.

The strongest predictors of AMI, when adjusting only for age (in years) and examination year (covariates for individual years), were pack-years smoked, serum ferritin concentration, maximal oxygen uptake (inversely), serum HDL₂ cholesterol concentration, ischemic ECG in exercise, blood hemoglobin, blood leukocyte count, systolic blood pressure, serum copper concentration, diabetes, blood glucose, serum apolipoprotein B and triglyceride concentrations, and diastolic blood pressure (Table 2). Serum LDL cholesterol concentration, plasma fibrinogen concentration, family history of ischemic heart disease, fasting serum insulin, and body mass index (kilograms per square meter) had nonsignificant

associations, and alcohol intake (not shown) had virtually no association with the risk of AMI, based on a relatively short follow-up.

Men who had an AMI also had higher age and examination year-adjusted mean serum ferritin concentration (231.8 $\mu\text{g/l}$; SD, 215.1 $\mu\text{g/l}$) than those who did not experience an AMI during the follow-up period (164.7 $\mu\text{g/l}$; SD, 146.5 $\mu\text{g/l}$; $p=0.002$ for difference). This difference remained statistically significant ($p=0.011$) after adjustments for all coronary risk factors shown in Table 2 as continuous variables. The distribution of serum ferritin concentration in men who developed an AMI and who did not develop an AMI is shown in Figure 1. There was a higher proportion of men with AMI in all categories above serum ferritin value 200 $\mu\text{g/l}$, which indicates iron accumulation.

Also in the multivariate Cox proportional hazards analysis, cigarette pack-years smoked was the strongest risk factor for AMI. When all risk factors (except diabetes, as it correlated strongly with blood glucose, blood hemoglobin, and diastolic blood pressure) that had significant age-adjusted associations with the risk of AMI were entered simultaneously, only cigarette pack-years ($z=4.45$, $p<0.001$) and serum ferritin concentration had statistically significant residual associations with the risk of AMI. When entered as a continuous variable, serum ferritin concentration was a statistically significant ($z=2.64$, $p<0.01$) risk factor for AMI even when all other risk factors shown in Table 2 (except hemoglobin) were entered simultaneously in the model as continuous variables (except binary variables as such). A log transformation in serum ferritin did not influence the relative hazard notably. The addition of hemoglobin (in grams per liter) and blood hematocrit reduced the excess risk associated with serum ferritin by 12%, but ferritin remained a significant risk factor ($z=2.13$, $p<0.05$). Neither blood hemoglobin nor hematocrit was a significant predictor when entered jointly with serum ferritin and other risk factors.

In a similar Cox model for estimated dietary iron intake, iron intake had a statistically significant residual association with the risk of AMI ($z=2.41$, $p<0.05$). For each milligram of iron daily, there was an increment of 5% in the AMI risk (relative hazard, 1.05; 95% CI, 1.01–1.09).

TABLE 2. Strongest Risk Factors for Acute Myocardial Infarction

Risk factor	Mean or proportion	SD	Range	Adjusted for age and exam year		
				Relative hazard of AMI	95% CI	<i>p</i>
Pack-years smoked	7.6	15.5	0.0–144.0	1.03	1.02–1.04	<0.001
Serum ferritin ($\mu\text{g/l}$)	166	149	10–2,270	1.002	1.001–1.003	<0.001
Maximal oxygen uptake ($\text{ml/min} \cdot \text{kg}$)	31.7	7.4	3.7–86.0	0.94	0.90–0.98	<0.01
Serum HDL ₂ cholesterol (mmol/l)	0.9	0.3	0.1–2.8	0.19	0.06–0.64	<0.01
Ischemic exercise ECG (yes vs. no)	17.9%	NA	0–1	2.28	1.29–4.04	<0.01
Blood hemoglobin (g/l)	147	9	105–181	1.04	1.01–1.07	<0.01
Blood leukocyte count ($10^9/\text{l}$)	5.6	1.6	2.4–18.9	1.20	1.05–1.37	<0.01
Systolic blood pressure (mm Hg)	134	17	88–213	1.02	1.005–1.03	<0.01
Serum copper (mg/l)	1.10	0.18	0.50–2.12	5.84	1.42–24.05	<0.05
Diabetes (yes vs. no)	3.7%	NA	0–1	2.82	1.12–7.14	<0.05
Blood glucose (mmol/l)	4.7	1.0	3.2–18.2	1.19	1.02–1.40	<0.05
Serum apolipoprotein B (g/l)	1.0	0.2	0.01–1.9	4.28	1.40–13.12	<0.05
Serum triglycerides (mmol/l)	1.3	0.7	0.2–10.9	1.38	1.03–1.85	<0.05
Diastolic blood pressure (mm Hg)	89	10	57–137	1.03	1.01–1.06	<0.05
Body mass index (kg/m^2)	26.7	3.5	18.8–48.5	1.05	0.98–1.13	NS
Plasma fibrinogen (g/l)	3.0	0.5	1.3–6.7	1.48	0.90–2.42	NS
Serum insulin (mU/l)	11.2	6.6	1.0–74.8	1.02	0.99–1.05	NS
Family history of IHD (yes vs. no)	45.9%	NA	0–1	1.59	0.91–2.77	NS
Serum LDL cholesterol (mmol/l)	4.0	1.0	0.7–8.1	1.22	0.94–1.59	NS

AMI, acute myocardial infarction; HDL₂, high density lipoprotein subfraction; IHD, ischemic heart disease; LDL, low density lipoprotein; NA, not applicable; NS, relative hazard did not deviate statistically significantly ($p > 0.05$) from the value 1.00.

When allowing for all significant risk factors in Table 2 as continuous variables (except diabetes, hemoglobin, and diastolic blood pressure), men with serum ferritin $\geq 200 \mu\text{g/l}$ had a 2.2-fold (95% CI, 1.2–4.0; $p < 0.01$) risk factor-adjusted risk of AMI compared with those with serum ferritin $< 200 \mu\text{g/l}$. When blood hemoglobin and hematocrit were entered as additional covariates, the relative hazard for serum ferritin $\geq 200 \mu\text{g/l}$ was 2.0 (95% CI, 1.1–3.8; $z = 2.30$, $p < 0.05$).

To test whether serum LDL cholesterol level modifies the relation between serum ferritin and AMI risk, this model was also fitted separately in 1,633 men with serum LDL cholesterol $< 5.0 \text{ mmol/l}$ (193 mg/dl) and in 298 men with serum LDL cholesterol $\geq 5.0 \text{ mmol/l}$.

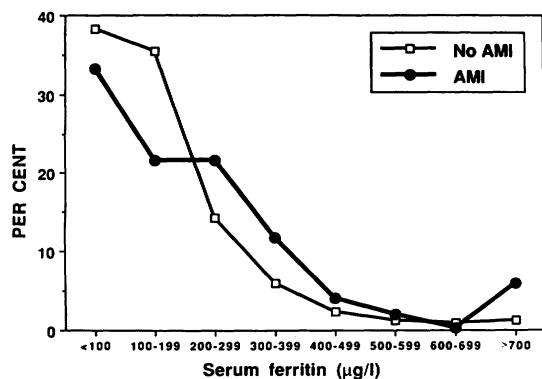


FIGURE 1. Graph of percentage frequency distribution of serum ferritin concentration in 51 men who experienced acute myocardial infarction (AMI) during follow-up and in 1,880 men who did not.

Thirty-seven men with low LDL cholesterol and 14 men with high LDL cholesterol experienced AMI during follow-up. The risk factor-adjusted relative hazard for serum ferritin $\geq 200 \mu\text{g/l}$ was 1.8 (95% CI, 0.9–3.5; $z = 1.59$, NS) in low LDL cholesterol men and 4.7 (95% CI, 1.4–16.3; $z = 2.45$, $p < 0.05$) in high LDL cholesterol men (Figure 2). The difference between these relative hazards was not statistically significant. The difference in relative hazards for serum ferritin concentration as a continuous variable in two separate Cox models with all other risk factors in men with low and in those with high

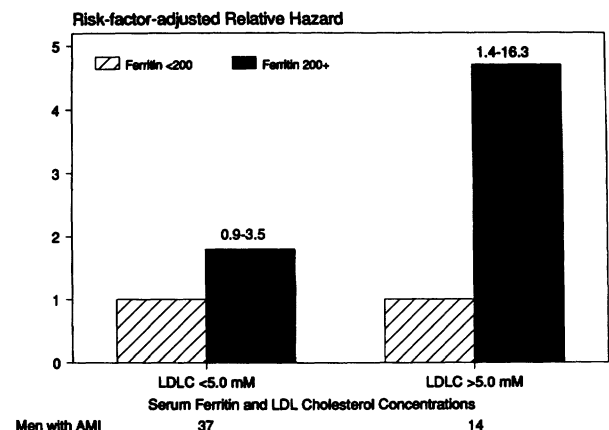


FIGURE 2. Bar graph of risk factor-adjusted relative hazard of acute myocardial infarction (AMI) associated with serum ferritin concentration $\geq 200 \mu\text{g/l}$ (with 95% CI) in men with serum low density lipoprotein cholesterol (LDLC) $\geq 5 \text{ mmol/l}$ and those with serum LDLC $< 5 \text{ mmol/l}$.

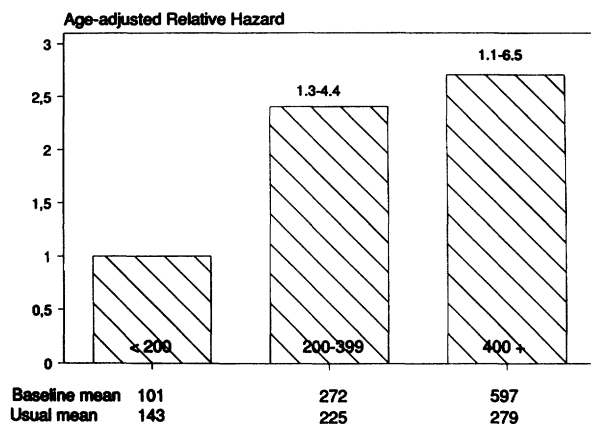


FIGURE 3. Bar graph of age-adjusted and examination year-adjusted relative hazard of acute myocardial infarction (with 95% CI) according to serum ferritin concentration.

serum LDL cholesterol was, however, statistically significant ($z=2.08$, $p<0.05$ for difference). The relative hazard for serum ferritin was almost identical in smokers and nonsmokers.

To estimate the dose-response relation between serum ferritin concentration and the risk of AMI, two indicator variables for ferritin values of 200–399 $\mu\text{g/l}$ (iron accumulation) and 400 $\mu\text{g/l}$ or more (iron overload) were entered in a Cox model, which also included age and examination years (Figure 3). The excess risks of AMI at serum ferritin levels 200–399 $\mu\text{g/l}$ and ≥ 400 $\mu\text{g/l}$ were statistically significant and almost identical. As indicated by the 73% reduction in the range of ferritin means between the lowest and the highest ferritin category from the baseline to the reexamination 1–5 years later, there was a strong regression toward the mean in serum ferritin concentration over time. On the basis of this Cox model, an increment of 170 $\mu\text{g/l}$ in the baseline (and that of 82 $\mu\text{g/l}$ in the usual) serum ferritin concentration was associated with a 2.4-fold age-adjusted and 2.3-fold risk factor-adjusted risk of AMI. An increment of 1% in serum ferritin concentration was associated with an $\approx 2.4\%$ increment (4.4% when corrected for the regression dilution bias) in the risk factor-adjusted risk of AMI.

To remove the possible effect of the acute phase of the disease on serum ferritin concentration, the Cox models were repeated, taking into account only myocardial infarctions that occurred more than 6 months after the baseline examination. The strength of the relations between serum ferritin concentration with the risk of AMI remained similar to that based on the entire follow-up period: The age and examination year-adjusted relative hazard for serum ferritin ≥ 200 $\mu\text{g/l}$ was 2.0 (95% CI, 1.1–3.6; $z=2.27$, $p<0.05$).

Discussion

Extensive reviews have been recently published concerning the role of iron in free radical reactions, such as lipid peroxidation.^{3–6} Briefly, except in states of iron overload, all iron in human serum is bound to proteins. About two thirds of body iron is found in hemoglobin, with smaller amounts in myoglobin, various enzymes, and the transport protein transferrin.⁶ Iron not required for these is largely stored in ferritin. To promote free

radical production, iron must be liberated from proteins. It is believed that oxidant stress itself can provide the iron necessary for formation of reactive oxygen species, for example, by mobilizing iron from ferritin or by degrading heme proteins to release iron.⁶ For instance, superoxide radicals have been observed to liberate iron from ferritin, promoting lipid peroxidation.^{6,26} Halliwell and Gutteridge⁶ have proposed that the general effect of iron catalysts is to convert poorly reactive free radicals into highly reactive ones, such as the hydroxyl radical.

Recently, Balla and coworkers²⁷ demonstrated that the combination of physiological concentrations of hydrogen peroxide and heme induce a rapid peroxidation of LDL in vitro and that free iron is released from the degraded heme ring. They also observed a simultaneous loss of reactive lysine amino groups of LDL, which has been shown to promote LDL uptake by scavenger receptors of macrophages leading to foam cell formation.¹ Also, transition metal ions are probably required for the peroxidation of LDL by monocyte/macrophages, smooth muscle cells, and endothelial cells.^{28,29} Oxyhemoglobin has been observed to stimulate lipid peroxidation.³⁰ Also, iron released from ferritin has been shown to stimulate the formation of hydroxyl radicals from superoxide radicals and hydrogen peroxide,³¹ whereas apoferritin appears to inhibit lipid peroxidation.³² In patients with iron overload consequent of hereditary hemochromatosis, nontransferrin-bound iron, reflecting free iron, is present in serum, and its concentration is highly correlated to that of serum ferritin, even at serum ferritin levels <400 $\mu\text{g/l}$.³³ Thus, the hypothesis that high iron status is associated with stimulated free radical reactions and accelerated lipid peroxidation in the human body appears to be plausible on the basis of free radical chemistry and animal experiments.

Iron loading has been observed to increase the susceptibility of rat hearts to oxygen reperfusion damage.^{6,34} There are a number of animal experiments suggesting that experimental ischemic myocardial injury can be limited or prevented by iron chelation therapy.^{3–8,34} The chelation of iron has been found to prevent postischemic lipid peroxidation in rats.³⁴ Recently, Williams et al⁸ found that desferrioxamine treatment improved the functional and metabolic recovery of isolated, perfused rabbit hearts after 30 minutes of ischemia. Korpela³⁵ observed increased hepatic and myocardial iron concentrations in pigs with microangiopathy (mulberry heart disease) compared with healthy pigs. Smith and coworkers³⁶ recently demonstrated catalytic iron in gruel samples from human advanced atherosclerotic lesions. The samples stimulated lipid peroxidation, and this was in most samples inhibited by the iron chelator desferrioxamine.

Murray and coworkers³⁷ measured the inhibitory effect on lipid auto-oxidation of the serum of milk-drinking nomads, who have nutritional iron and copper deficiency.³⁷ Twenty-two nomads were given 180 mg of iron daily for 60 days without change in diet. The mean percent inhibition of lipid auto-oxidation, as measured with the method of Stocks et al,³⁸ was reduced by 62% (from $81 \pm 3.7\%$ to $31 \pm 4.4\%$) during iron supplementation.³⁷ This experiment provides support to the role of iron as a catalyst of lipid oxidation in vivo. We observed in a nested case-control study in 60 Eastern Finnish men

a positive association between blood hemoglobin concentration and titer of autoantibodies against malondialdehyde-modified LDL ($r=0.27$, $p<0.05$), which is suggestive of a role of heme iron or the hemoglobin itself in lipid peroxidation *in vivo* in men.²

Sullivan^{7,12,39} has suggested that the higher incidence of CHD in men and postmenopausal women is due to higher levels of stored iron in these two groups. Sullivan bases his argument on the observations of 1) myocardial failure in patients with iron storage diseases, 2) accumulation of stored iron with age in men, and 3) the accumulation of stored iron after menopause to levels found in men and in rough proportion to the added risk.^{7,12} The cardiotoxicity of excessive amounts of stored iron is suggested by the finding of myocardial failure in hemochromatosis and diseases associated with large exogenous iron loads, such as thalassemia major.⁴⁰

In a small cross-population study comparing 10 countries, CHD mortality rates correlated strongly with the product of hepatic storage iron and serum cholesterol concentration in men ($r=0.72$) but only weakly in women ($r=0.38$).⁴¹ Our finding of the synergistic association of serum ferritin and LDL cholesterol concentrations with the risk of AMI is in agreement with this report and fits well in the theory that iron overload would elevate the risk of AMI through the promotion of oxidation of LDL.

An increase in the incidence of CHD and in the severity of the presenting diseases was noted in a cohort of 2,873 Framingham women, followed for 24 years, who had either natural or surgical menopause.⁴² The excess incidence was observed in all age groups (40–44, 45–49, and 50–54 years) and in women with natural or surgical menopause, whether ovaries were removed or not. This suggests that the protection against CHD was lost after simple premenopausal hysterectomy despite continued ovarian function and estrogen production.³⁹

In the Stockholm Prospective Study, there was an excess risk of myocardial infarction among men aged <60 years in the highest quintile of blood hemoglobin concentration.⁴³ Weak associations between high blood hemoglobin or hematocrit and the risk of CHD have also been reported from other prospective population studies.^{44,45} Hemoglobin and hematocrit are not, however, good measures of body iron status.^{46–48} There are no previous reports concerning the association of serum ferritin concentration with either the risk of or the mortality from CHD. We used serum ferritin concentration as an index of the amount of stored iron in the body. Serum ferritin is considered by many authors to be the best measurement of iron status.^{46–48} We did not measure serum iron concentration because it is susceptible to measurement error caused by hemolysis and does not indicate storage iron as well as ferritin.⁵

Besides by promoting lipid peroxidation, high iron status could increase the risk of AMI through the elevation of blood hematocrit and blood hemoglobin concentration. This increases the viscosity of blood, which could be related to thrombotic coronary events through a direct thrombogenic effect. In our study population, however, the association of serum ferritin both with blood hemoglobin ($r=0.21$) and with hematocrit ($r=0.16$) was quite weak. Also, there was a relation between serum ferritin concentration and the risk of AMI in our data even after controlling for blood

hematocrit and hemoglobin, whereas blood hematocrit and hemoglobin had no significant association with AMI risk when serum ferritin was allowed for. The association between serum ferritin and AMI risk was weakened by only 12% by the adjustment for hematocrit and hemoglobin. This suggests that the AMI risk-elevating effect of high serum ferritin is primarily through mechanisms other than increased blood viscosity.

Apo ferritin is a liver protein that is elevated in inflammatory conditions, even though not as much as the actual acute-phase proteins. To rule out the possibility that serum ferritin levels merely reflect the presence of an infection, inflammation, or chronic vascular disease, we adjusted for the blood leukocyte count in our statistical analysis. Serum ferritin had no association either with the concentration of plasma fibrinogen (an acute-phase protein) in the whole study population or with serum C-reactive protein or serum ceruloplasmin concentrations in a subsample. The impact of high serum ferritin on the risk of AMI did not attenuate when infarctions that occurred within 6 months of blood sampling were excluded from the statistical analysis.

Iron status was associated in our data with several risk factors for CHD. Serum ferritin had significant correlations (in order of strength) with blood glucose, serum triglycerides, systolic blood pressure, HDL₂ cholesterol concentration (inversely), and serum apolipoprotein B concentration. As serum ferritin had weak positive correlations with the intakes of alcohol, meat, and saturated fats, these associations may be partly of dietary origin. Serum ferritin also correlated inversely with maximal oxygen uptake, an indicator of cardiorespiratory fitness. This is a surprising finding, as high hemoglobin concentration enhances the transport of oxygen from the lungs to the muscles. There are two possible explanations for this observation: Most likely, high physical activity might increase iron excretion, as suggested earlier⁴⁹; theoretically, high iron status could also lower cardiorespiratory performance capacity through a direct effect on the cardiac muscle.

We found no reports concerning the effects of iron depletion by chelation therapy or phlebotomy on serum lipid and lipoprotein levels. In a cross-population comparison, hepatic iron stores correlated negatively with HDL cholesterol levels.⁴¹ In a small uncontrolled trial, systolic blood pressure was reduced by over 10% 14 days after phlebotomy in 15 patients with resistant essential hypertension.⁵⁰ Controlled clinical trials are needed to confirm whether the associations of body iron stores with lipids and blood pressure could be causal ones.

Theoretically, serum ferritin concentration could be a noncausal indicator of dietary and genetic etiologic factors rather than a true causal risk factor. The strongest dietary determinants of serum ferritin concentration in our data were the intakes of alcohol and meat. The consumption of alcohol was not associated with the risk of AMI in the present analysis. A high dietary intake of meat had a weak association with an increased risk of AMI. The consumption of meat also was associated weakly with serum LDL cholesterol and apolipoprotein B levels, which were controlled in our statistical analysis. High iron status of the body can also result from familial hemochromatosis. On the basis of the present data, we cannot exclude the possibility that the hemochromatosis gene would associate with CHD directly or

would covary with other genes that would be atherogenic.

The mean serum ferritin concentration in our study subjects was 166 $\mu\text{g/l}$. This is somewhat higher than means observed in adult men in most previous population studies. The median for men aged 18–45 years was 94 $\mu\text{g/l}$ in 1,564 people in the state of Washington.⁵¹ In a recent study in another Nordic population in Iceland, the mean serum ferritin concentration in 925 randomly sampled men aged 25–74 years was 198 $\mu\text{g/l}$.⁵² According to Munro and Linder,⁵³ the median value in adult men is 69–140 $\mu\text{g/l}$. In iron overload, serum ferritin ranges from 400 to 12,000 $\mu\text{g/l}$.⁵³ Six percent of our subjects had serum ferritin >400 $\mu\text{g/l}$ and over 25% had serum ferritin of at least 200 $\mu\text{g/l}$. If iron depletion is defined as serum ferritin <16 $\mu\text{g/l}$, there were only 20 of 1,931 (1%) iron-depleted men in our study population.

The present data provide the first empirical evidence in humans of the role of high stored iron measured as elevated serum ferritin concentration as a risk factor for ischemic heart disease. The association appears to be strong when one considers the sizable regression toward the mean over time of serum ferritin concentrations. A major proportion of our subjects had serum ferritin levels that put them at increased risk of AMI. If confirmed in subsequent studies, our present findings raise the issue of whether the current dietary recommendations emphasizing iron sufficiency should be revised to include aspects related to problems of excessive iron intake that might be relevant for men and possibly for postmenopausal women. Our findings do not undermine the role of LDL cholesterol in the etiology of CHD but rather help to explain why high serum LDL cholesterol concentration is more predictive of CHD in some individuals and populations than in others. The observed synergistic association of serum ferritin and serum LDL cholesterol concentration with the risk of AMI fits into the theory that iron overload would elevate the risk of AMI by promoting the oxidation of LDL.

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High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men.

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