Iron Stores Are Not Associated With Acute Myocardial Infarction

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Background  This study evaluated the relation between body iron stores and coronary artery disease. It has been suggested that total body iron stores are an independent risk factor for acute myocardial infarction (AMI).

Methods and Results  Our study population consisted of 46,932 members of a prepaid health plan who were ≥30 years old and who received a standard health check between 1969 and 1971. Blood collected during this examination was analyzed for serum iron and total iron-binding capacity. Transferrin saturation (TS), calculated as (serum iron/total iron-binding capacity) x 100, was categorized as low (<10%), normal (11% to 61%), or elevated (≥62%). Hospital stays for AMI were identified from the health plan’s computerized discharge records for its Northern California Region through December 31, 1991. Mean follow-up time was 14.1 years. During the follow-up period, 969 men and 871 women had an AMI-related hospital stay. Analysis of AMI-related hospital stays was performed overall and by sex. Age-adjusted incidence rates were obtained for each TS level, and proportional hazards regression models were used to assess the significance of TS as a risk factor for AMI, controlling for other known coronary disease risk factors. Our results did not show iron deficiency as defined by low TS to be protective against AMI. Subjects with increased iron stores indicated by TS ≥62% had a relative risk for AMI of 1.3, which was not statistically significant.

Conclusions  Our observations do not support the hypothesis that coronary artery disease risk is related to iron stores.

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Key Words  • coronary disease • ferritin • hemoglobin • iron • myocardial infarction • transferrin

Salonen et al 1 recently reported that high stored iron level as measured by serum ferritin was an independent risk factor for acute myocardial infarction (AMI). Sullivan 2 speculated that the extremely low incidence of ischemic heart disease in young menstruating women might be due in part to the protective effect of iron depletion. The Kaiser Permanente (KP) Multiphasic Health Check (MHC) was established at the Oakland KP Medical Center in 1951 as a thorough routine health check for adults that consists of administration of a standard health questionnaire, age- and sex-determined laboratory testing and cancer screening, history taking, and physical examination. Between 1969 and 1971, serum iron and total iron-binding capacity (TIBC) measurements were included in the MHC laboratory test panel. We performed a follow-up review of these patients to explore the relation of iron stores to subsequent hospitalizations for AMI.

Methods  
The study population consisted of 46,932 members of a prepaid health plan who were aged 30 years and older and who received an MHC between 1969 and 1971. Blood collected during the examination was analyzed for serum iron and TIBC. Transferrin saturation (TS) was calculated as (serum iron/ 

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TIBC) x 100. The study protocol was approved by the KP Medical Care Program, Northern California Region, Institutional Review Board.

AMI-related hospital stays through December 31, 1991, were identified from hospital admissions to KP Medical Centers, Northern California Region, by using the primary discharge diagnosis (ICD-8 and ICD-9 code 410). Because computerized data on hospital stays were incomplete before 1971, the follow-up period began 2 years after the MHC. Follow-up continued until first AMI-related hospital stay, death, or membership termination from the Kaiser Foundation Health Plan, or December 31, 1991, whichever was earliest.

TS was categorized as (1) <10% (low), (2) 11% to 61% (normal, used as referent), and (3) ≥62% (elevated). Analysis of AMI-related hospital stays was performed overall and by sex, and age-specific (<55, 55 to 64, 65 to 74, or ≥75 years) incidence rates were obtained for each TS level. Age-adjusted rates were calculated by using the direct method with the observed person-year distribution as the standard population. Proportional hazards regression models were used to assess the significance of TS as a risk factor for AMI while controlling for age, race, and risk factors for AMI as covariates. Statistical significance was considered at α = .05. The risk factor variables based on self-report were education, smoking status, alcohol consumption, family history of heart disease, and history of diabetes as diagnosed by a physician. Examination values for serum glucose, systolic blood pressure, cholesterol, and body mass index were also included as risk factors.

Between 1969 and 1971, neither triglyceride nor high-density lipoprotein cholesterol measurements were performed as part of the laboratory testing panel. The only lipid measurement available for analysis in this cohort of patients was the total serum cholesterol level. During this period, two different automated analyzers were used to measure serum cholesterol. Because these two automated analyzers produced cholesterol values with a mean that differed by 15
mg/dL, we used a standardized cholesterol value instead of the actual values. The standardized value for cholesterol was based on the automated analyzer used and was calculated as the difference between actual value and overall mean value for that analyzer divided by the standard deviation for the analyzer.

**Results**

Table 1 describes the characteristics of the study population, which was 32% men and 68% women with a mean age of 49.8 years. The study population was about 78% white, 14% black, and 8% other. Overall, 1.8% had TS ≤10%, and 2.3% had TS ≥62%. Mean follow-up time for the study population was 14.1 years.

Patients with low TS (≤10%) were more likely to have anemia (28.8% versus 2.0% in men and 45.7% versus 4.0% in women) and to have microcytosis (36.2% versus 2.9%) than those with TS >10% (P<.001 for all comparisons by χ² test of equality of proportions). Anemia was considered to be hemoglobin <13 g/L for men and hemoglobin <12 g/L for women; microcytosis was considered to be mean corpuscular volume ≤80 fl.

During follow-up, 969 men and 871 women were treated in the hospital for AMI. Table 2 shows age-adjusted AMI rates by TS level for men and women. The rate for men with TS level ≤10% was lower than for men with normal or elevated levels; among women, rates were similar for the two lower TS levels and somewhat higher for women with an elevated TS level.

Table 3 shows relative risk of AMI-related hospitalization for the low and the elevated TS level groups compared with the normal TS level group when the data were adjusted for other known coronary disease risk factors. The relative risk of 1.3 for the elevated TS level, observed both in men and women, was not statistically significant overall. Expected increased AMI risk was seen in the models for the covariates of age, systolic blood pressure, cholesterol level, body mass index, current or past smoker, family history of heart disease, and history of diabetes as diagnosed by a physician.

A test for linear trend using the three TS levels as an ordered variable (1, low; 2, normal; 3, elevated) was not significant (relative risk, 1.2; 95% confidence interval, 0.9 to 1.6). Results for TS were unchanged in analyses that excluded those who reported a history of AMI before MHC or in analyses that excluded subjects with TIBC <250 from those with TS ≤10%. Additional analyses performed on only those subjects with a total cholesterol level in the highest quartile found no relation between TS level and AMI-related hospital stay (Table 4).

**Discussion**

Sullivan et al proposed that reduced iron stores can protect against ischemic heart disease by inhibiting the oxidative modification of low-density lipoprotein (LDL) and possibly by decreasing posts ischemic myocardial injury. Salonen et al observed that serum ferritin was an independent risk factor for AMI in a cohort of 1931 randomly selected Finnish men who were followed for a mean of 3 years. Their observation that the association between ferritin and AMI was stronger in men with an elevated LDL level was considered to support the hypothesis of Salonen et al. Sullivan speculated that if iron stores did affect the modification of LDL cholesterol and myocardial reperfusion injury, maximal protection from coronary disease should be found among iron-deficient subjects. He further speculated that this protective effect might account in part for the very low incidence of coronary disease in premenopausal women. We looked for an association between AMI and stored iron among 46,932 subjects whose serum iron and TIBC were measured and who were followed for a mean of 14.1 years.

Both serum ferritin and TS <15% have been used to identify persons with anemia due to iron deficiency. However, Cook et al assessed a population of 1564 subjects for iron deficiency defined as TS <15%, ferritin <12 ng/mL, or erythrocyte protoporphyrin >100 μg/mL. They found that no one parameter was sufficient to
identify an iron-deficient population and that accuracy of iron deficiency detection in population surveys can be improved substantially by using two or three of these measurements. Neither erythrocyte protoporphyrin nor serum ferritin measurements were obtained for our subjects. We therefore used TS ≤ 10% to define our iron-deficient population. Considering the prevalence of anemia and microcytosis among our subjects with TS ≤ 10%, we are confident that this group included a substantial proportion of iron-deficient subjects. Our results did not show iron deficiency defined as TS ≤ 10% to be protective against AMI. The low TS group, however, was relatively small.

The anemia of chronic disease can be associated with low TS. Our results were unchanged after we excluded subjects with a TIBC < 250 from the group with TS ≤ 10%. As a result, a protective effect of iron deficiency against AMI was unlikely to be obscured by inclusion of subjects with chronic disease in our population of patients with low TS.

Salonen et al.1 found that the association between ferritin and AMI was stronger among men with elevated LDL cholesterol level than among those without elevated LDL cholesterol level. We did not have LDL cholesterol measurements for our study population, but we found no association between iron stores as determined by TS and AMI among study subjects with a total cholesterol level in the highest quartile.

Ferritin level measurements, an excellent method of assessing increased total body iron stores,9 were not performed in our study population. However, we used TS to identify a study population likely to have increased iron stores. In normal persons, iron absorption is inhibited as iron stores accumulate, and iron overload is prevented. In persons with hereditary hemochromatosis, feedback inhibition of iron absorption is impaired, and therefore increased iron stores are common.10 HLA-linked hereditary hemochromatosis is estimated to occur in 1 in 200 persons,11 and TS ≥ 62% is the best, simply measured indicator of homozygosity for the hemochromatosis gene.12 We therefore used TS ≥ 62% to identify a population likely to include many subjects with hemochromatosis and therefore to have increased iron stores. While our results suggested an increased AMI risk for this elevated TS group, the relative risk of 1.3, not statistically significant, was much lower than that reported by Salonen et al.1

Some authors have recommended that TS be measured when the patient is in a fasting state.13 Our subjects were not instructed to fast, but the time since they had last eaten was recorded. We found no relation between serum iron, TIBC, or TS and the time since our subjects had last eaten.

In summary, by using TS as a measure of iron stores, we have been unable to confirm Salonen’s observation that iron stores are an independent risk factor for AMI.

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References


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