Association of age, sex, and race with body iron stores in adults: Analysis of NHANES III data

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Background This study examined age-, sex-, and race- related increases in body iron stores that have been implicated in disease and the relative utility of the serum ferritin versus the percentage of transferrin saturation for population-based estimation of iron status.

Methods and Results Serum ferritin levels were examined by age, sex, and race, and values were compared with the percent transferrin saturation in 20,040 individuals >17 years of age from the third National Health and Nutrition Examination Survey (NHANES III) database. Body iron stores reflected by serum ferritin levels rose in the late teens in men and after menopause in women. This rise was more rapid and maximum ferritin levels were greater for blacks than whites and Hispanics of comparable age and sex. The distribution of values for the serum ferritin differed from the percent transferrin saturation.

Conclusions Different patterns of iron accumulation exist according to age, sex, and race. Serum ferritin levels reflect graded, population-based differences in body iron stores, but the percentage of transferrin saturation does not. The hypothesis that iron accumulation may contribute to higher morbidity and mortality rates can be tested in clinical trials of calibrated reduction of body iron stores in defined disease settings. (Am Heart J 2000;140:98-104.)

Iron is an essential mineral involved in oxygen transport and cellular oxidative metabolism but also is an environmental toxin.[1] Body iron stores rise over time in hereditary hemochromatosis (HH)[2] and in otherwise apparently healthy individuals in the absence of HH.[3-7] Although iron absorption can be regulated within limits,[8] iron accumulates because, like calories, no homeostatic mechanism exists for excreting excess quantities.[1] Unlike excessive calorie intake, rising iron stores cannot usually be recognized in the mirror, and the need for nutritional hygiene related to iron intake is neither defined nor part of public perception.

Possible toxic effects of rising iron stores over time have been implicated in the pathogenesis of several common diseases of aging including malignancy,[9] neurodegenerative disorders,[10] diabetes mellitus,[11] infections,[12,13] and atherosclerosis.[14-23] The explanation for the detrimental effect of iron rests in the same attribute that makes iron essential for life, namely its ability to reversibly cycle between highly reactive ferrous (Fe^{2+}) and relatively stable ferric (Fe^{3+}) oxidation states, resulting in formation of reactive oxygen species that are toxic to biomolecules.[1,24-26] Oxygen free radicals mediate DNA strand breaks and mutations to initiate carcinogenesis and promote tumor cell proliferation[1,9] and initiate lipid oxidation involved in atherogenesis.[1,9,24,26] Endogenous antioxidant mechanisms sufficient to counter damage from metabolism of essential levels of iron may be overwhelmed with an elevated pool of storage iron.

Sullivan[14,15] proposed that the reduced risk of myocardial infarction in premenopausal women compared with both men of comparable age and postmenopausal women might be explained by their lower iron stores reflected by serum ferritin levels. The effect of iron stores on the sex difference in vascular disease was distinguished from possible hormonal effects.[14,27] Reduction of iron stores (represented by a fall in the serum ferritin level) by phlebotomy in a cohort of men >50 years of age resulted in significantly decreased susceptibility of peripheral blood low-density lipoprotein to oxidation.[26] A longitudinal cohort study showed a highly significant correlation between serum ferritin and pathologic carotid artery wall thickening.[17] The ferritin concentration was a strong and independent risk factor for stroke in both men and women, and interactions were observed between ferritin levels and both low-density lipoprotein levels and smoking. Risk increased with ferritin levels >50 μg/L. Recently, the serum ferritin level has been associated with coronary risk in the elderly.[28]

Controversy over this concept is based on conflicting conclusions from epidemiologic studies, some of which used measures of transport iron rather than the

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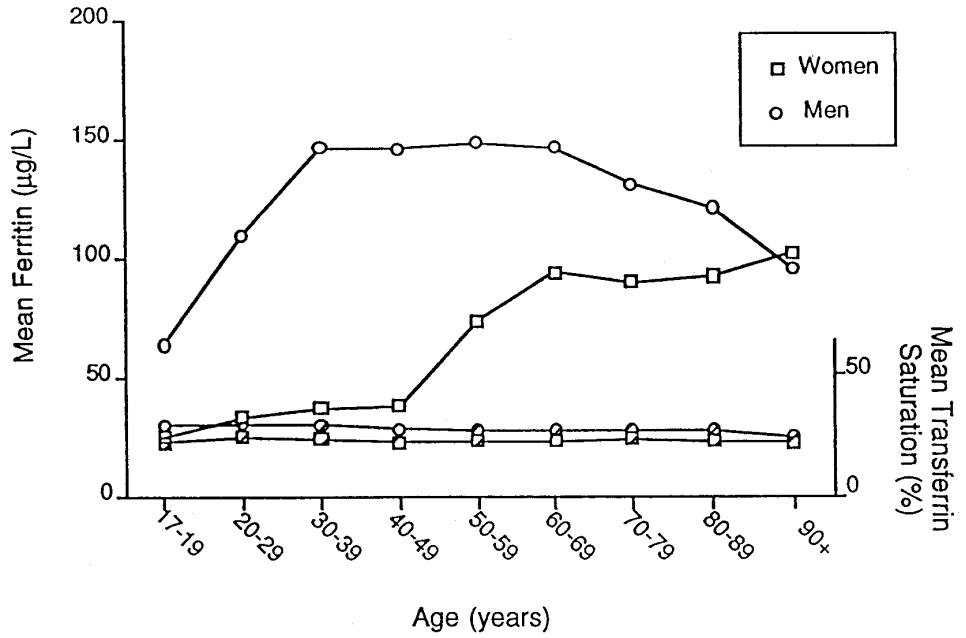
Figure 1



Distribution of serum ferritin level in micrograms per liter and transferrin saturation (%) by decade of age for women and men.

ferritin level.[22,23,29] Sullivan's hypothesis[14,15] was based on the incidence of ischemic heart disease derived from the Framingham Study[30-32] and on changes in ferritin levels by age and sex reported by Cook et al[3] in 1976. The latter data were from samples collected between 1968 and 1971 from 1564 individuals from 10 states in the Pacific Northwest. Blacks made up <3% of this population. The intent was to sample families in the lowest quartile of income. Thus uncertainty exists regarding the generalizability of these data and their current value for making epidemiologic correlations with disease. Relations between serum ferritin levels and both age and sex have been reported from other countries,[4,5] an ambulatory care setting in the United States,[6] and a subset of individuals in the National Health and Nutrition Examination Survey (NHANES) II database.[7] Blacks have been reported to have higher serum ferritin levels than whites.[33]

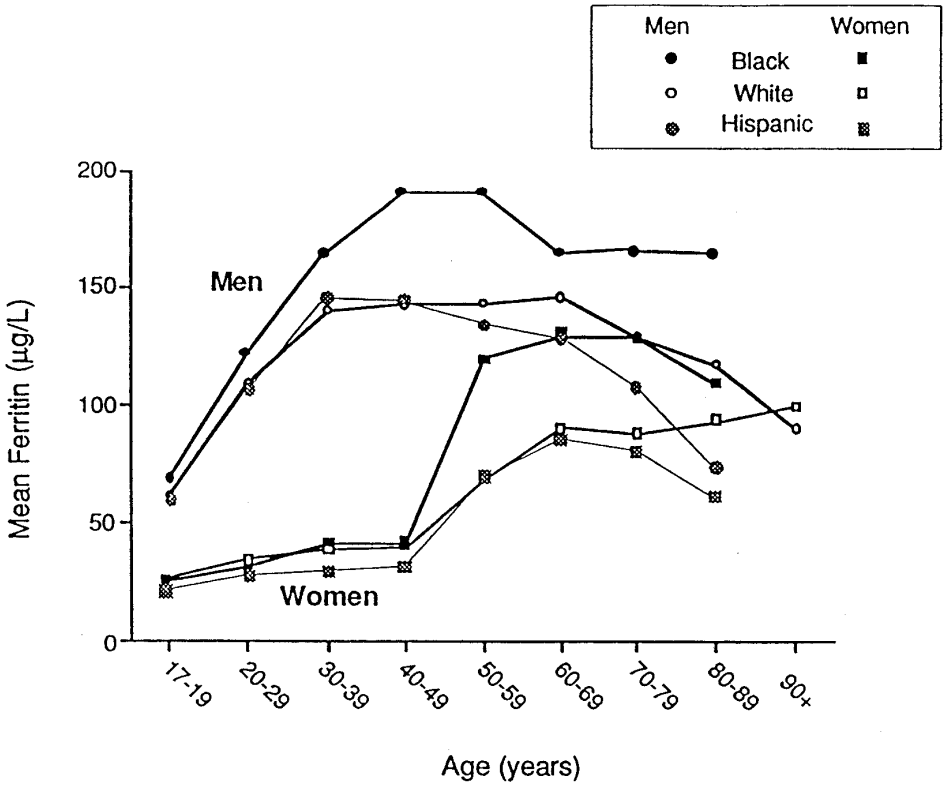
Our study was conducted to define the distribution of body iron stores in the current population of the United States and to compare population-based values for the serum ferritin with the percentage of transferrin saturation. If changes in iron stores over time indicate the contribution of iron to disease, then their portrayal would provide a benchmark for defining populations at risk. Serum ferritin levels, a surrogate for iron stores,[25] from subjects entered into NHANES III provided an opportunity to examine changes in iron stores by age, sex, and race in contemporary residents of the United States.

Methods

Data source

Data examined in this study are from NHANES III, the most recent (1988 to 1994) survey conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention, to assess the health and nutritional status of the civilian, noninstitutionalized population of the United States. Both the stratified, multistage probability sampling design and data collection methods have been described elsewhere.[34-37] Briefly, a national sample of approximately 34,000 individuals were studied by means of interviews, standardized medical examinations, and blood tests. We examined the distribution of the serum ferritin and the percentage of transferrin saturation in men and women ≥17 years of age. This lower age limit was selected because factors influencing body iron stores differ between adults versus children and early adolescents and because our focus was on possible correlates of iron stores with diseases of adults. The sample for our analyses consisted of 20,040 individuals identified by age, sex, and race that had ferritin and percent transferrin saturation determinations. Of these, 8477 were white, 5484 were black, 5304 were Hispanic, and 775 were of "other" race. Because the number of participants who were races other than black, white, and Hispanic was limited, analysis by race was limited to these three races. Age and race were self-reported, the lat-

Figure 2



Distribution of serum ferritin level in micrograms per liter by decade of age for women and men stratified by race.

ter based on the US census definitions. Ferritin and percent transferrin saturation assays were performed by methods described elsewhere.[37-39]

Analysis

The distribution for the mean serum ferritin in micrograms per liter and the percentage of transferrin saturation for adults is presented by deciles of age beginning at age 17 years (overall and stratified by black, white, and Hispanic race). Ten-year age categories were created to ensure sufficient numbers of unweighted observations (ie, >30) per stratum in all analyses as suggested in the NHANES III documentation. Because the values for ferritin within each age decile were strongly right-skewed, geometric means were used to best represent the central tendencies. The corresponding transferrin saturation distributions were only minimally skewed; consequently, arithmetic means are reported. All analyses incorporated sampling weights to adjust for differential probability of selection, given the complex sampling design and to account for nonresponse. All analyses used the SVY series of commands in STATA (College Station, Tex).

Results

The association of age and sex with the serum ferritin and percentage of transferrin saturation is shown for the entire population in Figure 1. Serum ferritin levels rose sharply in men toward the end of the adolescent growth spurt in the late teens and reached maximum in 30- to 39-year-olds. Levels remained constant thereafter until approximately age 70 years, after which they declined. By contrast, ferritin levels remained relatively low in women until after the fourth decade of life, after which they exhibited a steep rise resembling that observed in men approximately 30 years earlier. Maximum levels observed in women after menopause were approximately two thirds of those for men of comparable age. Ferritin levels for men and women converged in the oldest age group. Changes in ferritin levels by age and sex did not resemble the pattern observed for the percentage of transferrin saturation.

The association of race with the serum ferritin level by age and sex is shown in Figure 2. Ferritin levels in black men exceeded those in whites and Hispanics for each decade of life, and differences were amplified with age. Ferritin levels were comparable for black, white, and Hispanic women during the premenopausal years. However, after menopause, ferritin levels in black women rose more rapidly and exceeded those of white and Hispanic women. Overall, ferritin levels were approxi-

Table I. Comparison of patterns of iron accumulation related to versus not related to genetic hemochromatosis

Feature	HFe-related (HH)	Non–HFe-related	Reference
Total body iron accumulation over time	Yes	Yes	47
Degree of iron accumulation reflected by serum ferritin	Yes	Yes	26
Protection from accumulation in premenopausal women	Yes	Yes	48
Characteristic degree of iron accumulation	++++	+ to +++	4 through 8, 47
Percentage of transferrin saturation useful for diagnosis and population screening	Yes	No	3
Characteristic mutations of HH: Homozygosity or compound heterozygosity for C282Y and H63D; possibly other mutations	Present	Absent	49
Prevalence in population	Between 1 in 200 and 1 in 400 persons	Majority of adults	4 through 8, 49
Racial distribution	Primarily whites of northern European descent	All races, especially blacks	33, 49
Iron content of intestinal epithelial cells	Decreased	"Normal"	47
Intestinal epithelial cell expression of NRAMP-2 Iron transporter mRNA	Increased	"Normal"	50
Intestinal epithelial cell expression of ferric reductase activity	Increased	"Normal"	51
Primary site of iron accumulation	Parenchymal cells, eg, hepatocytes	Reticuloendothelial (monocyte-macrophage) system	52 through 54
Monocyte-macrophage phagocytic capacity	Decreased	"Normal"	55
Monocyte-macrophage iron regulatory protein activity	Increased	"Normal"	56
Reticuloendothelial system iron content	Decreased	Increased	52 through 54, 57, 58
Risk of atherosclerosis	Decreased	Increased	15 through 22, 46

mately 7% to 8% greater for blacks than for whites and Hispanics, and differences remained throughout the second half of life.

Discussion

We have documented different patterns for levels of the serum ferritin by age for sex and race (Figures 1 and 2). Serum ferritin levels rose sharply during the late teens in men and reached maximum in the 30- to 39-year-old age group. Thereafter, levels plateaued until approximately age 70 years, after which they declined. This decline with aging may be caused by either a decline in iron intake in later life or a selective disadvantage for survival of higher ferritin values in men. By contrast, ferritin levels remained relatively low in women until menopause, after which they rose but not to levels as high as in men of comparable age (Figure 1). Male/female differences were greater for blacks than for whites and Hispanics (Figure 2).

Iron accumulation and loss determine steady-state levels of body iron stores. Dietary iron absorption from the upper small intestine[40] increases with ferritin levels below approximately 60 μg/L.[8] Absorbed iron is recycled and conserved either in metabolically active form or in storage within the reticuloendothelial system, consisting of phagocytic monocytes/macrophages.[25] The relatively low iron stores typical of childhood, represented by serum ferritin values of approximately 25 μg/L, reflect the increased iron requirement for the expanding body mass. Similar low levels are observed in premenopausal women because of menstrual blood loss and pregnancy.[3] However, a 4- to 6-fold rise commences in men in the late teenage years and with menopause in women. There is no known physiologic requirement for this increase in iron stores. Lower iron stores characteristic of highly conditioned athletes and blood donors are compatible with excellent health.[41] A clue that such iron accumulation may be inappropriate is that accepted normal values for the ferritin level include an upper limit that may be 30-fold greater than the lower limit (300 vs 12 μg/L, respectively), a range wider than for other physiologic parameters.[42] Levels of transport iron such as the percentage of transferrin saturation are tightly controlled over a wide range of iron stores but may reflect either overt iron deficiency or gross excess characteristic of HH.[2,3] However, the percentage of transferrin saturation does not reflect graded changes in iron stores over time or show differences by age and sex in free-living human beings, as does the ferritin determination (Figure 1).

The pathologic significance of varying levels of body iron stores is controversial. Some have used measures of iron transport, such as the percentage of transferrin saturation, for epidemiologic correlations,[22,23,29] but these are of limited value (Figure 1). The mixed results from epidemiologic studies in men with the use of the ferritin assay[22,23,29] may be explained by the fact that

ferritin levels <50 μg/L are uncommon in male adults[3,6]; there is no naturally occurring male control population for comparison of risk. The use of the case-control strategy for epidemiologic analysis is of limited value because the ferritin may be altered by the disease itself[43] and by diagnostic phlebotomy.[44] After-the-fact assessment communicates little about the premorbid contribution of iron stores. Dietary surveys are problematic because estimates of iron intake calculated from nutritional tables vary widely from levels of iron measured in food.[45] The amount of iron obtained from nonprescription vitamin supplements and processed foods is poorly quantified, and dietary iron loading may have occurred many years earlier, obscuring temporal relations with presumed toxicity.

Confusion has also arisen because manifestations of iron toxicity in HH do not resemble diseases of aging such as atherosclerosis.[46] However, differences exist between iron accumulation with versus without HH. These differences are summarized in Table I.[3-8,15-22,26-33,46-58] Iron in HH is shunted relatively selectively to parenchymal cells, whereas the reticuloendothelial system, the primary site of non-HH storage iron, is relatively spared.[52] Interestingly, heterozygosity for HH, which is not associated with the HH phenotype characteristic of homozygotes, has been shown recently to be a risk factor for vascular disease.[59,60] These findings have been discussed in detail.[61]

Our results (Figure 2) raise the possibility that racial differences in iron stores may contribute to racial differences in disease. The rate of rise and the peak ferritin levels achieved were greater in black men beginning in early adulthood and in black women after menopause compared with whites and Hispanics. The relative contribution of nutritional versus genetic factors to exaggerated iron accumulation in American blacks is unknown, but studies in South African blacks have provided evidence for both mechanisms.[62] Increased dietary iron probably is not responsible for the higher ferritin levels in American blacks because consumption of meat and ready-to-eat cereals that are commonly supplemented with iron is less for blacks than whites.[63]

Examination of diseases that disproportionately affect blacks may provide clues to whether elevated iron stores influence health. The death rate from all causes in blacks is approximately 1.5 times that of whites. Compared with whites, blacks have worse survival after myocardial infarction,[64] a 2-fold-higher incidence of and morbidity from stroke,[65,66] and a higher risk of infrarenal peripheral vascular disease.[67] Morbidity and mortality rates from diabetes,[68] AIDS,[69] and cancer[70] are significantly higher for black men than whites. Differences in socioeconomic status and other risk factors are often invoked to explain the differences in disease prevalence between blacks and whites. However, increased iron stores may play a role because increased iron stores have been associated with impaired glucose tolerance[11] and cancer risk[71,72] as well as vascular disease risk.

If the iron hypothesis is correct, incentive would exist to monitor iron stores often, to define "normal" for body iron stores based on disease correlates, and to better understand the contribution of hereditary and environmental (dietary) factors to iron accumulation. Ferritin levels in the range of 15 to 50 μg/L may be optimal physiologically, on the basis of data showing correlations between serum ferritin levels >50 μg/L with vascular disease risk,[17] disregulation of iron absorption,[8] and increased risk of preterm delivery.[73] Cause-and-effect relations can be defined by prospective intervention studies in which a single variable, the levels of body iron measured by the serum ferritin concentration, is modified.[74] Reducing iron stores to the theoretical optimum of approximately 15 to 50 μg/L is feasible, safe, and inexpensive.[74] If the iron hypothesis is correct, disease prevention might be possible through laboratory monitoring and counseling about dietary iron intake, as would be done for lack of exercise, obesity, tobacco use, homocysteine levels, and dietary fat intake. The public health significance of controlling levels of iron stores might be considerable.

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