Is an elevated serum transferrin saturation associated with the development of diabetes?

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KEY POINTS FOR CLINICIANS

- Diabetes is a common comorbid condition of hemochromatosis and is suggested to be a complication of untreated hemochromatosis.
- Diabetes does not seem to be a complication of hemochromatosis.
- Screening for and treatment of hemochromatosis are justified for several complications but not indicated as a way to prevent development of diabetes.

■ OBJECTIVES Diabetes mellitus is a common comorbid condition of hemochromatosis and is often identified as a complication of untreated hemochromatosis. However, there are few primary data examining the development of diabetes secondary to hemochromatosis. Our objective was to determine the likelihood of developing diabetes in a nationally representative cohort of patients who have an elevated serum transferrin saturation rate but no current diagnosis of diabetes.

■ STUDY DESIGN This is a retrospective cohort study based on merging the National Health and Nutrition Examination Survey I (1971–1974; NHANES I) with the NHANES I Epidemiologic Followup Study (1992).

■ POPULATION Individuals aged 25 to 74 years at the time of the NHANES I without diabetes (n = 9274).

■ OUTCOMES MEASURED The outcome was development of diabetes according to patient report, proxy report, or death certificate by the time of the follow-up interview.

■ RESULTS The incidence of diagnosed diabetes in the cohort was 10.2%. Among individuals with serum transferrin saturation levels above 55%, 7.5% developed diagnosed diabetes compared with 10.2% with a serum transferrin saturation of no more than 45% (P = .38). The relation remained nonsignificant in models adjusted for risk factors of diabetes and in analyses that assumed 10% of patients had received treatment for hemochromatosis.

■ CONCLUSIONS In this nationally representative cohort of adults, elevated serum transferrin saturation was not significantly associated with the development of diabetes.

■ KEY WORDS Hemochromatosis; diabetes mellitus; cohort study (*J Fam Pract 2002; 52:933–936*)

Hemochromatosis is an autosomal recessive abnormality of iron regulation that results in excessive intestinal absorption and cellular deposition of iron.[1] Although hemochromatosis was once thought to be rare, many screening studies have established that it is among the most common inherited metabolic abnormalities.[2–6] The College of American Pathologists has recommended population-based screening for hemochromatosis with the use of the serum transferrin saturation level.[7] Although prevalent in the population, hemochromatosis is rarely diagnosed.[8] The pathologic iron accumulation resulting in hemochromatosis affects many organs including the liver, pancreas, and heart.[9–12] Because primary hemochromatosis is a common comorbid condition with diabetes,[13–15] most work on the relation between hemochromatosis and diabetes has focused on screening patients with diabetes for hemochromatosis.[16,17]

Clinical reviews have stated that, because diabetes is a serious complication of hemochromatosis, screening patients without diabetes for hemochromatosis might be a useful strategy to decrease the likelihood that they will develop diabetes.[15,18–20] However, there are few primary data to support this contention. There is some evidence to indicate that hemochromatosis has the pathogenic features of impaired insulin secretion and insulin resistance due to iron accumulation in the liver.[21] One study indicated that, in individuals with hemochromatosis but neither cirrhosis nor diabetes (n = 7), phlebotomy treatment normalizes serum ferritin levels, acute insulin response to glucose, and glucose tolerance.[22] In patients with hemochromatosis and newly diagnosed diabetes,

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phlebotomy did not affect glucose tolerance or insulin resistance. In a nationally representative cohort, we examined the likelihood that patients with an elevated serum transferrin saturation rate but no current diagnosis of diabetes would develop diabetes during 20 years of follow-up.

METHODS

This retrospective cohort study followed individuals without a diagnosis of diabetes, aged 25 to 74 years at the time of the index interview. We used the National Health and Nutrition Examination Survey I (1971–1974; NHANES I) merged with the NHANES I Epidemiologic Followup Study (1992; NHEFS).

The NHANES I was conducted between 1971 and 1975 and allowed for representative estimates of the non-institutionalized civilian US population. The NHEFS is a national longitudinal study of individuals assessed at the NHANES I baseline. The NHEFS initial population included the 14,407 participants who were 25 to 74 years of age when first examined in NHANES I. More than 98% of the individuals in the initial NHANES I cohort were traced and supplied data for the NHEFS.

The follow-up information was gathered in 3 ways. Surviving subjects were interviewed. If the subject was deceased or alive but incapacitated, a slightly modified version of the subject questionnaire was administered to a proxy respondent. For individuals who had died in the period between the NHANES I index interview and the follow-up interview, information from death certificates was recorded. A total of 1,681 proxy respondents was interviewed in the NHEFS.

Serum transferrin saturation was measured in the original NHANES I. We defined elevated serum transferrin saturation as greater than 45%, greater than 50%, greater than 55%, greater than 60%, or greater than 62%. All of these cutoff values had previously been proposed or used in population-based studies of elevated serum transferrin saturation.[4,5,23]

Diabetes was operationalized as a positive response to the question, Has a doctor ever told you that you have diabetes? This question was asked in the original NHANES I and in each wave of the follow-up survey (1982–1984, 1986, 1987, and 1992). For individuals who could not participate, proxy respondents were queried. In terms of individuals who died before the follow-up survey, we operationalized the development of diabetes as an ICD-9 diagnosis of 250.XX for underlying cause of death or any of the 20 other diagnoses listed on the death certificate.

We also assessed risk factors for diabetes available in the NHANES I, including obesity represented by a body mass index greater than 27 kg/m^2, race, sex, age, physician diagnosis of hypertension, and total serum cholesterol above 240 mg/dL as a way to increase our understanding of diabetes mellitus as a consequence of hemochromatosis.

Our index sample was limited to men and women 25 to 74 years of age in the NHANES I, who had a serum transferrin saturation rate recorded in the NHANES I, did not have diabetes at the initial index interview, and had information on the development of diabetes (n = 9724).

DATA ANALYSIS

We used sampling weights to calculate prevalence estimates for the civilian noninstitutionalized US population. Because of the complex sampling design of the survey, we performed all analyses with SUDAAN.[24]

We initially computed unadjusted estimates of the likelihood of development of diabetes for different levels of elevated serum transferrin saturation between 1971 and 1974. We attempted to compute analyses for serum transferrin saturation levels of 60% and 62%, but the number of people who developed diabetes with those levels was so small ($n < 10$) that stable estimates could not be computed. Consequently, analyses were limited to samples with serum transferrin saturations greater than 45%, greater than 50%, and greater than 55%. We then computed logistic regression models examining the independent effect of elevated serum transferrin saturation on the outcome of developing diabetes in the follow-up period and controlled for age, sex, race, obesity, high serum cholesterol, and physician diagnosis of hypertension.

Because we could not determine whether individuals with elevated serum transferrin saturation received treatment for hemochromatosis during the time of the study, we computed a series of analyses assuming that different proportions of individuals received treatment during the time frame. Some national evidence has suggested that few individuals are diagnosed with hemochromatosis. In fact, in the 1996, 1997, and 1998 National Ambulatory Medical Care Surveys, there were 7 visits for hemochromatosis of 64,001 total evaluated visits (0.01% of visits).[8] We recomputed the adjusted odds ratios for the samples of people with transferrin saturation rates greater than 45% and 50% after randomly selecting 10% of each group and treating those individuals as though they were undergoing therapeutic phlebotomies.

RESULTS

Table 1 presents the characteristics of the population with baseline characteristics and characteristics measured in the follow-up data collection. A substantial proportion of the adult population had elevated serum transferrin saturation greater than 45%, 50%, and 55%. The incidence of diagnosed diabetes in the cohort was 10.2%.

Among individuals with serum transferrin saturation levels greater than 45% at the NHANES I

TABLE 1

Baseline characteristics of the population collected in National Health and Nutrition Examination Survey I

Characteristic	Value
Male sex	47.7%
Race	
European American	90.7%
African American	8.7%
Other	0.6%
Age, mean ± standard error (y)	47.1 ± 0.2
Obesity (body mass index ≥ 27)	32.3%
Transferrin saturation (cumulative)	
> 45%	8.0%
> 50%	4.6%
> 55%	2.7%
> 60%	1.7%
> 62%	1.4%
Total serum cholesterol (>240 mg/dL)	32.0%
Hypertension (informed by physician)	13.6%
Collected in NHFES follow-up	
Developed diabetes	10.2%

NHFES, National Health and Nutrition Examination Survey I (NHANES I) merged with the NHANES I Epidemiologic Followup Study.

baseline, 8.9% developed diagnosed diabetes compared with 10.3% who did not have elevated serum transferrin saturation (P = .44). Similarly, among individuals with serum transferrin saturation levels greater than 50% at the NHANES I baseline, 8.1% developed diagnosed diabetes compared with 10.3% who did not have elevated serum transferrin saturation (P = .34); of individuals with transferrin saturation levels greater than 55%, 7.5% developed diabetes compared with 10.2% of those without elevated serum transferrin saturation (P = .38). Table 2 indicates that individuals with elevated transferrin saturation levels are not significantly more likely to develop diagnosed diabetes than individuals without elevated serum transferrin saturation. The lack of a significant relation is present in unadjusted and adjusted analyses.

When we reestimated the models assuming that 10% of the population with elevated serum transferrin saturation (> 45%) were successfully treated, individuals with elevated serum transferrin saturation were not significantly more likely to develop diagnosed diabetes than individuals without elevated serum transferrin saturation. This relation held in unadjusted and adjusted analyses. When we assumed that 10% of the population with elevated serum transferrin saturation at greater than 50% and greater than 55% were successfully treated, individuals with elevated serum transferrin saturation were not significantly more likely to develop diagnosed diabetes than individuals without elevated serum transferrin saturation. These relations remained consistent in unadjusted and adjusted analyses.

DISCUSSION

The findings of this study call into question the commonly held assumption that there is a causative relation between the presence of hemochromatosis and the subsequent development of diabetes mellitus. Although diabetes is a common comorbid condition with hemochromatosis,[13,14] this may be due to the fact that both conditions are relatively common, not that one disease leads to the development of the other. In this longitudinal analysis, even when examining the likelihood of developing diabetes at different levels of transferrin saturation, the findings suggested that hemochromatosis does not lead to diabetes.

Could the findings of the current study be explained by the fact that people were treated for hemochromatosis, thus reducing the subsequent development of complications such as diabetes? This seems unlikely because few people with hemochromatosis are routinely identified, and even fewer are treated on a chronic basis. On the contrary, the phenomenon that few people with hemochromatosis are diagnosed and treated is the rationale for recent recommendations for screening asymptomatic persons. Further, in unadjusted and adjusted analyses of the current study, people with elevated transferrin saturation were no more likely to develop diabetes than people without elevated transferrin saturation, even after assuming that 10% of the population with elevated transferrin saturation (> 45%, > 50%, and > 55%) were successfully treated.

TABLE 2

Unadjusted and adjusted odds of developing diabetes with an elevated serum transferrin saturation level

Transferrin saturation	Unadjusted OR (CI)	Adjusted* OR (CI)
Original data		
> 45%	1.17 (0.78–1.75)	0.89 (0.59–1.34)
> 50%	1.29 (0.73–2.29)	0.95 (0.53–1.70)
> 55%	1.40 (0.60–3.27)	1.03 (0.44–2.43)
Assuming 10% treatment		
> 45%	1.23 (0.8–1.9)	0.94 (0.61–1.47)
> 50%	1.29 (0.7–2.39)	0.96 (0.52–1.79)
> 55%	1.41 (0.56–3.58)	1.05 (0.41–2.67)

*Controlling for age, sex, race, hypercholesterolemia, obesity, and hypertension.
CI, 95% confidence interval; OR, odds ratio.

The findings of this study have implications for whether screening for hemochromatosis is worthwhile, assuming that prevention of diabetes is a goal. Hemochromatosis has many characteristics that make it attractive for screening: the disorder is common, it posseses a long asymptomatic phase, a simple screening test is available, and treatment is effective. To be a reasonable candidate for screening, the condition also needs to cause substantial morbidity or mortality, and treatment in the asymptomatic phase should be more effective than treatment initiated after the onset of symptoms.[25] The findings of this study suggested that screening for and treatment of hemochromatosis are not worthwhile as a way to prevent diabetes. However, the relation between hemochromatosis, treatment, and the development of cirrhosis or hepatocellular carcinoma may warrant screening for hemochromatosis. There is preliminary evidence from an observational study that diagnosing patients with hemochromatosis in the precirrhotic stage and treating them with phlebotomy results in a normal life expectancy, whereas those diagnosed with hemochromatosis and cirrhosis have a shortened life expectancy and a high risk of liver cancer, even when iron depletion has been achieved.[10]

Our study had several limitations. First, the estimate from the NHANES I was based on an elevated serum transferrin saturation level. This is an appropriate first step in a diagnosis of hemochromatosis. Some investigators have recommended that elevated serum transferrin levels should be confirmed with a second fasting level or an elevated ferritin level.[26,27] Further, we did not have access to liver biopsy data, which is considered the gold standard for diagnosing hemochromatosis. Thus, a single elevated transferrin saturation level may have resulted in overestimates of the prevalence of hemochromatosis in the study population. Second, the estimate also might have been affected by the use of the lower levels of serum transferrin saturation (> 45%, > 50%, or > 55%). Although using a more stringent level, eg, greater than 60%, might have strengthened the conclusions, so few people with this level developed diabetes that we could not accurately make a population estimate.

In summary, diabetes does not seem to be a likely complication of hemochromatosis as indicated by the presence of an elevated serum transferrin saturation. Consequently, cost-effectiveness models of screening for hereditary hemochromatosis may need to be reevaluated.

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