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Anti-Obesity and Pro-Diabetic Effects of Hemochromatosis

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Abstract

Objective—Levels of tissue iron contribute to determining diabetes risk, but little is known about the effects of higher iron levels on weight, nor on the interaction of weight and iron overload on diabetes risk. We therefore examined the effect of iron on body mass index and diabetes in individuals with iron overload from hereditary hemochromatosis (HH), compared to non-HH siblings and historical controls.

Methods—Chart reviews were performed on a cohort of adults (age ≥ 40, $N=101</math>) with the common C282Y/C282Y HFE genotype, compared to wild type siblings ($N=32</math>) and comparable NHANES cohorts, with respect to body mass index and diabetes status.$$

Results—Males with HH have lower body mass index (BMI) than control siblings. Females had a trend toward decreased BMI that was not significant, possibly related to decreased degrees of iron overload. In both males and females, increased rates of diabetes were seen, especially in the overweight or obese.

Conclusions—High tissue iron levels may be both pro- and anti-diabetic. The prevalence of obesity and diabetes in HH is likely dependent upon the degree of iron overload, caloric intake, and other genetic and environmental factors, contributing to the observed heterogeneity in the frequency of disease-related morbidities in HH.

Keywords

hereditary hemochromatosis; diabetes; iron overload; obesity

Introduction

Iron restriction causes adiposity in rats (1), and iron deficiency is associated with obesity in humans (2). Less is known about the effects of higher levels of iron on body weight. We therefore studied individuals with hereditary hemochromatosis (HH), an autosomal recessive disorder characterized by excessive iron storage affecting 0.3-0.5% of Caucasians (3). Two

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missense mutations in the *HFE* gene account for the majority of HH: C282Y and H63D (3, 4), with C282Y homozygotes having the highest risk (5). In the absence of normal HFE, hepcidin, a peptide that regulates iron entry into the circulation, is reduced and dietary iron absorption is high (6). As iron accumulates in tissues, clinical manifestations of cirrhosis, diabetes and other organ damage may ensue.

We previously analyzed individuals with HH and found a significant prevalence of diabetes (7). A mouse model of hemochromatosis with deletion of the *Hfe* gene demonstrates decreased insulin secretion and loss of beta cell mass, consistent with the human phenotype (8). Before the onset of diabetes in HH, both mice and humans exhibit increased insulin sensitivity, a phenomenon that in the mouse model is caused by increased expression of the insulin sensitizing hormone adiponectin (7, 9). Additionally, the mouse model was protected from high fat diet-induced obesity (10), and we therefore hypothesized that humans with HH might also be so protected. However, if diet-induced obesity ensued despite that relative protection, we hypothesized that the inability to compensate for the insulin resistance with increased insulin secretion would cause diabetes to occur at an increased frequency compared to non-HH individuals.

Methods

Subjects

The study participants were recruited from referrals to the Hemochromatosis Research Clinic at the University of Utah from 2000 to the present. *HFE* genotyping was performed using allele-specific PCR primers (7). All of the referred patients agreed to serve in the study and informed consent was obtained. Siblings and other relatives of the referred subjects were screened for hemochromatosis mutations and those relatives who were found to be homozygous wild type or heterozygous wild type/mutant at the *HFE* locus served as controls. (Heterozygotes for *HFE* mutations are not iron-overloaded and do not suffer associated morbidities (11)). All participants were Europoid whites. Because of the low number of wild type sibling controls, we also used comparator groups (non-Hispanic white, age >40) from the National Health and Nutrition Examination Survey (NHANES) (12, 13)). The study was approved by the University of Utah Institutional Review Board.

Clinical studies

Chart reviews were performed on 243 charts from hemochromatosis subjects studied from 2000 to the present. Because iron overload develops over the lifespan, subjects less than 40 years of age and those with incomplete data on documentation of diabetes status or height and weight were excluded. Ages did not differ among the groups (C282Y/C282Y: Males, N=67, 53.9±1.7 years; females, N=34, 57.2±2.5 years; Wild type or heterozygotes: Males, N=15, 54.6±1.1 years; females, N=17, 56.3±1.6 years). Statistical analyses used SPSS software (Chicago, IL).

Results

Because of heterogeneity in phenotypes among different HH genotypes (5), we included only C282Y/C282Y homozygotes in the HH group, all aged ≥40y. Body mass index (BMI)

was lower in males with HH (mean, 26.7 ± 0.5 kg/m², median 26.5), compared to wild type or heterozygote controls (mean, 30.5 ± 1.6 kg/m², median 29.3) (Fig. 1, $p=0.014$). We also compared these individuals to the 1999- 2002 NHANES cohort; most HH individuals were recruited in that interval, and we sought to minimize bias because of increasing BMI over time in the U.S. Non- Hispanic white men, age 40 in that cohort had an average BMI of 28.7 ± 0.3 (13), significantly greater than that of the HH group ($p < 0.05$) but not the sibling controls. Female C282Y/C282Y homozygotes by contrast, did not have significantly lower BMI than controls (HH, mean 26.0 ± 1.1 kg/m², median 23.9; controls 26.7 ± 1.1 kg/m², median 25.7; NHANES mean 28.3 ± 0.3 kg/m², $p=0.51$). Because women have lower serum ferritin values and consequently fewer clinical manifestations of HH than men (14), we assessed ferritin values and found that they trended lower in the females than in the men (females, 508 ± 150 ng/mL, normal 12-240 ng/mL; males 1038 ± 207 ng/mL, normal 30-490 ng/mL, $p=0.08$).

We next assessed diabetes frequency as a function of weight in HH subjects compared to control and NHANES cohorts, age 40. The fraction of all C282Y/C282Y homozygotes with diabetes ($23/92=0.25$) was higher than that of non-Hispanic white adults in the 1999-2000 NHANES cohort ($12/387/3602=.11$, $p < 0.001$ by Fisher's exact test). Our non-HH controls had a similar frequency of diabetes as the NHANES cohort (0/8 with normal weight, 1/8 with overweight, and 1/9 with obesity, overall frequency .08) although because of the small number on whom we had definitive data about diabetes, the frequency was not significantly different from the C282Y/C282Y homozygotes ($p=0.08$). When the C282Y/C282Y homozygotes were compared to the NHANES cohort by weight category (12), the frequency of diabetes was significantly higher in all groups ($p=0.025$, <0.0001 and 0.0048 in normal, overweight, and obese, respectively, Fig. 2). The absolute increase in prevalence of diabetes was highest in the obese HH group, with 44.4% diabetics compared to 15.5% in controls). The overall frequency of diabetes in C282Y homozygotes did not differ between males ($16/60=0.27$) and females ($7/32=0.22$, $p=0.80$ by Fisher's exact test).

Discussion

We demonstrate that iron overload in HH is associated with decreased weight in men. In addition, overweight and obesity significantly increase the prevalence of diabetes in HH. Obesity has been previously reported to be a risk factor for diabetes in HH (15). In addition to supporting this conclusion, the current study reports an extremely high prevalence of diabetes in obese hemochromatosis subjects.

The effects of HH were dampened in women, although in all cases the differences between HH subjects and controls trended in the same direction for both sexes. Complications of HH are seen at lower frequency in women, presumably related to decreased iron overload due in part to blood loss during menstruation and child birth (14), consistent with the observed trend toward lower ferritin values in the female HH subjects.

There are conflicting reports about the frequency of morbidity in HH. In a cross- sectional study, for example, Beutler et al. found no difference in self-reported symptoms among those with *HFE* mutations compared to controls with the exception of homozygotes

reporting a greater history of liver disorders (16). In contrast, two large studies that assessed severity of disease by objective criteria including liver biopsy found a higher frequency of morbidity (14, 17). This was true even in a clinically unselected cohort of relatives of patients with HH found to be homozygous for *HFE* mutations (14). The current data provide a possible explanation for these discrepancies, namely there may be competing morbid (e.g. insulin deficiency, cirrhosis) and protective (leanness) aspects of iron overload, that might be expected to be more or less present in populations with differing diets, environments, or genetic backgrounds.

There has also been controversy about the prevalence of diabetes in HH. Prior to the advent of genetic testing, there was selection bias for individuals with diabetes being identified as having hemochromatosis, but even after discovery of the *HFE* mutations, studies have yielded conflicting results. Some studies have detected no increase in diabetes prevalence in individuals with *HFE* mutations (16), although positive associations between diabetes and *HFE* mutations have been observed in several other studies (reviewed in (18)). The relative protection from obesity may explain some of the conflicting data on diabetes penetrance. In prior years when obesity was less prevalent, in populations with different risk for obesity, or with differing diets and prevalence of iron deficiency, the protection from obesity would vary in magnitude and thus affect the resultant overall frequency of diabetes.

The fact that diabetes risk is increased to a greater extent in HH individuals with overweight and obesity is consistent with our observations that the primary early effect of HH is loss of insulin secretory capacity (7, 8). Thus, obese individuals with HH are less able to compensate for insulin resistance with hyperinsulinemia because of less insulin secretory capacity (19). These results also speak to controversy over the relative contributions of insulin resistance and insulin secretion to diabetes in HH (18). Based on the current data, a significant number of HH diabetics would be insulin resistant based on their obesity, even though HH itself is not characterized by insulin resistance (7, 9). At the same time, it is also possible to lose almost all insulin secretory capacity in HH (7), explaining higher rates of diabetes even in lean HH subjects.

The mechanism for decreased weight in individuals with HH is not known. HH mice on a high fat diet are hypermetabolic, protected from obesity, and exhibit increased fatty acid oxidation and activation of AMPK (10, 20). Further mechanistic studies in humans are important given the conflicting effects of high iron on diabetes risk, namely protection from obesity but decreased insulin secretion. Given the broad 20-fold range of “normal” serum ferritin values, there likely exists a narrower range that supports both optimal weight and insulin secretion.

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What is known:

- Increased iron stores are a risk factor for diabetes
- Iron deficiency is associated with increased weight, although little is known about the effects of higher iron stores on weight

What this study adds:

- Iron overload in hereditary hemochromatosis is associated with lower body mass index
- Despite relative protection from overweight, individuals with obesity and iron overload have significantly higher rates of diabetes

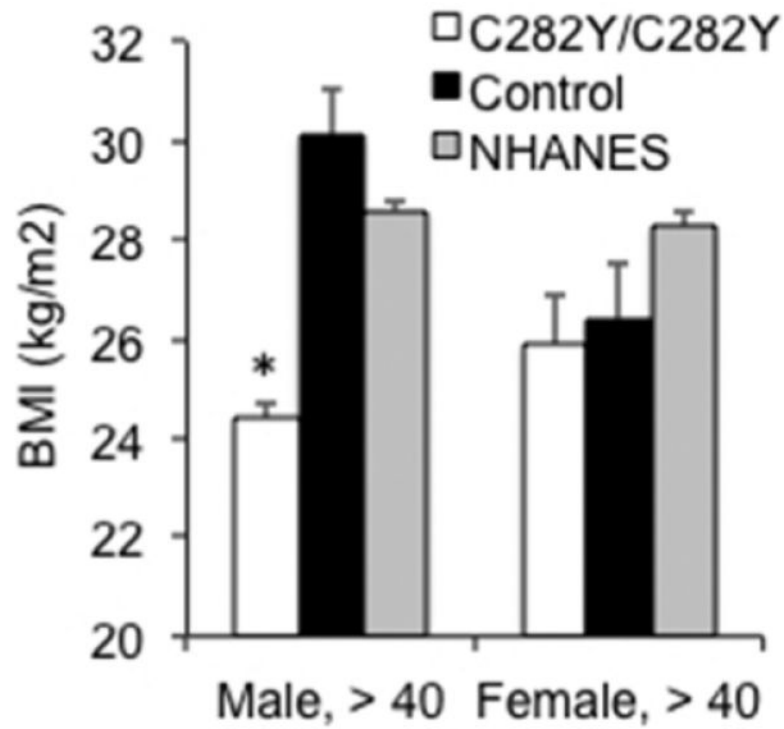


Figure 1. Average body mass index (BMI) in males and females homozygous for the C282Y HFE mutation compared to wild type or heterozygous siblings

BMI (mean±SEM) was determined in subjects over age 40 (N=67 male and 34 female C282Y homozygotes; 15 male and 17 female sibling controls). Data are also shown for the 1999-2002 NHANES cohort (13). Wild type denotes the phenotype and includes C282Y heterozygotes. * $p < 0.05$, C282Y vs. Control or NHANES, t-test

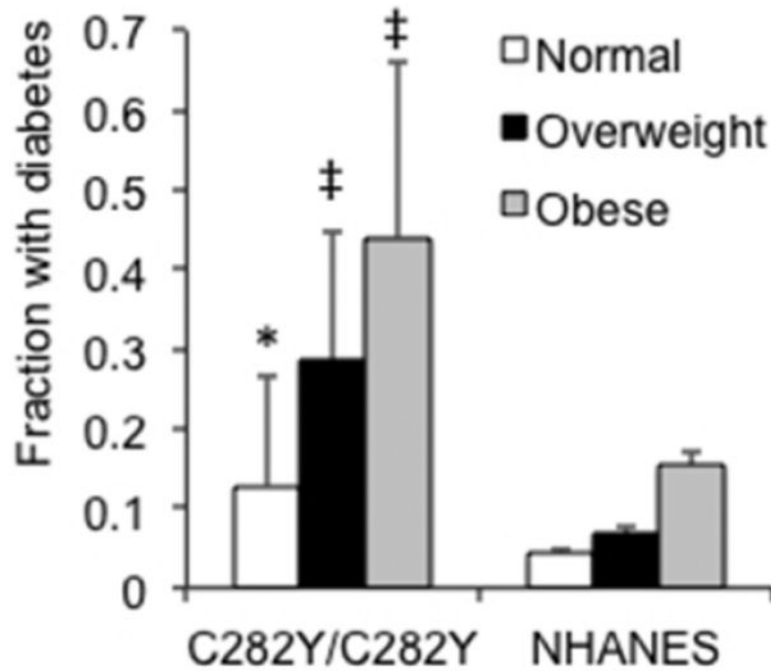


Figure 2. Fraction of individuals homozygous for the C282Y HFE mutation who have diabetes, by weight category, compared to the 1999-2002 study of the NHANES cohort

Individuals were ascertained as having diabetes by criteria of fasting blood glucose, glucose tolerance testing, or medical history and use of antidiabetic medications. Individuals whose glucose status was not known were excluded. Males and females were combined, but did not differ in overall diabetes frequency (total 16/60 males and 7/32 females). The number of sibling controls whose diabetes status was known was small but comparable to the NHANES cohort (0/8 normal weight, 1/8 overweight, 1/9=8% diabetic). The NHANES 1999-2002 cohort was chosen as the comparator because the diabetes assessment of most of the hemochromatosis cohort was performed in that time frame. (C282Y/C282Y, N=39 normal weight, 35 overweight, 18 obese; NHANES, N=5216 normal weight, 5202 overweight, 4633 obese). Error bars reflect 95% confidence intervals. * $p < 0.05$, ‡ $p < 0.001$ C282Y vs. NHANES