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Proton Pump Inhibitors and Lower Serum Ferritin Levels in 171 *HFE* C282Y Homozygotes in the Hemochromatosis and Iron Overload Screening Study

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Abstract

Background: In non-screening hemochromatosis patients with *HFE* C282Y homozygosity who achieve iron depletion, the proton pump inhibitor (PPI) omeprazole decreases non-heme iron absorption from test meals and decreases maintenance phlebotomy requirements. We sought to determine the effect of taking PPIs and histamine H2 receptor antagonists (H2RAs) on serum ferritin (SF) levels in C282Y homozygotes diagnosed in a screening study.

Methods: We compared mean ln SF in 171 homozygotes (60 men, 111 women) who reported taking and not taking PPIs and H2RAs. We performed linear regression on ln post-screening SF using age, sex, reports of taking PPIs and H2RAs, and free thyroxine levels.

Results: Eleven homozygotes (6.4%) took PPIs; twelve (6.7%) took H2RAs. Mean ln SF values of male and female homozygotes who took PPIs were ~one-half those of homozygotes without PPI reports, but the differences were not significant. In an initial five-factor regression model, H2RAs and free thyroxine levels were not significant predictors of ln SF. In a final three-factor regression model, taking PPIs was associated with lower ln SF ($p=0.0031$) after controlling for age and sex. The final model explained 31% of the variance in ln SF. Use of H2RAs was not independently associated with ln SF.

Conclusions: Taking PPIs is associated with lower SF levels in *HFE* C282Y homozygotes diagnosed in screening. Inorganic iron absorption may be decreased in some homozygotes who take PPIs; others who take PPIs may have upper gastrointestinal lesions that lower SF due to blood loss.

Keywords: Ferritin; Hemochromatosis; Histamine H2 receptor antagonist; Iron absorption; Proton pump inhibitor

Introduction

Hemochromatosis associated with homozygosity for the C282Y mutation of the *HFE* gene on chromosome 6p occurs in 2-6 per thousand whites of northwestern European ancestry. Increased iron absorption and consequent increased storage of iron are the predominant causes of hyperferritinemia in *HFE* C282Y homozygotes [1,2]. In the population-based HEIRS Study [3], elevated serum ferritin (SF) levels were observed in 88% of white men and 57% of white women discovered to have C282Y homozygosity [4].

Absorption of inorganic iron depends on its solubilization by gastric acid [5]. Amidated and non-amidated forms of the hormone gastrin stimulate and potentiate gastric acid secretion, respectively [6]. Non-amidated gastrins require ferric ions for biological activity *in vitro* [6]. Subsequent transport of soluble inorganic iron across the luminal surfaces of absorptive enterocytes depends on divalent metal transporter-1 (DMT1), a pH-dependent metal transporter [7]. In *HFE* C282Y homozygotes, serum gastrin levels are increased [6] and DMT1 expression is up-regulated [7,8]. These mechanisms could partly account for the increased absorption of inorganic iron in C282Y homozygotes. It is also plausible that decreasing gastric acid secretion could decrease solubilization of inorganic iron, DMT1 activity, and inorganic iron absorption, and decrease the rates of rise of storage iron and SF levels in C282Y homozygotes.

Proton pump inhibitors (PPIs) and histamine H2 receptor antagonists (H2RAs) decrease gastric acid secretion in short-term studies of persons without hemochromatosis [9-11]. In hemochromatosis patients with C282Y homozygosity previously treated with phlebotomy to achieve iron depletion, the PPI omeprazole decreased the absorption of non-heme iron from test meals and decreased maintenance phlebotomy requirements [12]. Observations regarding the effect of H2RAs on iron absorption or phlebotomy requirements in persons with hemochromatosis are very limited [13]. We postulated that reports of taking PPIs or H2RAs would be associated with lower SF levels in participants in the population-based HEIRS Study who were discovered to have *HFE* C282Y homozygosity. To test this postulate, we tabulated data on 171 euthyroid participants with *HFE* C282Y homozygosity. We computed the relationships of reports of taking PPIs or H2RAs to SF levels in specimens obtained at a post-screening clinical evaluation using univariable and multivariable

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methods. The implications of our results are discussed in the context of mechanisms of iron absorption and causes of hyperferritinemia in C282Y homozygotes.

Methods

Study approval

The local Institutional Review Boards of the HEIRS Study Coordinating Center, Central Laboratory, and each Field Center approved the Study protocol [3]. The Field Centers recruited participant's ≥ 25 years of age who gave informed consent.

Selection of study subjects

Participants were recruited from primary care clinics during the interval February 2001-February 2003 at HEIRS Study Field Centers [3,14]. All adult volunteers were eligible to participate in the HEIRS Study, but those who participated only because a family member participated or those who reported on their screening questionnaire that they had been previously diagnosed to have hemochromatosis or iron overload were excluded from the present analysis [15]. All C282Y homozygotes diagnosed in the HEIRS Study were invited to participate in a clinical examination that included listing of participants' medications, review of the listing by HEIRS Study personnel, and collection of blood samples for additional testing [3,14]. Herein, we included observations on euthyroid C282Y homozygotes because a previous report from the HEIRS Study revealed that hypothyroidism or hyperthyroidism affected SF levels significantly [14].

Laboratory methods for SF and serum thyroid-related measures

All measurements were performed at the HEIRS Study Central Laboratory at the University of Minnesota Medical Center-Fairview [3]. SF levels were measured using a turbidometric immunoassay (Roche Diagnostics/Hitachi 911, Indianapolis, IN) [3,14]. The SF reference ranges defined by the HEIRS Study were 15-200 $\mu\text{g/L}$ (women) and 15-300 $\mu\text{g/L}$ (men) [3,14]. Serum concentrations of thyroid-stimulating hormone (TSH) and free thyroxine (T4) were measured using a Siemens/Bayer ADVIA Centaur[®] immunoassay analyzer (Siemens Corporation, New York, NY) as described elsewhere [14]. Reference ranges were TSH 0.400-5.00 mIU/L and free T4 9.0-23.8 nmol/L [14]. We defined hypothyroidism as having TSH >5.00 mIU/L and free T4 <9.0 nmol/L, and hyperthyroidism as having TSH <0.400 mIU/L and free T4 >23.8 nmol/L, regardless of cause [14].

Medications

Obtaining information about participants' medications was performed in a prospective manner in the HEIRS Study. Participants brought their prescription and non-prescription medications and supplements to the post-screening clinical examination for review by HEIRS Study personnel. The name of each item was tabulated for the Study. These medication listings were subsequently reviewed and edited for correctness by a subcommittee of Study physician investigators. It was beyond the scope of the Study to record the dose and schedule of the respective medications and supplements or the indications for their use or to inquire about the compliance of the Study participants in taking the medications or supplements. PPIs taken by participants were esomeprazole, omeprazole, lansoprazole, and pantoprazole. H2RAs taken by participants were cimetidine, famotidine, and ranitidine.

Statistics

We reviewed post-initial screening observations on 176 *HFE* C282Y

homozygotes diagnosed in the HEIRS Study. Observations on three homozygotes were excluded because they had hyperthyroidism [14]. Two other homozygotes were excluded because some of their data were missing. Thus, the analytic dataset consisted of observations on 171 euthyroid C282Y homozygotes. Data tabulation and statistical analyses were performed using Excel 2000[®] (Microsoft Corp., Redmond, WA), and GB-Stat[®] (v.10.0, 2003, Dynamic Microsystems, Inc., Silver Spring, MD). SF levels less than 15 $\mu\text{g/L}$ were imputed as 7.5 $\mu\text{g/L}$. Free T4 and SF data were normalized using natural logarithm (ln) transformation for analysis [14]. Results were reported as anti-ln values. Descriptive data are displayed as enumerations, percentages, mean ± 1 SD, or geometric mean (95% confidence interval (CI)), as appropriate. Frequency values were compared using chi-square analysis or Fisher exact test, as appropriate. Mean values were compared using Student's two-tailed t-test. In univariable analyses, most observations in men and women were evaluated separately. Multiple regression analyses were performed using age, sex, use or non-use of PPIs and H2RAs, and ln free T4 as the independent variables; ln SF was the dependent variable. Values of $p < 0.05$ were defined as significant.

Results

General characteristics of 171 euthyroid *HFE* C282Y homozygotes

There were 60 men and 111 women. The predominance of women is consistent with the overall greater participation of women than men in the HEIRS Study [15]. The mean age of both men and women was 50 ± 13 (SD) years. The geometric mean SF level (95% CI) was 709 ng/mL (124, 4,057) in men and 199 ng/mL (15, 2,696) in women ($p < 0.0001$), consistent with the overall HEIRS Study results [15] and those of another large US clinic-based hemochromatosis and iron overload screening program [16]. A greater proportion of men had elevated SF levels than women (90.0% vs. 56.8%; $p < 0.0001$). A greater proportion of women had subnormal SF levels than men (4.5% vs. 0%; $p < 0.0001$). Taking PPIs was reported by 5.0% of men and 7.2% of women. Taking H2RAs was reported by 6.7% of men and 7.2% of women. In univariable analyses, mean SF levels in men and women who took PPIs were approximately one-half of the mean SF levels in men and women who did not take PPIs, although these respective differences did not achieve statistical significance (Table 1).

Predictors of ln SF in a regression analysis

Straight multiple regression was performed on ln SF using these independent variables: age, sex, use of PPIs, use of H2RAs, and free T4 levels. The respective values of p for these variables were < 0.0001 , < 0.0001 , 0.0023, 0.1020, and 0.2435. In a final three-factor model, taking PPIs was independently associated with lower ln SF ($p = 0.0031$) after controlling for the effects of greater age and male sex (both covariates, $p < 0.0001$). The final three-factor model explained 31% of the variance in ln SF (Table 2).

Discussion

A novel finding in the present study is that taking PPIs was a significant independent predictor of lower ln SF levels in 171 *HFE* C282Y homozygotes diagnosed in the HEIRS Study. This is consistent with a previous report that taking PPIs decreased the absorption of non-heme iron from a test meal and from the habitual diet in hemochromatosis patients with C282Y homozygosity diagnosed in medical care [12]. Achlorhydria or drugs that reduce gastric acid secretion decrease absorption of inorganic iron by reducing its solubility [17,18]. In addition, iron uptake into enterocytes mediated by DMT1

Table 1: Serum ferritin (SF) levels in 171 adult *HFE* C282Y homozygotes^a.

Medication	Men taking medication	Men not taking medication	Value of p ^a
Proton pump inhibitors	405 (4, 45784)	731 (158, 3370)	0.7163
Histamine-2 receptor antagonists	763 (385, 1512)	706 (117, 4263)	0.7540
Medication	Women taking medication	Women not taking medication	Value of p ^a
Proton pump inhibitors	90 (4, 1882)	212 (17, 2700)	0.1651
Histamine receptor-2 antagonists	109 (8, 1531)	209 (16, 2791)	0.2360

^aThere were 60 men and 111 women. Three men and eight women took proton pump inhibitors. Four men and eight women took histamine receptor-2 antagonists. Results are displayed as geometric means (95% CI). Student's two-tailed t-tests were performed using ln SF values.

Table 2: Parameters of a multiple regression analysis on ln serum ferritin level in 171 *HFE* C282Y homozygotes^a.

Independent variable	Beta coefficient	S.E. (Beta)	t-Value	Value of p
Age, y	0.0302	0.0068	4.4211	<0.0001
Male sex	1.22206	0.1800	6.7809	<0.0001
Proton pump inhibitors	-1.0659	0.3555	-2.9979	0.0031

^aMultiple R=0.5554; Multiple R²=0.31; S.E. estimate=1.1215; and constant=3.8717.

requires proton co-transport. It is presumed that the required protons are derived from gastric acid that enters the duodenum [19,20].

We observed that taking H2RAs was not a significant negative predictor of lower ln SF levels in the 171 *HFE* C282Y homozygotes diagnosed in HEIRS Study. H2RAs decreased dietary iron absorption in short-term studies of persons not diagnosed to have hemochromatosis [21], but continuous use of cimetidine for three years by persons without hemochromatosis did not alter hemoglobin or serum iron levels significantly [22]. A patient who took cimetidine for a long time nonetheless developed hemochromatosis with high transferrin saturation [13]. The greater influence of PPIs than H2RAs on ln SF levels in the present study could be explained by the direct inhibition of gastric acid secretion and longer duration of action characteristic of PPIs [9-11].

SF is the most commonly used surrogate measure of body iron stores. Measuring body iron stores either by quantitative phlebotomy or by analysis of liver biopsy specimens was not part of the original HEIRS Study. Although availability of post-screening therapeutic phlebotomy records was insufficient for their inclusion in the present study, SF levels in the present men and women are similar to corresponding initial screening SF levels in all HEIRS Study C282Y homozygotes [4,15], thus excluding strong selection bias in this ancillary study. Analyses of iron-related genes in these same *HFE* C282Y homozygotes revealed few mutations that would account for heterogeneity of iron phenotypes [23,24]. Diet or lifestyle factors may be important determinants of SF [25], but we did not evaluate reports of food choices and frequencies in the present analyses. It is unknown whether similar relationships of taking PPIs or H2RAs to SF levels or iron stores would be observed at diagnosis in hemochromatosis probands in medical care.

“Confounding by indication” is a concern in observational pharmacoepidemiology. This bias occurs if the clinical indications for prescribing a medication independently cause the outcome of interest. The aim of prescribing PPIs and H2RAs is almost always to control symptoms in the upper gastrointestinal tract caused by gastric acid secretion. Thus, “confounding by indication” is possible in the present study due to the known negative association between gastric pH and iron absorption [5]. We did not have measurements of gastric pH or iron absorption in the present subjects before or after they began taking PPIs or H2RAs to put in our model. In addition to indications for medication use, our results could be confounded by dose and schedule, dietary factors, acquired conditions, and genetic attributes. Our multivariable analyses included a limited number of variables that could confound the association between PPIs and H2RAs and ln SF.

Assessment of other potential confounders was beyond the design and scope of the present study. Some disorders, especially common liver conditions, may cause or contribute to hyperferritinemia in persons with or without C282Y homozygosity [26]. The significant negative association of taking PPIs with SF levels that we observed in multiple regression analyses is consistent with the relatively high compliance with and protracted use of PPIs (and H2RAs) for several common therapeutic indications [27-30] and with the measured effects of PPIs on inorganic iron absorption in C282Y homozygotes who had achieved iron depletion with phlebotomy [12]. It is also possible that some of the present C282Y homozygotes who reported taking PPIs or H2RAs had lower SF due to upper gastrointestinal lesions that caused blood loss.

We conclude that taking PPIs is associated with lower SF levels in *HFE* C282Y homozygotes diagnosed in a screening program. Inorganic iron absorption may be decreased in some homozygotes who take PPIs; others who take PPIs may have upper gastrointestinal lesions that lower SF due to blood loss.

Disclosures

The authors have no conflicts of interest to disclose.

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Author contributions: All authors contributed substantively to the design and data collection of the HEIRS Study. JCB conceived the present study, performed statistical analyses, and drafted the manuscript. MS and CEM participated in performing statistical analyses. PCA, RTA, CEM, MS, GDM, VRG, and JHE contributed substantive details of the study design, data interpretation, and manuscript formulation. All authors read and approved the final manuscript draft.

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Declaration of funding interests

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