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Calcium channel blocker use and serum ferritin in adults with hypertension

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Abstract Iron overload cardiomyopathy is becoming more prevalent, and early recognition and intervention may alter outcomes. Calcium channels are key transporters of iron under iron-overloaded conditions, and potentially represent a new therapeutic target for iron overload. The purpose of this study was to examine the relationship between Calcium channel blocker (CCB) use and serum ferritin among adults with diagnosed hypertension. We analyzed the nationally representative NHANES (National Health and Nutrition Examination Survey) 1999–2002 for adults ≥40 years with diagnosed hypertension. The association between CCBs and serum ferritin was assessed using a t-test and adjusted multiple regressions.The study population included 2143 individuals (representing 37.4 million individuals, 42.0 % males). 12.6 % of the population reported taking CCBs in the last month. Individuals taking CCBs had lower mean serum ferritin (129.3 ng/mL versus 154.5 ng/mL, $p = 0.02$). After adjusting for age, sex, menopause and hysterectomy status for women, race/ethnicity, and C-reactive protein, mean serum ferritin for individuals taking CCBs was 26.3 ng/mL lower than for those not taking CCBs ($p = 0.01$). In an adjusted regression, individuals who took CCBs and had a daily vitamin C intake of ≥500 mg had a mean serum ferritin that was 60.1 ng/mL lower than people not taking CCBs and with daily vitamin C < 500 mg ($p < 0.001$). In conclusion, this study found an association between use of CCBs and lower serum ferritin levels in individuals with hypertension. Further studies are needed to assess the possible use of CCBs as non-traditional chelating agents for treatment of iron overload cardiomyopathy.

Keywords Calcium channel blockers · Serum ferritin · NHANES

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Introduction

Iron overload is a condition that is not uncommon and has a variety of associated morbidities (Weinberg 2010). Iron overload cardiomyopathy is increasing (Gujja et al. 2010). It has been shown that early recognition and intervention may alter outcomes. Calcium channel blockers (CCBs) are being actively investigated as potential treatments for iron overload cardiomyopathy (Gujja et al. 2010; Murphy and Oudit 2010).

Cardiac L-type voltage-dependent Ca^{2+} channels are key transporters of iron into cardiomyocytes under iron-overloaded conditions, and potentially represent a new therapeutic target to reduce the cardiovascular burden from iron overload (Oudit et al. 2003). It has also been noted that iron-overloaded transgenic mice with cardiac-specific overexpression of the L-type calcium channel (LTCC) α1-subunit had 2-fold higher myocardial iron and oxidative stress levels, as well as greater impairment in cardiac function. LTCC blockade in these mice protected them from iron overload (Oudit et al. 2003). The above findings indicate the possible preventative and therapeutic roles of CCBs in iron overload cardiomyopathy.

Recent evidence suggests that cardiac iron uptake is strongly correlated with cardiac calcium stores and is significantly attenuated by a CCB, verapamil, suggesting that cardiac calcium and iron are related (Otto-Duessel et al. 2011). Importantly, verapamil treatment reduced both cardiac and hepatic iron levels significantly. Similarly, another CCB, nifedipine, mobilizes iron in animal models of iron overload. The mice studies show that nifedipine treatment mobilizes hepatic iron and stimulates renal iron excretion in animal models of primary and secondary iron overload (Ludwiczek et al. 2007).

The current research has been limited to animal models. Thus, it is unclear if CCB use is associated with decreased measures of iron level in humans. The purpose of this study was to examine the relationship between CCBs and serum ferritin in a sample of adults with diagnosed hypertension.

Methods

We conducted an analysis of the National Health and Nutrition Examination Survey (NHANES) 1999–2002. The NHANES is a nationally representative survey of the noninstitutionalized United States population, and provides the ability to make population estimates representative of the United States (NCHS, CDC 2011). The NHANES design includes interviews, laboratory tests, and physical examinations of the participants.

The study included adults aged 40 and older who answered yes to the question "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?" We chose this group to identify individuals who might be on a treatment regimen for hypertension of CCBs versus other treatment regimens.

Identification of calcium channel blocker use

During the NHANES household interview participants are asked if they have taken medications or dietary supplements in the past month. Those who answer 'yes' are asked to show the interviewer the containers of all the products used, or to verbally report the name of the product if the container is not available. Medication and supplement product names are matched to databases containing drug and supplement information. Drug ingredients are classified using the Multum Lexicon Therapeutic Classification Scheme. Participants were identified as taking CCBs if they reported taking a drug that was directly classified as a CCB or if they reported taking a drug classified as an Antihypertensive Combination that contained a drug ingredient that was classified as a CCB.

Serum ferritin

Serum ferritin was available in the NHANES 1999–2002 for adults and was measured using the Bio-Rad Laboratories' "Quantimune Ferritin IRMA" kit (Anaheim, California), which is a single-incubation two-site immunoradiometric assay (IRMA) (NCHS, CDC 2011; Addison et al. 1972; Miles 1977). People with unusually high serum ferritin (>2,000 ng/mL) were deleted from the sample.

Control variables

We included several control variables that might affect the relationship between CCBs and serum ferritin. These included respondent age, sex, menopause and hysterectomy status for women, race/ethnicity (non-hispanic white, non-hispanic black, hispanic, other), and C-reactive protein.

We were also interested in looking at the impact of ingestion of other substances that might increase ferritin levels, thereby blunting the relationship with calcium channel blockers. Specifically, we focused on the intake of dietary iron and iron supplements. We also were interested in the impact of vitamin C ingestion. Although vitamin C generally increases iron absorption, in the presence of a chelating agent it actually increases the amount of iron removed by a

chelator (O'Brien 1974). Since CCBs may be acting as a nontraditional chelator we wanted to examine whether people who were taking CCBs and ingesting high levels of vitamin C would have lower levels of serum ferritin than people taking CCBs alone.

To determine combined daily intake of iron and vitamin C, NHANES-calculated total dietary intakes of these nutrients from the dietary interview were added to supplement total intakes of iron and vitamin C that we calculated using product name, dosage and ingredient information from the NHANES supplements database, and supplement name, form, quantity, and frequency responses given during the household interview. Participants who did not complete the dietary interview, or who reported taking a supplement that contained more than 5 mg iron or more than 100 mg vitamin C and did not report their frequency of taking those supplements in the past month, were deleted from the sample. Also, participants with unusually high combined intakes of iron (>100 mg/day) or vitamin C (>2,500 mg/day) were deleted from the sample.

Analysis

The NHANES survey is based on a complex sampling design. Consequently, we used SUDAAN 10 software (Research Triangle Institute, Research Triangle Park, NC) to account for weighting and complex sampling design and to allow for us to make representative national estimates. χ^2 tests were used to compare the prevalence of demographic and nutrient intake characteristics for individuals in the CCB group versus the non-CCB group. A t-test was used to compare weighted mean ferritin levels for individuals taking CCBs versus not taking CCBs. Because of the observational design of this study we further evaluated the relationship of CCB use with serum ferritin through adjusted linear regressions, and computed mean serum ferritin levels adjusted for age, gender, menopause/hysterectomy status, race/ethnicity, and C-reactive protein.

Noting that vitamin C may accentuate the iron reducing effects of a chelator, we created a four-part variable which categorized the population as (a) those who took CCBs and whose daily vitamin C intake was ≥500 mg; (b) those who took CCBs and whose daily vitamin C intake was <500 mg; (c) those who did not take CCBs and whose daily vitamin C intake was ≥500 mg; and (d) those who did not take CCBs and whose daily vitamin C intake was <500 mg. We computed a model relating this 4 part CCB/vitamin C variable with serum ferritin, adjusting for age, gender, menopause/hysterectomy status, race/ethnicity and C-reactive protein.

Noting that the combined intake of iron from diet and supplements may partially counteract the iron reducing effects of CCBs, we created a four-part variable which categorized the population as (a) those who took CCBs and whose daily iron intake was ≤18 mg, (b) those who took CCBs and whose daily iron intake was >18 mg, (c) those who did not take CCBs and whose daily iron intake was ≤18 mg, and (d) those who did not take CCBs and whose daily iron intake was >18 mg. We computed a model relating this 4 part CCB/iron variable with serum ferritin, adjusting for age, gender, menopause/hysterectomy status, race/ethnicity, and C-reactive protein.

T-tests were used to evaluate differences between categorical beta estimates relative to each variable's reference level. For all analyses, $p < 0.05$ was determined to be significant.

Results

The demographics of the sample are presented in Table 1. CCBs were used by 12.6 % of the weighted population of adults with diagnosed hypertension. The weighted but unadjusted mean serum ferritin for individuals taking CCBs was 129.3 ng/mL, while it was significantly higher for individuals not taking CCBs at 154.5 ng/mL ($p = 0.02$). After adjustment for age, sex and menopause/hysterectomy status, race/ethnicity, and CRP, the mean serum ferritin for individuals taking CCBs remained significantly lower and was 26.3 ng/mL less than those not taking CCBs ($p = 0.01$).

Table 2 presents the results of the variables combining CCB use with high intakes of vitamin C or iron. In a model adjusting for age, sex and menopause/hysterectomy status, race/ethnicity, and CRP, compared to a reference group who did not take CCBs and had a daily vitamin C intake of less than 500 mg, individuals who took CCBs and whose daily vitamin C intake was less than 500 mg had serum ferritin reduced by a mean of 25.0 ng/mL ($p = 0.04$) while individuals who both took CCBs and had a daily

Table 1 Demographics and selected nutrient intake of adults (≥40 years old) with diagnosed hypertension by calcium channel blocker status

	Total sample	Taking a CCB	Not taking a CCB	*p*
Sample N	2143	307	1836	
Weighted N	37.4 million	4.7 million	32.7 million	
Age in years, %				<0.001
40–64	58.9	44.8	60.9	
65+	41.1	55.2	39.1	
Sex & menopause status				0.20
Male	42.0	38.7	42.4	
Female: premenopausal	8.1	5.5	8.5	
Female: postmenopausal or post-hysterectomy	50.0	55.9	49.1	
Race, %				0.03
NHW	75.4	71.1	76.0	
NHB	12.7	17.9	12.0	
Other	11.9	11.0	12.0	
Combined iron intake from diet & supplements				0.88
>18 mg/day	39.0	39.6	39.0	
≤18 mg/day	61.0	60.4	61.0	
Combined vitamin C intake from diet & supplements				0.18
≥500 mg/day	14.1	11.0	14.5	
<500 mg/day	85.9	89.0	85.5	
Mean CRP (mg/dL)	0.61	0.56	0.61	0.45

vitamin C intake of ≥500 mg had a mean serum ferritin that was 60.1 ng/mL ($p < 0.001$) lower than the reference group. This suggests an additive or synergistic effect of CCBs and high vitamin C on serum ferritin.

In terms of iron intake, a model adjusting for age, sex and menopause/hysterectomy status, race/ethnicity, and CRP, compared to a reference group who did not take CCBs and had high iron intake, individuals who took CCBs and had a low daily intake of iron had a mean serum ferritin that was 27.5 ng/mL lower, although not significantly different from the reference group ($p = 0.12$). For individuals who took both CCBs and had low iron intake, the model indicated a significantly lower mean (35.4 ng/mL; $p = 0.01$) compared to the reference group who did not take CCBs and had higher levels of iron intake.

Discussion

These findings suggest that calcium channel blockers may act as a nontraditional chelating agent. Due to the toxic side effects of a variety of traditional iron chelators, nontraditional chelators may be a positive strategy to attempt to prevent the deleterious effects of elevated iron (Chaston and Richardson 2003; Weinberg 2006). Although this study was not a clinical trial, these observational results indicate that individuals with hypertension who are on CCBs tend to have lower serum ferritin than those not on CCBs. These results function as a first step in translating the findings from mice studies to humans regarding CCBs as nontraditional chelators and potential treatments to avert iron overload cardiomyopathy and potentially other iron overload complications. Moreover, this study provides additional evidence of the potential of vitamin C intake to accentuate the iron removal capacity of a nontraditional chelator. This is important because of the side effect problems with traditional chelators by themselves and in the presence of high vitamin C (Nienhuis 1981).

Current national guidelines do not encourage screening and early treatment for iron overload in the general population, although a variety of studies have demonstrated that iron overload is associated

Table 2 Relationship between calcium channel blocker use and serum ferritin

	Difference in ferritin (ng/mL)	*p*	Mean ferritin (ng/mL)
CCB status			
Taking CCBs	−26.3	0.01	128.4
Not taking CCBs	REF	REF	154.7
CCB/Vitamin C status			
Taking CCBs, Daily vitamin C ≥500 g	−60.1	0.001	97.0
Taking CCBs, daily vitamin C <500 mg	−25.0	0.04	132.2
Not taking CCBs, daily vitamin C ≥500 mg	−16.7	0.07	140.4
Not taking CCBs, daily vitamin C <500 mg	REF	REF	157.2
CCB/Iron status			
Taking CCBs, daily iron ≤1 mg	−35.4	0.01	125.1
Taking CCBs, daily iron >18 mg	−27.5	0.12	133.1
Not taking CCBs, daily iron ≤18 mg	−9.5	0.30	151.0
Not taking CCBs, daily iron >18 mg	REF	REF	160.5

Values are adjusted for age, sex, race/ethnicity, menopausal/hysterectomy status, and CRP

REF reference group

with poor health outcomes, such as cardiomyopathy and liver disease (Qaseem et al. 2005; USPSTF 2006; Schmitt et al. 2005). Although treatments exist for identified iron overload, such as phlebotomy and the use of traditional iron chelators, these are not likely to be used as preventive measures or early treatments due to the associated inconvenience and risks. Thus, the investigation of nontraditional chelating agents may be useful, as they may present the opportunity for identifying convenient methods of preventing progression to overt iron overload. This study, taken together with previous animal studies, suggests that further evaluation of the chelating effects of CCBs is warranted, as this may provide another option for treatment of individuals with elevated iron and a predisposition for iron overload (Oudit et al. 2003; Ludwiczek et al. 2007).

There are several limitations to this study. As this is an observational study, we are unable to determine causation. An association between use of CCBs and lower ferritin levels is presented. Furthermore, ferritin is an acute phase reactant, and thus may be elevated due to conditions causing inflammation or tissue injury. We did however control for C-reactive protein as a way to control for inflammation and the relationship still remained. As this study only includes individuals with hypertension, it is unclear whether similar findings would be seen in the general population. Second, although the relationship between CCBs and lower serum ferritin was found in a general population of individuals with hypertension and elevated serum ferritin is a first step marker for iron overload cardiomyopathy, this study was not designed to investigate the direct association between use of CCBs and cardiomyopathy. Future studies, and in particular clinical trials, can investigate the utility of CCB therapy as a treatment for iron overload cardiomyopathy. Third, the association of CCB use and lower serum ferritin was enhanced by high ingestion of vitamin C, suggesting that the addition of other nontraditional chelators with CCBs might also enhance the effect. We were unable to include one of the more common nontraditional chelators, the beverage tea. Although tea ingestion is available in other years of the NHANES and has been used successfully by the research team (Matheson et al. 2011), it was not collected in 1999–2002 and was therefore not available to be examined in this study.

In conclusion, this study finds an association between use of CCBs and lower serum ferritin levels in individuals with hypertension. Further studies are needed to assess the possible use of CCBs as nontraditional chelating agents to be used as a treatment for elevated iron in general, as well as for iron overload cardiomyopathy.

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