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ASSOCIATION BETWEEN IRON STATUS AND CORONARY HEART DISEASE, DIABETES, AND STROKE: A POPULATION-BASED COHORT STUDY

Gemma Flores Mateo
Institut d'Investigació en Atenció Primària Jordi Gol - Reus

1. Abstract

Background and aims

Several studies aiming to determine the association between iron stores and coronary heart disease (CHD), stroke and type-2 diabetes have reported conflictive results. None of them have been performed in a Mediterranean region. Our aim is to assess the association between the levels of serum ferritin (SF) and the incidence of CHD, stroke and diabetes in a Mediterranean region.

Methods

We performed a cohort study using a primary healthcare population database. Primary outcome was incidence of CHD, stroke or diabetes. Subjects aged between 35 and 74 years old for whom SF measurements at baseline (1 January 2006 to 31 December 2008) were included. Cox regression models were used to compute hazard ratios (HRs) and 95% CIs for the association between SF and time until outcome (CHD, stroke or type 2 diabetes).

Results

We included 242,084 subjects with SF levels at baseline. Participants were observed for a median of 8.4 years, and during follow-up 1,106 incident cases of CHD were identified. People who had high SF had no increase in CHD risk at the time of follow-up (adjusted hazard ratio= 0.99; 95% CI 0.94 – 1.05; *P* = 0.86 in men, and 0.95; 95% CI 0.81 -1.13; *P* = 0.60 in women). Adjusted HR of SF and type 2 diabetes showed the following results: in women aged <50 years (HR=1.61; 95% CI 1.31, 1.98), in women aged >50 years (HR= 1.42,: 95% CI 1.27, 1.59) and in men (HR=1.22; 95% CI 1.17, 1.27). Adjusted hazard ratio Cox regression models found a significant association between SF and stroke in men (HR = 1.03, 95% CI 1.01 – 1.07; P = 0.04) and a non-significant association in women (HR = 1.01, 95% CI 0.95 -1.08; P 0.74).

Conclusions

Our study, by far the largest, showed that high levels of SF do not confer an increased risk of CHD, and questions its role as a risk factor for this disease. However, our results contribute to confirm that high SF levels increase the risk for type-2 diabetes. Therefore, assessment of iron status is recommended in the detection and management of type-2 diabetes in clinical practice.

Finally, we should determine sex-related differences in the regulation of iron metabolism that may contribute to the differences in progression of iron-overload cardiovascular disease such as stroke.

Introduction

Cardiovascular disease (CVD) is the main cause of death and morbidity worldwide. In this context, recent research has focused on the identification of non-traditional risk factors, such as iron biomarkers. Among the available iron biomarkers, serum ferritin (SF) is the most common measurement of body-iron status and correlates well with body-iron stores. Several cohort studies aimed to determine the association between SF and CHD have reported contradictory results. Moreover, there have been no previous studies analysing this association in a Mediterranean population. Given the special features of the Mediterranean diet and its protective role regarding the CHD, results of previous studies analysing the association between the iron status and the CHD may not be applicable in a Mediterranean population. The aim of our project is to determine the prognosis value of SF in the incidence of CHD, stroke and diabetes using real-world data,

Methods

Study design: Cohort study using a primary health care population database.

Source of data: Data were obtained from SIDIAP database ("*Sistema d'informació per al desenvolupament de la Investigació en Atenció Primària"*, www.sidiap.org), CMBD-AH ("*Conjunt mínim bàsic de dades*"). The SIDIAP database gathers anonymized information on medical records for >5.8 million patients (which covers >80% of the population of Catalonia). This database nourished itself from the electronic medical records software used by primary care professionals (ECAP), which contains information on demographic data (date of birth, sex, nationality), acute and chronic health conditions (ICD-10 Code), laboratory tests (taken directly from the laboratories), prescriptions dispensed by pharmacies (through pharmacy invoices) and referrals to the specialists.

Study participants: We included all subjects aged between 35 and 74 years old for whom serum ferritin measurements at baseline (January 1 2006 to December 31 2008) were available and without any known cardiovascular disease at baseline.

Exclusion criteria: All subjects with previous history of cardiovascular disease including CHD (angina, myocardial infarction, coronary revascularization procedures), stroke (ischemic or hemorrhagic, including transient ischemic attacks), and peripheral artery disease diagnosed with vascular imaging techniques were excluded. Further exclusions included: history of illegal drug use, chronic alcoholism (or total daily alcohol intake >50g/day). Participants were also excluded if they had or were diagnosed with haemochromatosis, chronic conditions (such as liver, rheumatic or kidney disease), acute infection or inflammation, as well as those institutionalized, those who used iron supplements or reporting high protein C reactive levels or low levels of haemoglobin (<10 g/dL), VCM (<80) or any other iron biomarker (in order to exclude patients with high levels of ferritin secondary to inflammatory disease).

Follow-up: Participants from 1 January 2006 until death, moving out of the catchment area or end of follow-up (31 December 2016).

Outcomes: Incidence of ischemic heart disease or CHD was defined as acute myocardial infarction (fatal or nonfatal or angina (ICD-10: I21, I210-I219, I22, I220-I240, I241, I248 and I249). Also, incidence for stroke and diabetes.

Clinical and biochemical variables: Sociodemographic data: age at baseline, sex. Classical cardiovascular risk factors were defined: hypertension patients with diagnostic codes (ICD10: I10 – I13) or treatment with antihypertensive drugs; dyslipaemia (diagnostic code E78.x or treatment with cholesterol-lowering drugs), type 2 diabetes (diagnostic codes E11.x or antidiabetic treatment (oral or insulin); smoking status (former/current/non-smoker), body mass index (BMI). All the diagnoses were recorded at baseline. Drug prescriptions were also assessed (identified from dispensing records): aspirin, and other antiplatelets.

Risk of alcoholism was measured with AUDIT test, and categorized from 0 (zero risk) to 3 (high risk). White blood cells counts was used as a measure of inflammation when available. SF levels were measured by immunoturbidimetry (intra- and interassay coefficients of variation <8).

Statistical analysis: Descriptive analyses of baseline characteristics were presented as mean, standard deviation, 95% confidence intervals, median, and interquartile range

(for continuous variables) or N (%) for categorical/binary data. SF variable was described as continuous variable, and also categorized into quartiles. Cox regression models were used to compute raw and adjusted (age, sex, BMI, smoking, diagnosis of hypertension, diabetes, dyslipidaemia, treatment of hypertension, diabetes, dyslipidaemia) hazard ratios (HRs) and 95% CIs for the association between the SF and the time until the CHD outcome, stroke or diabetes. We performed separate models for each outcome. Change in risk of outcomes per 1 increase standard deviations (SD) of SF was calculated. For ferritin quartiles the first quartile was used as reference. The level of statistical significance used for hypothesis testing was 0.05. Further sensitive analyses were carried out stratifying the results by sex. Analyses were carried out using program R version 3.2.5 for Windows.

Ethical considerations: The study was planned and executed in accordance with the principles laid down in the Helsinki declaration (World Medical Association) and the standards of good practice in clinical research. The study protocol was approved by the Ethics Committee at institution.

2. Results

1. **Serum ferritin and CHD**: We analysed a total of 242,084 subjects with ferritin levels at baseline and were observed for a median of 8.4 years (IQR from 7.6 to 9.1). During the follow-up period, 1,106 incident cases of CHD were identified out of 130,099 subject-analysed which represented a crude incidence rate of 10 cases per 10,000 persons/year. Cox regression models, compared with those in the first quartile of ferritin, only women over 50 years old in the 2nd, 3rd and 4th quartiles of SF reported a borderline statistically significant lower raw risk of being diagnosed with a CHD and adjusted for potential confounders models (HR of 0.74 95% CI 0.54 to 1.01, HR of 0.57, 95% CI 0.42 to 0.79 and HR of 0.71, 95% CI 0.51 to 1.00, respectively). This borderline association disappeared when using continuous levels of ferritin instead of quartiles.

2. **Serum ferritin and diabetes**: We included 117,233 individuals. The median follow-up was 8.4 years with an incidence of type 2 diabetes of 7,779 cases. SF concentrations in women aged <50 years (HR=1.61; 95% CI 1.31,1.98), in women

aged >50 years (HR= 1.42,: 95% CI 1.27, 1.59) and in men (HR=1.22; 95% CI 1.17,1.27).

3. **Serum ferritin and stroke**: Participants were observed for a median of 8.3 years (IQR from 7.6 to 9.1). During the follow-up, 3,856 incident cases of stroke were identified out of 130,099 subjects analysed representing a raw incidence of 37 cases of stroke per 10,000 persons/year. Adjusted hazard ratio Cox regression models found a significant association between SF and Stroke in men (HR = 1.03, 95% CI 1.01 – 1.07; P = 0.04) and a non-significant association in women (HR = 1.01, 95% CI 0.95 -1.08; P 0.74).

3. Future implications

Our study, by far the largest, showed that high levels of SF do not confer an increased risk of CHD, and questions its role as a risk factor for this disease in a Mediterranean population. However, our results contribute to confirm that high SF levels increase the risk for type 2 diabetes. Therefore, assessment of iron status is recommended in the detection and management of type 2 diabetes in clinical practice.

Finally, we should determine sex-related differences in the regulation of iron metabolism that may contribute to the differences in progression of iron overload cardiovascular disease such as stroke.