International Journal of Cardiology 172 (2014) 155–160

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Heme iron intake and acute myocardial infarction: A prospective study of men

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ARTICLE INFO

Article history:
Received 16 April 2013
Received in revised form 30 September 2013
Accepted 31 December 2013
Available online 7 January 2014

Keywords:
Acute myocardial infarction
Heme iron
Non-heme iron
Prospective cohort study

ABSTRACT

Background: Epidemiologic studies of heme iron and non-heme iron intake in relation to risk of acute myocardial infarction (AMI) are lacking. Therefore, we examine the associations between heme iron and non-heme iron intake and fatal and nonfatal AMI in men. Moreover, we investigated whether the associations were modified by intake of minerals (calcium, magnesium, and zinc) that decreases iron absorption.
Methods: The population-based prospective cohort of Swedish Men (COSM) included 36 882 men, aged 45–79 years, who completed a self-administered questionnaire on diet and had no history of coronary heart disease, stroke, diabetes, or cancer at baseline.
Results: During an 11.7 year follow-up, 678 fatal and 2593 nonfatal AMI events were registered. The hazard ratio (HR) of fatal AMI among men in the highest compared with the lowest quintile of heme iron intake was 1.51 (95%CI: 1.07–2.13, *P*-trend = 0.02). The association was confined to men with a low intake of minerals that can decrease iron absorption. Among men with combined intakes of calcium, magnesium, and zinc below the medians, the HR of fatal AMI was 2.89 (95%CI: 1.43–5.82) for the highest vs. the lowest quintile of heme iron intake. There was no association between heme iron intake and nonfatal AMI, or between non-heme iron intake and fatal or nonfatal AMI.
Conclusions: Findings from this prospective study indicate that a high heme iron intake, particularly with simultaneous low intake of minerals that can decrease iron absorption, may increase the risk of fatal AMI.

1. Introduction

According to the report of the American Heart Association approximately every 25 s somebody in USA has a coronary event, and every minute somebody dies from the disease. Almost half (48.5%) of the coronary heart disease (CHD) cases are myocardial infarctions (MI) [1]. Thus identification of factors that affect the risk of MI is of great relevance from a public health point of view.

Among many factors that increase the risk of MI, diet plays an important role [2]. Recently published studies indicate that high consumption of red and/or processed meat is related to increased risk of CHD [3] and stroke [4] as well as with cardiovascular disease (CVD) mortality [5]. These associations have been ascribed, at least partly, to heme iron content in red meat.

It is known that a high iron intake may lead to oxidative damage of body cells [6] and is associated with development of inflammation [7]. Studies have indicated that a high intake of heme iron is associated with increased risk of CHD incidence [8,9], stroke incidence [10] and CVD [11] mortality. Two prospective studies have examined dietary heme iron intake in relation to risk of nonfatal MI and CHD combined (249 nonfatal MI cases and 137 cases of coronary disease fatalities) [12] or fatal and nonfatal MI combined (124 cases of acute and subsequent MI) [13], with both studies showing a positive association. To our knowledge, no prospective study has examined heme iron and non-heme iron intake in relation to risk of fatal and nonfatal acute MI (AMI) separately.

Therefore, we conducted a prospective study to investigate the associations of heme iron and non-heme iron intake with risk of fatal and nonfatal AMI. Moreover, we examined whether these associations were modified by dietary intakes of minerals that can decrease iron absorption. We analyzed data from the prospective population-based Cohort of Swedish Men with a large number of fatal and nonfatal AMI.

2. Methods

2.1. Study population

The cohort of Swedish Men was established in central Sweden (Västmanland and Örebro Counties) in the late autumn of 1997. A questionnaire was sent to all men in the age from 45 to 79 years who lived in this area. Of the 48 850 men (49% of the source population) who returned a completed questionnaire, we excluded men with an

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http://dx.doi.org/10.1016/j.ijcard.2013.12.176

incomplete questionnaire and those with an erroneous or missing national identification number or implausible values for total energy intake (i.e. 3 SDs from the mean value for log-transformed energy). Moreover, we further excluded men with a history of stroke, coronary heart disease, diabetes or cancer (other than non-melanoma skin cancer) at baseline. After these exclusions, 36 882 men remained for analysis. The study was approved by the Regional Ethical Review Board at the Karolinska Institutet (Stockholm, Sweden).

2.2. Assessment of diet and other exposures

Diet was assessed with a 96-item food-frequency questionnaire (FFQ). Participants were asked to indicate how often, on average, they had consumed various foods and food groups over the previous year. Frequency of consumption was reported according to eight predefined categories: never/seldom, 1–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, once a day, 2 times a day, and ≥3 times per day. Intakes of total iron and other nutrients were calculated by multiplying the frequency of consumption of each food item by the nutrient content (obtained from the Swedish Food Administration Database [14]) of appropriate age-specific portion sizes. Total red meat consumption was calculated by using the frequency of consumption all types of fresh and minced pork, beef, and veal as well as processed meat (sausages, hot dogs, salami, ham, processed meat cuts, liver pate, and blood sausage).

The heme iron content in all meat and fish items was calculated using a method developed by Balder et al. [15]. The average of the measured values of heme iron content of specific types of meat reported in the published literature [15] was used to generate the heme iron specific factor for a given food item, ranging from 0.01 for shellfish to 0.70 for blood pudding. For each meat and fish item, the type-specific heme iron factor was multiplied with its total iron content to derive the heme iron content of that item. Non-heme iron was calculated as total iron intake minus heme iron.

The FFQ has been validated for nutrients among 248 Swedish men aged 40–74 years. The mean Spearman correlation coefficients between estimates from the FFQ and the mean of fourteen 24-h recall interviews were 0.65 for macronutrients and 0.62 for micronutrients [16].

Information on education, smoking status, body height and weight, physical activity, history of hypertension and high blood cholesterol levels, aspirin use, dietary supplement use, family history of myocardial infarction before age 60 years, and alcohol drinking habits was obtained at baseline by using a self-administered questionnaire. The participants were classified as having diabetes if they self-reported diabetes on the questionnaire or had a diagnosis of diabetes recorded in the Swedish National Inpatient Register or the Swedish National Diabetes Register. Assessment of total physical activity score, measured as metabolic equivalents (MET h/day), was created and described previously by Norman et al. [17]. Body Mass Index (BMI) was calculated by dividing the weight (kg) by the square of height (m). Pack–years of smoking history were calculated as the number of packs of cigarettes smoked per day multiplied by the number of years of smoking.

2.3. Case ascertainment

Dates of death were obtained from the Swedish Death and Population Registers at Statistics Sweden through December 31, 2010. Detailed information on causes of death was available from the Swedish Register of Death Causes at the National Board of Health and Welfare. Events of AMI were classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD code I21). In the present study, cases were all first-time events of AMI. Fatal AMI events were considered cases for which MI was specified as acute or with a stated duration of 4 weeks (28 days) or less from onset. Nonfatal AMI events were classified as those for which no death occurred or occurred later than 4 weeks from onset. Completeness of the registers is nearly 100%.

2.4. Statistical analysis

We used the Cox proportional hazards regression models with person time as the time scale to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of fatal and nonfatal AMI by quintiles of heme and non-heme iron intake.

The multivariable models included the following variables: age (continuous variable), education (less than high school, high school, or university), smoking status and pack–years of smoking (never; past <20, 20–39, or ≥40 pack–years; or current <20, 20–39, or ≥40 pack–years), BMI (<20, 20–24.9, 25–29.9, or ≥30 kg/m^2), total physical activity (quartiles, measured as metabolic equivalents), history of hypertension (yes or no), high blood cholesterol level (yes or no), ever aspirin use (yes or no), supplement use (yes or no), family history of myocardial infarction before age of 60 years (yes or no), alcohol consumption (quintiles) and quintiles of energy-adjusted intakes of protein, saturated fat, PUFA, cholesterol, fiber, vitamin E, β-carotene, vitamin C, potassium, sodium, calcium, magnesium, and zinc. All nutrients were energy-adjusted using the residual method [18]. Multivariable HRs were mutually adjusted for heme iron and non-heme iron intake.

The proportional hazards assumption was evaluated by regressing scaled Schoenfeld residuals against survival time. There was no evidence of departure from the assumption. To calculate *P* values for trend, the median values of quintiles of heme and non-heme iron intake were used as a continuous variable. Using the likelihood ratio test, we tested statistical interactions between heme iron and non-heme iron intake in predicting fatal and nonfatal AMI according to BMI, smoking status, physical activity, and alcohol consumption. Furthermore, stratified analyses were performed to investigate whether intakes of calcium, magnesium, and zinc modify the relation between heme and non-heme iron intake and fatal and nonfatal AMI. The cut-off points used to stratify were based on median energy-adjusted intakes of these minerals.

The statistical analyses were performed by using SAS version 9.2 (SAS Institute Inc., Cary, NC). All reported *P* values were 2-sided, and *P* values ≤0.05 were considered statistically significant.

3. Results

Among the 36 882 men who were followed up during 432 963 person–years (mean 11.7 years), we ascertained 678 fatal and 2593 AMI. Age-standardized characteristics of the study population by quintiles of energy-adjusted heme iron and non-heme iron intake are presented in Table 1. The Spearman's correlation coefficient between heme and non-heme iron intake was 0.18. Median intake of heme iron was 2.6-fold higher in the highest compared with the lowest quintile of heme iron. The median intakes of heme iron intake in the highest and lowest quintiles correspond to a red meat intake of 1037 g/week (including 611 g/week pork and 292 g/week beef) and 399 g/week (including 246 g/week pork and 104 g/week beef), respectively. The median intake of non-heme iron differed 1.8-fold between the highest and lowest quintiles of non-heme iron intake.

We observed a positive association between heme iron intake and risk of fatal AMI (Table 2). Compared with men in the lowest quintile of heme iron intake, those in the highest quintile had a 51% (95% CI: 7–113%) higher risk of fatal AMI. Adjustment for total red meat or processed meat consumption (in quartiles), which were both positively correlated with heme iron intake ($r = 0.64$ and $r = 0.44$, respectively), did not change the results materially; the HRs for the highest category of heme iron intake compared with the lowest category were 1.57 (95% CI: 1.09–2.26, *P*-trend = 0.02) and 1.45 (95% CI: 1.02–2.06, *P*-trend = 0.04), respectively. Neither red meat nor processed meat consumption was associated with risk of fatal AMI (highest vs. lowest quintile, HR: 0.94; 95% CI: 0.68–1.29 for red meat and HR: 1.17; 95% CI: 0.89–1.54 for processed meat). Moreover, intakes of total fat and saturated fatty acids were not associated with risk of fatal AMI (highest vs. lowest quintile, HR: 1.11; 95% CI: 0.59–2.11 for total fat and HR: 1.09; 95% CI: 0.77–1.54 for saturated fatty acids).

There was no association between heme iron intake and risk of nonfatal AMI or between non-heme iron intake and risk of fatal or nonfatal AMI (Table 2). Moreover, we observed no association between heme iron intake and risk of total AMI (HR for highest vs. lowest quintile: 1.05; 95% CI: 0.89–1.23, *P*-trend = 0.74).

Exclusion of the first year of follow-up did not change the results. Compared with men in the lowest quintile of heme iron intake, those in the highest quintile had a 50% higher risk of fatal AMI (95% CI: 5–113%; *P*-trend = 0.034) after excluding the first year of follow-up.

We next examined whether the associations between heme iron and non-heme iron intake and risk of fatal and nonfatal AMI were modified by intakes of minerals that can decrease iron absorption. We observed that the positive association between heme iron intake and risk of fatal AMI was confined to men with low intakes (below the median in the cohort) of calcium, magnesium, and zinc (Table 3). Among men with low intakes (below median) of all three minerals, the HR of fatal AMI was 2.89 (95% CI: 1.43–5.82) when comparing those in the highest quintile of heme iron intake with those in the lowest quintile. The *P* values for interaction between heme iron and calcium, magnesium, and zinc intakes were 0.059, 0.117, and 0.359, respectively. The associations between heme iron intake and nonfatal AMI and between non-heme iron intake and fatal and nonfatal AMI were not modified by intakes of calcium, magnesium, or zinc (all *P* values for interaction >0.3). We also tested whether the association between heme iron and fatal AMI was modified by vitamin C, which enhances iron absorption. The association was not stronger among men with a high vitamin C intake (above median) (highest vs. lowest quintile of heme iron intake,