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Original article

Plasma cis-vaccenic acid and risk of heart failure with antecedent coronary heart disease in male physicians

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SUMMARY

Background & aims: Although an inverse association of red blood cell cis-vaccenic acid and risk of myocardial infarction has been reported, it is unclear whether cis-vaccenic acid might lower the risk of heart failure (HF) with antecedent coronary heart disease (CHD). We sought to examine the relation of plasma cis-vaccenic acid with HF with antecedent CHD.

Methods: This nested case-control study was based on 788 incident HF cases (of whom 258 cases had antecedent CHD) and 788 controls. Each control was selected using a risk set sampling technique at the time of the occurrence of the index case and matched on year of birth, age at blood collection, and race. Fatty acids were measured using gas chromatography and incident HF was self-reported on annual questionnaires and validation in a subsample using medical records.

Results: In a multivariable conditional logistic regression, the odds ratio (95% confidence interval) for HF with prior CHD were 1.0 (ref), 0.72 (0.33–1.57), 0.28 (0.12–0.67), and 0.23 (0.09–0.58) across consecutive quartiles of cis-vaccenic acid (p_trend 0.0004). Each standard deviation of cis-vaccenic acid was associated with a 41% lower risk of HF with antecedent CHD (95% CI: 17%–59%) in a multivariable adjusted model.

Conclusions: Our data suggest that higher plasma levels of plasma cis-vaccenic acid may be associated with a lower risk of HF with antecedent CHD. Confirmation of these results in the general population including women and other ethnic groups is warranted.

1. Introduction

Heart failure (HF) is a clinical syndrome with multiple etiologies including ischemic heart disease, hypertensive heart disease, cardiomyopathy, valvular disease among others.[1,2] Despite progress in HF treatment, its mortality remains high,[3–6] underscoring the importance of novel prevention strategies. Fatty acids in the de novo lipogenesis play a role in cardiometabolic disorders as adult cardiomyocytes prefer fatty acids over glucose as energy source.[7,8] Excess carbohydrate or alcohol can enhance endogenous de novo lipogenesis[9] and byproducts of such pathway (14:0, 18:0, 16:0, 16:1n-7, 18:1 n-7) can affect the development of chronic disease. Recent data suggest that de novo lipogenesis plays a critical role in generating an endogenous ligand for peroxisome proliferator-activated receptor alpha (PPARα) in the liver.[10,11] Such ligand has been isolated as 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine (16:0/18:1-GPC).[10,12] PPARα is expressed in various tissues, but is enriched in liver, where it promotes fatty acid oxidation, lipid transport, and gluconeogenesis.[13] Palmitoleic acid can be desaturated to cis-vaccenic acid via stearoyl-CoA desaturase-1. Palmitic acid, palmitoleic and stearic acid (18:0) (major fatty acids from the de novo lipogenesis) have been associated with a higher risk of diabetes,[14,15] hypertension[16] and coronary heart disease.[17] Palmitoleic has also been associated with lower low-density lipoprotein cholesterol, higher high-density lipoprotein cholesterol, and lower fibrinogen.[18] Our group has recently reported an inverse association between red blood cell cis-vaccenic acid and the risk of myocardial infarction.[19] This suggests that cis-vaccenic acid may be associated with a

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lower risk of HF from ischemic origin (i.e., with antecedent coronary heart disease). However, no previous study has tested that hypothesis. Given the poor prognosis after HF onset, identification of factors that could lower the incidence of HF is critical for primary prevention. Hence, the current study sought to examine whether plasma phospholipid cis-vaccenic acid was associated with HF preceded by CHD. Our primary hypothesis was that cis-vaccenic acid would be associated with a lower risk of HF with antecedent CHD.

2. Methods

2.1. Study population

This ancillary study used a prospective nested case-control design built on the existing Physicians' Health Study, which is a completed randomized, placebo-controlled trial designed to study low-dose aspirin and beta-carotene for the primary prevention of cardiovascular disease and cancer.[20] Study base was restricted to participants that provided a blood sample at baseline (1982–1983). For each case of HF, we used a risk set technique to randomly select one control among participants who were alive and free of HF at the time of diagnosis of the index HF case. We matched each control to the index case on age at randomization (within 1 year for >95% of controls), race (white vs. non-white), year of birth (within 1 year), and time of blood collection (within 288 days). Current analyses are based on 788 pairs. Each participant signed an informed consent and the Institutional review Board at Brigham and Women's Hospital approved the study protocol.

2.2. Measurement of plasma phospholipids fatty acids

Plasma phospholipid fatty acids were measured using a method described by Cao et al.[21] For the extraction of plasma phospholipid fatty acids, we mixed 0.3 mL of plasma with 0.7 volume of 0.9% saline. Lipids are extracted from plasma with a mixture of chloroform:methanol (2:1, v/v), and cholesterol, triglycerides and phospholipid subclasses were then separated on a silica thin-layer chromatography plate in a solvent mixture of petroleum ether, diethyl ether, and glacial acetic acid (80:20:1, v/v/v). The band of phospholipids was harvested for the formation of methylesters. Fatty acid methylesters were prepared with 1.5 mL of 14% boron trifluoride in methanol, incubated at 80 °C for 90 min, and extracted with petroleum ether. The final product was then dissolved in heptane and injected onto a capillary Varian CP7420 100-m column with a Hewlett Packard 5890 gas chromatograph (GC) equipped with a HP6890A autosampler. We obtained adequate separation of fatty acid methylesters over a 80-min period with an initial temperature of 190 °C for 25 min. Fatty acid methylesters were separated, identified and expressed as percent of total fatty acids. The following coefficients of variations were obtained on 30 blind duplicates: eicosapentaenoic acid = 5.1%; docosapentaenoic acid = 3.8%; docosahexaenoic acid = 4.9%; 16:0 = 1.1%; 16:1n7cis = 1.8%; 18:0 = 3.5%; and 18:1n7 = 2.9%. Cases and matching controls were sent to the laboratory in the same batch and assayed at the same time. Lastly, laboratory personnel was blinded on the case-control status of each subject to enhance validity.

2.3. Ascertainment of incident HF

HF ascertainment in the PHS was initially achieved using yearly follow-up questionnaires (except during the first year when each participant completed two questionnaires six months apart). In addition, we have previously validated self-reported HF diagnosis in the PHS using the Framingham criteria[22] on supplemental questionnaires in a subsample as well as via chart review on limited number of HF.[23] Overall positive predictive value of self-reported HF was 90% in that subsample.[23]

2.4. Other variables

At baseline, each subject provided information on exercise [how often do you exercise vigorously enough to work up sweat? Possible answers included rarely/never, 1–3/month, 1/week, 2–4/week, 5–6/week, and daily]; smoking (never, former, and current smoker); and alcohol intake (rarely/never, 1–3 per month, 1 per week, 2–4/week, 5–6/week, daily, and 2+/day). Self-reported baseline weight (kg) was divided by height (meter squared) to compute body mass index. Information on comorbidity including hypertension, atrial fibrillation, hyperlipidemia, and diabetes was collected at baseline and through follow-up questionnaires. High-sensitive C-reactive protein (hsCRP) was measured using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics, Indianapolis, IN 46250). The inter-assay CV was 4.5%.

2.5. Statistical analyses

As we did not assume a priori linear relation of plasma cis-vaccenic acid with HF, we initially created quartiles of cis-vaccenic acid using its distribution in the control series. We created indicator variables for modeling using the first quartile as the reference. We fitted a conditional logistic regression to estimate relative risks of HF across exposure categories. The first model adjusted for matching variables, body mass index, plasma 18:0, oleic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and prevalent hypertension, coronary heart disease, atrial fibrillation, and diabetes. A full model also controlled for smoking (never, former, current smokers), vigorous physical activity (at least weekly vs. less frequent), alcohol consumption (rarely/never, <1, 1–6, and 7+ drinks per week), and docosapentaenoic acid (DPA). To calculate the p value for linear trend we used an indicator variable that treat quartiles as an ordinal variable. Of the 788 HF cases and 788 matched controls, 258 cases were preceded by CHD and were used to test the primary hypothesis. Alpha level was set at 0.05 and all tests were two-sided using SAS 9.3 for all analyses. To explore the shape of the association, we fitted restricted cubic splines with four knots at the tenth, 36.7th, 63.4th, and 90th percentile using cis-vaccenic value of 1.2 (50th percentile) as the reference in STATA/MP12.

3. Results

The average age was 58.8 ± 8.0 years. The mean plasma phospholipid cis-vaccenic acid (percentage of total fatty acids) was lower in cases (1.39 ± 0.23) than in controls (1.42 ± 0.21), Wilcoxon sign rank test $p = 0.02$. Cis-vaccenic acid was associated with older age, lower body mass index, higher concentration of oleic acid, DPA and DHA, lower prevalence of diabetes, hypertension, CHD, and current smoking and a high prevalence of vigorous exercise (Table 1). Plasma cis-vaccenic acid was inversely associated with HF preceded by CHD (p for trend 0.004, Table 2); each standard deviation higher cis-vaccenic acid was associated with a 41% lower risk of HF with antecedent CHD (95% CI: 17%–59%) in a fully adjusted model, Table 2. Using cubic splines to fit the data showed evidence for an inverse association (Fig. 1). In the control series, plasma cis-vaccenic acid was positively correlated with DHA, DPA, adiponectin, palmitoleic acid, and inversely related to body mass index, 18:0, and C-reactive protein (Table 3).