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Relation between Plasma Phospholipid Oleic Acid and Risk of Heart Failure

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Abstract

Background & aims: Although the association between monounsaturated fatty acids (MUFA) and risk factors for heart failure (HF) has been reported, it is unclear whether oleic acid, the predominant MUFA in olive oil, plays a role in the development of HF. Consequently, we sought to examine the relation of plasma phospholipid oleic acid with HF in a male cohort. In a secondary analysis, we examined the relation of the ratio of plasma monounsaturated-to-saturated fatty acids (MUFA:SFA) with HF.

Methods: This prospective nested case-control study was based on 788 incident HF cases and 788 controls from the Physicians' Health Study. Plasma phospholipid fatty acids were measured using gas chromatography and incident HF was self-reported via annual follow-up questionnaires and validated in a subsample using medical records.

Results: The mean age was 58.7 years at blood collection. In a conditional logistic regression, multivariable adjusted-odds ratio (95% confidence interval) for HF across consecutive quartiles of oleic acid were 1.0 (reference), 1.10 (0.79–1.54), 1.02 (0.72–1.44), and 1.05 (0.72–1.54). For MUFA:SFA ratio, corresponding odds ratios (95% CI) for HF were 1.0 (ref), 1.12 (0.80–1.58), 1.19 (0.84–1.68), and 0.97 (0.66–1.42).

Conclusions: Our data do not lend support to an association between plasma phospholipid oleic acid or MUFA:SFA ratio and the risk of HF. These results warrant confirmation in the general population including women and other ethnic groups.

Keywords

Heart failure; fatty acids; risk factor; nutrition; Mediterranean diet

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Introduction

Recognized predictors of heart failure (HF) include advanced age, hypertension, diabetes mellitus, obesity, valvular heart disease, and myocardial infarction [1,2]. While treatment for HF continues to improve, high mortality rates after diagnosis of HF and related health care costs necessitate the advancement of current prevention strategies for HF [3–6]. Previous studies have shown the usefulness of the Mediterranean diet on the primary prevention of myocardial infarction and hypertension, two major risk factors for HF [7]. It has been suggested that the observed benefits from the Mediterranean diet on cardiovascular health might be partially explained by the effects of olive oil and the monounsaturated fatty acids found within [8,9]. For instance, it has been shown that the ratio of monounsaturated fatty acids (MUFA) to saturated fatty acids (SFA) is significantly related to lower death rate from coronary heart disease [10]. Moreover, studies have demonstrated that a diet rich in MUFA can reduce blood pressure compared to a SFA-rich diet [11]. Many studies have investigated the role of oleic acid, the predominant MUFA in olive oil, in lowering insulin resistance and improving insulin transport in diabetics [9,12]. While the evidence suggests an inverse association between oleic acid and risk factors of HF, no previous study has examined whether oleic acid is associated with the risk of HF. Given the increasing impact of HF on the life expectancy of older adults, identification of nutrients with potential roles in dietary intervention for at-risk populations is critical. Hence the current study sought to primarily investigate whether plasma phospholipid oleic acid was associated with HF risk. In a secondary aim, we examined whether the ratio of MUFA:SFA was associated with the risk of HF.

Methods

Study population

We used a prospective nested case-control design among participants of the Physician's Health Study (a completed randomized, double-blind, placebo-controlled trial designed to determine whether low-dose aspirin decreases cardiovascular mortality) [13]. The study base was restricted to participants that provided a blood sample at baseline (1982–1983). For each new HF occurrence, we randomly selected one control subject that was alive and free of HF at the time of diagnosis of index HF; such control was matched on age, race, time of blood collection, and year of birth as described in detail previously [14,15]. Current analyses are based on matched 788 pairs. Every participant signed an informed consent and the Institutional Review Board at Brigham and Women's Hospital approved the study protocol.

Measurement of plasma phospholipid fatty acids

Plasma phospholipid fatty acids were measured using a method described previously [14,16]. In summary, lipids were extracted from plasma with a mixture of chloroform:methanol (2:1, v/v). Phospholipid subclasses were then separated from cholesterol and triglycerides on a silica thin-layer chromatography plate. Fatty acid methyl esters products were 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. Cases and matching controls were sent to the laboratory in the same batch and

assayed concurrently. Lastly, laboratory personnel were blinded on the case-control status of each subject to enhance validity.

Ascertainment of incident HF

For initial gathering of HF cases, participants were sent follow-up questionnaires about their compliance with the treatment regimen and the occurrence of any relevant events (including HF) every six months during the first year and annually thereafter. Validation of self-reported HF diagnosis via an independent chart review on a limited number of HF cases was previously reported with a confirmation rate of 91% [15].

Additional variables

Demographic information was obtained through self-report using questionnaires. At baseline, each subject provided information on exercise (How often do you exercise vigorously enough to work up sweat?) with possible answers including rarely/never, 1–3/month, 1/week, 2–4/week, 5–6/week, and daily; smoking (never, former, and current smoker); alcohol intake (rarely, monthly, weekly, daily). Self-reported baseline weight and height were used to compute body mass index. Data on comorbidity including hypertension, atrial fibrillation, hyperlipidemia, and diabetes were collected at baseline and through follow-up questionnaires.

Statistical analyses

We created quartiles of plasma phospholipid oleic acid or MUFA:SFA using their respective distributions in the control sample. We performed conditional logistic regression using 788 matched pairs to estimate the relative risk for HF using the lowest quartile of plasma phospholipid oleic acid as the reference category. The initial model adjusted for matching variables only (race, age, time of blood collection, and year of birth), while the final model additionally controlled for body mass index, prevalent diabetes, coronary heart disease, atrial fibrillation, hypertension, vigorous physical activity, smoking, alcohol consumption, palmitoleic acid, plasma phospholipid 18:0, and marine omega-3 fatty acids. Alpha level was set at 0.05 and all tests were two-sided using SAS 9.4 for all analyses.

Results

The average age was 58.7 ± 8.0 years among the 1576 male physician participants. Average follow-up time of participants was 17.0 years (SD=6.05 years). Average age at HF event was 75.7 years (SD=8.52 years). In the control series, mean plasma concentration of oleic acid was 9.5% (SD=1.1%) of total plasma phospholipids (range 6.2 – 16.0%). Concentration of plasma phospholipid oleic acid was associated with higher ratio of MUFA:SFA, higher concentration of palmitoleic acid, lower prevalence of hypertension, and a higher prevalence of smoking and exercise (Table 1).

We found no association between plasma phospholipid oleic acid and HF risk [multivariable adjusted OR (95% CI): 1.0 (ref); 1.10 (0.79–1.54); 1.02 (0.72–1.44); and 1.05 (0.72–1.54) across consecutive quartiles of oleic acid], Table 2. In a secondary analysis, the ratio of MUFA:SFA was not associated with HF risk (Table 3).

Discussion

In this prospective nested case-control study of apparently healthy male physicians, plasma phospholipid oleic acid concentration was not associated with HF risk, results that are contrary to our hypothesis of an inverse relation between oleic acid and HF. In a secondary analysis, our data also showed that the ratio of MUFA:SFA was not associated with the risk of HF. This is the first study to examine the relation of plasma phospholipid oleic acid with HF. A lack of an association between plasma phospholipid oleic acid and HF risk merits some comments. A possible explanation is that consumption of oleic acid in the US population is relatively low compared to Mediterranean countries, thereby making it a challenge to detect any benefits. Alternatively, evaluation of oleic acid as individual nutrient may not capture its effects if in reality oleic acid interacts with other nutrients to exert its health benefits. Since people usually consume oleic acid with other food groups, it is important to consider that the effects of an overall dietary pattern are far superior to the effect of a single nutrient. This suggests that future studies should emphasize more on dietary patterns rather than single nutrient of single food. Consistent with such hypothesis, Levitan et al. (2013) reported that adherence to the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets was associated with a lower risk of death among post-menopausal women with HF [17].

Currently, there are no data available on the primary prevention effects of Mediterranean diet on HF. Nonetheless, data from the PREDIMED study have shown the beneficial effects of the Mediterranean diet supplemented with extra virgin olive oil or mixed nuts in primary prevention of hypertension and major cardiovascular events including myocardial infarction, stroke, and death from cardiovascular causes [18,19]. A subgroup analysis of the PREDIMED trial showed that a Mediterranean diet enriched with extra virgin olive oil reduces the risk of diabetes [20]. Consistent with findings from the PREDIMED trial, two meta-analyses reported a lower risk of diabetes with adherence to a Mediterranean diet (ORs (95% CI): 0.77 (0.66–0.89) and 0.81 (0.73–0.90) [21,22].

Our study has several limitations. First, we had a single measurement of plasma phospholipid oleic acid and could not account for changes in that fatty acid over time. Inability to model oleic acid as time-varying exposure is certainly a limitation and could partially explain our results. However, our group showed comparable results between baseline and repeated measures of phospholipid fatty acids and risk of HF [23], suggesting that the use of a single measurement of MUFA is reasonable for epidemiologic studies. Second, extrapolation of these findings to the general population and other ethnic groups is limited due to the fact that all subjects were highly educated (physicians), predominantly white, and all male. Confirmation of these findings in other cohorts that include women and other ethnic groups is necessary. Third, data were not available for us to further classify HF based on etiology or left ventricular systolic function. Fourth, full adjustment for dietary patterns and other macro- and micronutrients was not possible due to lack of full food frequency questionnaire at baseline in this cohort. Fifth, HF diagnosis was a self-reported end-point by participants who were physicians and despite a 91% predictive value of self-reported HF against validation of medical records in a subsample, it is reasonable to assume some level of misclassification of HF. Lastly, another limitation to the study design includes

the inability to account for de novo lipogenesis (DNL), which may influence circulating plasma levels of MUFA independent of dietary intake. Several studies have examined factors affecting DNL[24–26]. Given the complexity and highly-regulated nature of endogenous production of fatty acids, there are undoubtedly numerous additional factors not yet studied affecting this process for which we currently cannot adjust in our measurements. Non-invasive techniques have been developed to determine levels of DNL in humans including stable isotope tracer studies, fatty acid profiling or indirect calorimetry [27] however, these techniques were not employed in the current study design.

Our study also has numerous strengths including a large number of participants; use of valid, reproducible, and accurate methods to assay phospholipid fatty acids; availability of data on numerous covariates; use of risk set technique to match cases and controls on relevant and potential confounders; and >90% positive predictive value of self-reported HF against review of medical records in a subsample.

In conclusion, our data suggest that neither plasma phospholipid oleic acid nor MUFA:SFA ratio is associated with the risk of HF.

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Abbreviations:

HF	heart failure
MUFA:SFA	monounsaturated-to-saturated fatty acids

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Table 1Characteristics of 1576 male physicians by quartiles of oleic acid.^a

Characteristics	Quartiles of plasma phospholipid oleic acid ^b			
	Q1 (low) 8.1 [6.2–8.7]	Q2 9.1 [8.7–9.4]	Q3 9.8 [9.4–10.1]	Q4 (high) 10.9 [10.1–16.0]
	(N= 388)	(N= 408)	(N= 386)	(N= 394)
Age (y)	58.0 ± 7.8	58.9 ± 7.8	58.7 ± 8.1	59.2 ± 8.4
Body mass index (kg/m ²)	25.4 ± 2.9	25.2 ± 2.9	25.2 ± 3.0	24.9 ± 2.8
Ratio of MUFA:SFA ^c	0.20 ± 0.01	0.22 ± 0.01	0.24 ± 0.01	0.27 ± 0.02
Plasma palmitoleic acid ^c	0.28 ± 0.09	0.31 ± 0.10	0.32 ± 0.13	0.39 ± 0.21
Plasma 18:0 ^c	14.3 ± 1.3	13.9 ± 1.2	13.9 ± 1.1	13.5 ± 1.2
Plasma marine n-3 ^c	5.3 ± 1.43	4.8 ± 1.4	4.5 ± 1.1	4.0 ± 1.0
Prevalent diabetes (%)	6.4	4.4	4.4	7.1
Prevalent CHD (%) ^d	16.5	15.4	16.3	12.7
Hyperlipidemia (%)	17.9	18.4	12.1	11.4
Hypertension (%)	34	29.8	29.8	31
Atrial Fibrillation	4.1	2.9	3.6	5.1
Current smoking (%)	6.4	10.8	11.4	16.2
Never smokers (%)	45.4	48.2	45.5	41.6
Current alcohol intake (%)	84.7	85.2	84.2	81.9
Vigorous exercise (%)	70.4	73.6	72.9	77.6
Aspirin use	53.6	48.28	45.1	50.1
Follow-up time (years)	17.4 ± 6.0	16.7 ± 6.0	17.5 ± 5.6	16.5 ± 6.6
Age at HF Event (years)	75.1 ± 8.2	76.1 ± 9.2	75.9 ± 8.3	76.0 ± 8.4

^aData are presented as medians (minimum-maximum), means ± standard deviation, or %. Few participants had missing data on hypertension (*n* = 10), smoking (*n* = 2), alcohol use (*n* = 6), and physical activity (*n* = 10).

^bQuartiles of oleic acid presented as percent of total fatty acids.

^cPlasma phospholipid fatty acids expressed as percentage of total plasma phospholipids (SFA: saturated fatty acids). Palmitoleic acid, 16:1.

^dCHD: coronary heart disease (myocardial infarction, coronary angioplasty or bypass surgery).

Table 2Odds ratios for heart failure by quartiles of plasma phospholipid oleic acid in the Physicians' Health Study.^a

Plasma phospholipid oleic acid quartiles ^b [minimum -maximum]	Cases	Odds ratio (95% CI) for heart failure	
		Model 1 ^c	Model 2 ^d
Q1 (low): 8.1 [6.2–8.7]	191	1.0	1.0
Q2: 9.1 [8.7–9.4]	210	1.10 (0.82–1.47)	1.10 (0.79–1.54)
Q3: 9.8 [9.4–10.1]	190	1.01 (0.75–1.35)	1.02 (0.72–1.44)
Q4 (high): 10.9 [10.1–16.0]	197	1.04 (0.78–1.39)	1.05 (0.72–1.54)
<i>p</i> for linear trend		0.91	0.94

^aData are presented as medians (minimum-maximum), means ± standard deviation, or %.^bQuartiles of oleic acid presented as percent of total fatty acids.^cAdjusted for matching variables (race, age, time of blood collection, and year of birth)^dAdjusted for matching variables plus body mass index, prevalent diabetes, coronary heart disease, atrial fibrillation, hypertension, vigorous physical activity, smoking, alcohol consumption, palmitoleic acid (16:1), plasma phospholipid 18:0, and marine omega-3 fatty acids.

Table 3

Odds ratios for heart failure by quartiles of ratio of MUFA:SFA in 1576 males of the Physicians' Health Study.

^a

MUFA:SFA quartiles $\pm$ SD ^b	Cases	Odds ratio (95% CI) for heart failure	
		Model 1 ^c	Model 2 ^d
Q1 (low): 0.20 $\pm$ 0.01	172	1.0	1.0
Q2: 0.22 $\pm$ 0.01	210	1.11 (0.83–1.49)	1.12 (0.80–1.58)
Q3: 0.24 $\pm$ 0.01	205	1.09 (0.82–1.46)	1.19 (0.84–1.68)
Q4 (high): 0.27 $\pm$ 0.02	201	0.93 (0.70–1.24)	0.97 (0.66–1.42)
<i>p</i> for linear trend		0.54	0.52

^aData are presented as medians (minimum-maximum), means $\pm$ standard deviation, or %.

^bSD = standard deviation.

^cAdjusted for matching variables (race, age, time of blood collection, and year of birth)

^dAdjusted for matching variables plus body mass index, prevalent diabetes, coronary heart disease, atrial fibrillation, hypertension, vigorous physical activity, smoking, alcohol consumption, palmitoleic acid, plasma phospholipid 18:0, and marine omega-3 fatty acids.