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Plasma phospholipid saturated fatty acids and heart failure risk in the Physicians' Health Study

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Abstract

BACKGROUND & AIMS—Previous studies have suggested that some plasma phospholipid saturated fatty acids (SFA) are associated with an increased risk of coronary heart disease and hypertension, major risk factors for heart failure (HF). However, little is known about the association between SFA and HF. This study examines associations of individual plasma phospholipid SFA with HF risk in US male physicians.

METHODS—The current ancillary study used a prospective nested matched case-control design to select 788 cases of incident HF and 788 controls. Plasma phospholipid SFAs were measured using gas chromatography. HF was self-reported on follow-up questionnaires and validated by review of medical records in a subsample. We used conditional logistic regression to estimate relative risks.

RESULTS—Mean age was 58.7±8.0 years. One standard deviation higher plasma phospholipid 16:0 was associated with an odds ratio (95% CI) of 1.20 (1.04, 1.38) controlling for established HF risk factors and other SFAs (p=0.042). However, this association was not significant after Bonferroni correction (p>0.008). We did not observe associations between other SFAs (14:0, 15:0, 18:0, 20:0, or 22:0) and HF risk (all p for trend > 0.05).

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CONCLUSIONS—Our data suggested no association between plasma phospholipid SFAs and HF in US male physicians.

Keywords

Saturated fatty acids; palmitic acid; heart failure

Introduction

Heart Failure (HF) is a common heart disease with nearly 700,000 new cases per year in the US. (1) The incidence of HF is high among elderly people, making it a major burden in developed nations with aging populations. (2, 3) Because mortality after HF onset remains high despite medical progress, it is important to evaluate novel modifiable determinants of HF that could lead to effective prevention. Two major risk factors of HF are coronary heart disease (CHD) and hypertension, and some previous studies suggest that plasma phospholipid saturated fatty acids (SFAs) may be associated with a higher risk of CHD and hypertension. (4, 5) Also, in cardiomyocytes, most of the energy is provided by oxidation of long-chain fatty acids (LUFAs) including SFAs. Early stage of ventricular failing shows abnormal metabolism of fatty acids, with a shift of energy provision from fatty acids to glucose, with more oxygen demand. (6) However, little is known about the association between SFAs and HF risk. Some experimental studies suggest beneficial effects of dietary SFA on cardiac function and HF survival in animal model. (7, 8) Of note is that circulating levels of the SFAs are largely driven by endogenous synthesis such as de novo lipogenesis rather than by SFA consumption. (9) On the other hand, several reports suggest toxic effect of free fatty acids on systolic function which might influence HF with depressed left ventricular function. (10) Limited studies have evaluated the relation of individual SFAs with HF. Hence, this study examines associations between individual plasma phospholipid SFAs and incident HF.

Methods

Study population

The PHS was a randomized, double-blind, placebo-controlled trial designed to test the effects of low-dose aspirin and beta carotene on cardiovascular disease and cancer among 22,071 US male physicians. A detailed description of PHS has been published previously. (11, 12)

For this ancillary study, we used a prospective nested case-control design to select all 788 incident HF cases with baseline blood sample (1982) from the PHS participants. For each case, we used a risk set technique to randomly selected one control subject who was alive and free of HF at the time of the index case diagnosis and matched on age at randomization (within 1 year), year of birth (within 1 years), and time of blood collection (within maximum 288 days), and race (white/non-white). Each case was eligible to serve as a control before HF diagnosis. Similarly, each control was eligible to later become a HF case to assure that controls were representative of a total population that gave rise to the HF cases. The investigation conforms with the principles outlined in the Declaration of Helsinki. Each participant gave written informed consent, and the Brigham and Women's Hospital (Boston, MA) Institutional Review Board approved the study protocol.

Measurement of plasma phospholipid SFAs

Baseline plasma phospholipid samples from all cases and controls were handled identically throughout sample collection, long term storage, sample retrieval, and assays. All investigators and laboratory personnel were unaware of participants' case- control status.

The fatty acid profile was measured in plasma using the method previously described by Cao et al. (13) For the extraction of plasma phospholipid fatty acids, 0.3 mL of plasma is mixed 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 are 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 is harvested for the formation of methyl esters. Fatty acid methyl esters are prepared with 1.5 mL of 14% boron trifluoride in methanol, incubated at 80°C for 90 minutes, and extracted with petroleum ether. The final product is 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. The GC is configured for a single capillary column with a flame ionization detector and interfaced with HP chemstation software. Adequate separation of fatty acid methylesters is obtained over a 50-min period with an initial temperature of 190°C for 25 minutes. The temperature is increased to 240°C at a rate of 2°C/min and held for 5 minutes. Fatty acid methylesters from 12:0 through 24:1n-9 are separated, identified and expressed as percent of total fatty acids. The following CVs were obtained on 30 blind duplicates as follows: 14:0, 5.2%; 15:0, 7.7%; 16:0, 1.4%; 18:0, 3.9%; 20:0, 6.9%; and 22:0, 6.5%.

We also assessed stearoyl-CoA desaturase-1 (SCD-1) activity defined as a ratio of product to substrate (16:1n-7/16:0), as SFAs are largely driven by de novo lipogenesis, particularly by SCD-1, and we wanted to evaluate the association between SFAs and risk of HF independent from de novo lipogenesis. A detailed description of measurement of SCD-1 activity has been published previously. (14)

Ascertainment of incident of HF

In PHS, ascertainment of endpoints including HF has been initially achieved using follow-up questionnaires. A questionnaire was mailed to each participant out every 6 months for the first year and has been mailed annually thereafter to obtain information on the incidence of HF. A detailed description of HF validation in the PHS has been published previously. (15) Briefly, two independent physicians reviewed medical records of a subsample of HF participants to validate self-reported diagnosis of HF. Positive predictive value of HF in this subsample was 91%.

Other variables

At baseline, we used a questionnaire to gather information on age, height, body weight, cigarette smoking, exercise, alcohol consumption, history of hypertension, diabetes mellitus, atrial fibrillation, and CHD defined as non-fatal myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft.

Statistical analysis

As we did not assume a particular shape of the relation between each plasma SFAs and incidence of HF, we initially used a more conservative approach. Each of plasma SFAs was divided into quartiles according to SFAs distribution among controls. The correlation among plasma SFAs was evaluated by using Spearman correlations. Baseline HF risk factors were compared according to quartiles of each plasma SFA, using ANOVA for continuous variables and χ^2 tests for proportions. We also evaluated the associations between each

plasma SFA and covariates included in the multiple conditional logistic regression using univariate regression among controls. We performed conditional logistic regression to examine the association between each plasma SFAs and HF. Odds ratios (95% CI) associated with each quartiles of plasma SFAs were obtained by using the lowest quartile as reference. The initial model controlled for matching factors. (Model 1) A second model controlled for BMI, smoking status (never, current, and past smokers), exercise (<1/week, =>1/week), alcohol consumption (rarely/none, 1–4/wk, 5–7/wk, 2+/day), diabetes mellitus, and atrial fibrillation. (Model 2) As for hypertension and CHD, we did not include these covariates into the second model, as we considered them as intermediate variables. Because correlations between plasma SFA were modest (all $r < 0.43$), we included indicator variables for each plasma SFA (14:0, 15:0, 16:0, 18:0, 20:0, and 22:0) into the same regression model to evaluate independent associations of each plasma SFA with HF controlling for other SFAs (Model 3). We additionally performed conditional logistic regression adjusted for covariates in Model 3 plus SCD-1 activity to evaluate the association between SFAs and risk of HF independent from SCD-1 activity. We tested for linear trend by fitting a continuous variable which assigned the median value of the each quartiles of plasma SFA. Because the quartile association was fairly linear, we also modeled each SFA as a continuous variable (OR for each standard deviation higher SFA using conditional logistic regression). All statistical tests were 2-sided and $p<0.05$ was considered significant. We used Bonferroni correction for final multivariate regression model to correct for inflation and used a p value of 0.0083 (0.05/6) to indicate statistical significance. Similarly, to achieve simultaneous 95% confidence intervals, we constructed 99.17% confidence intervals for each individual fatty acid's point estimate.

All analyses were completed using SAS, version 9.2 (SAS Institute, Cary, North Carolina).

Results

Mean age at blood collection was 58.7±8.0 years. Each of SFAs was fairly normally distributed in our study. For example, skewness and kurtosis of 16:0 (palmitic acid) were 0.37 and 0.54, respectively. Baseline characteristics of the participants are summarized in Table 1 according to quartiles of plasma palmitic acid, the most abundant plasma phospholipid SFA. In unadjusted data, higher plasma phospholipid palmitic acid concentration was associated with older age, higher body mass index, and higher proportion of hypertension. Spearman correlation coefficients between palmitic acid and other plasma SFAs varied from −0.43 to 0.25. Palmitic acid was inversely correlated with 18:0, 20:0, and 22:0, but positively correlated with 14:0 (Table 2).

From the lowest to the highest quartile of plasma phospholipid palmitic acid, multivariable adjusted odds ratios (95% CI) for HF were 1.0 (ref), 1.12 (0.80, 1.57), 1.11 (0.77, 1.59), and 1.68 (1.13, 2.50) controlling for matching factors, established HF risk factors, and other phospholipid plasma SFAs (p trend 0.01). Additional adjustment for potential intermediate factors including history of hypertension and CHD led to a modest attenuation of the odds ratios [1.0 (ref), 1.14 (0.81, 1.61), 1.11(0.76, 1.60), and 1.63 (1.09, 2.44) across consecutive quartiles of palmitic acid]. Also, additional adjustment for SCD-1 activity did not alter the association between palmitic acid and risk of HR at alpha of 0.05. [OR (95%CI): 1.0 (ref), 1.11 (0.79, 1.56), 1.08(0.75, 1.56), and 1.60 (1.07, 2.41) across consecutive quartiles of palmitic acid] When modeled as continuous variable, each standard deviation higher plasma phospholipid palmitic acid was associated with an odds ratio (95% CI) of 1.20 (1.04, 1.38) in the fully adjusted model (p value=0.042). However, we could not observe significant association after Bonferroni correction (all $p>0.008$). We did not observe an association between other plasma phospholipid SFAs (14:0, 15:0, 18:0, 20:0, or 22:0) and HF risk (all $p > 0.05$, Table 3)

Discussion

Summary of main findings

In this prospective nested case-control study, we found a positive association between plasma phospholipid palmitic fatty acid (16:0) and the risk of HF in US male physicians at nominal p value but not after Bonferroni correction for multiple testing ($p>0.008$). Other SFAs were not associated with HF risk at nominal p value or after Bonferroni correction (all $p >0.008$).

Plasma phospholipid palmitic acid (16:0) and HF

Few studies have evaluated the relation of palmitic acid concentrations with incident HF. Our findings of a positive association between palmitic acid and HF risk is consistent with the results from ARIC study, (16) which found that greater levels of plasma phospholipid palmitic acid was associated with a higher HF risk. They reported hazard ratio of HF for the highest versus the lowest quintiles of phospholipid plasma palmitic acid was 1.93 (p for trend across the quintiles=0.004) after the adjustment for age, sex, body mass index, systolic blood pressure, antihypertensive medication use, plasma total and high-density lipoprotein cholesterols, prevalent diabetes, smoking status, pack-years, alcohol intake, sports index, and education level in their prospective cohort study during 51,960 person-years of follow up of 3,575 white participants. Also, positive associations between plasma palmitic acid levels and hypertension as well as CHD were reported by other investigators. (4, 5) Contrary to those reports, our study did not reveal a statistically significant association of plasma palmitic acid with HF after adjustment for confounders and correction for multiple testing. A lack of a positive association between palmitic acid and risk of HF after Bonferroni correction ($p>0.008$), suggests that some of the fear against adverse health effects of saturated fats may not be fully substantiated. Further investigations are needed to evaluate the role of palmitic acid for risk of HF.

Palmitic acid is the most abundant fatty acid in plasma lipids, and it is largely driven by de novo lipogenesis, particularly by stearoyl-CoA desaturase-1 (SCD-1) activity. Our previous study showed that higher SCD-1 activity, defined as a ratio of product to substrate (16:1n-7/16:0), was associated with higher risk of HF. (14) Our data showed positive correlation between palmitic acid and both log transformed SCD-1 and 16:1n-7. [Spearman correlation coefficients for log SCD-1 and 16:1n-9 were 0.27 and 0.41, respectively. (both $p<0.001$)] However, conditional multiple logistic regression model (Model 3 in Table 3) additionally adjusted for SCD-1 did not alter the results. It may be important to account for dietary factors, as de novo lipogenesis is influenced by dietary carbohydrate, alcohol, and protein consumption. (9) Unfortunately, we did not have baseline information on carbohydrate or protein intake for further exploration.

Other SFAs and HF

Our results did not suggest association between other plasma SFAs and HF. These results are consistent with data from the ARIC study, which did not show significant associations between phospholipid myristic acid (14:0), margaric acid (17:0), and staric acid (18:0) and HF. (17) Furthermore, several large cohort studies did not show significant associations between plasma phospholipid stearic acid or myristic acid and HF risk factors including hypertension and CHD. (4) However, to the best of our knowledge, no previous study has evaluated the association between other plasma SFAs such as pentadecylic acid (15:0), arachidic acid (20:0) or behenic acid (22:0), and HF or HF risk factors.

Strengths and limitations

The current study has some limitations. First, we have only one measurement of plasma phospholipid SFAs, which are strongly influenced by endogenous synthesis (i.e. under carbohydrate intake or insulin resistance). Thus, we were not able to account for change in plasma SFAs over time during the follow-up period. Second, plasma phospholipids reflect concentration over only medium term (weeks to months) and are not as stable as red blood cell membrane phospholipids.

Third, we cannot exclude residual and unmeasured confounding as a partial explanation of our findings. Despite a reasonable positive predictive value for self-reported HF against validation via medical records in a subsample (91%), we cannot exclude possible misclassification of HF cases in this study. Fourth, our sample consists of only highly educated middle age male physicians in the US, thereby limiting the generalizability of our findings to other socioeconomic or ethnic groups and women. Fifth, as we did not have complete dietary information at baseline in this cohort, we could not evaluate the influence of other dietary factors including macro- and micronutrients on these results. Lastly, all the covariates were collected by self-reported questionnaires and we cannot exclude random misclassification.

Nevertheless, our study has several strengths, including a large sample size, matching on key confounders to minimize confounding, prospective study design, validation of incident HF and the use of reproducible biomarkers (plasma SFAs) to quantify SFA.

Conclusions

Our data are consistent with no association of various plasma phospholipid saturated fatty acids with HF after adjustment for multiple testing among US male physicians.

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Table.1

Characteristics of 1,576 participants according to quartiles of plasma phospholipid 16:0 fatty acid (Palmitic acid)*

	Quartiles of plasma phospholipid 16:0 fatty acid (% of total fatty acids)			
Characteristics	**Q1 [21.22–24.374] n=369**	**Q2 [24.375–25.325] N=384**	**Q3 [25.326–26.393] n=380**	**Q4(high) [26.394–33.579] n=443**
Age(year)	57.8±8.1	58.5±8.0	59.2±8.1	59.3±7.9†
Body mass index (Kg/m2)	24.9±2.6	25.0±2.9	25.4±3.2	25.4±2.9†
14:0(%)	0.25±0.07	0.27±0.07	0.29±0.08	0.30±0.08†
15:0(%)	0.19±0.04	0.20±0.04	0.20±0.04	0.19±0.05†
16:0(%)	23.58±0.64	24.86±0.28	25.82±0.31	27.39±0.93†
18:0(%)	14.51±1.06	14.18±0.10	13.84±1.05	13.19±1.22†
20:0(%)	0.28±0.14	0.26±0.13	0.24±0.13	0.23±0.13†
22:0(%)	0.72±0.22	0.70±0.24	0.68±0.24	0.64±0.23†
Current smoking (%)	9.8	9.9	11.8	13.1
Never smoking (%)	56.8	50.8	38.7	36.2†
Alcohol intake; None (%)	42.0	30.3	19.5	13.8
Alcohol intake; 1–4/week (%)	34.6	35.0	38.0	27.7
Alcohol intake; 5–7/week (%)	23.4	32.6	39.3	52.6
Current exercise (%)	76.4	71.7	73.8	72.8
Atrial fibrillation (%)	3.5	5.0	3.7	3.6
Coronary heart disease (%)	2.4	3.9	3.4	3.4
Hypertension (%)	28.5	25.0	35.5	34.3†
Diabetes (%)	4.6	3.7	5.8	7.9†

*Data are presented as Means ± standard deviation and quartiles are based on the distribution of 16:0 among controls

†$p<0.05$, across median values of plasma saturated fatty acids within each quartiles. ANOVA was used for continuous variables, and χ^2 test was used for categorical variables.

Table.2

Spearman correlation coefficients for plasma saturated fatty acids

	Plasma phospholipid saturated fatty acid					
	14:0	**15:0**	**16:0**	**18:0**	**20:0**	**22:0**
14:0						
15:0	0.28*					
16:0	0.25*	−0.02				
18:0	−0.05*	−0.07*	−0.43*			
20:0	−0.11*	−0.06*	−0.14*	−0.02		
22:0	<−0.01	0.04	−0.16*	0.11*	0.36*	

* p<0.05 for Spearman correlation.

Table.3

Odds ratio of heart failure according to plasma phospholipid saturated fatty acids in the Physicians' Health Study

	Cases	Odds ratio for heart failure					
		Model 1*		Model 2†		Model 3‡	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (99.17% CI)	P value
14:0 Q1	199	1	Ref	1	Ref	1	Ref
14:0 Q2	194	0.99(0.75, 1.30)	0.923	0.97(0.72, 1.31)	0.838	0.96(0.64, 1.46)	0.816
14:0 Q3	184	0.93(0.71, 1.23)	0.624	0.80(0.59, 1.09)	0.153	0.79(0.52, 1.22)	0.159
14:0 Q4	211	1.08(0.81, 1.44)	0.581	1.09(0.80, 1.49)	0.588	1.03(0.65, 1.64)	0.854
Per SD higher 14:0		1.03(0.93, 1.14)	0.572	1.03(0.92, 1.15)	0.585	1.02(0.86, 1.20)	0.719
15:0 Q1	218	1	Ref	1	Ref	1	Ref
15:0 Q2	187	0.88(0.66, 1.16)	0.359	0.76(0.56, 1.04)	0.083	0.78(0.50, 1.20)	0.122
15:0 Q3	217	1.00(0.76, 1.32)	0.996	0.89(0.65, 1.22)	0.482	0.95(0.61, 1.48)	0.415
15:0 Q4	166	0.77(0.57, 1.05)	0.096	0.71(0.50, 1.01)	0.055	0.73(0.44, 1.12)	0.101
Per SD higher 15:0		0.92(0.83, 1.03)	0.147	0.91(0.80, 1.02)	0.119	0.91(0.76, 1.07)	0.156
16:0 Q1	172	1	Ref	1	Ref	1	Ref
16:0 Q2	187	1.11(0.82, 1.49)	0.498	1.03(0.75, 1.42)	0.844	1.12(0.71, 1.77)	0.521
16:0 Q3	183	1.10(0.82, 1.48)	0.522	0.99(0.71, 1.39)	0.966	1.11(0.68, 1.81)	0.742
16:0 Q4	246	1.49(1.11, 2.00)	0.009	1.49(1.06, 2.09)	0.023	1.68(0.98, 2.87)	0.011
P for trend		0.01		0.02		0.01	
Per SD higher 16:0		1.15(1.03, 1.28)	0.010	1.14(1.01, 1.29)	0.042	1.20(0.99, 1.45)	0.014
18:0 Q1	185	1	Ref	1	Ref	1	Ref
18:0 Q2	186	1.02(0.76, 1.37)	0.890	0.92(0.67, 1.26)	0.581	1.01(0.64, 1.57)	0.979
18:0 Q3	185	1.01(0.75, 1.37)	0.925	0.86(0.62, 1.20)	0.374	1.02(0.63, 1.66)	0.901
18:0 Q4	232	1.28(0.95, 1.72)	0.101	1.04(0.75, 1.44)	0.816	1.28(0.78, 2.11)	0.189
Per SD higher 18:0		1.11(1.00, 1.23)	0.056	1.03(0.92, 1.16)	0.601	1.12(0.93, 1.35)	0.105
20:0 Q1	204	1	Ref	1	Ref	1	Ref
20:0 Q2	200	0.96(0.70, 1.31)	0.777	0.94(0.67, 1.33)	0.732	0.91(0.57, 1.48)	0.621
20:0 Q3	212	1.00(0.66, 1.50)	0.992	0.95(0.62, 1.48)	0.830	1.02(0.55, 1.88)	0.946
20:0 Q4	172	0.76(0.50, 1.17)	0.218	0.72(0.46, 1.15)	0.169	0.81(0.41, 1.59)	0.399

	Cases	Odds ratio for heart failure					
		Model 1*		Model 2†		Model 3‡	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (99.17% CI)	P value
Per SD higher 20:0		0.94(0.80, 1.10)	0.430	0.89(0.75, 1.06)	0.334	0.93(0.71, 1.23)	0.773
22:0 Q1	215	1	Ref	1	Ref	1	Ref
22:0 Q2	191	0.85(0.62, 1.15)	0.291	0.87(0.62, 1.21)	0.409	0.91(0.57, 1.46)	0.314
22:0 Q3	194	0.85(0.61, 1.17)	0.314	0.78(0.55, 1.11)	0.170	0.82(0.48, 1.38)	0.305
22:0 Q4	188	0.80(0.56, 1.14)	0.223	0.74(0.50, 1.09)	0.126	0.86(0.46, 1.56)	0.503
Per SD higher 22:0		0.93(0.82, 1.06)	0.279	0.89(0.77, 1.03)	0.118	0.93(0.74, 1.16)	0.366

*Conditional logistic regression matched for matching factors age, race, year of birth, the date of blood kid returned,

†Adjusted for matching factors and body mass index, smoking status, exercise level, alcohol consumption, history of diabetes, and history of atrial fibrillation.

‡Adjusted for matching factors and covariates in model 2 plus all of saturated fatty acids.

alpha=0.0083 (0.05/6) and 99.17% CI were used to construct individual confidence intervals to achieve an overall 95% confidence intervals using Bonferroni correction.