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Omega-6 and trans fatty acids in blood cell membranes: a risk factor for acute coronary syndromes?

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Abstract

Background—Although fatty acid intake has been associated with risk of coronary disease events, the association between blood omega-6 and trans-fatty acids (FAs) at the time of an acute coronary syndrome (ACS) is unknown.

Methods—The relationship of blood FA composition to ACS was analyzed in 768 incident cases and 768 controls (matched on age, sex, and race).

Results—Compared to controls, ACS cases' blood cell membrane content of linoleic acid was 13% lower ($p<0.0001$); arachidonic acid was 3.6% higher ($p<0.001$); the *trans* isomer of oleic acid was 13.3% higher ($p<0.0001$); and the *trans-trans* isomer of linoleic acid was 13.3% higher ($p=0.003$). In multivariable analyses, a 1-standard deviation (SD) decrease in linoleic acid was associated with >3 times the odds for being a case {OR=3.23 {95% CI, 2.63–4.17}}. The relationship of arachidonic acid to ACS was U-shaped; compared to the first quartile of arachidonic acid, the ORs for case status in the second, third and fourth quartiles were 0.73 (95% CI: 0.47–1.13), 0.65 (95% CI: 0.41–1.04), and 2.32 (95% CI: 1.39–3.90). The OR for a 1-SD increase in *trans* oleic acid was 1.24 (95% CI: 1.06 to 1.45) and for *trans-trans* linoleic acid, 1.1 (95% CI: 0.93–1.30). All associations were independent of membrane omega-3 FA content.

Conclusions—High blood levels of linoleic acid but low levels of *trans* oleic acid are inversely associated with ACS. The relationship of arachidonic acid to ACS appears more complex.

INTRODUCTION

In the US, the predominant dietary *trans* FAs are the 18-carbon isomers of oleic and linoleic acids (1). Dietary intake of *trans* FAs and CHD risk have been positively correlated in several cohort studies (2–4) and a case-control study (5). However, biomarker-based case-control studies correlating *trans* FAs with risk for cardiac events have not been consistent. Some have reported adverse associations (1,6,7), others no correlation (8,9) and one study demonstrated a paradoxical, beneficial association (10).

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Disclosures
None

A class of FAs that has been traditionally considered “heart healthy” is the omega-6 FAs, in particular linoleic acid, which is found in abundance in most vegetable oils (11). However, in recent years questions have been raised as to whether the consumption of linoleic acid has become excessive (12), to the point of actually contributing to an increased risk for CHD via its conversion to arachidonic acid (the predominant substrate for proinflammatory prostaglandins, leukotrienes, thromboxane, and prostacyclin (13)).

METHODS

Selection of Cases

See Figure 1 for a study recruitment description. Cases were drawn from a registry of patients with a confirmed diagnosis of either acute myocardial infarction or unstable angina as previously described (14). Three physicians reviewed the charts of all patients for whom diagnostic uncertainty remained and attained consensus on the final diagnosis. In total, 1,059 consecutive patients met the inclusion criteria. Data from 768 of these patients were successfully matched to control patients (described below) and used in this study.

Selection of Controls

Outpatient controls having blood drawn for routine clinical testing were recruited from blood drawing centers at Saint Luke’s Hospital (where 88% of the cases were derived). The other 12% were derived from Truman Medical Center. They were all recruited between March 8, 2004 and March 1, 2005. Permission was sought from men and non-pregnant women age 35 and older to obtain one additional 10 ml blood sample, and they were asked to complete a 2-page questionnaire. A history of CHD did not exclude either cases or controls as this study investigated the relationship between fatty acid content and incident ACS. Control samples were individually and matched to cases by age (5-yr windows), sex and race (Caucasian vs. non-Caucasian). The study was approved by the Institutional Review Boards of both hospitals.

Laboratory Methods

Blood cell FA composition was measured as previously described (14). For the present study, we focused on two omega-6 FAs (linoleic and arachidonic acids), and three *trans* FAs (*trans* palmitoleic, *trans* oleic and *trans trans* linoleic acid). The latter two are representative of the major *trans* species derived by partial hydrogenation of oleic and linoleic acids, respectively. The total *trans* FAs was defined as the sum of these three, recognizing that very small amounts of many more *trans* isomers were also present in these samples. Serum lipids were measured in the hospital clinical laboratory by routine enzymatic methods. In those samples with triglycerides under 400 mg/dL, low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation (15); otherwise LDL-C was not reported.

Statistical Analysis

Descriptive statistics were used to compare characteristics of patients with and without ACS using paired t-tests, McNemar’s test, or Bowker’s test of symmetry, as appropriate. Non-linear relationships of continuous variables were determined using restricted cubic spline terms with non-linear variables then treated categorically(16). A reference level was chosen by finding the lowest odds point on the curve for each FA. To prevent erroneous model-predicted values in the tails of the distributions we constrained the restricted cubic spline predicted values for graphs to those subjects with fatty acid values between the 10th and 90th percentile of that fatty acid’s distribution.

Information on one (n=159, 10%) or more (n=164, 11%) covariates was missing and was assumed to be missing at random (i.e., non-informatively missing given the available observed

data). Values were thus independently imputed 5 times using multiple imputation methods to allow incorporation of all patients in the analysis and to account (in an unbiased manner) for uncertainty due to missingness. The imputation model consisted of all variables used in the multivariable model. Analyses were replicated on the 5 imputed data sets and pooled to obtain final model estimates. Analyses were also performed excluding subjects with any missing variables to ensure that imputation did not alter the results.

Multivariable conditional logistic regression models were used to determine the independent effects, expressed by the odds ratio (OR) and 95% CI, of linoleic acid, arachidonic acid, and the *trans* FAs of interest on ACS status. To prevent confounding, the following covariates were included in the models: lipid levels (LDL, HDL, log-triglycerides, total cholesterol/HDL ratio), body mass index, diabetes mellitus, hypertension, family history of coronary artery disease, personal history of myocardial infarction or revascularization, alcohol consumption (less than moderate, moderate [= 1–2 drinks, 2–6 days each week], or more than moderate), smoking habits (currently smoking vs. not), statin, aspirin, or anti-platelet drug use, education level (some college vs. none) and blood cell content of the two omega-3 fatty acids, eicosapentaenoic acid (EPA) + docosahexanoic acid (DHA). To determine if the effect of each FA was mediated through effects on lipids or the proportion of EPA+DHA, the effect of removing these two factors collectively and separately from the regression model was also assessed. To adjust for potential unmeasured confounders, we added a statistical interaction term separately for level of education and a prior diagnosis of cardiovascular disease to the model. C-statistics were calculated for logistic regression models for each fatty acid of interest adjusting for matched variables and not conditional on the matched pairs. Statistical significance for variables in the logistic regression models was defined by a two-sided *p*-value of <0.05. All analyses were conducted using SAS software, release 9.1 (SAS Institute, Cary, North Carolina) and R version 2.6.0. (R Foundation for Statistical Computing, Vienna, Austria). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Of the 768 ACS cases, 29% had unstable angina and 71% MI, with the latter group being evenly split between ST- and non-ST- Elevation MIs.

Case-Control Differences

Because of matching, the age, sex, and race distributions of the cases and the controls were virtually identical (Table 1). For ACS cases, blood cell linoleic acid content was 13% lower than in controls ($p<0.0001$) whereas arachidonic acid was 3.6% higher ($p<0.001$) (Table 1). In ACS cases, blood cell content of the major *trans* isomer of oleic acid (elaidic acid) was 13.3% higher than in controls ($p<0.0001$), the *trans-trans* isomer of linoleic acid was 13.3% higher ($p=0.003$), and the sum of these two *trans* FAs (plus *trans* palmitic acid) was 13.1% higher ($p<0.0001$). Linoleic and arachidonic acids composed 15% and 14% of total FAs, respectively, whereas total *trans* FAs composed only about 4% of total FAs. For the total population, *trans* oleic acid composed 74% of total *trans* FAs and this proportion was consistent for cases and controls. The distribution of other fatty acids that compose the total proportion of blood cell fatty acids in cases and controls, are displayed in Table 1.

Blood Cell Membrane Omega-6 and Trans Fatty Acid Content and Odds for ACS

Restricted cubic spline analyses for each fatty acid are shown in Figure 2. The relationships with ACS for all fatty acids of interest were generally linear except for arachidonic acid, which had a U-shaped relation with the odds for ACS; having very low or very high levels of arachidonic acid associated with an increased the odds of being an ACS case.

In multivariable analyses (Figure 3), a 1-standard deviation (SD) increase in linoleic acid was associated with an OR for case status of 0.30 (95% CI, 0.24–0.38). The OR did not change appreciably when excluding from the model both lipids and EPA+DHA (OR 0.35; 95% CI 0.29–0.43), and it changed even less when each alone was excluded (data not shown).

Compared to the lowest quartile of arachidonic acid (reference group), the OR for case status was 0.73 (95% CI: 0.47–1.13) in the second quartile, 0.65 (95% CI: 0.41–1.04) in the third quartile, and 2.32 (95% CI: 1.39–3.90) in the highest quartile. When excluding lipids (LDL, HDL, log-triglycerides and the total cholesterol/HDL ratio) and EPA+DHA from the model, the presence of an arachidonic acid content in the second (OR 0.66; 95% CI 0.45–0.97) and third (OR 0.60; 95% CI 0.40–0.89) quartiles was negatively associated with ACS and content in the highest quartile remained positively associated with ACS (OR 1.67; 95% CI 1.08–2.57). The curved relationship of arachidonic acid with ACS was still present after adjusting for palmitic acid (a prominent saturated FA) or when excluding lipids and EPA+DHA from the model.

The OR for a 1-SD increase in *trans* oleic acid was 1.24 (95% CI; 1.06 to 1.45), for *trans* linoleic acid 1.10 (95% CI; 0.93–1.30), and for total *trans* FA, 1.31 (1.11–1.55). Overall logistic regression model discrimination was quite good with c-statistics of 0.82 for all fatty acids in Figure 2 with the exception of linoleic acid, which had even greater discriminative ability ($c=0.87$). As for linoleic acid, excluding lipids and EPA+DHA together and separately from these models did not significantly change the relationship of these *trans* fatty acids with ACS and the relationships for all FAs of interest with ACS also held in bivariate analyses. The results were also unchanged when models excluded subjects with any missing variables and level of education or a prior diagnosis of cardiovascular disease did not affect the results (interaction p -values >0.2). None of the fatty acids of interest were independently associated with the total cholesterol/HDL ratio (all p -values >0.05).

DISCUSSION

ACS incident cases had a lower proportion of linoleic acid and a greater proportion of the 18-carbon *trans* oleic acid but not the 18-carbon *trans trans* linoleic acid in their blood cell membranes than subjects not experiencing an ACS. Importantly, these associations were independent of EPA+DHA (14), and the total cholesterol/HDL ratio, a robust predictive metric for cardiovascular events (17), known to be altered by fatty acid intake (18). Linoleic acid was most strongly associated with ACS, having a robust negative relationship that was even greater than that for EPA+DHA. The n6/n3 ratio was higher in the cases than the controls owing to the fact that, in the cases, the n3 fatty acids were depressed to a greater extent than were the n6 fatty acids. The value of the n6/n3 ratio has recently been questioned (19,20).

Higher linoleic acid intakes tend to lower serum LDL-C levels (21) and CHD death rates in the US have dropped markedly over the decades when linoleic acid intakes have increased (22). Intake of linoleic acid has also been directly associated with a 12–15% reduction in the incidence of coronary heart disease in four high linoleic acid intake intervention trials (23–26). Similarly, the risk of coronary heart disease and intake (or plasma/serum levels) of linoleic acid were inversely correlated in four large prospective studies (27–31). The current study found that high linoleic acid levels (unlikely to be altered by an ACS (32,33)) were inversely related to ACS despite the fact that LDL levels were slightly higher in subjects with higher membrane LA content. These data suggest that, although linoleic acid is the major dietary fatty acid regulating LDL metabolism (34), its cardioprotective effects could be mediated through other metabolic pathways. Moreover, the adjusted odds for ACS for those with the lowest content of linoleic acid was almost twenty times higher than those at the other extreme.

Consumption of *trans* FAs, which are produced largely by partial hydrogenation of vegetable oils (and to some extent by prolonged heating) (35), has been associated with a pooled relative

risk of 1.23 for every 2% increase in energy intake. This relationship with diet has been demonstrated in four of the more recent case-control studies (1,6,7,36). Although *trans* FAs can alter a variety of risk factors for CHD, notably lipids, endothelial function, and inflammatory markers (35), the link between *in vivo* *trans* FA levels and risk for CHD has not been demonstrated in all studies (8,9). Despite the fact that biomarkers may be more reliable than dietary measures as indicators of exposure, they are not without shortcomings (22). For example, blood values of the nutritional biomarkers folate and homocysteine can vary substantially between laboratories due to a lack of standardization and establishment of reference ranges (37). Other factors that can lead to invalid correlation of biomarkers with disease status include genetic, environmental, behavioral, and health status factors, sampling error, and measurement error. Such issues may explain why a number of retrospective case-control studies have demonstrated inconsistent results (6,7,10). In the current study, high levels of *trans* oleic acid were associated with ACS whereas levels of *trans trans* linoleic acid, although higher in cases, were not significantly so. This study is unique in that it had nearly twice the number of subjects than two prior biomarker studies (1,36) combined and a distinct outcome of ACS (MI and unstable angina), as opposed to sudden cardiac death, with or without fatal MI.

Perhaps the most novel finding of this study was the U-shaped relationship between blood cell arachidonic acid content and ACS case status. Although risk tended to be lower in the second and third quartiles as compared with the first, it was considerably higher in the highest quartile. The explanation for this is not readily apparent, but it may depend on which FAs are being replaced by arachidonic acid. However, this hypothesis will be difficult to test as fatty acids are measured as proportions and, in that sense, are interdependent. Interestingly, the presence of an arachidonic acid level in the highest quartile was associated with ACS despite progressively increasing levels of EPA+DHA in each successively higher quartile. A meta-analysis of fourteen prior case-control and prospective cohort studies published between 1966 and 2005 found that increased arachidonic acid content in phospholipid or triglyceride was not significantly associated with CHD events except when measured in adipose tissue (triglyceride fraction; positive association (38). Other authors have concluded that phospholipid arachidonic acid content does not correlate with CHD (34,39). These findings support further research as a U-shaped relationship of arachidonic acid to ACS was not described in any of these prior investigations.

Although the Framingham Risk Score predicts CHD events with 70–80% accuracy (40,41), it could still be improved upon. Thus, the benefits of measuring tissue fatty acids should be investigated. First, fatty acid profiles may serve as a clinical screening tool to assess cardiovascular risk (42). Second, they could guide dietary interventions using an evidence-based approach. Third, as aspirin and atorvastatin are commonly used in patients at risk for CHD, and each appears to affect levels of potentially protective lipid mediators from fatty acids (43), the interaction between these agents and tissue fatty acids appears to warrant investigation.

STRENGTHS AND LIMITATIONS

Strengths of this study include a large sample size, a rigorously-defined ACS population, detailed FA analysis, the inclusion of plasma lipid covariates, and the use of a biomarker of FA intake that is unlikely to be affected by an ACS(32,33). Potential limitations include the fact that this study was conducted in a single metropolitan area, thus restricting the range of observed FA levels. Second, focusing exclusively on ACS patients excluded individuals in the community succumbing to out-of-hospital sudden cardiac death. Exclusion of these patients, who could theoretically have especially high *trans* FA values, would tend to select patients with lower levels and to minimize case-control differences. Third, different methods were used

to collect demographic and health history data from cases and controls. Although the same questions were asked of each, the former were obtained by personal interview and chart review, while the latter came from self-administered questionnaires. This could theoretically have led to inaccurate adjustment for covariates, although such a problem would not have altered the unadjusted relationships between ACS risk and blood FA content. Fourth, although we were able to control for serum lipids, data were not available on other known (e.g. current blood pressure, marital status, socioeconomic class, exercise) or emerging (e.g. inflammatory mediators(44)). Finally, since our study included few minorities and mostly men, our findings may have limited generalizability.

CONCLUSION

An increased blood cell content of *trans* oleic acid was independently associated with increased odds of ACS case status whereas an increase in the principal omega-6 FA, linoleic acid, was associated with decreased odds. The association of blood cell arachidonic acid content with ACS was U-shaped with levels in the highest quartile being robustly associated with odds for ACS case status. The prognostic and/or diagnostic value of these FA markers as they relate to ACS, and the extent to which their modification by diet will alter risk for ACS, are both currently unknown and warrant further study.

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Figure 1.

Figure 2.

Graphs representing the relationship of each fatty acid of interest with ACS, with 95% confidence intervals, were created using restricted cubic spline terms. To ensure data stability, each spline plot represents data from those subjects with a proportion of each fatty acid of interest between 10 and 90% of total fatty acids.

Figure 3.

Odds for acute coronary syndrome (ACS) case status. Odds for arachidonic acid are relative to the lowest quartile (reference group) and odds for all other fatty acids are for a 1 SD increase in blood cell membrane content. Odds were calculated in the multivariable logistic regression model previously described. Blood cell content of EPA+DHA was included in the model for all non-omega-3 FAs. Data are presented as point estimates with 95% confidence intervals.

Table 1

Description of Cases and Controls

Variable	Cases (n = 768)	Controls (n = 768)	P-Value
Age (years)	61.0 ± 12.1	61.0 ± 12.0	0.18
Male	509 (66%)	509 (66%)	1.0
Caucasian	704 (92%)	704 (92%)	1.0
Diabetes mellitus	193 (25%)	120 (17%)	.0003
Body mass index (kg/m ²)	29.5 ± 6.1	28.3 ± 5.8	<.0001
Currently smoking	268 (35%)	106 (14%)	<.0001
Education level - No college	393 (52%)	168 (22%)	<.0001
Moderate alcohol use (1–2 drinks 2–6 days/week)	341 (45%)	446 (59%)	<.0001
Hypertension (by history)	487 (63%)	408 (55%)	.001
Myocardial infarction or revascularization (by history)	216 (28%)	104 (14%)	<.0001
Family history of premature CHD	404 (53%)	270 (36%)	<.0001
Total cholesterol (mg/dL)	180 ± 43	191 ± 45	<.0001
Triglycerides (mg/dL)	183 ± 142	165 ± 128	.02
High density lipoprotein cholesterol (mg/dL)	42 ± 15	51.0 ± 16	<.0001
Low density lipoprotein cholesterol (mg/dL)	104 ± 36	108 ± 38	.007
Linoleic acid (% total FA)	14.26 ± 2.51	16.45 ± 2.57	<.0001
Arachidonic acid (% total FA)	14.21 ± 3.70	13.72 ± 2.39	.0007
Omega-6/omega-3 ratio	7.09 ± 2.16	6.14 ± 2.10	<.0001
Total <i>trans</i> -fats (% total FA) ^I	3.78 ± 1.40	3.34 ± 1.29	<.0001
<i>Trans</i> -oleic acid (% total FA)	2.81 ± 0.81	2.48 ± 0.84	<.0001
<i>Trans, trans</i> -linoleic acid (% total FA)	0.17 ± 0.13	0.15 ± 0.08	.003
<i>Trans</i> palmitic acid (% total FA)	0.80 ± 1.04	0.70 ± 1.0	0.02
Palmitic acid (% total FA)	22.71 ± 2.74	21.46 ± 1.91	<.0001
Stearic acid (% total FA)	14.34 ± 1.93	14.31 ± 1.48	0.77
Palmitoleic acid (% total FA)	1.54 ± 0.77	1.46 ± 0.65	0.02
Oleic acid (% total FA)	18.00 ± 3.67	17.29 ± 2.63	<.0001
Alpha-linoleic acid (% total FA)	0.31 ± 0.17	0.48 ± 0.25	<.0001
Eicosapentaenoic acid (% total FA)	0.46 ± 0.29	0.72 ± 0.53	<.0001
Docosahexaenoic acid (% total FA)	2.93 ± 1.40	3.53 ± 1.57	<.0001
Eicosadienoic acid (% total FA)	0.25 ± 0.07	0.25 ± 0.05	0.2
Eicosatrienoic acid (% total FA)	1.74 ± 0.40	1.71 ± 0.38	0.2
Docosatrienoic acid (% total FA)	2.80 ± 0.95	2.49 ± 0.69	<.0001
Statin use	340 (44%)	295 (38%)	.02
Aspirin or other antiplatelet drug use	387 (50%)	241 (31%)	<.0001

^I sum of *trans* C16:1n7, *trans* C18:1n9, and *trans, trans* C18:2n6 isomers

The other fatty acids not reported here (2–3% of the total) included dimethylacetals, odd chain fatty acids, and very minor *cis*- and *trans*-positional isomers of palmitic, oleic and linoleic acids.

Values for continuous variables are means ± SD.