Arachidonic Acid in Adipose Tissue Is Associated with Nonfatal Acute Myocardial Infarction in the Central Valley of Costa Rica[1]

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ABSTRACT Arachidonic acid (AA), a precursor of prothrombotic eicosanoids, is potentially atherogenic, but epidemiologic data are scarce. We evaluated the hypothesis that increased AA in adipose tissue is associated with increased risk of nonfatal acute myocardial infarction (MI), and if so, whether this association is related to dietary or adipose tissue linoleic acid. We studied the association between AA and MI in 466 cases of a first nonfatal acute MI, matched on age, gender, and residence to 466 population controls. Fatty acids (FA) were assessed by GC in adipose tissue samples collected from all subjects. Odds ratios (OR) and 95% CI were calculated from multivariate conditional logistic regression models. Subjects in the highest quintile of adipose tissue AA (0.64% of total FA) had a higher risk of nonfatal acute MI than those in the lowest quintile (0.29% of total FA), after adjusting for potential confounders including (n-3) and *trans* FAs (OR = 1.94, 95% CI: 1.07, 3.53, *P* for trend = 0.026). Adipose tissue AA was not correlated with dietary AA ($r = 0.07$), linoleic acid ($r = 0.04$), or other dietary (n-6) FAs, or with adipose tissue linoleic acid ($r = -0.07$). These data suggest that the association between MI and adipose tissue AA is not related to dietary intake of (n-6) FAs including linoleic acid. Better understanding of the metabolic factors that increase AA in adipose tissue is urgently needed. J. Nutr. 134: 3095–3099, 2004.

KEY WORDS: • *arachidonic acid* • *fatty acids* • *myocardial infarction* • *adipose tissue* • *risk factors*

Arachidonic acid (AA)[3] is a long-chain (n-6) fatty acid (FA) [20:4(n-6)] that results from the elongation and desaturation of linoleic acid [18:2(n-6)] or directly from the diet (1). Because AA is a precursor of proinflammatory and proaggregatory eicosanoids, it was hypothesized that diets rich in (n-6) FAs, specifically linoleic acid, can have detrimental health effects (2,3). However, intervention studies showed that AA does not accumulate in human tissues after major increases in dietary linoleic acid (4–7). These observations question the potential adverse health effects that may occur with dietary linoleic acid. The conversion of linoleic acid to AA could be modified by the (n-3) FA content of the diet, e.g., α-linolenic acid [18:3(n-3)] because these 2 FA families compete for the same desaturases in the metabolic pathways (8). Thus, increasing dietary (n-3) FAs could reduce the formation of AA and its effect on coronary heart disease (CHD) (8). Most epidemiologic studies show a cardiovascular protective effect of (n-6) PUFA, (9–12) but studies on the direct effect of AA on CHD are scarce (13,14). Interestingly, the variant form of the 5-lipoxygenase gene that codes for the enzyme involved in the first step of AA conversion to eicosanoids increases atherosclerosis, particularly among consumers of diets high in AA (15). We tested the hypothesis that increased AA in adipose tissue is associated with increased risk of nonfatal acute myocardial infarction (MI), and if so, whether this association is related to linoleic or α-linolenic acid in adipose tissue and in the diet.

SUBJECTS AND METHODS

Study population. The study design and population were described previously (16). Eligible case subjects were men and women who were diagnosed as survivors of a first acute MI by 2 independent cardiologists at any of the 3 recruiting hospitals in the Central Valley of Costa Rica (17). All cases met the WHO criteria for MI, which require typical symptoms plus either elevations in cardiac enzyme levels or diagnostic changes in the electrocardiogram (18). Enrollment was carried out while cases were in the hospital's step-down unit.

One free-living control subject for each case, matched for age (±5 y), sex, and area of residence (county), was randomly selected using the information available at the National Census and Statistics Bureau of Costa Rica. Participation was 97% for cases and 90% for controls. All subjects gave informed consent on documents approved by the Human Subjects Committee of the Harvard School of Public Health and the University of Costa Rica.

Data collection. All cases and controls were visited at their homes for data collection. Anthropometric measurements and biological specimens were collected in the morning at the subject's home, after an overnight fast (16,17). A subcutaneous adipose tissue biopsy was collected from the upper buttock and stored at −80°C until analysis (19). Adipose tissue was sampled an average of 3 wk after acute nonfatal MI. Adipose tissue was selected because it was

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[3] AA, arachidonic acid; CHD, coronary heart disease; FA, fatty acid; MI, myocardial infarction.

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established that it has a very long half-life (1–2 y) (6) and it is not affected by acute events (20). Sociodemographic characteristics, smoking, socioeconomic status, and medical history data were collected during an interview using a questionnaire. Dietary intake was collected using a FFQ that was developed and validated specifically to assess FA intake among the Costa Rican population (19,21). Although the main exposure is adipose tissue AA, dietary information from the FFQ is useful to understand the characteristics of the study population and to investigate whether nutrients not measured in adipose tissue could confound the association between adipose tissue AA and MI. Self-reported diabetes and hypertension were validated as previously described (17).

Fatty acid analysis. Fatty acids from adipose tissue were quantified by GLC (19). Peak retention times and area percentages of total FA were identified using known standards (Nu-Chek-Prep), and analyzed with the Agilent Technologies ChemStation A.08.03 software. Duplicate samples ($n = 12$), indistinguishable from others, were analyzed throughout the study. The between assay CV for linoleic and AA were 5.5 and 11.2%, respectively.

Statistical analysis. All data were analyzed with the Statistical Analysis Systems software (SAS Institute). Of the 1061 subjects that were recruited, 466 cases and 466 controls with complete data on adipose tissue FA and potential confounders were used in the final analysis. The significance of differences in crude means and frequencies for health characteristics and potential confounders were assessed by paired *t* tests and McNemar's test. Spearman correlation coefficients were calculated to show the association between FAs in diet and adipose tissue and within FAs in adipose tissue. Odds ratios (OR) and 95% CI for adipose tissue AA quintiles were estimated from multiple conditional logistic regression models. Confounders were selected among potential risk factors for MI if they were associated with AA among the controls (exposure) and had an effect on the AA-MI association, or if they were biologically relevant. Variables included in the final models were waist-to-hip ratio (quintiles), household income (quintiles), history of diabetes (yes/no), history of hypertension (yes/no), smoking status (never, past, <10 cigarettes/d, 10–20 cigarettes/d, >20 cigarettes/d), adipose tissue linoleic (quintiles), adipose tissue α-linolenic (quintiles), adipose tissue total *trans* (quintiles), saturated fat intake (quintiles), alcohol intake (never, past intake, current intake divided in tertiles), and total energy intake (quintiles). Other potential confounders examined but not included in the final models were BMI, physical activity, history of hypercholesterolemia, multivitamin use, aspirin use, nonsteroidal anti-inflammatory drugs, intake of vitamin E, vitamin C, folate, fiber, dietary cholesterol, and total fat. In adipose tissue, we examined oleic acid, γ-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid as potential confounders, in addition to those included in the final model (linoleic acid, α-linolenic, and total *trans*). Tests for trend were performed across quintiles, using the median value for each of the quintiles modeled as a continuous variable. We tested for the statistical significance of interactions between adipose tissue AA and other variables using the likelihood ratio test.

RESULTS

The basic characteristics of the study population are described in **Table 1**. In univariate analysis, the relation between adipose (n-6) FAs and MI varied according to desaturation and chain elongation. Linoleic acid [18:2(n-6)], the precursor FA of the (n-6) family and γ-linolenic acid [18:3(n-6)] the first product of desaturation, were significantly lower in cases than in controls. In contrast, FAs that result from increasing carbon chain length and desaturation [20:3(n-6), 20:4(n-6), and 22:4(n-6)] were significantly higher in cases than in controls.

Weight, waist to hip ratio, sex, history of hypertension, and diabetes, 20:2(n-6), 20:3(n-6), 22:4(n-6), 18:3(n-3), and total *trans* in adipose tissue were associated with AA in adipose tissue **(Table 2)**. The main contributors of dietary AA in this population, that is, eggs, chicken, fish, and meats were not correlated with AA in adipose tissue. Neither dietary AA nor dietary linoleic acid were correlated with adipose tissue AA ($r = 0.07$, $P = 0.15$ and $r = 0.04$, $P = 0.41$, respectively), but, as expected, dietary linoleic acid was strongly correlated with adipose linoleic acid ($r = 0.57$, $P < 0.0001$). Furthermore, adipose tissue linoleic acid was correlated with adipose tissue 18:3(n-6) ($r = 0.43$, $P < 0.0001$) but not with adipose tissue AA ($r = -0.07$, $P = 0.11$), and weakly correlated with 20:3(n-6) ($r = 0.18$, $P = 0.0001$) or 22:4(n-6) ($r = -0.14$, $P = 0.003$). These findings confirm a strong metabolic regulation of AA formation, and suggest that dietary linoleic acid does not increase AA in tissues within the range of intake in this population (3.1–6.7% of energy for the median values of quintile 1 vs. 5).

Adipose tissue AA was associated with increased risk of MI (**Table 3**). The age-sex-residence adjusted model shows an OR of 2.32 for subjects in the 5th quintile (AA = 0.64%) compared with subjects in the 1st quintile (AA = 0.29%). This association remained significant, although somewhat attenuated (OR = 1.94, (95% CI 1.07, 3.53), after adjusting for potential confounders (established risk factors, other adipose tissue FA, and dietary variables). Further adjustment for other dietary variables, such as intake of fiber, folate, or cholesterol, did not change the results. AA and dihomo-γ-linolenic [20:3(n-6)], an immediate precursor of AA, were highly correlated ($r = 0.60$); thus, statistical adjustment was not possible. The OR for the highest quintile of dihomo-γ-linolenic acid was 2.85 (95% CI = 1.37, 5.94), although most likely the effect of dihomo-γ-linolenic on MI is due to AA.

Adipose tissue linoleic acid was associated with MI in the univariate analysis (OR = 0.68 95% CI 0.44, 1.04 for the highest vs. lowest quintile, *P* for trend = 0.0422), but this association was attenuated and no longer significant (*P* trend

TABLE 1

Characteristics of MI cases and population-based controls in Costa Rica[1]

n	Controls 466	Cases 466	*P*-value
Age, *y*	57 ± 11	57 ± 11	—
Waist-to-hip ratio	0.93 ± 0.07	0.95 ± 0.07	<0.0001
BMI, *kg/m²*	25.8 ± 4.0	26.0 ± 3.9	0.6663
Physical activity, *METS/d*	1.55 ± 0.63	1.45 ± 0.64	0.0174
Income, *$US/mo*	568 ± 483	455 ± 424	0.0006
Gender, *% female*	27	27	—
Diabetes, %	11	24	<0.0001
Hypertension, %	26	44	<0.0001
Current smokers,[2] %	28	43	<0.0001
NSAID intake, %	27	24	0.2643
Aspirin intake ≥ 1/wk, %	11	8	0.1167
	g/100 g total fatty acids		
Adipose tissue			
18:2(n-6)	13.4 ± 3.2	12.9 ± 3.1	0.0196
18:3(n-6)	0.30 ± 0.18	0.27 ± 0.17	0.0094
20:2(n-6)	0.22 ± 0.06	0.22 ± 0.06	0.8044
20:3(n-6)	0.32 ± 0.12	0.35 ± 0.13	<0.0001
20:4(n-6)	0.43 ± 0.13	0.47 ± 0.14	<0.0001
22:4(n-6)	0.22 ± 0.07	0.24 ± 0.08	<0.0001
Σ (n-6) fatty acids	15.3 ± 3.3	14.9 ± 3.2	0.0466

[1] Values are means ± SD or %.
[2] Smoke ≥ 1 cigarette/d.
[3] METS, metabolic equivalents; NSAID, nonsteroidal anti-inflammatory drug.

TABLE 2

Distribution of potential confounders by quintiles of adipose tissue AA in Costa Rican population-based controls[1]

	Quintiles of arachidonic acid in adipose tissue				
	1	2	3	4	5
Median adipose tissue AA	0.28	0.36	0.43	0.49	0.62
Waist-to-hip ratio	0.91	0.94	0.94	0.94	0.95[2]
BMI, *kg/m*^{2}	23.6	24.8	25.4	27.3	28.2[2]
Physical activity, *METS/d*	1.63	1.66	1.44	1.46	1.50
Income, *$US/mo*	598	520	565	535	615
Sex, % *female*	18	15	23	37	38[2]
History of diabetes, %	3	13	11	17	13[2]
History of hypertension, %	16	20	24	39	35[2]
Current smokers,[3] %	26	37	28	20	32
NSAID intake, %	15	20	23	19	23
Aspirin intake ≥ 1/wk, %	7	11	11	16	11
Dietary variables					
Energy, *MJ/d*	9.9	9.5	9.8	9.9	9.6
Total fat, % *energy*	33.0	33.7	33.6	33.3	32.9
Saturated fat, % *energy*	11.7	11.9	11.6	11.6	11.2
Monounsaturated fat, % *energy*	12.3	12.6	12.7	12.5	12.3
Polyunsaturated fat, % *energy*	5.5	5.6	5.6	5.6	5.6
Alcohol,[4] *g/d*	12.2	12.3	13.6	18.4	17.2
Foods, *g/d*					
Eggs	23	27	25	34	25
Meats	59	60	60	54	60
Fish and chicken	63	64	67	69	71
			g/100 g total fatty acids		
Adipose tissue					
18:2(n-6)	13.5	13.7	13.4	13.4	12.8
18:3(n-6)	0.34	0.33	0.30	0.27	0.25
20:2(n-6)	0.20	0.22	0.22	0.22	0.24[2]
20:3(n-6)	0.22	0.29	0.31	0.36	0.40[2]
22:4(n-6)	0.14	0.18	0.22	0.24	0.31[2]
Σ (n-6) fatty acids	15.1	15.5	15.3	15.4	15.1
18:3(n-3)	0.58	0.58	0.55	0.53	0.49[2]
Σ *trans* fatty acids	3.42	3.16	3.17	3.01	2.85[2]

[1] Values are means or %, $n = 466$.
[2] P for trend < 0.05.
[3] Smoke ≥ 1 cigarette/d.
[4] Among alcohol drinkers ($n = 217$).
[5] METS, metabolic equivalents; NSAID, nonsteroidal anti-inflammatory drug.

= 0.14) after adjusting for potential confounders, particularly adipose tissue α-linolenic acid, which is strongly protective in this population and is present in many oils and foods that contain linoleic acid (16).

DISCUSSION

This study shows that increased AA in adipose tissue is associated with a 94% increase in nonfatal acute MI, and

TABLE 3

ORs for the risk of nonfatal acute MI by quintile of AA in adipose tissue in Costa Rica[1]

Quintile	1	2	3	4	5	*P* for trend
Median adipose AA	0.29	0.37	0.44	0.51	0.64	
Ratio controls/cases	111/75	101/86	100/86	77/110	77/109	
Age-sex-residence adjusted	1.00	1.29 (0.85,1.96)	1.32 (0.86,2.03)	2.31 (1.48,3.60)	2.32 (1.49,3.63)	<0.0001
Model 1	1.00	1.29 (0.79,2.10)	1.29 (0.78,2.14)	1.78 (1.04,3.06)	2.03 (1.18,3.51)	0.0069
Model 2	1.00	1.29 (0.78,2.15)	1.40 (0.82,2.38)	1.88 (1.05,3.37)	2.12 (1.19,3.77)	0.0077
Model 3	1.00	1.22 (0.71,2.09)	1.37 (0.78,2.40)	1.65 (0.91,3.01)	1.94 (1.07,3.53)	0.0226

[1] Values are OR (95% CI).
[2] Model 1: adjusted for waist-to-hip ratio, income, history of diabetes, history of hypertension, cigarette smoking status; Model 2: Model 1 + adipose tissue fatty acids (linoleic, α-linolenic, total *trans*); Model 3: Model 2 + dietary variables (saturated fat, alcohol intake, total energy intake. Adjusting for other dietary variables did not change the results).

supports the hypothesis that AA is detrimental to cardiovascular health (2,3). The observed association was independent of confounders, particularly other FAs that increase (*trans* and SFA) or decrease (α- linolenic and linoleic acid) the risk of MI in this population (16,22,23). The validity of our findings is enhanced by the population-based, case-control design with high participation (97 and 90%, respectively), the standardized study procedures for inclusion of cases of a first MI, the large number of case subjects, and the assessment of exposure using adipose tissue, a stable marker of FAs after acute MI because of its slow turnover (6).

Results in the Costa Rican population are supported by those of a recent study in Israel (13) in which the risk of MI was 97% higher among subjects with the highest adipose tissue AA (3rd tertile) compared with the lowest, after adjusting for confounders. It is noteworthy that these findings are similar even with the large diet differences between Israel and Costa Rica. For example, polyunsaturated vegetable oils are used extensively in Israel, and this high level of intake is reflected in a very high proportion (25%) of linoleic acid in adipose tissue (13). In contrast, the use of palm oil is common in the Costa Rican population, where linoleic acid represents only 13% of total FAs in adipose tissue. Other studies did not detect significant associations between adipose tissue AA and MI (24–26). Yet, case subjects from these studies tended to have higher AA adipose tissue levels than controls (24–26).

A few studies examined the association between AA in blood and MI (24,27,28). Consistent with our observation, AA in erythrocytes was higher in cases of cardiac arrest compared with controls (28). In contrast, other studies showed that AA in platelets or plasma was significantly lower among cases than in controls (14,24). Interestingly, discrepant results were observed even in the same study in which an association with MI was found with lower platelet AA, but not with lower adipose tissue (24), or with lower AA in serum phospholipids, but not with serum triglyceride or cholesterol esters (27). There are several possible explanations for these conflicting results. Fatty acid biomarkers in blood (e.g., plasma, RBC) and adipose tissue can result in different outcomes because they could reflect tissue-specific properties. In muscle, phospholipid AA is positively related to insulin sensitivity (29). However, Phinney et al. (30,31) reported altered AA homeostasis in obese Zucker rats, in which a metabolic shift of AA was observed from phospholipids to cholesterol esters in liver. Thus, although obese rats had lower proportions of AA in liver phospholipids, they had higher proportions in cholesterol esters. Furthermore, the absolute amount of AA in carcass fat was 5 times higher in obese than in lean rats (30,31). In our study, we analyzed AA in RBC and adipose tissue in a subset of 200 controls. Consistent with data from animal studies, we found that the correlation between AA in RBC (mostly phospholipids) and adipose tissue AA was very low ($r = 0.11$), but when restricting the analysis to obese subjects (BMI $\geq$30), the correlation becomes negative ($r = -0.45$ in men and $r = -0.24$ in women) (unpublished data). Thus, it is possible that individual tissues reflect different metabolic pools of AA, and our findings in adipose tissue do not necessarily reflect potential associations with other tissues.

The association between adipose tissue AA and MI could be related to the role of AA as a precursor of eicosanoids (2,3). Although adipose tissue FA concentrations do not necessarily represent flux through the tissues, increased AA in adipose tissue could reflect increased mobilization of AA in other important tissues such as the arterial intima. The association between AA and MI could also be mediated by insulin sensitivity in adipose tissue or elsewhere. Altered distribution of AA in tissues was correlated with alterations in lipogenesis and insulin action (8,30,32,33). Also, increased adipose tissue AA is associated with BMI (8,30,32,33). In fact, in our study, we found a relatively high correlation between AA and BMI, particularly among men ($r = 0.40$). AA is an activator of the peroxisome proliferator-activated receptors that modulate insulin sensitivity (34), and it is more adipogenic than (n-3) FAs (35). Still, we cannot rule out that the effects of AA on MI could reflect lower (n-3) FAs or a correlation with increased *trans* FAs, both predictors of MI in our population (16,22). In our analysis, we adjusted for these factors; however, although it is unlikely, residual confounding remains a possibility.

Our data suggest that at the current intake of our population, dietary linoleic acid intake does not result in increased AA in adipose tissue because there was no association between adipose tissue AA and dietary or adipose linoleic acid, a finding consistent with a study in another population (13). These observations are supported by feeding studies showing either no change (4,5) or even lower (7) AA levels in tissues after subjects consumed diets rich in linoleic acid. In the classic study by Dayton et al. (6) in which 393 subjects consumed an experimental diet rich in unsaturated FA for 5 y, linoleic acid in serum was substantially higher among subjects in the experimental diet compared with those in the control diet, but no differences in AA levels were observed even after 3 y of follow-up (6). These studies clearly show that AA is likely to be subjected to tight metabolic control, and its dietary precursor linoleic acid does not increase its concentration in tissues. Thus, it is unlikely that a diet high in linoleic acid increases the risk of MI because of its conversion to AA; in fact, both epidemiologic studies and clinical trials show that linoleic acid is protective.

In conclusion, we found that increased adipose tissue AA is associated with MI. Our results suggest that this association is independent of dietary and adipose tissue linoleic acid, as well as of other (n-6) and (n-3) FAs. Human studies that investigate how AA levels are regulated in vivo are warranted. Identification of these pathways could lead to novel targets to lower the risk of coronary disease.

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