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Erythrocyte Saturated Fatty Acids and Systemic Inflammation in Adults

Lin Mu, BS, BA[1], **Kenneth J. Mukamal, MD, MPH, MA**[1,2,3], and **Asghar Z. Naqvi, MD, MPH, MNS**[1,2]

[1]Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, MA

[2]Harvard Medical School, Boston, MA

[3]Harvard School of Public Health, Boston, MA

Abstract

Objective—The role of saturated fatty acids (SFAs) in chronic disease remains controversial; inflammation is one pathway by which SFAs influence the risk of chronic disease. We aim to investigate the associations between red blood cell (RBC) phospholipid SFAs and systemic inflammation.

Methods—As part of a randomized controlled trial, we measured RBC phospholipid FA composition among 55 generally healthy adults twice at three-month intervals. We estimated associations of RBC total SFAs and two major SFA subtypes, palmitic and stearic acids, with C-reactive protein (CRP), interleukin-6 (IL-6), white blood count (WBC), and a composite inflammation measure using generalized estimating equations in multivariable FA substitution models.

Results—Mean (±SD) SFA level across both visits was 45±3% of the total RBC FAs, mainly palmitic (21±1%) and stearic (17±3%) acids. In models adjusted for age, sex, race, smoking, BMI, statin use, aspirin use, transunsaturated FAs, and ω3FAs, SFAs were significantly associated with IL-6 (20% increase per 1 SD increment; 95% CI: 0.03%, 43%; P=0.05) and the composite inflammation measure (P=0.05) and marginally associated with CRP (34% increase; − 1%, 81%; P=0.06), but not associated with WBC. Stearic acid was positively associated with CRP (35% increase; 2%, 79%; P=0.04). Palmitic acid was marginally associated with the composite inflammation measure (P=0.06) and, upon additional ω6FA adjustment, significantly associated with IL-6 (15% increase; 0.4%, 27%; P=0.006).

Corresponding Author Contact: Asghar Z. Naqvi, MD, MPH, MNS 330 Brookline Avenue, Yamins 102-D Boston, MA 02215 United States Telephone: 617-754-9600 Facsimile: 617-667-8665 anaqvi@bidmc.harvard.edu.

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Conclusions—RBC SFAs, which represent longer-term dietary intake, are positively associated with inflammation. In particular, palmitic acid was associated with IL-6, and stearic acid was associated with CRP after multivariable adjustment.

Keywords

C-Reactive Protein; Interleukin-6; White Blood Count; Palmitic Acid; Stearic Acid; Erythrocyte Phospholipid; Saturated Fat

INTRODUCTION

The role of saturated fatty acids (SFAs) in chronic diseases such as coronary heart disease (CHD) and cancer remains an area of ongoing controversy. For example, a 2010 meta-analysis of 16 prospective cohorts found that dietary SFA intake is not significantly associated with risk for CHD [1]. A systematic review based on the Bradford Hill guidelines also concluded that insufficient evidence relates SFA intake with CHD [2]. By contrast, a pooled analysis of 11 cohorts [3] and a meta-analysis of 8 randomized controlled trials [4] suggested that isocaloric replacement of SFAs with polyunsaturated FAs reduces coronary events and deaths.

Similarly, a meta-analysis found that higher SFA intake was associated with lower risk of breast cancer in 19 cohort studies but higher risk in eight case-control studies, although neither relation was significant [5]. Similar controversies exist in ovarian [6–9], prostate [10–12], and pancreatic cancers [13–16]. In reconciling these discrepancies, the accuracy of dietary assessment instruments, particularly food frequency questionnaires (FFQs), has been critiqued for contributing to the contradictory research results [17, 18].

One pathway by which SFAs have been proposed to influence risk of chronic disease is inflammation. A recent systematic review suggested that the current evidence regarding the association of SFA with inflammation remains inconclusive; however, it pointed to a potential positive relationship between SFA and C-reactive protein (CRP) [19]. In the Whitehall study of older men, plasma lipid SFA level was positively correlated with plasma CRP and fibrinogen levels [20]. In addition, among healthy men fed controlled diets, consumption of combined lauric, myristic, and palmitic acids increased plasma CRP, fibrinogen, and interleukin-6 (IL-6) concentrations [21]. Surprisingly, the consumption of stearic acid alone, which appears to be non-hypercholesterolemic [22–24], also appears pro-inflammatory [21].

To date, few studies have related measured levels of SFAs to systemic inflammation. To evaluate the potential effect of SFAs and their two most prevalent subtypes (palmitic and stearic acids) on systemic inflammation, we assessed the associations of systemic CRP and IL-6 concentrations and white blood count (WBC) with red blood cell (RBC) phospholipid SFAs on two occasions in a cohort of generally healthy adults with periodontitis. Periodontitis is a common, chronic inflammatory disease with a global prevalence exceeding 10% in 2010 [25]; studying healthy adults with periodontitis allows us to include individuals with a broad range of inflammation levels. RBC SFAs are objective physiological measurements that reflect dietary intake within the past three months and thus allow for

more direct assessment of the SFA physiological role in inflammation than dietary survey methods [26].

SUBJECTS AND METHODS

Subjects

This study analyzed data from a randomized control trial conducted at Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA that examined the effect of supplementation of docosahexaenoic acid (DHA), a marine-source omega-3 fatty acid (ω3FA), on adults aged 40 years and older with moderate periodontitis. Relevant exclusion criteria included pregnancy, diabetes, rheumatic diseases, cirrhosis, cancer, hemorrhagic stroke, gastrointestinal bleeding, poorly controlled hypertension, conditions requiring antibiotic prophylaxis, systemic steroids, immune-modulatory therapies, warfarin, clopidogrel, end-stage renal disease, severe caries or periodontitis, recent antibiotic or periodontal therapy or ω3FA use, and regular use of non-steroidal anti-inflammatory drugs other than aspirin. A total of 560 potential participants who responded to advertisements underwent a pre-screening telephone interview and, if eligible by history, underwent a screening appointment at the BIDMC Clinical Research Center within two weeks. From June 2009 to December 2011, 55 eligible participants underwent randomization in a parallel, double-blinded design to receive either 2 g/day DHA or corn/soy oil placebo for three months (Supplemental Figure 1). All participants also received 81 mg aspirin, which prolongs the anti-inflammatory effect of DHA *in vitro* [27, 28]. We provided participants with standard oral hygiene instructions but asked them not to undergo periodontal treatment, alter diet, or change physical activity for the duration of the study. Each participant received $100.00 remuneration. The study was approved by the Committee on Clinical Investigations, and all participants gave written informed consent.

Laboratory measurements

Blood specimens were collected after an overnight fast at baseline and three-month follow-up. Complete blood count and high sensitivity CRP concentration were both assessed at Laboratory Corporation of America (Raritan, NJ), using a Sysmex X-series analyzer (Sysmex Corporation, Kobe, Japan) and a particle enhanced turbidimetric assay on a COBAS INTEGRA system (Roche Diagnostics, Mannheim, Germany), respectively. RBC FAs were quantified in the Department of Nutrition at Harvard School of Public Health (Boston, MA), using gas–liquid chromatography on a fused silica capillary cis–trans column SP2560 (Supelco, Bellefonte, PA) with peak retentions analyzed in Agilent Technologies ChemStation A.08.03 software. Individual RBC FA was reported as a proportion of total phospholipid FAs. Serum IL-6 concentration was measured at the Harvard Catalyst Central Laboratory (Boston, MA) using access chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA). The intra-assay coefficients of variation for CRP, IL-6, palmitic, and stearic acids were 1.3%, 1.7–4.6%, 5%, and 19%, respectively.

Statistical analysis

We analyzed data using the Statistical Analysis Software (version 9.3, 2011, SAS Institute Inc). Baseline participant characteristics across tertiles of SFA were compared using simple

linear regression for trends in continuous variables or Fisher's exact test for categorical variables. RBC FA data generally followed a normal distribution, which we rescaled in units of their standard deviations before analysis. CRP, IL-6, and WBC data were right-skewed and log-transformed. We also created a composite measure of inflammation by averaging the standardized levels of log-transformed CRP, IL-6, and WBC.

We used generalized estimating equations (PROC GENMOD) to evaluate the association between inflammation measures and SFAs accounting for repeated measures within-individual. We first adjusted for age and sex, and then additionally controlled for race, smoking (current, former, never), BMI, statin use, aspirin use (two individuals at baseline and all at follow-up), and levels of transunsaturated FA (TFA) and ω3FA.

Because individual FA levels represent proportions of RBC FAs and hence sum to 1, adjustment for TFA and ω3FA (but not MUFA or ω6FA) represents a substitution model, in which the estimate for SFA represents the effect of substituting SFAs for an equivalent amount of MUFAs and ω6FAs, which we considered physiologically neutral. In models where MUFA and ω6FA appeared to show heterogeneous associations with inflammation, we additionally adjusted for ω6FA. We further applied these models to examine the individual effects of palmitic and stearic acids, the two most prevalent SFA subtypes, adjusting for the modest levels of other SFAs. To maximize model convergence, we specified 1) a Poisson distribution and a log link in CRP and IL-6 models and 2) a Gaussian distribution and an identity link in models of WBC and composite inflammation. We tested for linearity with fractional polynomials and tests of heterogeneity across quartiles of SFA, palmitic, and stearic acids.

RESULTS

Table 1 shows the baseline characteristics of the study participants. Except for moderate periodontitis, participants were generally healthy. Among all 55 participants across both visits, the mean (±SD) SFA level was 45 (±3) % of the total RBC FAs, which were mainly palmitic acid (21±1%) and stearic acid (17±3%). As expected, CRP and IL-6 concentrations were strongly correlated (Spearman r=0.54, P<0.001), and each was marginally correlated with WBC (CRP: r=0.16, P=0.13; IL-6: r=0.19, P=0.08).

In age and sex adjusted models, SFA was positively, albeit not significantly, associated with inflammation. Further adjustment for confounders strengthened this association. In multivariable models, SFA was significantly associated with IL-6 (P=0.05) and the composite inflammation measure (P=0.05) and marginally associated with CRP (P=0.06), but not with WBC (Table 2). Among all covariates, BMI was the main confounder and most significantly associated with CRP (P<0.001), conferring a 13% (95% CI: 7%, 19%) increase in CRP concentration per 1 unit BMI increment; it was also significantly associated with the composite inflammation measure (P=0.03) and marginally associated with IL-6 (P=0.10). We did not find TFA or ω3FA to associate significantly with any inflammatory biomarker, likely due to their relatively low levels; the mean (±SD) TFA and ω3FA levels across both visits were 0.9 (±0.4) % and 6 (±2) %, respectively. MUFA and ω6FA exhibited marginally different associations with IL-6 only (P=0.07); in IL-6 models with additional adjustment for

ω6FA, 1 SD increment of SFAs was associated with 30% (95% CI: 4%, 62%; P=0.02) increase in IL-6 levels.

In assessments of major SFA subtypes, palmitic acid was not consistently associated with inflammatory biomarkers (Table 2), although it had a marginally significant and moderately positive association with the composite inflammation measure (P=0.06). On the other hand, stearic acid tended to be associated with higher levels of inflammation measures, particularly with CRP in the multivariable model. In addition, adjustment for ω6FA strengthened associations between SFA subtypes and IL-6 levels: 1 SD increments of palmitic acid and stearic acid were associated with 15% (95% CI: 4%, 27%; P=0.005) and 15% (95% CI: −9%, 45%; P=0.26) increases, respectively, in IL-6 levels. Finally, we observed a significant quadratic association between stearic acid and the composite inflammation measure (P=0.01). Relative to the levels in the first quartile, the lowest composite inflammation levels were seen in the second quartile (Beta=−0.30, SE=0.18) and the highest in the fourth quartile (Beta=0.06, SE=0.39, P=0.09 for heterogeneity). We observed no other non-linear relationships.

DISCUSSION

By examining a healthy population with a wide range of inflammation, obtaining two measures of exposure and outcome within individuals, using gold-standard RBC FA measurement, and analyzing three complementary measures of inflammation, this study provides evidence to the growing literature on the positive links between SFA, its subtypes, and inflammation. Specifically, we found that SFAs were positively associated with inflammation, mainly due to the significant effects of palmitic acid and stearic acid on IL-6 and CRP, respectively.

Few clinical trials and cohort studies have assessed the roles of SFA in systemic inflammation, and they have yielded mixed results. For example, although most feeding trials suggest postprandial elevation in CRP following an SFA-rich meal, postprandial changes in other inflammatory markers such as IL-6 and tumor necrosis factor-alpha (TNFα) are largely inconsistent [29–32]. In cohort studies using dietary assessment, even the association between SFA intake and CRP has yet to be established, with results ranging from null [33], borderline positive [34], to significant in males only [35]. At least one study has applied both semi-quantitative FFQs and plasma lipid FA measurements [36]. In that study of 374 healthy adults, dietary SFA was significantly associated only with IL-6, not CRP; by contrast, plasma SFA was significantly associated with both IL-6 and CRP, which is consistent with our findings and those from the Whitehall study [20]. This seems to suggest a higher consistency across studies assessing measured levels of SFA than using dietary instruments alone, although the limited number of studies reporting measured SFA levels precludes definitive conclusions at this time.

Our results also suggest a pro-inflammatory role of both palmitic and stearic acids. This is supported by a previous feeding trial, in which the consumption of stearic acid alone increased CRP concentration [21]. It is also substantiated by the PIVUS study, which found a significant association between CRP and stearic acid among 264 elderly Swedes [37].

However, these results are not entirely consistent. For example, in a prospective cohort of 395 Portuguese, neither palmitic nor stearic acid intake was associated with CRP [35]. In a cross-sectional survey among 489 healthy Japanese adults, CRP was found to have a significant and positive association with serum palmitic but not stearic acid, and this relationship was only observed in men [38]. In another cross-sectional study of 528 young Canadian adults, CRP was found to have a significant and positive association with plasma palmitic acid but a significant and inverse association with stearic acid; these correlations were only observed in women and were independent of ethnicity [39]. The effects of individual SFA subtypes warrant further research, especially using erythrocyte measures that best reflect longer-term intake.

Our observed associations concord with emerging evidence in cellular and animal studies that suggest biological mechanisms through which SFAs induce inflammation. In cocultures of murine macrophages and adipocytes, SFAs, but not unsaturated FAs, increase TNFα mRNA levels by stimulating toll-like receptor 4 and activating nuclear factor kappa B (NFκB) [40, 41]. This likely results from the metabolism of SFA into ceramide, which amplifies the lipopolysaccharide response in human monocytes and macrophages [42]. Cellular studies also point to heterogeneous roles of palmitic and stearic acids in inflammation. Palmitate increases monocyte chemoattractant protein-1 expression in hypertrophied adipocytes via c-Jun NH_2- terminal kinase and NFκB signaling [43] and causes endoplasmic reticulum stress eliciting apoptosis [44]. It also induces IL-6 production and TNFα expression in adipocyte and skeletal muscle cells [45–47]. In contrast, stearate does not affect NFκB transactivation or monocyte chemoattractant protein-1 expression in adipocytes [48], but it more potently induces IL-6 mRNA in macrophages than palmitate [49]. Our study results support the biological link between palmitate and IL-6 production, although we did not find stearic acid to be associated with IL-6.

The limitations of our study include its observational design, which hinders our ability to draw causal inferences. The cohort was also small, although we included multiple measures within each person. In addition, our study is limited by the lack of certain data that may relate to inflammation including physical activity and dietary habits other than fats. Further, even though RBC SFA measurement allows for more definitive studies of the role of SFA in inflammation than calculated values from dietary assessments, it reflects more than mere dietary intake; therefore, dietary recommendations may not be directly extrapolated from this current study. Finally, an observational analysis of a clinical trial such as this may be subject to bias related to selection into the trial. In this trial, most exclusions related to insufficient or excessive oral disease. As a result, participants of this study had moderate but not severe periodontitis, which allowed us to include individuals with a broad range of inflammation levels, but our findings may not be generalizable to other populations.

CONCLUSIONS

Higher RBC SFAs are associated with increased systemic inflammation. In particular, palmitic acid was associated with elevated IL-6, and stearic acid was associated with higher CRP after multivariable adjustment. Larger prospective cohort studies and clinical trials are

needed to clarify the potential pro-inflammatory effects of SFAs and their major subtypes in other clinical populations and the general public.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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We acquired data of this study from a clinical trial on docosahexaenoic acid (DHA) and periodontitis, which received a donation of DHA and placebo capsules from Martek Corporation. Martek provided no other resources or funds and has no role in the conduct or analysis of this study. Martek had no role whatsoever in the current manuscript. There are no other competing interests to disclose.

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Table 1

Baseline Participant Characteristics according to Red Blood Cell Saturated Fatty Acid Levels[a]

	SFA Tertiles (Ranges in %)			
	T1 (40–43)	**T2 (43–46)**	**T3 (46–51)**	**P value[b]**
No. of Participants	17	17	17	
Demographic Characteristics				
Age (years)	55 (10)	55 (10)	56 (8)	0.90
Sex (female)	8 (47%)	6 (35%)	7 (41%)	0.94
Race				0.42
White	13 (76%)	11 (65%)	7 (41%)	
African American	3 (18%)	3 (18%)	7 (41%)	
Asian	1 (6%)	2 (12%)	2 (12%)	
Multi-Racial	-	1 (6%)	1 (6%)	
Smoking Status				0.80
Former	6 (35%)	3 (18%)	3 (18%)	
Current	2 (12%)	2 (12%)	3 (18%)	
BMI (kg/m^2)	30.0 (4.5)	28.1 (5.9)	27.3 (4.5)	0.12
Overweight (25–30)	5 (29%)	5 (29%)	7 (41%)	
Obese (>30)	8 (47%)	6 (35%)	4 (24%)	
Blood Pressure (mmHg)	137 (19) / 79 (10)	132 (14) / 78 (9)	136 (15) / 80 (10)	0.94 / 0.81
Hypertension	3 (18%)	3 (18%)	3 (18%)	1.00
Hyperlipidemia	5 (29%)	5 (29%)	2 (12%)	0.43
Clinical Characteristics				
TG (mg/dL)	133 (62)	96 (30)	94 (35)	0.02
HDL (mg/dL)	60 (22)	52 (10)	59 (22)	0.94
LDL (mg/dL)	117 (31)	131 (67)	104 (30)	0.45
CRP (mg/L)	2.89 (3.41)	1.67 (2.26)	1.82 (2.48)	0.27
IL-6 (pg/mL)	2.57 (1.82)	2.85 (1.66)	2.40 (1.07)	0.75
WBC (k/μL)	6.6 (2.1)	7.3 (2.3)	5.9 (1.1)	0.29
PD (mm)	2.6 (0.4)	2.8 (0.4)	2.6 (0.4)	0.81
Red Blood Cell Phospholipid Fatty Acids (%)				
SFA	42 (0.9)	44 (0.9)	48 (1.5)	<0.001
Palmitic Acid	21 (0.8)	21 (1.1)	22 (1.4)	0.02
Stearic Acid	15 (1.1)	17 (1.1)	20 (1.5)	<0.001
TFA	0.7 (0.2)	0.8 (0.3)	1.2 (0.3)	<0.001
MUFA	19 (1.5)	17 (1.1)	16 (1.1)	<0.001
ω3FA	7 (1.5)	6 (1.1)	5 (1.3)	0.01
ω6FA	32 (2.3)	32 (1.8)	29 (2.1)	<0.001

Abbreviations: BMI: Body Mass Index, TG: Triglycerides, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, CRP: C-Reactive Protein, IL-6: Interleukin-6, WBC: White Blood Count, PD: mean periodontal Pocket Depth, SFA: Saturated Fatty Acids, TFA: Trans-Fatty Acids, MUFA: Mono-Unsaturated Fatty Acids, ω3FA: Omega-3 Fatty Acids, ω6FA: Omega-6 Fatty Acids.

[a]Data are means (SD) or number (%). Four participants were missing baseline SFA measurements.

[b] P values were based on the simple linear regression for continuous variables or Fisher's exact test for categorical variables.

Table 2

Change of Inflammatory Marker Levels per 1 SD Increment of SFAs

	CRP (mg/L)		IL-6 (pg/mL)		WBC (k/μL)		Inflammation	
	% Change (95% CI)	P	% Change (95% CI)	P	% Change (95% CI)	P	Beta (95% CI)	P
Saturated Fatty Acids								
Age-sex adjustment*	4 (−13, 24)	0.68	4 (−5, 13)	0.40	0.7 (−4, 5)	0.76	0.08 (−0.03, 0.20)	0.15
Multivariable†	35 (−1, 84)	0.06	20 (0.03, 43)	0.05	6 (−8, 22)	0.42	0.24 (0.002, 0.48)	0.05
Palmitic Acid								
Age-sex adjustment*	−15 (−34, 8)	0.18	4 (−4, 13)	0.37	−0.3 (−5, 5)	0.91	0.07 (−0.07, 0.21)	0.35
Multivariable†	−2 (−17, 17)	0.85	8 (−1, 18)	0.10	−4 (−18, 13)	0.65	0.11 (−0.004, 0.23)	0.06
Stearic Acid								
Age-sex adjustment*	7 (−9, 25)	0.40	2 (−7, 11)	0.66	1 (−4, 6)	0.69	0.07 (−0.04, 0.19)	0.21
Multivariable†	35 (1, 80)	0.04	7 (−12, 31)	0.50	10 (−4, 27)	0.16	0.16 (−0.09, 0.40)	0.21

Abbreviations: BMI: Body Mass Index, CRP: C-Reactive Protein, IL-6: Interleukin-6, WBC: White Blood Count, SFA: Saturated Fatty Acids, TFA: Trans-Fatty Acids, ω3FA: Omega-3 Fatty Acids.

*N is 87, 92, 91, and 96 in CRP, IL-6, WBC, and Inflammation models, respectively.

†N is 85, 89, 88, and 93 in CRP, IL-6, WBC, and Inflammation models, respectively. Additional adjustment included race, smoking, BMI, statin use, aspirin use, TFA, and ω3FA.