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Fatty Acids and Osteoarthritis: The MOST Study

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Abstract

Objective: Inflammation worsens joint destruction in osteoarthritis (OA) and aggravates pain. Saturated and n-6 fatty acids (FAs) increase, whereas n-3 FAs reduce inflammation. We examined whether FA levels affected the development of OA.

Design: We studied participants from the Multicenter Osteoarthritis study (MOST) at risk of developing knee OA. After baseline, repeated knee x-rays and MRIs were obtained and knee symptoms queried through 60 month follow-up. Using baseline fasting samples, serum FAs were analyzed with standard assays. After excluding participants with baseline OA, we defined two sets of cases: those developing radiographic OA and those developing symptomatic OA (knee pain and

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AUTHOR CONTRIBUTIONS

- Conception and design: DTF, DM
- Analysis and interpretation of the data: ML, XC, AL, NM
- Drafting of the article: DTF, DM
- Critical revision of the article for important intellectual content: MC, CEL, ML, XC, AL, NM, JT, MCN
- Final approval of the article: All Authors
- Provision of study materials or patients: CEL, JT, MCN
- Statistical expertise: ML
- Obtaining of funding: DTF, CEL, JT, MN
- Administrative, technical, or logistic support: MC
- Collection and assembly of data: MC, MN

COMPETING INTERESTS

No author has competing interests that might bias this work.

radiographic OA). Controls did not develop these outcomes. Additionally, we examined worsening of MRI cartilage loss and synovitis and of knee pain using WOMAC and evaluated the number of hand joints affected by nodules. In regression models, we tested the association of each OA outcome with levels of saturated, n-3 and n-6 FAs adjusting for age, sex, BMI, education, race, baseline pain and depressive symptoms.

Results: We studied 260 cases with incident symptomatic and 259 with incident radiographic OA. Mean age was 61 years (61% women). We found no signficant nor suggestive associations of FA levels with incident OA (e.g. for incident symptomatic OA, OR per s.d. increase in n-3 FA 1.00 (0.85, 1.18) nor with any OA outcome in knee or hand.

Conclusion: Despite previously described effects on systemic inflammation, blood levels of FAs were not associated with risk of later knee OA or other OA outcomes.

Keywords

Knee Osteoarthritis; n-3 Fatty Acids; Saturated Fatty Acids; Pain; Cartilage

INTRODUCTION

Among the lipid abnormalities most likely to be associated with OA are elevated levels of circulating fatty acids (FAs). FAs varying in chain length and degree of saturation. These differences can affect FA induced inflammatory responses, a critical element of OA pathogenesis[1,2]. There is considerable evidence that **saturated FAs** are generally proinflammatory[3,4]. They activate macrophages in adipose tissue to secrete TNFα and IL-1[5]. In a study using a destabilizing meniscal injury and controlled for weight gain, mice given diets rich in saturated FAs had increased OA severity, while diets rich in n-3 (omega 3) FAs mitigated injury induced OA[6]. Alvarez-Garcia and colleagues[7] compared fibroblast-like synoviocytes isolated from young healthy donors and patients undergoing knee replacement surgery for OA. The synoviocytes were exposed to palmitic acid (16:0), a saturated FA or oleic acid (18:1), a monounsaturated FA. Relative to oleic acid, caspase activation and cell death were upregulated 14 by palmitic acid, which, in turn, upregulated the expression of IL-6 and COX-2 in both 15 chondrocytes and synoviocytes. Extracellular matrix degradation occurred with palmitic acid.

N-3 FAs abrogate inflammation through effects on prostaglandin synthesis. Two recent studies in mice have shown that increasing blood levels of n-3 FAs, either by diet or through the introduction of the fat-1 transgene that endogenously converts n-6 to n-3 polyunsaturated FAs, reduces the development of post-traumatic knee OA[6,8]. Our group[9] has reported that n-3 FA levels in serum were negatively associated with patellofemoral (but not tibiofemoral) cartilage loss, and arachidonic acid levels (an **n-6 FA**) were positively associated with synovitis.

While *in vitro* models and animal studies have suggested a major role for inflammation in contributing to joint damage in OA, human studies of knee OA have been consistently unrevealing. For example, a positive assoication has been identified between metabolic syndrome and OA. However, this association was not observed with knee OA, after

adjusting for body mass index[10]. In contrast, middle-aged HIV positive men with metabolic syndrome as a consequence of treatment have been reported to have high rates of hand OA[11]. This discrepancy might be attributable to different contributions of mechanically driven damage for knee OA relative to non-weightbearing locations.

We carried out our primary study examining FAs and their relationship with incident OA focusing initially on knee OA and its subphenotypes. We then carried out exploratory analyses testing the association of FAs with hand OA to examine whether factors influencing systemic inflammation might be easier to detect using a hand OA phenotype. Based on the evidence above, we focused our testing on four different lipid variables, total saturated FAs, monounsaturated FAs, n-3 FAs, and n-6 FAs. We selected monounsaturated FA's because that have been used as controls in studies of n-3 FA interventions[12,13]. To our knowledge, there have been no longitudinal investigations of these FAs and the development of OA in humans.

METHODS

Study sample

MOST is a large NIH-funded longitudinal observational study focused on symptomatic and radiographic knee OA in a cohort of community dwelling older adults with or at high risk for knee OA[14]. The study enrolled 3026 participants age 50–79 years from 2003–2006 at two clinical sites (Iowa City, Iowa and Birmingham, Alabama). Participants were followed with repeated examinations at 15, 30, and 60 months after baseline.

Weight-bearing, semi-flexed posteroanterior (PA) and lateral views of the knees were obtained at baseline and at each exam according to the MOST radiograph protocol[15]. Two readers interpreted and graded all radiographs according to Kellgren-Lawrence (KL) grade and if they disagreed, readings were adjudicated by a panel of three readers[16]. MRIs of the knee without contrast were acquired at each visit using a 1.0 T magnet (OrthOne, ONI Inc., Wilmington, MA, USA) and a circumferential extremity coil. As in previous work[2] we read one randomly selected knee MRI per person. This was done for budgetary reasons and because of the high rate of symmetry in knee MRIs. The MRIs were read by two experienced musculoskeletal radiologists using the Whole Organ MRI Score (WORMS)[17].

Synovitis and cartilage morphology were scored in MRIs at baseline,15, 30, and 60 months with good interobserver agreement for each of the features[18]. At each examination, participants completed the WOMAC questionnaire, reporting on the amount of pain experienced during activities in each knee.

At the baseline examination, trained examiners, following a written protocol, characterized each DIP and PIP hand joint as having bony enlargement consistent with a diagnosis of Heberden's or Bouchard's nodes. Weight and height were measured as previously described.[2] BMI was calculated as weight in kilograms divided by the height in meters squared.

OA Outcomes

We defined two primary knee outcomes: incident radiographic OA and incident symptomatic OA both up to 5 years after baseline and created two separate nested case control studies. In the first of these, the outcome was incident radiographic knee OA among the subset of participants who had no radiographic OA in either knee (both knees with Kellgren and Lawrence grade <2 in the tibiofemoral and patellofemoral compartments at baseline). Those participants who developed either radiographic knee OA (KL≥2) or had a knee arthroplasty in either knee by follow-up were defined as having incident radiographic knee OA. In the second case control study, we focused on symptomatic OA. It was defined in a person when they had the combination of frequent knee pain (saying yes to the question, Do you have pain, aching or stiffness in either knee on most days?) and had concurrent radiographic OA in that knee or had a knee arthroplasty at follow-up. Persons with symptomatic OA at baseline in either knee were excluded from both case control studies, and for each of these studies, we followed participants for 5 years to identify incident cases. For each of these case groups, we used risk set sampling to select controls randomly from eligible participants at baseline. The first risk set used 15-month follow-up and randomly selected controls who were not cases then, and so forth up to the third risk set at 60 months. Subjects who were selected as controls for early exams could become cases at later ones.For both case control studies, we selected 2 controls per case.

To further investigate potential associations of FA levels with outcomes, we assessed several secondary knee based outcomes including cartilage loss and change in synovitis based on MRI readings and pain using the WOMAC pain score. These analyses were performed in the combined sample of all cases and controls. Within each of 14 subregions in each knee, cartilage morphology was scored 0–6 using the WORMS scale[17]. We defined worsening cartilage morphology by analyzing each sub-region and characterizing each as worsening when the score increased by 1 point (an exception to this was that for a subregion scored 0, there needed to be an increase in score to >=2 since a WORMS score of 1 does not represent morphologic change). Sub-regions with baseline scores of 6 were excluded. Second, we examined change in synovitis. Each region (infrapatellar, intercondylar and suprapatellar) was scored 0–3 based on volume at each timepoint, and the scores were then summed (0–9). We defined worsening synovitis as an increase in the summed score of one or more, excluding knees with synovitis scores of 9 at baseline[19]. We assessed one knee pain outcome (change in WOMAC pain) and calculated changes in pain as the difference of WOMAC pain score from baseline to the last available follow-up up to 60 months in each knee.

In exploratory analyses, we examined the number of hand joints affected by nodal OA as assessed by standardized physical examination.

Fatty Acid Profiles

Potential Confounders

Blood draws were performed at the time of the baseline visit following an overnight fast. Blood samples were allowed to clot at room temperature for 30 minutes, and serum was separated by centrifugation at 1,500 g at 4°C for 20 minutes. Aliquots were stored at -80°C in the MOST repository. For the determination of lipid profiles, matched case-control

samples (N=994) were shipped overnight on dry ice to the Cardiovascular Nutrition Laboratory at the Jean Mayer USDA Human Nutrition Research Center of Aging at Tufts University. Aliquots of plasma were thawed and analyzed for phospholipid (PL) fatty acid profiles. The mol% of each individual fatty acid was assessed as the primary fatty acid measure used in analyses. Detailed methodology and temporal stability of frozen samples have been published[20–24]. Data will be expressed as percentage (mol%) relative to the internal standard. The intra- and inter-assay coefficient of variation25 for fatty acids range from 0.5 to 4.3% for fatty acids present at levels >5%, from 1.8 to 7.1% for fatty acids present at levels between 1–5 mol%, and from 2.8 to 11.1% for fatty acids present at levels <1 mol%.

As indicated for each analysis, the data were adjusted for participants' age, sex (men, women), education (college or above, yes vs. no), physical activity (Physical Activity Scale for the Elderly [PASE], continuous), smoking (never, past, current), BMI (kg/m^2, continuous) and statin use (yes/no) all based on baseline data. We used an indicator variable to adjust for race (white vs. non-white) and clinic site. For all pain outcomes, we included depressive symptom score (Center for Epidemiologic Studies Depression [CES-D], scale score ≥16, yes vs. no as a covariate). For knee pain analyses, we adjusted for baseline WOMAC pain score (continuous). For analyses of number of nodes with OA in the hands, we adjusted for age, sex, BMI, education, race, and clinic site.

Statistical Analyses

Our analytic sample consisted of MOST participants who were either selected as cases or controls in one of our case control studies (incident x-ray OA or incident symptomatic OA) and who had an archived baseline fasting serum sample. They had to be followed until at least the second MOST exam at 30 months. Our analyses looked at the range of FAs on OA outcomes, testing each on a continuous basis and examining risk per s.d. increase.

Analyses of radiographic OA and incident symptomatic OA were at the level of the person. For each case control study, we used logistic regression to analyze the association of the fatty acid level at baseline with the OA outcome. The dependent variable for each of these analyses was cumulative incidence of the OA outome over 5 years. We carried out logistic regression in analyses of MRI findings and of WOMAC pain. We used a minimal worsening threshold for WOMAC pain (score worsening >=2) and classified participant knees as worsened or not. For MRI cartilage loss, any increase in score in any subregion defined the knee as having cartilage loss and for synovitis, any worsened composite score was worse. These changes were defined by change from baseline to last available follow-up.

For analyses of knee OA, we carried out several sensitivity analyses. First, because of concerns that baseline levels of fatty acids might not accurately reflect levels up to 5 years later, we carried out analyses limiting incidence to 30 months. Second, some incident OA is caused by injury which would tend to cause unilateral disease. We wanted to focus on those with systemic factors affecting disease, so in another sensitivity analysis, we defined cases as those who during follow-up developed incidence in both knees, either contemporaneously (e.g both at 30 months) or sequentially (e.g. one knee at 30 months, the other at 60 months.

For exploratory analyses of nodal hand OA which produces a count of the number of affected joints, we used negative binomial regression.

While we carried out multiple analyses, we did not adjust for multiple comparisons given the biological plausibility of all of the examined associations. Further, as Rothman has suggested[26], in exploratory analyses, adjustment for multiple comparisons can eliminate meaningful associations. All analyses were carried out using SAS version 9.4.

Institutional review board approvals were obtained from University of California, San Francisco, Boston University, University of Alabama at Birmingham and The University of Iowa. All participants provided written consent for study participation.

RESULTS

In our nested case control study of incident radiographic knee OA, there were 622 subjects (Table 1). In the study of incident symptomatic knee OA, there were 599 subjects. As expected, cases were slightly older and had higher BMI's than controls, but fatty acid levels were similar in cases and controls for both studies.

Baseline values of saturated fatty acids, n-3 fatty acids and arachidonic acid were not significantly associated with incident x-ray or symptomatic knee OA (Table 2). Sensitivity analyses were carried out exploring whether effects were seen when fatty acid levels were associated with risk of OA at 30 months or were associated with bilateral incident OA and for these analyses. The results were similar and null (data not shown).

We next examined the association of these fatty acid measures and change in WOMAC knee pain, loss of cartilage (an increase in WORMS score) and worsening synovitis (see table 3). We found no signficant or suggestive associations of any of the fatty acid levels at baseline with these knee outcomes.

Lastly, we turned to nodular hand OA where we carried out cross sectional analyses (Table 4). We again found no signficant association of FAs with this OA phenotype.

DISCUSSION

While fatty acids levels affect systemic inflammation and might thereby influence the occurrence of OA, we found no association of fasting levels of FAs previously associated with inflammation and OA. In exploratory analyses, we did not identify any association between levels of FAs and nodular hand OA and therefore could not confirm that systemic factors may have a greater influence on hand than knee OA.

Other studies examining the association of FA's with OA have been conflicting. In a large cross sectional study, Loef et al[27] reported that high postprandial levels of all of the FA categories were associated with modest increases in the prevalence of hand but not knee OA, a finding more prominent in men. In the study by Loef et al, analyses of fasting FA levels showed no associations with OA, a finding more consistent with this study. In an attempt to confirm their findings of sex specific associations, we carried out sex specific analyses and

found no clear association of FA's with OA in males but ironically found an association of high levels of n-3 FAs with a lower than expected number of nodular OA hand joints (adjOR = 0.90, p = 0.04, interpreted as the mean count of nodes was 10% lower per standard deviation increase in n-3 FAs) in women only. We found no other signficant assocations of FAs with OA in men or women.

In longitudinal data from a study of persons with OA, our group reported[9] that high fasting levels of n-3 FAs were assocated with less cartilage loss in the patellofemoral but not tibiofemoral compartment. (Our analysis focused on tibiofemoral cartilage loss). High levels of n-6 FAs were assocated with more synovitis. And in an important clinical trial, Hill et al[12] found no difference in pain or cartilage loss among persons with knee OA treated with n-3 FA supplements than those treated with oleic acid supplements. The findings from this combination of studies suggest that, even though FAs affect inflammation, a primary target of treatment development in OA, they are unlikely to have effect short or long term outcomes at least in knee OA.

There may be some evidence that hand OA is more likely to be influenced by systemic inflammatory factors than knee OA which is predominantly driven by mechanical influences even though we could not confirm this hypothesis. In a systematic review Li and Felson[10] reported that metabolic syndrome was not associated with knee OA especially after studies adjusted for BMI. The evidence linking metabolic syndrome and hand OA is more conflicting, however. In one important study men with metabolic syndrome from long-standing HIV therapy had a high prevalence of nodal hand OA[11]. Other studies of hand OA have shown less consistent associations, some positive[28] and some negative[29].

Among the strengths of our study which were its large sample size and its longitudinal design. Fasting bloods were analyzed using state-of-the-art methods.

Our study however had a number of limitations.First, we selected a case control sample of incident knee OA and there may well have been a biased selection of cases for examination of the hand OA. When we compared the prevalence of and burden of hand OA in our selected sample versus the larger MOST cohort, there was no difference. Another potential weakness is that we may have failed to include important confounders or a relevant FA and that the FA levels measured may have been transient and therefore not terribly relevant to longer-term outcomes. This concern motivated us to carry out a sensitivity analysis in which we limited outcomes to 30 months, and results were no different. We did not measure FA levels repeatedly over time which would have provided a better idea of chronic exposures. Also, we note that we tested FA levels in those who were mostly not taking FA supplements, and it is possible that supplementation with high doses of n-3 FAs, for example, may affect OA outcomes. However, this possibility was tested in a large trial that reported null findings. Lastly, we carried out many analyses. Even so, all of our analyses examining fatty acids and OA were null.

In conclusion, fatty acid levels in blood were unassociated with knee or hand OA outcomes. Our findings combined with those from other studies do not support a major role for fatty acid supplementation at least in knee OA.

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Table 1:

Description of Study Participants According to Case Control Study

	Incident Radiographic OA (N=622)		Incident Symptomatic OA (N=599)	
	Cases (n=260)	Controls (n=362*)	Cases (n=259)	Controls (n=340*)
Mean Age (years, s.d.)	60.8 (8.0)	60.2 (7.6)	62.7 (8.2)	61.3 (7.9)
Female	62%	60%	63%	57%
Mean BMI (s.d.)	30.5 (5.3)	28.7 (4.7)	31.0 (5.5)	29.2 (4.8)
Some college education	79%	76%	74%	77%

* Number of control persons is less than 2 per case for each exam. Based on risk set sampling, some controls were used more than once as controls, but we counted them only once here.

Table 2:

Associations of Fatty Acids with Incident Knee OA: Results of Logistic Regression Analyses*

	Mean (mol%)		Adj OR with 95% CI (per SD of FA)	P value
	Cases	Controls		
Incident Knee Radiographic OA(cases/controls=260/520)				
Saturated FA	38.0 (1.6)	37.8 (1.6)	1.02 (0.86, 1.20)	0.84
Monounsaturated FA	12.8 (1.3)	12.8 (1.3)	1.00 (0.85, 1.18)	0.98
n-6 Polyunsaturated FA	41.9 (2.3)	41.9 (2.3)	1.08 (0.91, 1.28)	0.37
n-3 Polyunsaturated FA	5.0 (1.1)	5.1 (1.3)	0.86 (0.72, 1.02)	0.09
trans FA	2.3 (0.7)	2.3 (0.8)	0.96 (0.82, 1.13)	0.65
Incident Symptomatic Knee OA(cases/controls=259/518)				
Saturated FA	37.9 (1.5)	37.9 (1.7)	1.00 (0.85, 1.17)	0.99
Monounsaturated FA	12.9 (1.4)	12.8 (1.4)	1.01 (0.86, 1.19)	0.91
n-6 Polyunsaturated FA	41.7 (2.4)	41.8 (2.4)	1.00 (0.85, 1.18)	0.98
n-3 Polyunsaturated FA	5.2 (1.3)	5.2 (1.3)	1.00 (0.85, 1.18)	0.98
trans FA	2.3 (0.7)	2.3 (0.8)	0.97 (0.83, 1.14)	0.75

*Adjusted for age, sex, BMI, physical activity, race and clinic site; Symptomatic OA adjusted for the same variables + depressive symptoms

Table 3:

Associations of Fatty Acids with Worsening Synovitis or Pain and with Cartilage Loss *

	Worsening Synovitis (by knees: 121 worsening synovitis / 400 not worsen)		WOMAC Pain Worsening (by knees: 484 worsen/ 1500 not worsen)		Cartilage Loss (by number of knee regions: 973 with loss / 7404 no loss)	
	adjOR (95% CI)	**P value**	**adjOR (95% CI)**	**P value**	**adjOR (95% CI)**	**P value**
Saturated FA (per s.d.)	1.16 (0.93, 1.44)	0.18	0.92 (0.82, 1.04)	0.18	0.98 (0.88, 1.08)	0.65
Monounsaturated FA (per s.d.)	1.06 (0.84, 1.34)	0.62	0.92 (0.81, 1.04)	0.17	0.91 (0.81, 1.03)	0.13
n-6 Polyunsaturated FA (per s.d.)	1.00 (0.80, 1.24)	0.98	1.03 (0.91, 1.16)	0.65	1.11 (1.00, 1.23)	0.06
n-3 Polyunsaturated FA (per s.d.)	0.88 (0.72, 1.09)	0.25	1.11 (0.98, 1.24)	0.09	0.96 (0.87, 1.07)	0.47
trans FA (per s.d.)	0.84 (0.68, 1.04)	0.12	1.07 (0.94, 1.21)	0.31	0.96 (0.87, 1.05)	0.35

* For 60 month synovitis worsening and cartilage loss, we carried out logistic regression analyses adjusted for age, sex, race, BMI, PASE score, race and clinic site. For WOMAC pain, we adjusted additionally for depressive symptoms and baseline WOMAC pain score).

Table 4.

Association of Fatty Acids with Nodal Hand OA

	Nodal Hand OA	
	adjOR (95% CI)	**P value**
Saturated FA (per s.d.)	1.03 (0.95,1.11)	0.48
Monounsaturated FA (per s.d.)	1.06 (0.98, 1.14)	0.12
n-6 FA (per s.d.)	0.97 (0.90, 1.05)	0.46
n-3 FA (per s.d.)	0.94 (0.87, 1.02)	0.12
Trans FA (per s.d.)	1.01 (0.94, 1.09)	0.72

Nodal Hand OA is adjusted for age, sex, BMI, education, race, clinic site.