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SATURATED AND MONOUNSATURATED FATTY ACID STATUS IS ASSOCIATED WITH BONE STRENGTH ESTIMATED BY CALCANEAL ULTRASONOGRAPHY IN INUIT WOMEN FROM NUNAVIK (CANADA): A CROSS-SECTIONAL STUDY

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Abstract: *Objective:* The aim of this study is to examine the relationship between the status in selected saturated (SFAs) and monounsaturated (MUFAs) fatty acids and the Stiffness Index (SI) in Inuit women from Nunavik (Northern Quebec, Canada). *Design:* Cross-sectional descriptive study. *Setting:* Inuit population from 14 communities who participated to Qanuippitaa? How are we? Nunavik Inuit Health Survey in 2004. *Participants:* 187 Inuit women aged 35-72 years. *Measurements:* SI was determined by ultrasonography (Achilles InSight device) at the right calcaneus of participants. SFAs and MUFAs contents of erythrocyte membrane phospholipids were measured after transmethylation by gas chromatography coupled with a flame ionization detector. Several factors known to be associated with bone strength were concomitantly recorded. Multiple linear regression was used to investigate relations between selected SFAs, MUFAs and SI, taking into consideration several potential confounders and covariates. *Results:* Total SFAs, in particular behenic acid, and cis-vaccenic acid among MUFAs were negatively associated with SI (β = -0.028, SE = 0.011, p = 0.0084; β = -0.060, SE = 0.023, p = 0.0093 and β = -0.087, SE = 0.019, p <0.0001, respectively), whereas total cis-MUFAs and specifically oleic acid were positively associated with SI (β = 0.036, SE = 0.011, p = 0.0008; β = 0.037, SE = 0.011, p = 0.0014, respectively) after adjustment for several covariates. *Conclusion:* Saturated and monounsaturated fatty acid status is associated with bone strength estimated by calcaneal SI values in Inuit women from Nunavik.

Key words: Bone strength, Inuit, saturated and monounsaturated fatty acids.

Background

Osteoporosis is "a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures" (1). This multifactorial polygenic disease comprises genetic determinants that are modulated by hormonal, environmental, and nutritional factors (2), is asymptomatic and progress silently with age (3). Eighty one percent of all fractures in women aged 50 years and older can be attributed to osteoporosis (4). Osteoporotic fractures, such as those of the hip, spine and wrist, often appear in older people following minor trauma. Hip fractures lead to rehabilitation problems and greatly decrease the quality of life (5, 6).

Bone parameters measured by quantitative ultrasonography (QUS) reflect the intrinsic quality and biomechanical properties of bone and provide information complementary to that of bone mineral density (BMD) on bone strength (7). Recent studies reported that bone parameters measured by QUS of the calcaneus can predict fractures as effectively as dual-energy x-ray absorptiometry (DXA) in postmenopausal women and men aged of 65 years and more (8, 9). Values of QUS parameters are generally lower in osteoporotic patients than in healthy subjects (10).

Ultrasound bone measurement has several advantages: it is a simple technique, fast, non-invasive, radiation-free and inexpensive (11). Furthermore, ultrasound bone measurement devices are portable and easy to use in remote, isolated regions, such as those inhabited by Aboriginal communities, where measurement of BMD cannot be performed by DXA, the reference method for the diagnosis of osteoporosis according to World Health Organization (8).

Inuit people living in circumpolar regions experience extreme climatic conditions and exhibit unique lifestyle and dietary habits, such as their traditional diet based on local game and marine species harvesting. Inuit consume large amounts of fatty fish and marine mammal meat and fat (12) that are important sources of some saturated (SFAs), monounsaturated (MUFAs) and polyunsaturated (PUFAs) fatty acids. This dietary pattern explains for example their higher omega-3 PUFA intake (13) compared to that of other Aboriginal (14) and non-Aboriginal populations (15). During the last decades, Inuit people have gradually moved away from their traditional diet to adopt a Western diet that provides a high intake of trans-fatty acids (trans-FAs), carbohydrates and sodium, with potentially negative health impacts.

Intakes of omega-3 and omega-6 PUFAs in balanced proportions seem essential for proper cellular function, the prevention of several pathologies, such as inflammatory, autoimmune and cardiovascular diseases, diabetes, and obesity (16), and maintenance of healthy bones (17). In humans, several studies have reported a beneficial effect of an elevated omega-3 PUFA intake and low omega-6/omega-3 ratio on bone

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health and prevention of osteoporosis (18, 19). For example, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) contents of erythrocyte membrane phospholipids and the omega-3/omega-6 PUFA ratio were positively associated with increased broadband ultrasound attenuation (BUA, dB/mHz) values at the calcaneus measured after a follow-up of two years in Inuit women from Nuuk (Greenland) (13, 14). We previously reported that a higher omega-3 PUFA content of erythrocyte membrane phospholipids, especially EPA, was also significantly associated with greater Stiffness Index (SI, %) in Inuit women from Nunavik (14).

In contrast, high-fat diets rich in SFAs and trans-MUFAs increase low-density lipoprotein cholesterol (LDL-C) levels, leading to excessive accumulation of dietary energy and fat mass storage, and are strongly linked to obesity and the risk to develop diabetes, hypertension, and some cancers (20). Conversely, reduced fat intake, low fatness, and normal plasmatic concentrations of LDL-C were associated with high bone mineral density (BMD) at lumbar spine and femoral neck in women (21).

Negative associations have been reported between fat intake, BMD at several skeletal sites (22, 23) and the risk of fracture (24). Food with high SFA content or low in nutrients were found to be detrimental to bone health in menopausal women (25). Elevated dietary SFA intake was also associated with lower BMD at the femoral neck in men (26) and with a higher hip fracture risk in postmenopausal women (27). In contrast, an elevated MUFA intake was positively and significantly associated with BMD in men and women (28) and with a lower fracture risk in postmenopausal women (27). Evidence exists to support the implication of unsaturated fatty acids, including oleic acid (OA), in bone cell metabolism (29).

As mentioned previously, profound dietary changes have occurred in the Inuit population over the last decades; with the diet shifting towards a Western style diet, MUFA and SFA intake increases. El Hayek et al. (30) recently reported that MUFA intake was positively associated with calcaneal BUA values in 3-5 year-old Inuit children from Nunavut (Northern Canada). No other information is available regarding the status of MUFAs and SFAs in this population and its relation with bone quality measures, osteoporosis or risk of fractures.

The aim of our study was to examine the relationship between the proportions of certain SFAs and MUFAs contents in erythrocyte membrane phospholipids and bone strength estimated by Stiffness Index (SI) – a synthetic QUS index which reflects the structural parameters and elastic properties of the calcaneus – in Inuit women living in Nunavik (Canada).

Materials and methods

Population

The Inuit Health Survey entitled "Qanuippitaa? How are we?" was organized by the Nunavik Regional Board of Health and Social Services and took place from August 27 to October 1st, 2004, in the 14 Inuit communities of Nunavik (located north of the parallel 55°N in Québec, Canada) (31).

The target population for the survey was the entire population living permanently in Nunavik (9632 inhabitants according to the 2001 Canadian census), with the following exclusions: a) households where there was no adult Inuit aged 18 years and over; and b) residents of collective dwellings (houses, hotels, nursing homes, hospitals and prisons). The target population represented 91% of the total population of Nunavik (31). The survey plan was a complex two-stage stratified random sampling. The first stage was the selection of a random sample of private Inuit households stratified by community, with proportional allocation according to the community size. In the second stage, all eligible individuals living in these households were asked to participate in the survey. Among the 677 eligible households, 521 agreed to participate in the survey, which represents a total weighted response rate of 77.8%. These 521 houses have generated 2,550 individuals (31).

Participants answered a series of validated questionnaires available in English and Inuktitut that were administered by the research staff. Those aged 18 to 74 years also participated in a clinical session which involved collection of blood samples and anthropometric measurements. All women aged 35-74 years who responded to the household questionnaire were eligible for QUS measurement. Among the 317 eligible women, 207 (aged 35-72 years) underwent QUS measurement. The weighted mean proportion of participants to this measure was therefore 65.5% and the global weighted response rate was 51.0% (31). Among the 207 participants, 20 of them were excluded (3 were not Inuit, 3 had no anthropometric measurements, 13 had no sufficient blood samples for biochemical analysis and 2, including one without plasma sample, were pregnant at the time of the study). Therefore, 187 Inuit women completed the study.

The project was approved by the Comité d'éthique de la recherche de l'Université Laval and the Comité d'éthique de santé publique du Québec. Participation in the study was voluntary and a consent form was signed by each participant. All information regarding the participants was kept strictly confidential.

Measurements and analyses

Bone measurements

SI was measured at the right calcaneus of participants using the portable ultrasound instrument Achilles Insight (GE Healthcare Lunar, Madison, WI, USA). SI value was calculated automatically by the instrument from two QUS parameters, the speed of sound (SOS, m/s) and BUA (dB/MHz), using the formula from the manufacturer: [SI% = (0.67 * BUA) + (0.28 * SOS) – 420].

The inspection of the instrument membranes was performed daily before the first measurement of the day, followed by a quality control test. The instrument was calibrated daily using

the bone-mimicking phantom provided by the manufacturer. The accuracy was assessed in vitro based on 36 repeated measurements conducted with the phantom of the manufacturer; the average coefficient of variation for SI was 0.15%.

Anthropometric measures

Body weight, fat and lean mass (Kg; balance beam scale), height and abdominal circumference (cm) were measured by research nurses using standardized techniques.

Laboratory analyses

Fasting blood samples were processed within 2 hours of collection. The fatty acid composition of phospholipids in erythrocyte membranes was determined following transmethylation with a HP5890 gas chromatograph (Hewlett Packard, Toronto, ON) equipped with a HP8823 capillary column, a flame ionization detector (FID) and a HP7673A automatic injector at the Centre de recherche sur les maladies lipidiques (Centre de Recherche CHU de Québec, QC, Canada) according to the method previously described (32). SFA, MUFA and PUFA contents were expressed as the percentage of all fatty acids in membrane phospholipids.

SFAs include the following fatty acids: myristic (tetradecanoic; C14:0), palmitic (hexadecanoic; C16:0), stearic (octodecanoic; C18:0), arachidic (eicosanoic; C20:0), behenic (BA; docosanoic acid; C22:0) and lignoceric acid (tetracosanoic; C24:0).

MUFAs include both cis isomers and trans isomers. Cis MUFAs comprise the following fatty acids: myristoleic (9-cis-tetradecenoic acid; C14:1 cis-9), palmitoleic (9-cis-hexadecenoic acid; C16:1 cis-9), vaccenic (VA; 11-cis-octadecenoic acid; C18:1 cis-11), oleic (OA; cis-9-octadecenoic acid; C18:1 cis-9), petroselinic (cis-6-octadecenoic acid; C18:1 cis-6), gondoic (cis-11-eicosenoic acid; C20:1 cis-11), cis-8-eicosenoic acid (C20:1 cis-8), erucic (cis-13-docosenoic acid; C22:1 cis-13), nervonic acid (cis-15-tetracosenoic acid; C24:1 cis-15). Trans MUFAs include palmitelaidic (trans-9-hexadecenoic acid; C16:1 trans-9), trans-vaccenic (trans-VA; trans-11-octadecenoic acid; C18:1 trans-11), elaidic (trans-9-octadecenoic acid; C18:1 trans-9), trans-11-eicosenoic acid (C20:1 trans-11) and petroselaidic acid (trans-6-octadecenoic acid; C18:1 trans-6).

Total omega-3 PUFAs comprises the following fatty acids: alpha-linolenic (ALA, C18:3n-3), eicosapentaenoic (EPA, C20:5n-3), docosahexaenoic (DHA, C22:6n-3), C22:5n-3, C18:4n-3, C20:3n-3 and C20:4n-3. Total omega-6 PUFAs refer to the sum of linoleic acid (LA, C18:2n-6), arachidonic acid (AA, C20:4n-6), C18:3n-6, C20:2n-6, C20:3n-6, C22:2n-6, C22:4n-6 and C22:5n-6.

Concentrations of LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol and triglycerides (mmol/L) in plasma samples were also determined by enzymatic methods on an Auto-analyser II instrument (Technicon Instruments Corporation, Tarrytown, NY) in the Centre de recherche sur les maladies lipidiques. The HDL-C fraction was obtained after precipitation of LDL-C in the infranatant with heparin and manganese chloride as previously described (31).

Plasma analyses for polychlorinated biphenyls (PCBs) and blood analyses for metals/metalloids analyses were conducted in the Laboratoire de Toxicologie of the Institut National de Santé Publique du Québec (INSPQ, Québec, Canada). Purified extracts were analyzed for 45 PCB congeners, including PCB 153 (a surrogate for exposure to the majority of organochlorines present in plasma samples), by gas chromatography coupled to electron capture negative ion mass spectrometry, as previously described (32). Methods for quantifying blood levels of lead, cadmium, selenium, plasma retinol (vitamin A) and C-Reactive Protein (CRP) concentrations, fasting glucose level and serum vitamin D [25(OH)D] concentrations, have been published elsewhere (31, 33).

Questionnaires

Questionnaires were administered to document socio-demographic variables (date and place of birth; geographical region of residence: Hudson/Ungava), lifestyle habits (smoking during the last year, yes/no; leisure physical activity: active/inactive) and gynaecological history (menopausal status, non-menopausal/postmenopausal; parity, yes/no).

Physical activity was evaluated using the section of "The Actimeter" questionnaire pertaining to leisure time physical activity (34). A dichotomous variable was created from the values of the Energy Expenditure Index (EEI): EEI = 0 (the median of recorded values) defines inactive women, whereas IDE > 0 defines active women.

Women were considered postmenopausal if they had no menstrual period for one year before their recruitment in the study. Medical files were consulted to document the use of calcium and vitamin D supplements (yes/no) and medications/affections in the past 12 months that constitute causes of secondary osteoporosis (35) (CSO, yes/no).

Statistical analyses

Descriptive statistics (mean, standard error of the mean, minimum, maximum for quantitative variables or numbers and % per modality for categorical variables) were presented for the 187 participants.

Pearson correlation coefficients were calculated between age, SI and contents of total or specific SFAs, cis-MUFAs and trans-MUFAs in erythrocyte membrane phospholipids. The relationship between SFAs, MUFAs and SI were examined using multiple linear regression models: three models were proposed that included different sets of covariates. Multicollinearity diagnostics were performed for all independent variables. For continuous variables, normality, linearity and homoscedasticity of residuals were tested

graphically and by hypothesis testing. Box-Cox procedures were used to resolve problems encountered with the hypotheses of normality and/or homoscedasticity in the multiple regression models; SI was subsequently log-transformed.

A population weight was calculated for each participant by the Institut de la Statistique du Québec (ISQ). Population weights were used to obtain all statistical estimates; standard errors were computed using the bootstrap procedure (31). ISQ considered that 500 sub-samples were sufficient to provide bootstrap weights for the survey.

Table 1
Characteristics of Inuit women from Nunavik

Variables	N[a] (N[b])	Mean[c] (SE)[d]	Range	GM[e] (SE)[d]
SI (%)	1097 (187)	78.60 (0.99)	39-135	
Age (years)	1097 (187)	48.33 (0.45)	35-72	
Weight (kg)	1097 (187)	66.33 (1.01)	37.6-117.9	
Height (cm)	1097 (187)	152.27 (0.31)	142-164	
Fat mass (kg)	1097 (187)	23.57 (0.73)	3.1-56.2	
Abdominal circumference (cm)	1097 (187)	94.15 (0.95)	69-130	
Vitamin D (nmol/L; serum)	1097 (187)	29.95 (0.73)	5.93-67.50	
Vitamin A (µmol/L; plasma)	1072 (184)	2.16 (0.04)	1.04-3.57	
Fasting glucose (mmol/L; plasma)	1097 (187)	4.78 (0.07)	2.80-10	
Omega-3 PUFA (%)[f]	1097 (187)	11.91 (0.21)	1.65-19.53	
Omega-6 PUFA (%)[g]	1097 (187)	23.27 (0.26)	12.58-32.39	
Ratio omega-3/omega-6 PUFA	1097 (187)	0.54 (0.01)	0.12-1.28	
Total triglycerides (mmol/L; plasma)	1097 (187)	1.17 (0.04)	0.45-4.16	
Total cholesterol (mmol/L; plasma)	1097 (187)	5.37 (0.06)	2.90-8.55	
Total cholesterol/HDL-C ratio	1097 (187)	2.93 (0.06)	1.67-6.84	
C-Reactive Protein (mg/L; plasma)	1090 (186)	3.59 (0.48)	0.10-94	
Lead (µmol/L; blood)	1097 (187)	0.29 (0.01)	0.04-1.50	0.23 (0.01)
Cadmium (nmol/L; blood)	1097 (187)	36.47 (1.83)	3.40-130	26.43 (1.61)
Selenium (µmol/L; blood)	1097 (187)	76.69 (4.49)	1.5-458.5	40.08 (3.70)
PCB 153 (ng/L; plasma)	1097 (187)	4222.60 (326.25)	150-3000	2460.0 (152.8)
	N[h] (%)	**N[b]**		
Menopausal status	1096.52	187		
Non-menopausal	627.48 (57.22)	111		
Postmenopausal	469.04 (42.78)	76		
Geographical region	1096.52	187		
Hudson area	681.85 (62.18)	114		
Ungava area	414.68 (37.82)	73		
Parity	1096.52	187		
Yes	1030.86 (94.01)	177		
No	65.66 (5.99)	10		
Smoking status	1096.52	187		
Yes	805.10 (73.42)	140		
No	291.42 (26.58)	47		
Physical activity	1056.90	179		
Active	332.70 (31.48)	56		
Inactive	724.19 (68.52)	123		
Supplements use[i]	1096.52	187		
Yes	115.41 (10.53)	19		
No	981.11 (89.47)	168		
Causes of secondary osteoporosis	1096.52	187		
Yes	125.36 (11.43)	22		
No	971.16 (88.57)	165		

Note: LDL-C (mmol/L) : N[a] = 1097 (N[b] = 187), mean[c] = 2.88, SE[d] = 0.06, Range = 1.22-6.14; HDL-C (mmol/L) : N[a] = 1097 (N[b] = 187), mean[c] = 1.95, SE[d] = 0.04, Range = 0.86-3.11. Statistical parameters for these variables are provided for informative purposes; they were not used as adjustment factors in multivariate models presented in Table 3. a. Weighted and rounded size; b. Sample size; c. Arithmetic mean; d. Standard error; e. Geometric mean; f. Omega-3 PUFA = ∑C18:3n-3 + C18:4n-3 + C20:3n-3 + C20:4n-3 + C20:5n-3 + C22:5n-3 + C22:6n-3; g. Omega-6 PUFA = ∑C18:2n-6 + C18:3n-6 + C20:2n-6 + C20:3n-6 + C20:4n-6 + C22:2n-6 + C22:4n-6 + C22:5n-6; h. Weighted size; i. Calcium and vitamin D supplements in the last 12 months.

A p value < 0.05 in the bilateral situation was considered statistically significant. Statistical analyses were performed with SAS version 9.2 software (SAS Institute Inc., Cary, NC, USA) and SUDAAN version 11.0 software.

Results

Characteristics of participants

The main characteristics of the participants are listed in Table 1. Most Inuit women lived in the Hudson Bay area, were aged between 35 and 72 years and were predominantly non-menopausal. A majority of participants had children, were smokers and physically inactive. A low proportion of Inuit women were taking supplements of calcium and vitamin D and had CSO.

Most Inuit women (61.6%) had a waist circumference ≥ 88 cm (abdominal obesity according to Health Canada) (36). With respect to body mass index (BMI, kg/m^2), according to Health Canada criteria (36), 1.1% of Inuit women were underweight (BMI < 18.5), 31.3% had a normal BMI (between 18.5 and 24.9), 30.8% were overweight (BMI between 25.0 and 29.9 kg/m^2) and 36.8% were obese (BMI ≥ 30 kg/m^2). A large majority of Inuit women (93.7%) displayed minimal serum 25(OH)D levels (<50 nmol/L) (35).

SFAs and MUFAs profiles are listed in Table 2. The most abundant SFA was palmitic acid, representing 49.4% of total SFAs, followed by stearic (34.4%) and lignoceric (9.7%) acids. Among cis-MUFAs, the most abundant was OA (62.6%), followed by nervonic (25.5%) and cis-VA (6.1%) acids. Elaidic acid represented 53.5% and trans-VA 43.6% of the total trans-MUFA content.

Pearson's correlation coefficients (r).

SI (log) values were negatively correlated with age (r = -0.57, p < 0.0001). Total cis-MUFAs were positively correlated with age (r = 0.31, p < 0.0001, in particular nervonic acid, r =

Table 2

Saturated and monounsaturated fatty acids in phospholipids of erythrocytes membranes in Inuit women from Nunavik

Main exposure variable (N[a] = 1097; N[b] = 187)	Mean (SE)	Range	% of detected values
Saturated fatty acids (%)			
Myristic acid (C14:0)	0.28 (0.01)	0.00-0.51	91.41
Palmitic acid (C16:0)	21.09 (0.12)	18.96-28.40	100
Stearic acid (C18:0)	14.70 (0.06)	12.25-17.70	100
Arachidic acid (C20:0)	0.48 (0.01)	0.28-0.95	100
Behenic acid (C22:0)	1.99 (0.04)	1.06-5.34	100
Lignoceric acid (C24:0)	4.14 (0.05)	2.63-7.15	100
∑SFAs[c]	42.68 (0.21)	38.84-59.86	100
Monounsaturated fatty acids (%)			
cis-Isomers			
Myristoleic acid (C14:1 cis-9)	0.004 (0.002)	0.00-0.21	1.94
Palmitoleic acid (C16:1 cis-9)	0.56 (0.01)	0.00-1.41	98.25
Vaccenic acid (C18:1 cis-11)	1.29 (0.04)	0.00-3.05	91.17
Oleic acid (C18:1 cis-9)	13.22 (0.08)	10.25-16.86	100
Petroselinic acid (C18:1 cis-6)	0.16 (0.01)	0.00-0.77	54.4
Gondoic acid (C20:1 cis-11)	0.39 (0.01)	0.00-0.83	93.76
C20:1 cis-8	0.008 (0.003)	0.00-0.27	3.92
Erucic acid (C22:1 cis-13)	0.12 (0.03)	0.00-2.55	6.3
Nervonic acid (C24:1 cis-15)	5.38 (0.07)	3.15-9.63	100
∑cis-MUFAs[d]	21.13 (0.12)	17.66-26.99	100
trans-Isomers			
Palmitelaidic acid (C16:1 trans-9)	0.02 (0.01)	0.00-1.10	7.95
Vaccenic acid (C18:1 trans-11)	0.44 (0.03)	0.00-2.16	74.52
Elaidic acid (C18:1 trans-9)	0.54 (0.03)	0.00-3.44	65.79
C20:1 trans-11	0.006 (0.003)	0.00-0.27	3.1
Petroselaidic acid (C18:1 trans-6)	0.004 (0.003)	0.00-0.597	0.58
∑trans-MUFAs[e]	1.01 (0.04)	0.00-4.63	86.32
Ratio			
Behenic/Palmitic acid	0.094 (0.002)	0.05-0.21	100
Oleic/Stearic acid	0.90 (0.01)	0.67-1.24	100

a. Weighted and rounded size; b. Sample size; c. ∑SFAs = C14:0 + C16:0 + C18:0 + C20:0 + C22:0 + C24:0; d. ∑cis-MUFAs = C14:1 cis-9 + C16:1 cis-9 + C18:1 cis-11 + C18:1 cis-9 + 6c-C18:1 cis-6 + C20:1 cis-11 + C20:1 cis-8 + C22:1 cis-13 + C24:1 cis-15; e. ∑trans-MUFAs = C16:1 trans-9 + C18:1 trans-11 + C18:1 trans-9 + C20:1 trans-11 + C18:1 trans-6.

Table 3
Results of multiple linear regression analyses: SI (log) models

Main exposure variable	R^2	Model I[a] (N^d = 1097; N^e = 187) Regression coefficient (SE)	p-Value[f]	R^2	Model II[b] (N^d = 1097; N^e = 187) Regression coefficient (SE)	p-Value[f]	R^2	Model III[c] (N^d = 1026; N^e = 175) Regression coefficient (SE)	p-Value[f]
SFAs									
Myristic acid	0.3651	-0.141(0.109)	0.1973	0.4391	-0.167 (0.117)	0.1553	0.4373	-0.134 (0.123)	0.2768
Palmitic acid	0.3642	-0.009 (0.007)	0.1687	0.4334	-0.005 (0.017)	0.7888	0.4348	-0.009 (0.012)	0.4530
Stearic acid	0.3705	-0.027 (0.014)	0.0480	0.4365	-0.019 (0.019)	0.3162	0.4390	-0.024 (0.018)	0.1711
Arachidic acid	0.3618	-0.080 (0.097)	0.4118	0.4336	0.047 (0.121)	0.7000	0.4341	0.072 (0.114)	0.5259
Behenic acid	0.3758	-0.045 (0.018)	0.0114	0.4510	-0.060 (0.023)	0.0093	0.4537	-0.062 (0.024)	0.0102
Lignoceric acid	0.3601	-0.004 (0.019)	0.8523	0.4342	-0.016 (0.028)	0.5751	0.4357	-0.023 (0.030)	0.4358
∑SFAs[g]	0.3711	-0.009 (0.004)	0.0199	0.4505	-0.028 (0.011)	0.0084	0.4480	-0.017 (0.007)	0.0180
MUFAs									
Palmitoleic acid	0.3651	-0.075(0.052)	0.1470	0.4378	-0.085 (0.064)	0.1903	0.4359	-0.046 (0.055)	0.3967
cis-Vaccenic acid	0.4081	-0.086 (0.020)	<0.0001	0.4750	-0.087 (0.019)	<0.0001	0.4590	-0.067 (0.021)	0.0015
Oleic acid	0.3728	0.020 (0.009)	0.0333	0.4598	0.037 (0.011)	0.0014	0.4556	0.029 (0.010)	0.0046
Gondoic acid	0.3608	-0.040 (0.079)	0.6120	0.4333	0.014 (0.076)	0.8573	0.4349	-0.036 (0.078)	0.6495
Nervonic acid	0.3639	0.015(0.013)	0.2602	0.4411	0.028 (0.019)	0.1264	0.4392	0.021 (0.016)	0.2063
∑cis-MUFAs[h]	0.3638	0.008 (0.007)	0.2436	0.4589	0.036 (0.011)	0.0008	0.4480	0.019 (0.007)	0.0100
trans-Vaccenic acid	0.3618	-0.019 (0.024)	0.4202	0.4334	-0.008 (0.033)	0.8083	0.4344	-0.003 (0.028)	0.9121
Elaidic acid	0.3612	-0.014 (0.027)	0.6093	0.4356	-0.022 (0.028)	0.4316	0.4458	-0.047 (0.026)	0.0636
∑trans-MUFAs[i]	0.3635	-0.023 (0.029)	0.4313	0.4353	-0.020 (0.029)	0.4954	0.4442	-0.044 (0.029)	0.1204
Ratio fatty acids									
Behenic/Palmitic	0.3736	-0.923 (0.412)	0.0256	0.4516	-1.231(0.453)	0.0068	0.4513	-1.154 (0.494)	0.0199
Oleic/Stearic	0.3869	0.381 (0.115)	0.0009	0.4586	0.405 (0.130)	0.0019	0.4536	0.349 (0.133)	0.0087

a. Model adjusted for age only; b. Model adjusted for: age, body weight, height, serum vitamin D, fasting glucose, % omega-3 PUFA, % omega-6 PUFA, total plasma cholesterol, total plasma triglycerides, blood lead, blood cadmium, menopausal status, smoking status, parity, supplements use, geographical region; c. Model adjusted for: age, blood lead, total plasma triglycerides, menopausal status, parity, omega-3/omega-6 PUFA ratio, total cholesterol/HDL-cholesterol ratio, C-Reactive Protein, PCB 153, vitamin A, blood selenium, causes of secondary osteoporosis, physical activity, fat mass, abdominal circumference, total cis-MUFAs (if the main exposure variable is an SFA) or total SFAs (if the main exposure variable is a MUFA); d. Weighed and rounded size; e. Sample size; f. Wald Chi Square Test with Satterthwaite correction for the degrees of freedom; g. ∑SFAs = C14:0 + C16:0 + C18:0 + C20:0 + C22:0 + C24:0; h. ∑cis-MUFAs = C14:1 cis-9 + C16:1 cis-9 + C18:1 cis-11 + C18:1 cis-9 + C18:1 cis-6 + C20:1 cis-11 + C20:1 cis-8 + C22:1 cis-13 +C24:1 cis-15; i. ∑trans-MUFAs = C16:1 trans-9 + C18:1 trans-11 + C18:1 trans-9 + C20:1 trans-11 + C18:1 trans-6.

0.36, p <0.0001), whereas total trans-MUFAs were negatively correlated with age (r = -0.39, p < 0.0001, and mostly, elaidic acid r = - 0.26, p = 0.0003). Total or individual SFAs were not significantly correlated with age; only BA showed a correlation of borderline significance (r = - 0.14, p = 0.0608).

Results from multivariate analyses

Main exposure variables

Among SFAs, only BA was negatively and significantly associated with SI (log) in all models (model I: adjusted only for age; models II and III: each adjusted for 16 covariates; Table 3). The total of six SFAs was also negatively and significantly associated with SI (log) in all models. Increasing ratios of behenic/palmitic acids were significantly associated with decreasing SI (log) values (Table 3).

Among cis-MUFAs, OA was positively and significantly associated with SI (log) while cis-VA was negatively associated with SI (log) in all models. The total cis-MUFA content was also positively and significantly associated with SI (log) in models adjusted for a larger number of covariates (models II and III; Table 3). No association was found between specific trans-MUFAs isomers, or total trans-MUFAs and SI (log). An increased oleic/stearic acid ratio was associated with elevated SI (log) values in all models (Table 3).

Independent factors significantly associated with SI (log)

In all multivariate models adjusted for several covariates (models II and III), age and menopausal status were negatively and significantly associated with SI (log). Other factors negatively associated with SI (log) were blood lead level (models II for total cis-MUFAs, total trans-MUFAs and myristic, stearic, arachidic, behenic, lignoceric, oleic and elaidic acids), total SFAs (models III for OA and total cis-MUFAs) and total omega-6 PUFAs (models II for OA and total cis-MUFAs). Factors positively and significantly associated with SI (log) were total plasma triglyceride level (models II and III for total trans-MUFAs and myristic, palmitic, arachidic, behenic, lignoceric, palmitoleic, gonodic, nervonic, trans-vaccenic and elaidic acids; model III for cis-VA), parity (models II for total SFAs and OA), total cis-MUFAs (model III for total SFAs) and total omega-3 PUFAs (models II for OA and total cis-MUFAs) (data not shown).

Discussion

We have investigated the relation between the proportions of selected SFAs and MUFAs in erythrocyte membrane phospholipids and bone strength assessed by SI in a representative sample of Inuit women from Nunavik. Total SFAs, in particular BA, and cis-VA were negatively associated, whereas OA and total cis-MUFAs were positively associated with SI in multivariate models adjusted for several covariates.

The mean SI value of 78.6% reported here for Inuit women from Nunavik is lower than that of 91.5% measured using the same instrument (Achilles InSight) at the right calcaneus of 249 Cree women (mean age of 48 years; 41% postmenopausal) from East of James Bay, another aboriginal population of Northern Quebec (Canada) (14).

Unpublished data on fatty acid content in erythrocyte membrane phospholipids in 254 Cree women can be used to compare levels of SFAs and MUFAs reported here for Nunavik women. The average total SFAs content (weighted mean of 42.68%) of erythrocyte membrane phospholipids in Inuit women from Nunavik was similar to that of Cree women (weighted mean of 43.17%). BA content in Inuit women from Nunavik (weighted mean of 1.99%, representing 4.66% of total SFAs) was similar to that of Cree women (weighted mean of 1.82% representing 4.22% of total SFAs). Mean total cis-MUFAs content (weighted mean of 21.13%) in Inuit women from Nunavik appears to be slightly higher than that of Cree women (weighted mean of 19.09%). OA content in Inuit women from Nunavik (weighted mean of 13.22% representing 62.57% of total cis-MUFAs) was slightly greater than that of Cree women (weighted mean of 11.63%, corresponding to 60.92% of total cis-MUFAs). Cis-VA content in Inuit women from Nunavik (weighted mean of 1.29%, representing 6.11% of total cis-MUFAs) was similar to that of Cree women (weighted mean of 1.10% corresponding to 5.76% of total cis-MUFAs).

Only a few studies have investigated the relationship between dietary intakes of SFAs or MUFAs and BMD at different skeletal sites, the risk of osteoporosis and fragility fractures (25-28). Corwin et al. reported that an elevated dietary saturated fat intake (median value of 35 g) was inversely associated with BMD at the femoral neck (linear trend, $p=0.004$) in men aged <50 years who participated in the NHANES III Study (26). Higher SFA consumption was also associated with higher risk of hip fracture [quartile 4 multivariate-adjusted hazard ratio (HR): 1.31, p for trend = 0.001] in postmenopausal women enrolled in the Women's Health Initiative (27). In the same study, lower total fracture risk was associated with a higher MUFA intake (quartile 3 HR: 0.94, p for trend = 0.05) (27).

Even less information is available regarding the relation between specific SFAs and bone quality. Griffith et al. reported significant differences in proportions of cis-7-hexadecenoic acid and BA in bone marrow fatty acids between subjects (men and women, mean age 69.7 years) with low bone mass (% mean ± SD: 0.90% ± 0.16 for cis-7-hexadecenoic acid and 0.03% ± 0.02 for BA, respectively) and those with osteoporosis (0.78% ± 0.15 and 0.06% ± 0.08, respectively) (37). While significant differences were observed, cis-7-hexadecenoic acid and BA are minor constituents, accounting for <1% and <0.1% of the total marrow fatty acid composition, respectively (37). Nevertheless, results indicating higher BA content in subjects with osteoporosis are in agreement with the negative association observed between BA status and SI in our study.

Dietary BA is hydrolysed shortly after absorption into shorter-chain SFAs, particularly stearic, palmitic, myristic and lauric acids (38). Despite its low bioavaibility compared to OA, BA is known as a total cholesterol and LDL-cholesterol-raising fatty acid in humans (38). However, in our study, neither BA nor other SFA were correlated with total cholesterol and LDL-C plasma levels. No study could be located concerning the effect of BA on bone tissues.

FAs present in the body originate from the diet as well as de novo fatty acid synthesis. An endogenous pathway for lipid synthesis is de novo lipogenesis (DNL), wherein carbohydrates and proteins are converted to fatty acids (39). The main product of DNL is palmitic acid which can be metabolised either by delta-9 desaturation to palmitoleic acid and then by elongation to cis-VA, or by elongation to stearic acid followed by desaturation to OA (40).

Cis and trans MUFAs isomers possess different physical, chemical, biological and physiological properties: cis-MUFAs are generally considered "healthy" and trans-MUFAs "unhealthy" (41). Trans-MUFAs and mostly those from partially hydrogenated vegetable oils (a typical example is elaidic acid), were associated with an increase risk of cardiovascular disease, decreased insulin sensitivity in adipose tissue, increased total cholesterol and LDL-C levels, systemic inflammation and endothelial dysfunction (42-45). Natural trans-MUFAs are produced in the rumen of ruminants through partial hydrogenation and/or isomerisation of cis-MUFAs present in the feed, which is catalysed by bacterial enzymes (46). Trans-VA is the predominant natural trans-MUFA in the fat and milk of ruminant (47) produced during the partial biohydrogenation of LA and ALA (48). Trans-VA acts as precursor for the endogenous synthesis of cis-9, trans-11-conjugated linoleic acid (CLA) via the action of the 9-desturase enzyme in animals and humans (49). Next, trans-VA is converted to stearic acid. In the case of VA, the trans-isomer does not seem detrimental (50) and is rather beneficial to human health (47), while the cis-isomer was associated with reduced kidney function (reduced glomerular filtration rate) in Chinese-American men and women aged 45-84 years, participating in the Multi-ethnic Study of Atherosclerosis (MESA) (51). Kidney dysfunction may contribute to an increase in bone loss and constitutes a CSO (35). In our study, trans-VA was not associated with SI, whereas cis-VA was negatively associated with SI in all statistical models.

There is evidence supporting an effect of unsaturated fatty acids on bone cell metabolism. Both EPA and OA increased gene expression of type I collagen and fibronectin via a

transforming growth factor-beta-independent mechanism in cultured osteoblast-like human cells (29). Diets rich in OA have beneficial effects in inflammatory-related diseases (52). It was suggested that OA could exert its anti-inflammatory effect by decreasing oxidative stress and the production of AA metabolites. Competitive substitution of membrane AA by OA in male Sprague-Dawley rats reduced pro-inflammatory eicosanoid production, in particular that of prostaglandin (PG)E2, the main prostaglandin involved in bone resorption, and decreased mucosal AA concentrations as well as AA/EPA ratio (52, 53).

In addition, dietary FAs such as EPA, DHA, CLA and OA induce anti-inflammatory effects through several mechanisms that include activation of the 5'adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma (PPAR-γ), suppression of toll-like receptors (TLRs) and nuclear factor-KB (NF-KB) pathways (54). For example, OA can reduce the inflammatory effects of long-chain SFAs in human aortic endothelial cells through reducing cellular stearic acid incorporation and NF-KB activation (55).

MUFAs also reduce the secretion of pro-inflammatory cytokines by adipocytes (56). In individuals with abdominal obesity, adipose tissue inflammation is induced by high-SFA, but not high-MUFA diets (57). High MUFA diets reduce expression of lipoprotein lipase and increase phosphorylation of hormone-sensitive lipase (54).

It was also reported that intakes of OA and LA can significantly reduce serum C-reactive Protein (CRP) – a marker of systemic inflammation – in Japanese men and women aged 35-60 years, especially when the intake of long-chain omega-3 PUFAs (EPA+DHA) is at a moderate level (0.30-0.51% of energy in men and 0.21-0.38% in women), after adjustment for confounding factors (58).

In our study, a large proportion of women were considered obese according to international criteria, such as BMI and abdominal circumference. However, in Inuit women from Nunavik, anthropometric parameters were not associated with SI in multivariate models. Furthermore, among Inuit, compared to the general population, the measure of obesity based on BMI may not be appropriate because of the higher sitting height measures in Inuit (59).

Recent epidemiologic studies show that a high level of fat mass is detrimental to bone mass and fat mass itself may be a risk factor for osteoporosis and fragility fractures (60, 61). High body fat percentage and waist circumference have been related to low BMD and vertebral fracture (62).

As previously reported in Inuit, obesity may not reflect the same degree of metabolic risk: for each level of BMI or waist circumference, the Inuit had lower values of metabolic indicators such as plasma lipids or blood pressure than Euro-Canadians (59, 63). This appears in agreement with our results indicating that neither the weight, nor the amount of body fat nor the abdominal circumference was associated with the bone strength estimated by SI.

Strengths and limitations of our study

Our study has several strengths. Firstly, the data used in this work were obtained from a large health survey conducted in the Inuit population of Nunavik. Our population sample was likely representative of the women aged 35 to 72 years of Nunavik, because of the study design, the recruitment strategy and the weighting scheme that takes into account non-response and refusals to participate. Secondly, we considered a large number of covariates as adjustment factors in our multivariate models. Thirdly, measurement biases on the dependent variable or exposure variables are unlikely. QUS parameters, anthropometric measures and biological sampling were all performed by research nurses using standardized techniques.

However, this study has some limitations. Firstly, the main methodological limitation is its cross-sectional design, with exposure and the dependent variable measured at the same time, such that the temporal sequence of cause and effect cannot be determined. Secondly, the participation rate of women aged between 35 and 72 years old at QUS measurements was relatively small, which can suspect a selection bias. However, this bias is quantitatively unimportant, since it is unlikely that the characteristics of the subjects included in the study are different from those of all eligible persons. Regarding the non-response and refusal to participate in the study, it is unlikely that these subjects have different levels in SFAs or MUFAs or SI values, compared with participants; the recruitment of participants was made for a survey of general health and not specifically for the purpose of our study.

In conclusion, we observed that OA status has a positive relation with SI in Inuit women from Nunavik. In contrast, their status in total SFAs (especially of BA) and cis-VA has a negative relation with calcaneal SI values. OA, the most abundant MUFA in erythrocyte membrane phospholipids, favours bone strength in this population of Inuit women aged 35 to 72 years.

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