

A high activity index of stearoyl-CoA desaturase is associated with increased risk of fracture in men

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Abstract

Summary The activity index of stearoyl-CoA desaturase (SCD), a key enzyme in lipogenesis, was associated with increased risk of fracture in a longitudinal population-based cohort of men. This indicates that elevated levels of endogenous lipogenesis increase the risk of fracture and suggest a role for saturated fat in the pathogenesis of osteoporosis.

Introduction Osteoblasts and marrow adipocytes are derived from a common mesenchymal progenitor, and experimental studies have indicated that increased adipogenesis can occur at the expense of osteoblasts, leading to bone loss. Stearoyl-CoA desaturase (SCD) converts saturated to monounsaturated fatty acids and is a key enzyme in lipogenesis.

Methods Analysis was performed in a population-based, longitudinal cohort study of men ($n=2009$). A product-to-precursor index (palmitoleic acid/palmitic acid) was used to

estimate SCD activity in fasting serum analyzed in samples obtained at enrollment at age 50 years. Fractures were documented in 422 men during 35 years of follow-up. Cox regression analysis was used to determine the risk of fracture according to SCD activity index.

Results The risk of fracture was highest among men with the highest levels of SCD activity index. Multivariable analysis of the risk of fracture in the highest quintile as compared to the lowest one showed that the rate ratio was 1.71 (95% CI 1.26–2.33) for any fracture, with an estimated population attributable risk of 15%. The risk was further increased within the highest quintile.

Conclusions Our results indicate that elevated levels of endogenous lipogenesis increase the risk of fracture and suggest a role for saturated fat in the pathogenesis of osteoporosis.

Keywords Fat · Fracture · Lipogenesis · Men · Nutrition · Osteoporosis

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Introduction

In the last few years, it has become apparent that there is a reciprocal relationship between the development of bone and fat. Osteoblasts and marrow adipocytes share a common mesenchymal progenitor and bone loss is associated with an expansion of adipose tissue in the marrow [1]. Recent animal studies have shown that the peroxisome proliferator-activated receptor gamma (PPAR γ) pathway, i.e., the dominant regulator of adipogenesis, inhibits osteoblast differentiation [2], and that leptin, an anorexigenic metabolic hormone that is secreted in proportion to fat mass, is a regulator of both bone formation and resorption [3–5].

We hypothesized that a key enzyme in lipogenesis, stearoyl-CoA desaturase (SCD) may be of particular interest in this context. SCD is involved in the cellular biosynthesis of monounsaturated fatty acids (MUFAs) from saturated fatty acid (SFA) substrates (mainly palmitic and stearic acid). As a result of substrate channeling the major MUFAs generated by SCD, i.e., palmitoleic and oleic acid, represent the main substrates for synthesis of triglycerides, cholesterol esters and phospholipids. The palmitoleic/palmitic acid (16:1/16:0) index in serum, also known as the “desaturation index” has been used to estimate SCD activity [6, 7]. Consistent with a role as a key point of metabolic control, SCD activity is tightly regulated, being decreased by polyunsaturated fatty acids (PUFAs) and increased by SFAs [8]. Interestingly, SCD-1-null mice display resistance to obesity and hyperlipidemia [9]. The levels of palmitoleic acid have been shown to be significantly associated with abdominal adiposity in obese female twins [10] and in obese children [11]. We have recently shown that the SCD activity index is significantly associated with obesity in both men and women [12] and that PPAR γ function appears to have a pivotal role in SCD regulation [7]. This is the first study to investigate the relation between the SCD activity and risk of fracture.

Methods

Subjects

The Uppsala Longitudinal Study of Adult Men (ULSAM) has been described previously [13, 14]. Briefly, from 1970 to 1973, we invited all 2,841 men, born 1920–1924, living in the municipality of Uppsala, Sweden, to participate in a health survey, the Uppsala Longitudinal Study of Adult Men. A total of 2,322 men (82% of those invited), 49 to 51 years of age, agreed to participate. At 60 years of age 1,860 men took part in a second evaluation, at 70 years 1,221 men took part in a third evaluation, and at 77 years 839 men participated and finally 530 participated in the final evaluation at age 82 years. At end of follow-up (Dec 31, 2005), 1,295 (56% of the cohort) of these men had died.

SCD activity index

Fasting serum palmitoleic acid and palmitic acid in ULSAM were analyzed in cholesterol esters by gas-liquid chromatography after separation of serum lipids by thin-layer chromatography as previously described [15–17]. Briefly, serum was extracted with a hexane-isopropanol solution and cholesteryl esters (only lipid esters that were measured at baseline) were separated from the extract by thin-layer chromatography before inter-esterification with

acidic methanol was performed. Free cholesterol that had been liberated in the reaction was removed by aluminium oxide to avoid contamination of the column. The composition of methylated fatty acids was determined by gas chromatography (25 m NB-351 silica capillary column) with a flame ionization detector and helium as carrier gas. Every 25th sample was a serum control pool. The CV between successive gas chromatography runs was 0.2–5%. A product-to-precursor index (palmitoleic acid 16:1 n-7/palmitic acid 16:0) was used to estimate SCD activity index for the 2,009 men for which data were available at baseline.

Identification of cases of fractures

We sought to identify all fractures that occurred among the study participants after enrollment. We matched the study cohort to the Hospital Discharge Register to identify cases treated on an inpatient basis. All orthopaedic records, radiographic records and outpatient registries at the local hospitals in areas where the participants in the initial investigation resided were reviewed to identify out-patient treated fractures. We censored six cases of fracture caused by metastatic cancer. Seven cases of fractures due to suspected high-impact trauma were retained in the analysis since there are indications of comparable increases of low and high trauma fracture risk with decreasing bone density in elderly.

Statistical analysis

We used Cox proportional-hazards models to estimate rate ratios, with 95% confidence intervals calculated as measures of associations in the same way as previously described for serum retinol in the ULSAM cohort [13]. For each man, the number of years of follow-up was calculated from the date of enrollment (i.e., the date of the first investigation) until the date of a first fracture or the end of the follow-up period (December 31, 2005). Dates of deaths were based on data from the continuously updated Swedish National Population Register.

SCD activity index levels at baseline at 50 years of age were evaluated both as a continuous variable and as a categorical variable, in quintiles. Separate analyses were performed for fractures specifically designated as osteoporotic (i.e., fractures of the hip, pelvis, spine, distal forearm, and proximal humerus). The results were similar whether or not we included the seven cases of fractures due to suspected high-impact trauma, and these cases were therefore retained in the analyses. We then estimated the trend in the risk of fracture by restricted cubic-spline Cox regression with five “knots” (SCD activity index percentiles 5, 27.5, 50, 72.5, and 95), which enabled us to investigate extreme SCD values. We used the midpoint of the first

quintile, i.e., percentile 10, as reference point in this analysis. The results of this analysis are presented as smoothed plots with 95% CI for the overall risk of fracture.

In addition, since fatty acids were analyzed in half of the men participating in the third evaluation at 70 years ($n=611$), we could examine the change of SCD activity index from age 50 to 70 years and the risk of fracture (in tertiles). Baseline in this particular analysis was age at the third investigation and fractures among these 611 men after this investigation were used as outcome ($n=66$).

We considered a crude and a multivariable model. The latter included age, weight, height, serum retinol (all continuous), smoking (never, former, current), diabetes, (yes, no), marital status (single, divorced/widowed, married/cohabitee), any cardiovascular disease (yes, no), self-rated health (good, not good), and physical activity (low, medium, high). The estimates remained similar when we also included sedimentation rate (at age 50), as well as alcohol intake, dietary energy intake and use of oral calcium and vitamin D (all at the age of 70 years). Consequently, these variables were omitted from the reported analyses.

The population attributable risk for fracture among those with a specific SCD-1 level was calculated by

$$\frac{p(RR - 1)}{[p(RR - 1) + 1]}$$

where p is the prevalence of the investigated SCD level among the fracture cases.

Results

Characteristics of the participants according to the quintile of SCD-1 activity index at baseline are shown in Table 1. There was a tendency toward higher weight, higher serum retinol values, more current smokers, more singles and divorced men, more circulatory system disease, lower self-rated health, and lower physical activity in higher quintiles of SCD-1 activity index. During 51,707 person-years of follow-up, we identified 422 men (21%) with any fracture after study entry.

The overall risk of fracture increased by 31% for every increase of 1 SD in SCD activity index. The increment was mainly concentrated in the highest quintile for SCD; multivariable rate ratio for any fracture, as compared with the lowest quintile, 1.71 (95% CI 1.26–2.33) (Table 2), with an estimated population attributable risk of 15%. For fractures at sites that are typical of osteoporotic fractures, the multivariable rate ratio was 1.91 (95% CI 1.26–2.91). There was also a trend towards increased risk of hip fractures when analyzed as a continuous variable ($p=0.04$), but the multivariable rate ratio for the highest quintile as compared with the lowest quintile did not reach statistical significance, HR 1.4 (95% CI 0.8–2.6).

The risk of fracture was further increased in the highest quintile for SCD. Subjects with SCD levels in the 95th percentile had an overall risk of fracture that was about twice the risk among those with lower levels (crude rate ratio 2.8 (95% CI 2.0–4.0), multivariable rate ratio 2.2

Table 1 Base-line characteristics of the study participants according to the quintile of SCD activity index levels (SD in parentheses)

Characteristic	Quintile 1 (0–0.251) $N=401$	Quintile 2 (0.251–0.286) $N=402$	Quintile 3 (0.286–0.325) $N=402$	Quintile 4 (0.325–0.387) $N=403$	Quintile 5 (>0.387) $N=401$
Age (years)	49.7 (0.6)	49.7 (0.6)	49.7 (0.6)	49.6 (0.6)	49.7 (0.6)
Height (cm)	176.4 (5.9)	176.3 (6.2)	176.4 (5.9)	176.2 (6.1)	175.5 (5.6)
Weight (kg)	75.0 (9.2)	76.0 (10.3)	78.3 (10.8)	79.8 (12.1)	79.8 (12.2)
Serum retinol ($\mu\text{g/l}$)	626.8 (140.4)	649.6 (124.5)	649.3 (112.7)	655.1 (121.0)	719.4 (147.1)
Circulatory system disease					
Yes	3 (0.7%)	7 (1.7%)	7 (1.7%)	9 (2.2%)	11 (2.7%)
Marital status					
Divorced	13 (3.2%)	19 (4.7%)	14 (3.5%)	14 (3.5%)	32 (8.0%)
Married	356 (88.8%)	345 (86.0%)	361 (90.0%)	353 (87.6%)	316 (79.0%)
Single	26 (6.5%)	32 (8.0%)	22 (5.5%)	32 (7.9%)	44 (11.0%)
Widower	6 (1.5%)	5 (1.2%)	4 (1.0%)	4 (1.0%)	8 (2.0%)
Self-rated health					
Good	319 (82.0%)	335 (84.6%)	326 (84.2%)	321 (81.7%)	301 (77.0%)
Physical activity					
Low	37 (9.7%)	57 (14.7%)	49 (13.1%)	58 (15.3%)	80 (20.7%)
Medium	145 (37.9%)	136 (35.1%)	121 (32.3%)	145 (38.3%)	149 (38.5%)
High	201 (52.5%)	195 (50.3%)	205 (54.7%)	176 (46.4%)	158 (40.8%)
Smoking					
Current smoker	193 (48.1%)	189 (47.0%)	202 (50.2%)	198 (49.1%)	247 (61.6%)
Former smoker	88 (21.9%)	100 (24.9%)	89 (22.1%)	101 (25.1%)	92 (22.9%)
Never smoked	120 (29.9%)	113 (28.1%)	111 (27.6%)	104 (25.8%)	62 (15.5%)
Diabetes					
Yes	9 (2.2%)	4 (1.0%)	5 (1.2%)	3 (0.7%)	8 (2.0%)

Table 2 Rate ratios (RRs) with 95% confidence intervals (95% CI) of any fracture by SCD activity index at baseline at 50 years

Category	<i>n</i> fractures	Univariate analysis		Multivariable* analysis	
		RR	95% CI	RR	95% CI
Quintile 1	83	1.0	Ref	1.0	Ref
Quintile 2	84	1.03	0.76–1.40	1.04	0.77–1.41
Quintile 3	77	1.05	0.77–1.43	1.09	0.80–1.50
Quintile 4	73	1.08	0.79–1.48	1.07	0.77–1.47
Quintile 5	105	1.91	1.43–2.55	1.71	1.26–2.33
Per 1 SD		1.38	1.26–1.50	1.31	1.19–1.44
<i>P</i> value		<0.001		<0.001	

* Adjusted for age, height, weight, serum retinol (all continuous), smoking status (never, former, current smoker), diabetes (yes/no), marital status (single, divorced/widowed, married/cohabiting), circulatory system disease (yes/no), self-rated health (good, not good), and physical activity (low, medium, high).

(95% CI 1.5–3.2), whereas subjects in the 99th percentile had an overall risk that exceeded the risk among men with levels by a factor of about five (crude rate ratio 6.1 (95% CI 3.3–11.5), multivariable rate ratio 4.52 (95% CI 2.33–8.75) (Fig. 1).

In half of the men examined at 70 years of age, serum palmitoleic and palmitic acid were measured ($n=611$). Using only fracture data that occurred in this sub-group (66 fractures), we found a significant correlation between the change in SCD index and fracture risk (crude rate ratio for third vs. lowest tertile 3.23 (95% CI 1.50–6.93), multivariable rate ratio 2.16 (95% CI 1.17–3.98), indicating that when the SCD activity index increases over time, so does the risk of fracture. In 454 men waist circumference was measured at enrollment. There was a moderate, but highly significant, correlation between SCD activity index and waist circumference ($r=0.22$, $p<0.001$).

Discussion

SCD is a key enzyme in the biosynthesis of MUFAs from SFAs, i.e., in lipogenesis. In this prospective, population-based cohort study of men, the overall risk of fracture was substantially increased among the men with high levels of estimated SCD activity. The risk was concentrated in the highest quintile, with a continuous increase within this category, and it was independent of BMI. Thus, despite a positive effect of increased fat mass on weight-bearing, our results indicate that increased endogenous lipogenesis has negative effects on bone. Although we could only analyze a subgroup, the finding that an increase in SCD activity index from 50 to 70 years is associated with an even higher risk, gives further support to this.

We included not only height and weight in our multivariable model, but also a number of lifestyle factors. Adjustment for these factors had only modest effects on the estimates, indicating that the association between SCD activity index and fracture risk cannot be explained by these potential confounders. Instead our results suggest that the dietary fat quality and endogenous fatty acid metabolism may be important. It should be emphasized that increased SCD activity index does not directly reflect increased proportions of palmitoleic acid in the diet, since the content of this fatty acid is normally small in the diet. Rather, it reflects increased endogenous desaturation of palmitic acid by SCD leading to increased palmitoleic acid, as a consequence of a high intake of palmitic acid in the diet [11]. Interestingly, in glycogen storage disease type 1, the synthesis of palmitic acid is increased 40-fold [18] and osteopenia is a known complication in this disease [19–22]. Furthermore, in animal studies, inclusion of palmitic acid as the major source of fat causes a reduction in bone ash and bone calcium levels [23, 24].

Alternatively, although unlikely in a Western diet with a high dietary intake of fat [25], an increased SCD activity index could be a consequence of a high intake of carbohydrates. At low fat intakes, the amount of palmitoleic acid in serum has been reported to reflect the hepatic pool of carbon flux from carbohydrates to fatty acids [26], e.g., in rats rendered obese by sucrose administration, SCD activity index increases dramatically in liver and plasma [27].

SFAs, high carbohydrate diets, and insulin all appear to be able to induce SCD expression, whereas dietary PUFAs and leptin seem to inhibit SCD mRNA transcription [11]. Therefore, the relationship between SCD and risk of fracture may reflect compensatory up-regulation of SCD to continuous intake of e.g., a diet high in SFAs (such as dairy products, solid margarines, and meat products) and low in PUFAs, rather than a metabolically harmful effect of increased activity in itself [17]. Consistent with this, a

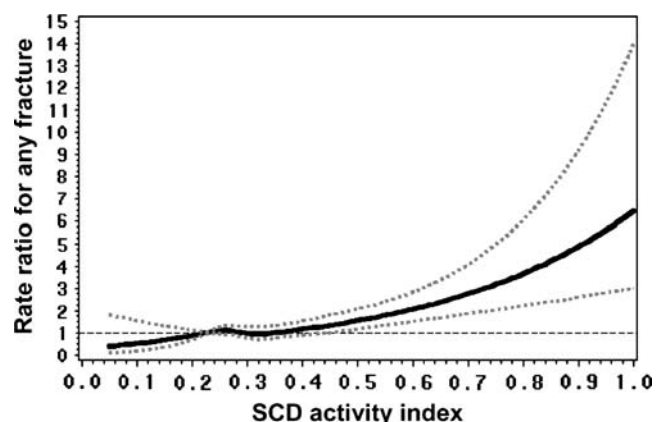


Fig. 1 Smoothed plot of rate ratios for any fracture according to the adjusted SCD activity index level at baseline

recent analysis of NHANES III by Corwin et al. [28] found that SFAs are inversely associated with bone density at several hip sites, particularly in men <50 years of age.

SCD activity can also be estimated as the oleic/stearic acid (18:1/18:0) ratio [6]. However, the predictive value of this ratio in serum in the ULSAM cohort has previously been shown to be considerably less than for palmitoleic/palmitic acid due to a much higher dietary proportion of oleic acid [17], and was therefore not analyzed in this study.

Mounting evidence indicates an important role of PPAR γ in skeletal metabolism. PPAR γ haploinsufficient mice have increased bone mass and decreased adipogenesis, whereas activation of PPAR γ with the agonist rosiglitazone causes bone loss and increased bone marrow adiposity in mice [29, 30]. Thiazolidinedione use has recently been shown to cause bone loss also in humans [31]. In a randomized clinical trial rosiglitazone increased SCD activity index, and in one patient with partial lipodystrophy and type 2 diabetes due to dominant-negative mutation in the PPAR γ gene, it restored SCD activity index, indicating a pivotal role of PPAR γ function in SCD regulation, at least in adipose tissue [7]. The activation of PPAR γ by natural ligands, such as oxidized fatty acids, plays an important role in the development of atherosclerosis [32]. Oxidized lipids also inhibit osteoblast development in vitro and bone formation in vivo, and serve as substrates for PPAR γ , which redirects differentiation of mesenchymal cells from osteoblasts to adipocytes. PPAR also enhances many adipocyte genes and diminishes Cbfa1/Runx2, needed for osteoblast development. All these effects could reduce bone formation and promote atherogenesis [33]. Atherosclerosis could be one of the common factors which would explain the reported relationship between cardiovascular disease and osteoporosis [34]. Our findings are consistent with previous findings from the ULSAM cohort regarding serum fatty acid profile and the risk of developing cardiovascular disease [16, 35]. Moreover, inflammation plays an important role in atherogenesis. Part of the inflammatory response is activation of T cells with release of cytokines, especially of RANKL, which is a key molecule in bone resorption [33].

We have previously found an association between serum retinol and fracture risk in ULSAM (12). Retinol is a fat-soluble vitamin found in dietary fat from animal sources, i.e., in food that may also contain high levels of SFAs. However, inclusion of retinol in the multivariable model had only minor effects on the rate ratio.

Our population-based study had the advantage of involving men with similar age followed from a time before they reached the high incidence ages for fractures, and we used hospital-record verification of fractures. In addition, we used serum levels of individual fatty acids, rather than dietary assessments of fat intake.

There are some limitations of this study. The study population consisted only of men and therefore our results need to be verified in women. Since direct measures of SCD activity is very difficult to obtain in larger studies, we used the ratio between two fatty acids. Whether the ratio mainly reflects SCD activity in adipose tissue, liver, or both still remains to be elucidated. Unfortunately, bone mineral density data were not available. Another limitation of the study is the lack of dietary records at baseline and the resulting lack of knowledge about the intake of e.g., SFAs and PUFAs in the studied population.

In conclusion, the results of our study suggest that a high SCD activity, indicating elevated endogenous lipogenesis, substantially increases the risk of fractures. Previous experimental work showing a reciprocal relationship between bone and fat supports this conclusion.

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Conflicts of interest None.

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