Serum Adiponectin in Elderly Men Does Not Correlate with Fracture Risk

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Context: Recent evidence suggests that adiponectin may play a role in bone metabolism, but studies of the correlation between serum adiponectin and bone mineral density (BMD) have given conflicting results, and the impact on fracture risk is unknown.

Objective: Our objective was to investigate the association between serum adiponectin levels and BMD and fracture risk.

Design, Setting, Participants, Main Outcome Measures: We used regression analyses to estimate the relationship between adiponectin and BMD in the Prospective Investigation of the Vasculature in Uppsala Seniors cohort of 441 men and 457 women aged 70 yr. The association was thereafter analyzed in the Uppsala Longitudinal Study of Adult Men (ULSAM), in which adiponectin was analyzed at age 70 yr and BMD at 82 yr in 507 men. Fractures in the ULSAM were documented in 314 men during 15 yr follow-up. Cox regression analysis was used to determine the risk of fracture according to serum adiponectin levels.

Results: In multivariable analysis a negative association between adiponectin and BMD was found in both cohorts. When individuals in the highest quintile of adiponectin were compared with those in the lowest quintile, adjusted BMD was 9.7% lower at the lumbar spine, 7.1% lower at the proximal femur, and 5.2% lower for total body in the Prospective Investigation of the Vasculature in Uppsala Seniors ($P < 0.001$ for all three), and 8.1, 5.1, and 4.1% ($P < 0.003$ for all three), respectively, in the ULSAM. However, the hazard ratio for fracture per 1 SD of serum adiponectin was 0.99 (95% confidence interval 0.89–1.11).

Conclusion: Although adiponectin was a negative determinant of BMD in two independent cohorts, it was not associated with fracture risk in men. **(*J Clin Endocrinol Metab* 93: 4041–4047, 2008)**

Advances in obesity research have led to the recognition that adipose tissue is an active endocrine organ that secretes multiple bioactive factors (adipokines). One such factor is adiponectin, which has gained considerable interest due to its positive effects on insulin sensitivity (1, 2), atherosclerosis (3), and inflammation (4, 5). It is highly abundant in serum, but unlike other adipokines (*e.g.* leptin), serum concentrations of adiponectin are inversely correlated to total fat mass (6).

Adiponectin and its receptors have recently been produced also by human bone-forming cells (7, 8), suggesting that adiponectin may have a functional role in bone homeostasis, and that adiponectin may be a hormone linking bone and fat metabolism. The exact function in bone has not yet been clarified, and *in vitro* (9–14) and animal studies (10, 15) show conflicting results. Adiponectin has stimulated human osteoblast proliferation and differentiation (9, 12) but also increased the number of osteoclasts indirectly through stimulation of the synthesis of re-

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; HR, hazard ratio; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; ULSAM, Uppsala Longitudinal Study of Adult Men.

ceptor activator of nuclear factor-κB ligand and inhibited osteoprotegerin production in osteoblasts (11). In contrast, Yamaguchi *et al.* (13) reported an inhibition of osteoclasts. Treatment of mice with adenovirus expressing adiponectin showed an increased trabecular bone mass accompanied by a decreased number of osteoclasts and levels of plasma NTx, a bone resorption marker (10), whereas Shinoda *et al.* (15) who analyzed transgenic mice overexpressing adiponectin in the liver, found no abnormality in the bone.

Previous human studies that have evaluated the relationship between serum adiponectin and bone mineral density (BMD) are also inconsistent (16–27). Whether serum adiponectin levels are associated with the most important outcome, fracture, has not yet been studied. Therefore, we examined the influence of adiponectin levels on BMD and on fracture risk.

Subjects and Methods

Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)

The PIVUS (http://www.medsci.uu.se/pivus/pivus.htm) has been described in detail previously (28–30). Briefly, all 70-yr-old individuals living in Uppsala, Sweden, in 2001–2004 were eligible for the PIVUS, and 2025 randomly selected individuals were invited within 2 months of their 70th birthday from April 2001 to June 2004. Of these, 1016 (50%) participated in the study. At the examination the participants underwent a blood pressure measurement and anthropometry, blood sampling after an overnight fast, routine medical history, and assessment of BMD using dual-energy x-ray absorptiometry (DXA) as described below. All participants provided written informed consent, and the study was approved by the Ethics Committee of the Uppsala University.

Uppsala Longitudinal Study of Adult Men (ULSAM)

The ULSAM (http://www.pubcare.uu.se/ULSAM) has also been described in detail previously (31–33). Briefly, from 1970–1973, all 2841 men born in 1920–1924 and living in the municipality of Uppsala, Sweden, were invited to participate in a health survey. A total of 2322 men (82% of those invited), 49–51 yr of age, agreed to participate. At 60 yr of age, 1860 men took part in a second evaluation, and at 70 yr, 1221 men took part in a third evaluation. The latter forms the baseline for the present study. Serum adiponectin levels were available for 1205 of these men. In addition, at 77 yr 839 men participated in a fourth investigation, and at the fifth one, at age 82 yr, there were 530 participants. Fasting blood samples were collected at each investigation in addition to a questionnaire survey regarding medical history, lifestyle habits, and regular medication. The study was approved by the Ethics Committee of the University of Uppsala.

DXA

At the fifth ULSAM at age 82 yr, *i.e.* on average 12 yr after the analysis of serum adiponectin at baseline, 507 of the 530 men agreed to undergo measurements of BMD (g/cm^2) and bone area (cm^2) of the total body, femoral neck region of the hip, total proximal femur, total legs and arms, the skull, and the lumbar spine (vertebrae L2–L4), as well as total lean and fat mass, by DXA (DPX Prodigy; Lunar Corp., Madison, WI). When applicable, both extremities were used in the calculation. The same DXA equipment was also used to examine, in a similar manner, 898 participants of the PIVUS cohort on average 2 yr after their baseline investigation. By triple measurements in 15 subjects, the precision error of the DXA measurements in our laboratory has been calculated to be between 0.8 and 1.5% for BMD, depending on site, and between 0.7 and 1.6% for bone areas. Total fat mass had a precision error of 1.5% and total lean mass 1.0%.

Identification of fractures

We sought to identify all first fractures that occurred in study participants after enrollment. Using the Swedish personal identification number of every participant, we matched the study cohorts to the national Hospital Discharge Register to identify all cases of fractures treated on an inpatient basis. Fractures were also confirmed by linkage, with the use of the personal identification number, to radiographic records and county outpatient registries. All orthopedic records at the local hospitals in areas where the participants in the initial investigation resided were reviewed to identify fractures according to the type and circumstances of the injury, as previously described (31, 33).

Analysis of adiponectin and leptin

Serum from the third investigation at age 70 yr of the ULSAM cohort and plasma at baseline from the PIVUS cohort were collected in the morning after fasting overnight and stored at −70 C from baseline to the time of assay. The analysis of serum adiponectin in the ULSAM cohort has previously been described (34, 35). Briefly, it was analyzed using a time-resolved immunofluorometric assay based on commercial reagents from R & D Systems (Abingdon, UK) (36), with an intraassay coefficient of variation (CV) of less than 5% and interassay CV of less than 6%. Plasma adiponectin in the PIVUS cohort was measured using a human RIA kit (LINCO Research, Inc., St. Charles, MO) as previously described (37), with an intraassay CV of 3.6% and interassay CV of 9.3%. In addition, in the PIVUS cohort, serum leptin was analyzed with a RIA kit with intraassay and interassay CVs of 6.2 and 8.3%, respectively (37).

Statistical analysis

All statistical calculations were performed using SAS (SAS 9.1; SAS Institute Inc., Cary, NC). The association between adiponectin, fat mass, and leptin (only in the PIVUS) and BMD was primarily analyzed by ordinary linear regression models. Adiponectin and leptin displayed a skewed distribution, and they were thus log transformed to achieve a normal distribution. We further categorized the exposures by quintiles, and the least square means of BMD for each quintile was estimated on the basis of the regression estimates by the procedure general linear model of SAS. All estimates are adjusted by age at the DXA measurement and height (both continuous) and in the PIVUS cohort also by sex.

In addition, we included adiponectin, leptin, and fat mass simultaneously in the simple primary model. Furthermore, we evaluated a more sophisticated multivariable model, including also leisure physical activity (low, medium, high), smoking status (never, former, current), Framingham heart index, serum low-density lipoproteins, serum high-density lipoproteins, serum triglycerides, serum cholesterol, serum calcium, plasma glucose, body weight or body mass index, lean body mass, serum creatinine (all continuous), educational level (low, medium, high), statin use, diabetes, hypertension, and heart failure (all dichotomous). These variables had only modest impact on our estimates and were thus not included in the results presented.

Fracture risk associated with serum adiponectin was then analyzed. We used Cox proportional-hazards models to estimate hazard ratio (HR) [with 95% confidence intervals (CIs)] as a measure of the association. For each man the number of years of follow-up was calculated from the date of enrollment (*i.e.* the date of the third investigation at age 70 yr) until the date of a first fracture, the date of death, or the end of the follow-up period (December 31, 2007). Dates of deaths and moves were based on data from the continuously updated Swedish National Population Register. We first estimated fracture risk per 1 SD increase in serum adiponectin. We then modeled the nonlinear trend in the risk of fracture by a restricted cubic-spline Cox regression analysis (38) with three "knots" (serum adiponectin percentiles 10, 50, and 90) and percentile 20 as reference. The results of this analysis are presented as a smoothed plot with 95% CIs for the overall risk of fracture. Proportional-hazards assumptions were confirmed by Schoenfeld's tests. We considered two separate

models: a univariable and a multivariable model. The multivariable model included age, weight, height, BMI, and waist to hip ratio at enrollment (all continuous), smoking status (never, former, current), physical activity (low, medium, high), and diabetes mellitus (yes/no). In addition, we included insulin resistance, determined with the euglycemic insulin clamp technique and using the insulin sensitivity index (M/I) as described for this cohort previously (35), but the estimates remained similar.

Results

Characteristics of the participants in the two cohorts are displayed in Table 1. There were 441 men and 457 women in the PIVUS cohort and 507 men in the ULSAM cohort. Both baseline data of the ULSAM cohort and data at the final investigation at age 82 yr are presented.

We first investigated the correlations between adiponectin, fat mass, and in the PIVUS, also leptin. There was a modest negative correlation between fat mass and adiponectin in both cohorts (Table 2), but a strong positive correlation between leptin and fat mass (0.75; $P < 0.0001$). We also observed a crude negative correlation between adiponectin and BMD at all three sites but positive correlations between both total fat mass and BMD. These estimates were similar in both men and women, and in the two cohorts.

The negative association between adiponectin and BMD persisted at all sites after adjustment for sex, age,, and height as well as after adjustment for fat mass and leptin (Table 3). Fat mass was a positive predictor of BMD independently of adiponectin and leptin, whereas the positive association between leptin and BMD was no longer evident after adjustment for fat mass ($P > 0.3$ at all sites; data not shown). When individuals in the highest quintile of adiponectin in the PIVUS were compared with those in the lowest quintile, adjusted BMD means were 9.7% ($P < 0.0001$) lower at the lumbar spine, 7.1% ($P < 0.0001$) lower at the proximal femur, and 5.2% ($P < 0.0001$) lower for the total body. The corresponding numbers in the ULSAM (Table 4) were 8.1% ($P = 0.003$), 5.1% ($P < 0.0001$), and 4.1% ($P = 0.001$). Further adjustment for total fat mass (and in the PIVUS, also leptin) had only minor effects. For every 1 SD increase in adiponectin, the adjusted mean for BMD decreased by 0.041 g/cm^2 at the lumbar spine, 0.024 g/cm^2 at the proximal femur, and 0.018 g/cm^2 for total body in the PIVUS. In the ULSAM these β-estimates were quite similar: 0.034, 0.032, and 0.016 g/cm^2/SD, respectively.

Surprisingly, there was no association between adiponectin levels and fracture risk (Fig. 1). The crude HR for fracture per 1 SD of adiponectin was 0.99 (95% CI 0.89–1.11) and the adjusted HR 0.97 (95% CI 0.86–1.10). This analysis included 314 men with fractures. If we only considered the 86 hip fractures, the crude HR/SD was 1.06 (95% 0.86–1.31) and the adjusted HR/SD 1.00 (95% 0.80–1.26).

Discussion

To our knowledge this is the first published report on adiponectin and fractures. Somewhat surprisingly, adiponectin did not correlate with fracture risk. In both elderly men and women, increasing adiponectin levels were significantly associated with a decrease in BMD. The association persisted across all measured anatomical sites and was independent of our selected covariates. An unusual strength of the BMD part of our study is the independent replication of the findings in a second population-based cohort. We are not aware of any osteoporosis study outside the field of genetic associations with this design. Although adiponec-

TABLE 1. Characteristics of participants in the two cohorts at baseline, and for the ULSAM, also at the final investigation at age 82 yr when BMD was measured

	PIVUS		ULSAM study of men (n = 507)	
Baseline data	Women (n = 457)	Men (n = 441)	Baseline	Final investigation
Age (yr)	72.1 (0.9)	71.9 (0.8)	71.0 (0.6)	81.7 (0.9)
Weight (kg)	70.2 (12.9)	82.6 (12.8)	79.7 (10.4)	78.1 (11.1)
Height (cm)	161.7 (5.7)	175.3 (6.5)	174.9 (5.4)	173.0 (5.5)
BMI (kg/m^2)	26.9 (4.8)	26.9 (3.7)	26.0 (3.1)	26.1 (3.4)
Total fat mass (kg)	27.8 (9.2)	23.4 (8.2)	NA	22.7 (8.0)
Plasma/serum adiponectin (μg/ml)	8.7 (4.7)	5.4 (3.1)	10.3 (4.2)	NA
Plasma leptin (ng/ml)	19.4 (11.6)	7.9 (5.5)	NA	NA
BMD total body	1.06 (0.10)	1.21 (0.11)	NA	1.18 (0.11)
BMD proximal femur	0.88 (0.13)	1.02 (0.15)	NA	0.99 (0.16)
BMD lumbar spine	1.09 (0.20)	1.29 (0.24)	NA	1.32 (0.26)
Smoking habits, no. (%)				
Never smoker	249 (54.5)	186 (42.3)	219 (43.2)	185 (36.5)
Former smoker	157 (34.4)	212 (48.2)	232 (45.8)	292 (57.6)
Current smoker	51 (11.2)	42 (9.6)	56 (11.1)	30 (5.9)
Physical activity, no. (%)				
Low	30 (6.8)	33 (7.6)	11 (2.2)	68 (13.4)
Medium	220 (49.9)	211 (48.8)	171 (33.7)	186 (36.7)
High	191 (43.3)	188 (43.5)	325 (64.1)	253 (49.9)

Plasma adiponectin was analyzed in the PIVUS, and serum adiponectin was analyzed in the ULSAM. The BMD for the PIVUS was obtained on average 2 yr after baseline. Values are expressed as means (SD). NA, Not applicable.

TABLE 2. Pearson correlation coefficients between adiponectin levels, total fat mass, and bone densities of the total body, proximal femur, and lumbar spine in the PIVUS and ULSAM cohorts

	Plasma adiponectin	Serum leptin	BMD of total body	BMD of proximal femur	BMD of lumbar spine
Women in the PIVUS					
Plasma adiponectin (*P* value)	1.0	−0.13 (0.004)	−0.15 (0.001)	−0.17 (0.0004)	−0.16 (0.001)
Total fat mass (*P* value)	−0.17 (0.0004)	0.75 (<0.0001)	0.39 (<0.0001)	0.32 (<0.0001)	0.30 (<0.0001)
Men in the PIVUS					
Plasma adiponectin (*P* value)	1.0	−0.15 (0.0006)	−0.19 (0.0001)	−0.14 (0.003)	−0.17 (0.0003)
Total fat mass (*P* value)	−0.17 (0.0005)	0.75 (<0.0001)	0.37 (<0.0001)	0.35 (<0.0001)	0.26 (<0.0001)
	Serum adiponectin				
ULSAM male cohort					
Serum adiponectin (*P* value)	1.0	NA	−0.16 (0.0007)	−0.19 (<0.0001)	−0.13 (<0.005)
Total fat mass (*P* value)	−0.21 (<0.0001)	NA	0.30 (<0.0001)	0.24 (<0.0001)	0.26 (<0.0001)

NA, Not applicable.

tin was analyzed with two different methods, and although BMD was measured a decade after the measurement of adiponectin in the ULSAM cohort, the results were strikingly similar in the two cohorts. Despite these clear and consistent BMD results, adiponectin levels were not associated with the most important outcome, fracture.

Published results on the relationship between adiponectin and BMD are conflicting. Seven studies have reported a negative correlation (18, 21, 24–27, 39), three studies have not found any significant association (16, 17, 23), and three studies have shown mixed results depending on the measured site (19, 20, 22); one of these latter studies found a positive correlation at the distal radius (20).

Previous studies have often been small and performed in selected subjects: Lenchik *et al.* (39) studied 38 women and 42 men with type 2 diabetes; Kontogianni *et al.* (16) 25 premenopausal

TABLE 3. Plasma adiponectin and total fat mass, and their association with BMD in the PIVUS cohort

	Quintiles						
	Q1	Q2	Q3	Q4	Q5	β/SD	*P* value
Adjusted means, BMD of the lumbar spine (g/cm^2)							
Adiponectin (μg/ml)	<3.2	3.2–5.2	5.3–7.4	7.5–10.5	>10.5		
Model 1 (*P* value)[a]	1.24 (ref)	1.22 (0.39)	1.20 (0.08)	1.16 (0.001)	1.12 (<0.0001)	−0.041 (0.008)	<0.0001
Model 2 (*P* value)[b]	1.23 (ref)	1.21 (0.47)	1.19 (0.13)	1.16 (0.007)	1.14 (0.0002)	−0.031 0.008	<0.0001
Total fat mass (kg)	17.8	17.8–22.5	22.6–27.0	27.1–33.2	>33.2		
Model 1 (*P* value)[a]	1.10 (ref)	1.17 (0.001)	1.17 (0.001)	1.22 (<0.0001)	1.27 (<0.0001)	0.060 (0.007)	<0.0001
Model 2 (*P* value)[b]	1.12 (ref)	1.18 (0.03)	1.17 (0.11)	1.21 (0.003)	1.25 (0.0002)	0.053 (0.012)	<0.0001
Adjusted means, BMD of the proximal femur (g/cm^2)							
Adiponectin (μg/ml)	<3.2	3.2–5.2	5.3–7.4	7.5–10.5	>10.5		
Model 1 (*P* value)[a]	0.98 (ref)	0.96 (0.22)	0.96 (0.34)	0.94 (0.04)	0.91 (<0.0001)	−0.024 (0.005)	<0.0001
Model 2 (*P* value)[b]	0.97 (ref)	0.95 (0.22)	0.96 (0.49)	0.95 (0.18)	0.92 (0.004)	−0.015 (0.005)	0.003
Total fat mass (kg)	17.8	17.8–22.5	22.6–27.0	27.1–33.2	>33.2		
Model 1 (*P* value)[a]	0.88 (ref)	0.93 (<0.0001)	0.94 (<0.0001)	0.98 (<0.0001)	1.02 (<0.0001)	0.048 (0.005)	<0.0001
Model 2 (*P* value)[b]	0.90 (ref)	0.94 (0.002)	0.94 (0.007)	0.97 (<0.0001)	1.01 (<0.0001)	0.041 (0.008)	<0.0001
Adjusted means, BMD of the total body (g/cm^2)							
Adiponectin (μg/ml)	<3.2	3.2–5.2	5.3–7.4	7.5–10.5	>10.5		
Model 1 (*P* value)[a]	1.16 (ref)	1.15 (0.36)	1.14 (0.27)	1.13 (<0.0001)	1.10 (<0.0001)	−0.018 (0.004)	<0.0001
Model 2 (*P* value)[b]	1.15 (ref)	1.14 (0.40)	1.14 (0.43)	1.13 (0.09)	1.11 (0.002)	−0.011 (0.003)	0.002
Total fat mass (kg)	17.8	17.8–22.5	22.6–27.0	27.1–33.2	>33.2		
Model 1 (*P* value)[a]	1.08 (ref)	1.12 (<0.0001)	1.12 (<0.0001)	1.15 (<0.0001)	1.19 (<0.0001)	0.038 (0.003)	<0.0001
Model 2 (*P* value)[b]	1.10 (ref)	1.13 (0.006)	1.12 (0.06)	1.15 (0.002)	1.18 (<0.0001)	0.032 (0.005)	<0.0001

ref, Reference.

[a] Adjusted for sex, age at the DXA measurement, and height (both continuous).

[b] Adjusted as that in footnote "[a]" and also including adiponectin and total fat mass, respectively, as well as serum leptin.

TABLE 4. Serum adiponectin and the association with BMD in the ULSAM male cohort

						β/SD	*P* value
Quintiles	Q1	Q2	Q3	Q4	Q5		
Plasma adiponectin (μg/ml)	<7.1	7.1–8.7	8.8–10.4	10.5–13.4	>13.4		
BMD of the lumbar spine (g/cm^2)	1.36	1.30	1.34	1.33	1.25	−0.034 (0.012)	0.005
P value	ref	0.12	0.53	0.44	0.003		
BMD of the proximal femur (g/cm^2)	1.05	0.99	0.99	0.99	0.94	−0.032 (0.008)	<0.0001
P value	ref	0.01	0.023	0.014	<0.0001		
BMD of the total body (g/cm^2)	1.21	1.19	1.19	1.18	1.16	−0.016 (0.005)	0.0009
P value	ref	0.20	0.39	0.04	0.001		

Adjusted by age and height. ref, Reference.

plus 55 postmenopausal healthy women; Huang *et al.* (17) 105 nondiabetic female adolescents; Oh *et al.* (19) 80 men; Jürimäe *et al.* (18) 21 premenopausal plus 17 early postmenopausal women; Chanprasertyothin *et al.* (23) 200 premenopausal women; Jurimae and Jurimae (25) 42 premenopausal and 111 postmenopausal women; Misra *et al.* (21) 17 anorectic and 19 control adolescent girls; Jurimae and Jurimae (26) 98 middle-aged premenopausal women; Richards *et al.* (24) 1735 nondiabetic women; Tamura *et al.* (20) 28 men and 12 women with type 2 diabetes; Buday *et al.* (22) 20 healthy and 51 glucose intolerant women; and during the preparation of this manuscript, Peng *et al.* (27) published a study of 232 Chinese men. Therefore, the limited sample size in many of these studies may be one important reason for the diverging results. Other reasons may be the heterogeneity and different selection criteria of the studied populations, *i.e.* differences in age, sex, menopausal status, concomitant diseases (such as diabetes), *etc.* Our study is the first in which all studied individuals have the same age. This should be

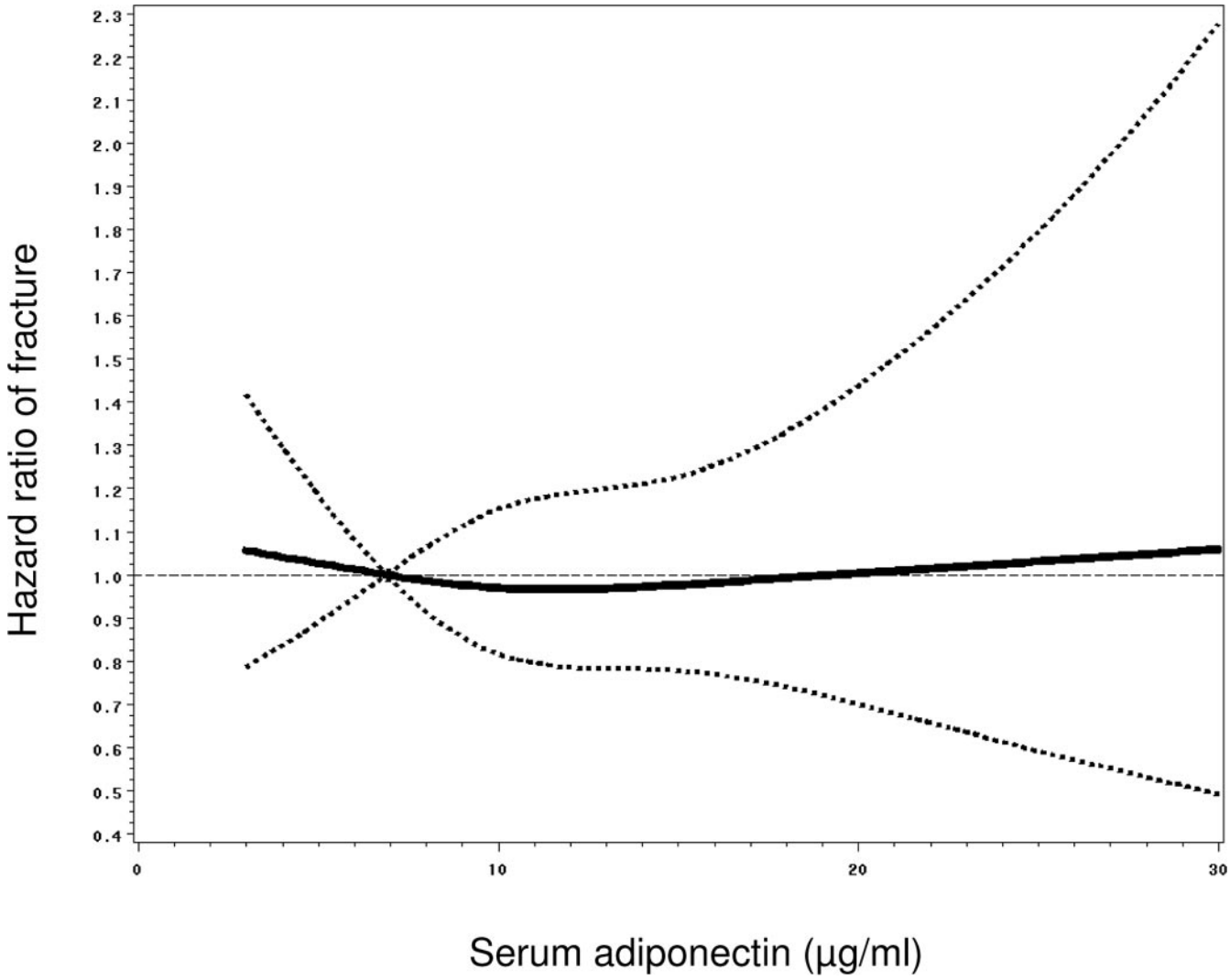

FIG. 1. Smoothed plot of HRs for fracture according to the serum adiponectin level in the ULSAM male cohort. The HRs (*solid line*) and 95% CIs (*dotted lines*) were estimated by restricted cubic-spline Cox regression analysis, with the serum adiponectin percentile 20 as the reference value.

an important strength because adiponectin levels changes through life due to endogenous (*e.g.* menopause) or exogenous factors, and usually increase with age (24). The majority of previous studies have focused on women and have not included elderly. In addition, adjustment for fat mass has not been done in all studies, and in the recent large study of 1735 nondiabetic women, Richards *et al.* (24) demonstrate the importance of menopausal status. No discernible relationship between adiponectin and BMD was observed in premenopausal women once measures of adiposity were controlled for, but a strong relationship was demonstrated in postmenopausal women. Thus, the results of our study, in which all women were postmenopausal and the negative association remained highly significant also after adjustment for total fat mass, are consistent with the study by Richards *et al.* (24). A negative relationship to BMD has also been found in three of the four previous studies in men (19, 20, 27, 39).

Despite our finding of an inverse relationship between adiponectin and BMD in two independent community based cohorts, the risk of fracture remained independent of circulating adiponectin. As seen in Table 4, the decrease in BMD per 1 SD of adiponectin was about 3% at both the lumbar spine and proximal femur in the ULSAM. This would be expected to correspond to about a 30% increase in fracture risk (40). The 95% CI showed that our sample size was sufficient to detect a considerably smaller difference in fracture risk of about 10%. Thus, the lack of association between adiponectin and fracture risk is unlikely to be due to a lack of statistical power. An alternative explanation would be that adiponectin also increases the bone size. However, we did not find any significant effects of adiponectin on the bone areas at any site, although we acknowledge the limitations of DXA regarding bone size measurements.

We hypothesize that the lack of association with fracture risk is due to other important effects of adiponectin. Adiponectin is an insulin-sensitizing hormone (1, 2). It has also been reported to have antiatherogenic and antiinflammatory properties (4, 5). Low adiponectin levels correlate with obesity, especially central adiposity, and are associated with insulin resistance and the development of type 2 diabetes, as well as with increased risk of coronary heart disease (35, 41–44). Increasing evidence suggests that older patients with type 2 diabetes have an increased risk of fractures, even when the higher body mass and BMD associated with diabetes are considered (45, 46). Recent metaanalyses support these results (47). Thus, the conceivable negative effects of adiponectin on BMD may be counterbalanced by the effects on insulin resistance and type 2 diabetes, and possibly also by increased atherogenesis and inflammatory processes, on fracture risk. Further studies will be needed to clarify this.

There are some limitations of this study. The risk of fracture was only evaluated in the ULSAM, which consisted of men, and, therefore, our results need to be verified in women. Adiponectin was analyzed with two different methods in the two cohorts, giving different cutoff values for the quintiles. Moreover, the BMD measurements in the ULSAM were performed a decade after the adiponectin levels were analyzed. However, the results obtained in the PIVUS were essentially the same, indicating that adiponectin levels remain relatively stable over time in elderly. Less than half the men in the ULSAM for whom we had serum adiponectin levels were examined with DXA, but the adiponectin levels among these men did not differ from those who were not examined ($P = 0.77$). An additional limitation is the approximately 2-yr time gap between the baseline adiponectin assay and the BMD measurement in the PIVUS cohort.

In conclusion, although increasing adiponectin levels were associated with a substantial decrease in BMD in two independent population-based cohorts, there were no effects on fracture risk in men. These results may have important implications for future pharmacological interventions aimed at increasing serum adiponectin in diabetes and atherosclerosis.

Acknowledgments

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