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High-Sensitivity CRP Is an Independent Risk Factor for All Fractures and Vertebral Fractures in Elderly Men: The MrOS Sweden Study

Anna L Eriksson,[1] Sofia Movérare-Skrtic,[1] Östen Ljunggren,[2] Magnus Karlsson,[3] Dan Mellström,[1] and Claes Ohlsson[1]

[1]Centre for Bone and Arthritis Research, Institute of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
[2]Department of Medical Sciences, Uppsala University Hospital, Uppsala, Sweden
[3]Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences, Lund University and Department of Orthopaedics, Malmö University Hospital, Sweden

ABSTRACT

Epidemiological studies have shown low-grade inflammation measured by high-sensitivity C-reactive protein (hs-CRP) to be associated with fracture risk in women. However, it is still unclear whether hs-CRP is also associated with fracture risk in men. We therefore measured serum levels of hs-CRP in 2910 men, mean age 75 years, included in the prospective population-based MrOS Sweden cohort. Study participants were divided into tertile groups based on hs-CRP level. Fractures occurring after the baseline visit were validated (average follow-up 5.4 years). The incidence for having at least one fracture after baseline was 23.9 per 1000 person-years. In Cox proportional hazard regression analyses adjusted for age, hs-CRP was related to fracture risk. The hazard ratio (HR) of fracture for the highest tertile of hs-CRP, compared with the lowest and the medium tertiles combined, was 1.48 (95% CI, 1.20–1.82). Multivariate adjustment for other risk factors for fractures had no major effect on the associations between hs-CRP and fracture. Results were essentially unchanged after exclusion of subjects with hs-CRP levels greater than 7.5 mg/L, as well as after exclusion of subjects with a first fracture within 3 years of follow-up, supporting that the associations between hs-CRP and fracture risk were not merely a reflection of a poor health status at the time of serum sampling. Femoral neck bone mineral density (BMD) was not associated with hs-CRP, and the predictive role of hs-CRP for fracture risk was essentially unchanged when femoral neck BMD was added to the model (HR, 1.37; 95% CI, 1.09–1.72). Exploratory subanalyses of fracture type demonstrated that hs-CRP was clearly associated with clinical vertebral fractures (HR, 1.61; 95% CI, 1.12–2.29). We demonstrate, using a large prospective population-based study, that elderly men with high hs-CRP have increased risk of fractures, and that these fractures are mainly vertebral. The association between hs-CRP and fractures was independent of BMD. © 2014 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals, Inc. on behalf of the American Society for Bone and Mineral Research. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEY WORDS: FRACTURE RISK; AGING, DXA; LOW GRADE INFLAMMATION; hs-CRP

Introduction

Osteoporosis-related fractures constitute a major health concern not only in women but also in men. In Sweden the lifetime risk of a hip, spine, or forearm fracture, which are common osteoporosis-related fractures, at the age of 50 years is 46% for women and 22% for men.[1] These fractures are associated with increased morbidity and mortality, and pose a substantial burden to the individual, the healthcare system, and society in general.[2,3] It is thus important to elucidate the pathogenesis of osteoporosis in men, in whom it has been less extensively studied than in women, to aid in prevention and treatment. Risk factors for fractures in men that we know of today include poor neuromuscular function, age, physical inactivity, low levels of estrogens, low bone mineral density (BMD), and bone geometry.[4]

It is well known that chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and chronic obstructive pulmonary disease (COPD) are associated with bone loss and an enhanced fracture risk,[5–9] indicating a relationship between the immune system and bone. It has also been shown that certain proinflammatory cytokines are involved in the pathogenesis of osteoporosis.[10,11] Moreover, the detrimental effects of estrogen deficiency on bone are to a certain extent

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Address correspondence to: Claes Ohlsson, MD, PhD, Centre for Bone and Arthritis Research, Vita Stråket 11, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden. E-mail: claes.ohlsson@medic.gu.se

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mediated via these cytokines.[12] Chronic low-grade inflammation is involved in the pathophysiology of a large number of conditions, including dementia,[13] cardiovascular disease,[14] and diabetes mellitus.[15] Lately, the question has arisen as to whether also low-grade inflammation, as estimated by high-sensitivity C-reactive protein (hs-CRP), is a risk factor for fractures. There is indeed epidemiological data supporting an association between hs-CRP and fracture risk.[16–19] However, these studies have been conducted either in women only, or in mixed cohorts in which the number of men with fractures has been too low to clarify the relationship between hs-CRP level and fracture risk specifically in men.

We hypothesized that there is also an association between hs-CRP and fracture risk in men and that such an association can be found if a large study, well-powered enough for the purpose, was used. We therefore investigated associations between hs-CRP and fracture risk in Osteoporotic Fractures in Men (MrOS) Sweden, which is a large prospective population-based cohort of elderly Swedish men.

Materials and Methods

Study subjects

The Osteoporotic Fractures in Men (MrOS) study is a multicenter, prospective study including older men in Sweden (3014), Hong Kong (~2000), and the United States (~6000). In the present study, associations between serum hs-CRP and fractures that occurred after the baseline visit were investigated in the Swedish cohort (Table 1), which consists of three subcohorts from three different Swedish cities ($n = 1005$ in Malmö, $n = 1010$ in Göteborg, and $n = 999$ in Uppsala). Study subjects (men aged 69–81 years) were randomly identified using national population registers, contacted, and asked to participate. To be eligible for the study, the subjects had to be able to walk without assistance, provide self-reported data, and sign an informed consent; there were no other exclusion criteria.[20] The study was approved by the ethics committees at the Universities of Göteborg, Lund, and Uppsala. Informed consent was obtained from all study participants.

Assessment of covariates

We used a standardized questionnaire to gather information about self-reported previous fractures after 50 years of age, amount of physical activity, nutritional intake, smoking, use of alcohol, prevalent major diseases (eg, diabetes, stroke, chronic obstructive pulmonary disease [COPD], cancer, and rheumatoid arthritis), and medication use (Table 1). Physical activity was the subject's average total daily walking distance, including both walking as a means of exercise and leisure and as a means of outdoor transportation in activities of daily life. Calcium intake

Table 1. Baseline Characteristics by Tertiles of hs-CRP

Characteristic	All subjects ($n = 2910$)	Tertile group for hs-CRP level: 1 (Low) ($n = 971$)	2 (Medium) ($n = 970$)	3 (High) ($n = 969$)	p
Age (years)	75.4 ± 3.2	75.4 ± 3.2	75.4 ± 3.2	75.5 ± 3.1	0.36*
Height (cm)	174.8 ± 6.6	175.2 ± 6.5	174.7 ± 6.4	174.4 ± 6.7	0.007*
Weight (kg)	80.7 ± 12.1	78.1 ± 11.1	81.4 ± 11.7	82.7 ± 13.1	<0.001*
BMI (kg/m^2)	26.4 ± 3.6	25.4 ± 3.2	26.6 ± 3.5	27.2 ± 3.8	<0.001*
Femoral neck BMD (g/cm^2)	0.83 ± 0.13	0.82 ± 0.13	0.84 ± 0.13	0.83 ± 0.14	0.09*
Physical activity (km)	3.9 ± 3.1	4.2 ± 3.2	4.1 ± 3.2	3.5 ± 3.0	<0.001*
Grip strength (kg)	39.9 ± 7.5	40.4 ± 7.2	40.0 ± 7.9	39.3 ± 7.4	0.003*
Smoking (%)	246 (8.5)	60 (6.2)	70 (7.2)	116 (12.0)	<0.001*
Alcohol ≥3 units per day (%)	76 (2.6)	19 (2.0)	25 (2.6)	32 (3.3)	0.18*
Calcium intake (mg)	898 ± 435	893 ± 403	895 ± 429	906 ± 470	0.51*
hs-CRP	2.17 (1.67–3.26)	1.51 (1.31–1.67)	2.17 (1.98–2.40)	4.31 (3.26–7.92)	NA
Major prevalent diseases, *n* (%)					
Cancer	450 (15.5)	151 (15.6)	157 (16.2)	142 (14.7)	0.65
COPD	245 (8.5)	63 (6.5)	59 (6.1)	123 (12.8)	<0.001
Diabetes	276 (9.5)	90 (9.3)	87 (9.0)	99 (10.2)	0.63
Stroke	189 (6.5)	55 (5.7)	69 (7.1)	65 (6.7)	0.41
Rheumatoid arthritis	43 (1.5)	12 (1.2)	12 (1.2)	19 (2.0)	0.31
Fractures at >50 years old	501 (17.3)	160 (16.6)	172 (17.9)	169 (17.6)	0.73
Subjects with validated incident fractures					
All fractures	377 (23.9)	110 (20.4)	116 (21.6)	151 (30.1)	0.01
Nonvertebral osteoporosis fractures	159 (9.7)	51 (9.1)	49 (8.8)	59 (11.2)	0.57
Hip fractures	89 (5.4)	27 (4.8)	28 (5.0)	34 (6.4)	0.61
Clinical vertebral fractures	125 (7.6)	39 (6.9)	34 (6.1)	52 (9.9)	0.11

Values are given as mean ± SD, median (interquartile range) or *n* (%). For fractures, the numbers of subjects with first fractures are given, with the incidence/1000 person-years shown in parentheses. Some subjects, included in the group of "all fractures," had more than one type of first fracture, and therefore, these subjects were included in more than one of the different subtypes of fractures. Nonvertebral osteoporosis fractures are defined as fractures in hip, distal radius, proximal humerus, and pelvis.

hs-CRP = high-sensitivity C-reactive protein; BMI = body mass index; BMD = bone mineral density; NA = data not applicable; COPD = chronic obstructive pulmonary disease.

*p for trend.

was calculated using information from the questionnaires. Use of alcohol was expressed as three or more glasses of alcohol-containing drinks per day, calculated from the reported frequency and amount of alcohol use. Grip strength was analyzed using Baseline equipment (Baseline, Chattanooga, TN, USA), and the average of two consecutive measurements was used in the analyses. Standard equipment was used to measure height and weight.

Assessment of incident fractures

Participants were followed for 5.4 years on average after the baseline examination. The follow-up time was recorded from the date of the baseline visit to the date of the first fracture or the date of death. When a subject sustained a first fracture at different sites during the follow-up, the various fractures and the follow-up time for each respective first fracture type were included in the analyses. Central registers covering all Swedish citizens were used to identify the subjects and the time of death for all subjects who died during the study, and these analyses were performed after the time of fracture validation. At the time of fracture evaluation, the computerized X-ray archives in Malmö, Göteborg, and Uppsala were searched for new fractures occurring after the baseline visit, using the unique personal registration number, which all Swedish citizens have. All validated fractures were included in the main analyses, followed by exploratory subanalyses of fracture type. In the latter, we studied the associations between hs-CRP and validated fractures, divided into three main groups: (1) X-ray–verified clinical vertebral fractures; (2) nonvertebral osteoporosis fractures at the major osteoporosis-related locations (defined as hip, distal radius, proximal humerus, and pelvis); and (3) hip fractures (Table 1). Fracture rates were expressed as the number of subjects with first fractures per 1000 person-years (Table 1).

Assessment of BMD

Areal BMD (aBMD, g/cm^2) of the femoral neck was assessed via dual-energy X-ray absorptiometry (DXA) using the Lunar Prodigy DXA ($n = 2004$ from the Uppsala and Malmö cohorts; GE Lunar Corp., Madison, WI, USA) or Hologic QDR 4500/A-Delphi ($n = 1010$ from the Göteborg cohort; Hologic, Waltham, MA, USA). The coefficients of variation (CVs) for the aBMD measurements ranged from 0.5% to 3%. To be able to use DXA measurements performed with equipment from two different manufacturers, a standardized BMD (sBMD) was calculated, as described.[20]

Serum analyses

CRP was measured by an ultrasensitive particle-enhanced immunoturbidimetric assay (Orion Diagnostica, Espoo, Finland). The analyses were performed on a Konelab 20 autoanalyzer (Thermo Fisher Scientific Inc, Waltham, MA, USA), with a sensitivity of 0.1 mg/L. Interassay CV for the Konelab analyses was below 5%.

Statistical analyses

The characteristics of the subjects were compared by tertiles of CRP using linear regression for continuous variables and chi-square tests for categorical variables. Non-normally–distributed variables were log-transformed.

Associations among variables were examined by Pearson's correlation. Cox proportional hazards models were used to study the associations between hs-CRP and fracture outcomes. The proportional hazard assumption for the main analysis as well as for exploratory subanalyses was assessed by the graphical log-log method using stphplot in Stata 12. Tertiles of hs-CRP were used in the primary analysis, and in subsequent analyses tertiles 1 and 2 were pooled into one group. Age-adjusted HRs, with 95% confidence intervals (CIs) within parentheses, versus the combined group of tertiles 1 and 2, were calculated. Further adjustments for height, weight, calcium intake, physical activity, grip strength, cigarette smoking, use of alcohol, COPD, stroke, diabetes, cancer, rheumatoid arthritis, prevalent fractures, and medication use (corticosteroids, statins, thiazide diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs], osteoporosis medications, testosterone, antidepressants, hypnotics and sedatives, and antiandrogens) were made to investigate the independent effects of hs-CRP on fracture outcome. Finally, adjustments were made also for femoral neck BMD. All validated fractures were included in the main analyses, followed by exploratory subanalyses of fracture type.

Results

Characteristics of the study subjects

Baseline characteristics of the study subjects, including the number and incidence per 1000 person-years of validated fractures having occurred after the baseline visit of the older men in the MrOS Sweden cohort, are shown in Table 1. In total, 377 subjects had at least one validated incident fracture, and the average follow-up time of the 2910 subjects was 5.4 years. Study participants were divided into tertile groups based on hs-CRP level. Serum levels of hs-CRP were [<1.81], [≥ 1.81, <2.76], and [≥ 2.76] mg/L in the lowest, medium, and highest tertiles, respectively. CRP was directly associated with baseline weight, body mass index (BMI), proportion of smokers, and prevalence of COPD, and inversely associated with grip strength (Table 1).

hs-CRP as a predictor of fractures

Cox proportional hazards models demonstrated that high serum hs-CRP was related to an increased risk of first fracture (age-adjusted HR, 1.25; 95% CI, 1.10–1.42 per tertile increase in hs-CRP). The fracture risk for subjects in the highest CRP tertile was clearly increased compared with subjects in the lowest tertile (HR, 1.54; 95% CI, 1.20–1.97), whereas the fracture risk was similar in the medium CRP tertile compared with the lowest CRP tertile (HR, 1.10; 95% CI, 0.85–1.43). Therefore, the lowest and the medium tertiles were pooled into one group in the subsequent analyses. The HR of fracture for the highest tertile of hs-CRP, compared with the lowest and the medium tertiles combined, was 1.48 (95% CI, 1.20–1.82; Fig. 1*A*).

Exploratory subanalyses of fracture type demonstrated that hs-CRP was clearly associated with clinical vertebral fractures (HR, 1.61; 95% CI, 1.12–2.29; tertile 3 versus tertiles $1 + 2$). There was no significant association between hs-CRP and hip fractures and nonvertebral osteoporosis-related fractures, respectively (Fig. 1*A*).

hs-CRP as an independent predictor of fractures

Multivariate adjustment for other risk factors for fractures (age, height, weight, calcium intake, physical activity, grip strength, cigarette smoking, use of alcohol, COPD, stroke, diabetes, cancer, rheumatoid arthritis, prevalent fractures, and medication use)

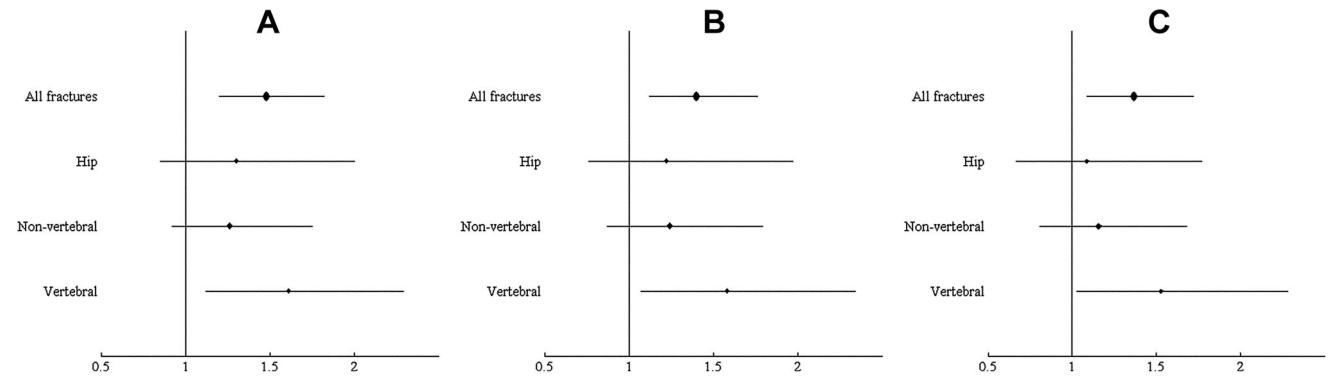

Fig. 1. Forest plot of Cox proportional hazard ratio (HR) and 95% CI of fracture by hs-CRP (highest tertile versus medium and lowest tertiles combined). (*A*) Adjusted for age. (*B*) Adjusted for age, height, weight, calcium intake, physical activity, grip strength, cigarette smoking, use of alcohol, chronic obstructive pulmonary disease (COPD), stroke, diabetes, cancer, rheumatoid arthritis, prevalent fractures, and medication use (corticosteroids, statins, thiazide diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), osteoporosis medications, testosterone, antidepressants, hypnotics and sedatives, antiandrogens). (*C*) Further adjusted for femoral neck sBMD.

had no major effect on the associations between hs-CRP and fracture (Fig. 1*B*).

Femoral neck BMD was not significantly associated with hs-CRP (p for trend 0.09; Table 1), and the predictive role of hs-CRP for fracture risk was essentially unchanged after adjustment was also made for femoral neck BMD (HR, 1.37; 95% CI, 1.09–1.72; tertile 3 versus tertile 1 + 2; Fig. 1*C*).

Exclusion of subjects with hs-CRP levels greater than 7.5 mg/L ($n = 258$), had essentially no effect on the results obtained for all fractures (HR, 1.39; 95% CI, 1.09–1.77, tertile 3 versus tertiles 1 + 2; multivariate-adjusted) and for vertebral fractures (HR, 1.66; 95% CI, 1.10–2.52; tertile 3 versus tertiles 1 + 2; multivariate-adjusted).

Long-term effects of hs-CRP on fracture risk

To explore the possibility that hs-CRP only reflected a poor health status at the time of serum sampling, we performed the Cox proportional hazards models comparing the HR of fracture in the highest tertile of hs-CRP with the medium and lowest tertiles combined, excluding all fractures occurring within the first 3 years of follow-up. The start time in these exploratory subanalyses was adjusted to begin at 3 years after study start. hs-CRP remained a significant predictor for fractures in this model. Interestingly, hs-CRP tended to be an even stronger predictor for all fractures when long-term effects were investigated (HR, 1.61; 95% CI, 1.18–2.20; multivariate-adjusted; tertile 3 versus tertiles 1 + 2). This was true also for vertebral fractures (HR, 1.89; 95% CI, 1.19–3.02; multivariate-adjusted HR, 2.29; 95% CI, 1.37–3.81; tertile 3 versus tertiles 1 + 2). Inclusion of femoral neck BMD in the models had no influence on the associations between hs-CRP and long-term risk of fracture (Table 2).

Discussion

As hypothesized, in this prospective population-based study, men with slightly elevated levels of hs-CRP, suggesting a low-grade inflammation, had an increased risk of fractures. The associations between hs-CRP and fracture risk in our cohort were largely independent of other known risk factors for fracture, including physical performance, smoking, use of alcohol, previous fractures, several chronic conditions, and medication use. The associations between hs-CRP and fractures were also independent of BMD.

Previous epidemiological research on associations between hs-CRP and incident fractures has been carried out primarily in women. Pasco and colleagues[16] showed a dose-response relationship between hs-CRP and fractures in Australian women

Table 2. Cox Proportional HR and 95% CI of Fracture by hs-CRP, Excluding All Fractures During the First 3 Years of Follow-Up

	All fractures	Hip	Nonvertebral	Vertebral
Age-adjusted	1.62 (1.22–2.16)	1.23 (0.70–2.16)	1.00 (0.63–1.60)	1.89 (1.19–3.02)
Multivariate adjusted[a]	1.61 (1.18–2.20)	1.23 (0.66–2.29)	1.05 (0.62–1.75)	2.29 (1.37–3.81)
Multivariate adjusted[b]	1.58 (1.15–2.16)	1.14 (0.61–2.13)	0.98 (0.58–1.64)	2.22 (1.33–3.69)

Values are HR (95% CI).

HR = hazard ratio; CI = confidence interval; hs-CRP = high-sensitivity C-reactive protein; COPD = chronic obstructive pulmonary disease; NSAID = nonsteroidal anti-inflammatory drug; sBMD = standardized BMD.

[a]Highest tertile versus medium and lowest tertiles of hs-CRP combined. Adjusted for age, height, weight, calcium intake, physical activity, grip strength, cigarette smoking, use of alcohol, COPD, stroke, diabetes, cancer, rheumatoid arthritis, prevalent fractures, and medication use (corticosteroids, statins, thiazide diuretics, NSAIDs, osteoporosis medications, testosterone, antidepressants, hypnotics and sedatives, antiandrogens).

[b]Further adjusted for femoral neck sBMD.

(median age 77 years, 96 fractures). In a cohort of Japanese women (mean age 74 years, 50 limb or vertebral fractures), Nakamura and colleagues[18] found an increased risk for fractures in the medium and highest tertiles compared to the lowest tertile of hs-CRP. In a recent study of American women (mean age 46 years, 194 fractures), by Ishii and colleagues,[19] fracture hazard increased significantly for values of hs-CRP above 3 mg/L.

Schett and colleagues[17] studied Italian women and men (mean age 59 years, 69 hip or vertebral fractures). Individuals in the highest tertile of hs-CRP had a clearly increased risk of nontraumatic fracture. However, only 19 of the fractures occurred in men, making it difficult to draw firm conclusions on the relationship between hs-CRP and fractures in men from this study. A mixed cohort was also used by Cauley and colleagues[21] (U.S. men and women, mean age 74 years, 253 fractures), but in this study results were not statistically significant for hs-CRP. Borderline significance was reached in a multi adjusted model comparing the highest quartile of hs-CRP (Q4) to Q1, Q2, and Q3 combined. Results for men were not reported separately. Thus, there has definitively been a lack of well-powered studies on the associations between hs-CRP and fracture risk in men, and this is where our large cohort, which included as many as 377 men with at least one fracture, adds new knowledge.

Several risk factors for fracture such as smoking, low physical activity, malignancies, and chronic inflammatory diseases are associated with elevated levels of hs-CRP,[22–24] and the associations between hs-CRP and fracture risk could thus be mediated via these conditions. However, our data are very robust; adjustments for multiple known risk factors for fracture including smoking, physical activity, previous fractures, concomitant diseases, and medication use had no major effects on the results. The same was true when individuals with hs-CRP above 7.5 mg/L or fractures occuring during the first 3 years of follow up were excluded from the analyses. This makes it highly unlikely that our results are due to increased fracture risk in individuals with frailty or undiagnosed concomitant diseases associated with elevated hs-CRP levels.

Moreover, the high number of fractures enabled us to study individual fracture types, and it appears that in men, hs-CRP mainly is a predictor of fractures in the vertebrae because the associations with vertebral fractures prevail after adjustments for a wide range of risk factors as exemplified in Figure 1.

In our study, there were no associations between hs-CRP and BMD, and the predictive role of CRP for fracture risk was independent of BMD. This is in line with findings of the other studies on hs-CRP and fracture in which BMD by DXA[16–18,21] or bone ultrasonographic data at the heel[17,21] were measured. However, there are also studies indicating that there actually is an association between hs-CRP and BMD, including a large study by Koh and colleagues[25] in healthy Korean women in which a negative association between hs-CRP and BMD was found, and a study by Ding and colleagues[26] in which there were negative associations between hs-CRP and longitudinal change in BMD, whereas others reported no associations.[27–29] All of these studies were conducted in women.

The mechanism behind the associations between hs-CRP and fracture risk in our study is thus not an effect on BMD as measured by DXA. However, it is still possible that aspects of bone quality other than BMD, such as quality of the collagenous matrix, bone microarchitecture, or bone size, mediate the effects of low-grade inflammation on fracture risk. In the study by Ishii and colleagues,[19] femoral neck composite strength indices were calculated using DXA-derived measurements. CRP was inversely associated with these strength indices, as well as with bone size factors, but not with BMD. Some, but not all, of the association between high hs-CRP and increased fracture risk in their study was explained by the decrement in composite strength indices with high hs-CRP. It thus appears that low-grade inflammation can affect the balance between bone strength and load.

The associations between bone microarchitecture and hs-CRP were recently investigated by Rolland and colleagues[30] in a cohort of 1149 men aged 19 to 87 years. As in several other studies, there were no associations between hs-CRP and aBMD. Interestingly however, in men aged $\geq$72 years, but not in younger men, there was an association between bone microarchitecture, as measured by high-resolution pQCT (HR-pQCT), and hs-CRP. In the distal radius, men in the highest quartile of hs-CRP had 6.6% lower trabecular volumetric BMD and 4.5% lower trabecular number compared with the other quartiles combined. They also had a higher trabecular spacing, and more heterogeneous trabecular distribution than men with lower hs-CRP.[30] Inflammation upregulates osteoclasts and downregulates osteoblasts[11] and it is thus not surprising to see an effect of low-grade inflammation in the metabolically more active trabecular bone compartment as in the study by Rolland and colleagues.[30] Fracture prevalence increased with increasing hs-CRP concentration in the study by Rolland and colleagues,[30] but in contrast to our prospective study, this was a cross-sectional study in which peripheral fractures were self-reported and only vertebral fractures were verified by X-ray.

Thus, the studies by Ishii [19] and Rolland [30] give suggestions on how the associations between high hs-CRP and an increased fracture risk are mediated. Because data on neither bone microarchitecture nor bone strength indices are available for the men in our study we do not know if these parameters were affected in our cohort. There are yet other possible explanations not investigated so far, including bone composition, falls, and neuromuscular function.

Our study has a number of strengths. The population-based nature, the large number of study subjects, the complete follow-up and the X-ray validation of fractures all contribute to the validity of the results. There were, however, also limitations. No other inflammatory markers were measured and therefore the potential causal mechanism underlying the associations between hs-CRP and fractures could not be studied. hs-CRP was measured only once, and that might underestimate the effect size. Moreover, markers of bone turnover were not measured and thus it is not possible to investigate associations between bone turnover and hs-CRP.

In summary, we show that in elderly Caucasian men, higher levels of hs-CRP are associated with an increased risk of fractures. We thus propose that low-grade inflammation leads to an increased risk for fractures in men. Our study is the first to convincingly show the association between hs-CRP and fractures in men.

Disclosures

All authors state that they have no conflicts of interest.

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