High-Sensitivity C-Reactive Protein and Risk of Nontraumatic Fractures in the Bruneck Study

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Background: Chronic inflammatory diseases are associated with bone loss and an enhanced fracture risk. It is unknown, however, whether low-grade inflammation in healthy individuals, as estimated by the high-sensitivity C-reactive protein (hs-CRP) level, interferes with bone metabolism and affects the risk of nontraumatic fractures.

Methods: Lifetime bone fractures were carefully recorded in the cohort of the population-based Bruneck Study (n=919) along with information on the date of occurrence and associated circumstances. The serum level of hs-CRP was measured from blood samples collected during the 1990 baseline examination and the 1995, 2000, and 2005 follow-up examinations. In addition, lifestyle and demographic characteristics, bone ultrasonographic data at the heel, and variables of bone metabolism were assessed.

Results: Between September 1, 1990, and August 31, 2005, 69 subjects experienced nontraumatic hip or vertebral fractures. The incidence of nontraumatic fractures was 1.3, 3.8, and 13.9 per 1000 person-years in the tertile groups for hs-CRP. In multivariate pooled logistic regression analysis, the adjusted relative risk (95% confidence interval) of nontraumatic fracture in the highest vs lowest tertile group for hs-CRP was 9.4 (3.6-24.8) (P<.001). The exclusion of subjects with cardiovascular disease, dementia, malignancies, and chronic inflammatory disease had little effect on the results obtained. The hs-CRP level was unrelated to ultrasonographic measures of bone density, but showed an inverse relation to laboratory markers of bone turnover, like β-crosslaps and osteocalcin concentration (P<.001).

Conclusions: The hs-CRP level is a significant and independent risk predictor of nontraumatic fracture. This finding is consistent with the hypothesis of a tight interplay between low-grade inflammation and bone turnover.

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STUDY SUBJECTS

The Bruneck Study is a prospective population-based survey of the epidemiology and pathogenesis of atherosclerosis and disorders of the brain and bone. The study protocol was reviewed and approved by the appropriate ethics committees. All study subjects gave their written informed consent. At the 1990 baseline, the study population was recruited as an age- and sex-stratified random sample of all inhabitants of Bruneck (125 women and 125 men in each of the fifth to eighth decades of age). A total of 93.6% participated, with data assessment completed in 919 subjects. Thirteen subjects with nontraumatic fractures before baseline were excluded, leaving 906 men and women for the current analysis. Follow-up examinations were performed every 5 years (1995, 2000, and 2005), and information on fractures was available for 93.6% of participants, thereby using 3 sources of information: the subject’s self-report, a medical record from the study hospital or general practitioner, and a standardized evaluation of all radiographs ever taken of study subjects. The situation in Bruneck is unique in that (1) the only x-ray filming facility in the whole district is located at the hospital and all radiographs ever taken of study subjects were available for review, (2) radiographs were obtained in virtually all cases of injury and in moderate-to-severe or long-lasting back pain, and (3) population mobility in the survey area was low during the past 15 years. For all radiologically confirmed fractures, localization, date of occurrence, and associated circumstances were recorded. Fractions were classified as nontraumatic if resulting from a fall from standing height or less or manifesting without any trauma. Vertebral fractures were diagnosed according to established criteria.

Clinical history taking and examination

Lifetime fractures were carefully recorded for all study participants, thereby using 3 sources of information: the subject’s self-report, a review of medical records from the Bruneck Hospital and general practitioners, and a standardized evaluation of all radiographs ever taken of study subjects. The situation in Bruneck is unique in that (1) the only x-ray filming facility in the whole district is located at the hospital and all radiographs ever taken of study subjects were available for review, (2) radiographs were obtained in virtually all cases of injury and in moderate-to-severe or long-lasting back pain, and (3) population mobility in the survey area was low during the past 15 years. For all radiologically confirmed fractures, localization, date of occurrence, and associated circumstances were recorded. Fractions were classified as nontraumatic if resulting from a fall from standing height or less or manifesting without any trauma. Vertebral fractures were diagnosed according to established criteria.

Lifestyle variables were assessed in 1990, 1995, 2000, and 2005. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Smoking status and alcohol consumption were recorded as detailed previously. The activity score was composed of the scores for work (3 categories) and sports/leisure activities (0, ≤2, or >2 h/wk). Socioeconomic status was defined with a 3-category scale (low, medium, and high) based on information about occupational status and educational level of the person with the highest annual income in the household. Diabetes mellitus was diagnosed according to American Diabetes Association criteria, with a cutoff level of fasting plasma glucose of 126 mg/dL or more (≥7.0 mmol/L). Autoimmune diseases were identified by an extensive 2-phase screening procedure detailed previously. A diagnosis of malignancy required confirmation by histological/cytological examinations. Dementia was coded present if predefined by a neurologist and/or in case of a Mini-Mental State Examination score of less than 24. Cardiovascular disease subsumes fatal and nonfatal strokes (National Survey of Stroke criteria), fatal and nonfatal definite myocardial infarctions (World Health Organization definition), and definite peripheral artery disease. Bone ultrasonographic data (broadband ultrasonic attenuation and speed of sound) were assessed in 2000 and 2005 at the heel bones using quantitative ultrasonographic equipment (SAHARA; Hologic, Inc, Bedford, Mass).

LABORATORY PROCEDURES

Blood samples were drawn after an overnight fast and 12 hours of abstinence from smoking, and were available from 919 subjects in 1990, 826 subjects in 1995, 700 subjects in 2000, and 372 subjects in 2005. Samples taken in 1990 and 1995 were analyzed in 2005 after 10 and 15 years of storage at −70°C (without any cycle of thawing-freezing), and 2000 and 2005 samples were immediately processed. The hs-CRP level was analyzed with an immunoniturbimetric latex CRP assay (OLYMPUS OS68199; Olympus Diagnostics, Melville, NY) with an IFCC/BCR/CAP CRM 470 CRP standard. Serum levels of osteocalcin, parathyroid hormone, and β-crosslaps were measured by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany), 25-hydroxyvitamin D by automated chemiluminescence assay (Nichols Advantage; Nichols Institute Diagnostics, San Juan Capistrano, Calif), and soluble receptor activator of nuclear factor κB ligand and osteoprotegerin by a commercial sandwich enzyme-linked immunosorbent assay (Biomedica, Vienna).

STATISTICAL ANALYSIS

Person-years of follow-up for each participant were accrued from the 1990 baseline until diagnosis of nontraumatic fracture, death, or October 1, 2005, whichever came first. Participants experienced nontraumatic vertebral or hip fractures. Participants were divided into 3 approximately equal groups according to tertiles of hs-CRP. Relative risks were estimated with rate ratios comparing the incidence of nontraumatic fractures in each tertile with that of the lowest (referent) tertile. Risk factor–adjusted relative risks were estimated from pooled logistic regression analyses. This technique treated each observation period (1990-1995, 1995-2000, and 2000-2005) as a mini follow-up study in which updated risk factor measurements were used to predict fracture risk (ie, risk factor levels assessed in 1990 were used to predict the risk of fractures occurring in 1990-1995, risk factor levels assessed in 1995 were used to predict the risk of fractures occurring in 1995-2000, and risk factor levels assessed in 2000 were used to predict the risk of fractures occurring in 2000-2005). Updates were performed for all variables in the analyses and not only for hs-CRP level. In case of a missing hs-CRP level, follow-up measurement during the subsequent 5-year period was not considered in the analysis. Observations over all 3 periods were pooled into a single sample, as usual in pooled logistic regression models. The pooled logistic regression approach has been shown to be asymptotically equivalent to the Cox proportional hazards regression model, with time-dependent covariates given short intervals between reevaluations and low rates of events. Multivariate models were adjusted for age (in years), sex (men, premenopausal women, and postmenopausal women), follow-up period (1990-1995, 1995-2000, or 2000-2005), income (low, medium, or high), smoking (number of cigarettes smoked daily), alcohol consumption (measured in grams per day), physical activity (score), diabetes mellitus (no or yes), body mass index, creatinine levels (measured in milligrams per deciliter), sex hormone therapy (no or yes), and facultative variables of bone metabolism. We performed tests for linear trend by treating the medians in each category of CRP level as a continuous variable. All reported P values are 2-sided, and all analyses were prespecified except for the subgroup analyses in subjects with prominent inflammation arbitrarily defined by an hs-CRP cutoff of 7.5 mg/L.

RESULTS

Levels of hs-CRP in the Bruneck cohort were lower than those recently reported from a standard US population (Table 1). The Bruneck participants are quite lean and
that might explain the relatively low CRP level. Geometric means of hs-CRP level in the 1990, 1995, 2000, and 2005 assessments were highly consistent when accounting for the continuous aging of study subjects and minor shifts in sex ratios (1.7, 1.8, 2.0, and 2.2 mg/L), which suggests considerable stability of CRP level in frozen samples.19 Individual levels of hs-CRP were stable during a 5-year period, as indicated by Spearman rank correlation coefficients of 0.65, 0.64, and 0.64 for assessments 1990 vs 1995, 1995 vs 2000, and 2000 vs 2005, respectively. The intraclass correlation calculated for all assessments and the entire 15-year follow-up was high, at 0.52. Classification of hs-CRP level into tertile groups showed a considerable agreement during the three 5-year assessments and the entire 15-year follow-up was high, according to tertile groups for hs-CRP are depicted in Table 2. The hs-CRP level was significantly and inversely associated with variables of bone turnover, such as β-crosslaps and osteocalcin concentration (P<.001), whereas it emerged as unrelated to bone ultrasonographic data of the heel. These findings did not apply to the small subsegment of subjects with hs-CRP levels exceeding 7.5 mg/L in whom hs-CRP level showed a positive correlation with β-crosslaps (eg, 1990 baseline: r = 0.28, P=.03) and an inverse correlation with ultrasonographic measures of bone density (eg, 2005 follow-up examination: bone ultrasonographic data, r = –0.33 [P=0.007]; and speed of sound, r = –0.32 [P=0.009]).

Between 1990 and 2005, 69 men and women experienced nontraumatic hip and vertebral fractures. The incidence of nontraumatic fractures varied from 1.3 per 1000 person-years in the lowest tertile to 13.9 per 1000 person-years; multivariate OR, 9.1 [95% CI, 3.1-27.2] for subjects in the highest vs lowest tertile group for hs-CRP level (P=.004 for trend) and in women (n=50; incidence, 8.8 per 1000 person-years; multivariate OR, 8.0 [95% CI, 1.06-69.6] for subjects in the highest vs lowest tertile group for hs-CRP level; P=.02 for trend) and nontraumatic vertebral fractures (n=58; incidence, 5.2 per 1000 person-years; multivariate OR, 9.9 [95% CI, 3.4-28.7] for subjects in the highest vs lowest tertile group for hs-CRP level; P<.001 for trend). The exclusion of subjects with malignancies, autoimmune disease, cardiovascular disease, and dementia and of those with an hs-CRP level greater than 7.5 mg/L had little effects on the results obtained (Table 4). Results were also confirmed when log-transformed hs-CRP level was treated as a continuous variable (multivariate OR, 1.8 [95% CI, 1.4-2.3] per 1-U increase; P<.001) or hs-CRP categorization other than the predefined tertile groups were applied (multivariate OR, 3.5 [95% CI, 1.3-9.2] and 7.5 [95% CI, 2.8-19.8] for subjects with an hs-CRP level of 1-3 and >3 vs <1 mg/L; P<.001) (Table 1); the multivariate OR values were 1.0 (95% CI, 0.3-4.3), 2.8 (95% CI, 0.8-9.0), 5.1 (95% CI, 1.7-15.6), and 7.1 (95% CI, 2.4-21.3) for subjects in the second to fifth vs first quintile group, respectively, for hs-CRP level (P<.001).

When restricting the analysis to the 2000 to 2005 period and allowing for ultrasonographic measures of bone density (2000), this variable showed the expected inverse relation to fracture risk (OR, 4.5 [95% CI, 1.7-12.2] and 2.5 [95% CI, 0.9-7.2] in the lowest and middle vs highest tertile group for bone

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**Table 1. Baseline hs-CRP Level of 906 Subjects According to Age and Sex in the Bruneck Study From 1990**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.0 ± 6.0</td>
<td>1.4 (0.8-3.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.1 ± 7.0</td>
<td>1.6 (0.8-3.1)</td>
</tr>
<tr>
<td>Female</td>
<td>2.9 ± 4.8</td>
<td>1.4 (0.8-3.0)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>2.0 ± 2.8</td>
<td>1.1 (0.6-2.4)</td>
</tr>
<tr>
<td>50-59</td>
<td>2.5 ± 6.3</td>
<td>1.4 (0.8-2.8)</td>
</tr>
<tr>
<td>60-69</td>
<td>2.8 ± 5.6</td>
<td>1.6 (1.0-3.2)</td>
</tr>
<tr>
<td>70-79</td>
<td>4.9 ± 8.4</td>
<td>2.2 (1.1-4.5)</td>
</tr>
</tbody>
</table>

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range.

*Data are given as percentage of subjects. Percentages may not total 100 because of rounding.
ultrasonographic data; \( P = .002 \) and the association between fracture risk and hs-CRP tertile groups remained virtually unchanged.

In contrast to nontraumatic vertebral and hip fractures, other (traumatic) fractures (n=312) were not related to hs-CRP level in multivariate pooled logistic regression analysis (OR, 1.0 [95% CI, 0.7-1.4] and 1.1 [95% CI, 0.8-1.6] in the middle and highest vs lowest tertile group for hs-CRP level; \( P = .65 \)).

### Table 2. Baseline Distribution of Demographic and Lifestyle Variables, Indicators of Bone Metabolism, Bone Ultrasonographic Data, and Medication According to Tertile Group for hs-CRP Level in 906 Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tertile Group for hs-CRP Level</th>
<th>( P ) Value for Trend†</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP level, median (range), mg/L</td>
<td>1 (Low) (n = 346)</td>
<td>2 (Medium) (n = 292)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>56.7 (10.8)</td>
<td>58.9 (11.2)</td>
</tr>
<tr>
<td>Sex†</td>
<td>49.1</td>
<td>50.0</td>
</tr>
<tr>
<td>Physical activity score</td>
<td>4.5 (1.5)</td>
<td>4.4 (1.5)</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>3.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Body mass index§</td>
<td>23.7 (3.1)</td>
<td>25.0 (3.6)</td>
</tr>
<tr>
<td>Bone metabolism and renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteocalcin level, µg/L</td>
<td>30.2 (20.6)</td>
<td>27.4 (13.0)</td>
</tr>
<tr>
<td>( \beta )-Crosslaps, ng/mL</td>
<td>0.51 (0.38)</td>
<td>0.44 (0.25)</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D, ng/mL</td>
<td>33.7 (13.4)</td>
<td>31.6 (12.3)</td>
</tr>
<tr>
<td>Parathyroid hormone, pg/mL</td>
<td>49.3 (29.1)</td>
<td>52.0 (26.8)</td>
</tr>
<tr>
<td>RANKL, pmol/L</td>
<td>1.15 (0.66)</td>
<td>1.21 (1.25)</td>
</tr>
<tr>
<td>Osteoprotegerin, pmol/L</td>
<td>3.5 (1.9)</td>
<td>3.6 (1.5)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.94 (0.21)</td>
<td>0.89 (0.15)</td>
</tr>
<tr>
<td>Bone ultrasonographic data†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUA, dB/MHz</td>
<td>71.7 (18.6)</td>
<td>72.4 (17.2)</td>
</tr>
<tr>
<td>SOS, m/s</td>
<td>154.6 (3.2)</td>
<td>154.5 (3.0)</td>
</tr>
<tr>
<td>Change in BUA, dB/MHz</td>
<td>-1.1 (6.9)</td>
<td>-1.9 (7.5)</td>
</tr>
<tr>
<td>Change in SOS, m/s</td>
<td>0.1 (7.8)</td>
<td>-0.5 (2.0)</td>
</tr>
<tr>
<td>Medication‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Coumarin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Statins</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>10.2</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Abbreviations: BUA, broadband ultrasonographic attenuation; hs-CRP, high-sensitivity C-reactive protein; NA, data not applicable; RANKL, receptor activator of nuclear factor \( \kappa \) ligand; SOS, speed of sound.

†Conversion factors: To convert \( \beta \)-crosslaps to picomoles per liter, multiply by 8.557; to convert creatinine to micromoles per liter, multiply by 88.4; to convert 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496; and to convert osteocalcin to nanomoles per liter, multiply by 0.171.

‡Data are given as unadjusted mean (SD) unless otherwise indicated. The slightly unequal sampling in the tertiles is because the cutoffs for the definition of tertile groups were based on all (ie, the 1990, 1995, and 2000) measurements.

§Variable levels across hs-CRP tertile groups were compared by means of generalized linear models (continuous variables) and logistic regression analysis (categorical variables). Analyses were adjusted for age and sex/menopausal status. \( P \) values for age and sex were unadjusted. Tests for linear trend were performed by treating the medians in each category of hs-CRP level as a continuous variable.

‡Data are given as percentage of each group. Percentages may not total 100 because of rounding.

§Calculated as weight in kilograms divided by the square of height in meters.


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monly regarded as low-grade inflammation. Subjects in the bottom and top tertile groups for hs-CRP level differed in their fracture risk by a factor of 7.8 (lower limit of the 95% CI, 3.1). This finding emerged as largely independent of age, sex, menopausal status, lifestyle characteristics, and laboratory variables of bone metabolism. The conjecture is similar to that observed in cardiovascular disease. There is solid evidence of an enhanced burden of vascular disease in patients with chronic inflammatory diseases, like rheumatoid arthritis, systemic lupus erythematosus, chronic infections, and common allergic disorders, and hs-CRP level is a well-established predictor of vascular risk in healthy individuals.

Several observations suggest that the key finding of our study is not based on chance: (1) The association obtained was strong, specific for nontraumatic fractures and of a dose-response type and remained robust after correction for potential confounders and in several sensitivity analyses. (2) P values for the main findings were in a comfortable range well below .001. (3) Data were highly consistent in all three 5-year intervals and various subgroups according to age, sex, and menopausal state. Furthermore, we considered the possibility that subjects in the highest tertile group for hs-CRP level have confounding diseases featured by elevated hs-CRP levels and an increased fracture risk. Autoimmune diseases and malignancies are such conditions, as are cardiovascular disease and dementia. The latter conditions confer a higher risk of falls and may affect fracture risk. Actually, exclusion of subjects with any of these diseases and/or those with an hs-CRP level greater than 7.5 mg/L of unknown origin had little effect on the results obtained (Table 3). The possibility of unidentified confounding, however, cannot be excluded.

More important, hs-CRP level was not related to bone density and both measures predicted the risk of nontraumatic fractures independently of each other. These findings, however, should be interpreted in view that ultrasonographic data were assessed at the heel and standard radiological measurements of bone density at predilection sites of osteoporosis were not available. Nevertheless, fracture risk is not exclusively determined by bone density but is also influenced by other factors, like age...
and genetic variables,\(^2\) that also affect bone quality aside from bone mass. More important, levels of osteocalcin and \(\beta\)-crosslaps decreased with increasing hs-CRP concentration, suggesting a state of low bone turnover and reduced bone remodeling. Speculatively, this could affect bone microarchitecture and quality and account for the elevated fracture risk.\(^3\) An inhibitory effect of inflammation on osteoblast differentiation is known from experimental models and may indirectly also affect osteoclast maturation via coupling mechanisms.\(^4\) In contrast, the conjecture in subjects with autoimmune disease\(^5,\)\(^6\) and in the small segment of the general community with more prominent inflammation (hs-CRP level, >7.5 mg/L) seems to be characterized by a preferential up-regulation of bone resorption.

The strength of this population study is its representative nature for the general community, which is ascertained by (1) near complete participation and follow-up and (2) a broad age range between 40 and 94 years and a high degree of accuracy in assessing and classifying fractures. Furthermore, assessments of risk estimates for other variables were consistent, revealing established variables, such as sex, menopausal state, age, alcohol consumption, and physical activity, and newly identified variables, such as receptor activator of nuclear factor \(\kappa\) ligand level, as relevant for fracture risk.\(^7\) One potential limitation is the fact that clinically unapparent vertebral fractures were not assessed. Radiographic measures detect fractures that are clinically unapparent and the prevalence of these events is higher than that of clinically symptomatic fractures. Estimates suggest that every third vertebral fracture is clinically apparent.\(^3,\)\(^4\) However, the relevance of such events is small from a clinical viewpoint, and nonassessment of minor disease phenotypes may be expected to weaken evident relations rather than to create spurious ones. Another limitation is that bone density has been assessed by heel ultrasonography rather than dual x-ray absorptiometry of the spine or hip. It can, thus, not be fully excluded that the association between CRP level and fracture risk is independent from bone mineral density, because bone ultrasonographic data, although well correlated with dual x-ray absorptiometry measures, do not formerly measure bone mineral density.\(^3,\)\(^5\) However, most studies\(^7-\)\(^12\) show that the prognostic validity of bone ultrasonography for vertebral and hip fractures is at least as good as that of hip and vertebral dual x-ray absorptiometry, suggesting no major effect on the strength of association between CRP level and fracture risk.

In summary, this study demonstrates that hs-CRP level predicts the risk of nontraumatic fractures at levels previously shown to be linked with cardiovascular disease and diabetes mellitus. This finding is intriguing from a pathophysiological viewpoint, suggesting a tight interplay between the immune system, inflammation, and bone quality, and may well find clinical application if confirmed in independent population samples.

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