Tumour necrosis factor-related apoptosis-inducing ligand and osteoprotegerin serum levels in psoriatic arthritis

L. C. Hofbauer, M. Schoppet†, M. Christ‡, J. Teichmann¹ and U. Lange²

Objectives. The degree of bone loss in patients with psoriatic arthritis (PsA) has not been well-defined. We tested the hypothesis, whether serum levels of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), a pro-apoptotic cytokine and osteoprotegerin (OPG), an anti-osteoclastic cytokine, are associated with changes in biochemical markers of bone turnover or bone mineral density (BMD) in patients with PsA.

Methods. In a cross-sectional study, we evaluated biochemical markers of bone turnover, BMD and serum levels of TRAIL and OPG in 116 patients with PsA (mean age: 52±13 yrs).

Results. In patients with PsA, osteopenia was present in one-third of women and men, while osteoporosis was more frequent in men (10.2%) than in women (1.75%). Serum levels of TRAIL were significantly higher in patients with PsA (66.1±45.3 pmol/l) compared with controls (50.0±20.1 pmol/l, P<0.01), whereas OPG serum levels were not different. There were no associations between TRAIL or OPG serum levels with BMD and biochemical markers of bone turnover. However, TRAIL serum levels were associated with C-reactive protein (CRP) levels (R = 0.201, P<0.05), whereas OPG serum levels were associated with the erythrocyte sedimentation rate (R = 0.215, P<0.05).

Conclusion. In summary, BMD is decreased in one-third of patients with PsA, and predominantly men with PsA suffer from osteoporosis. While TRAIL serum levels are increased in PsA and correlated with CRP levels, neither TRAIL nor OPG serum levels are correlated with BMD or markers of bone metabolism.

KEY WORDS: Bone metabolism, Inflammatory arthritis, Osteoprotegerin, Psoriatic arthritis, Tumour necrosis factor-related apoptosis-inducing ligand

Introduction

Patients with psoriatic arthritis (PsA) have local and systemic bone loss, and may be at an increased risk of suffering from osteoporotic fractures [1–5]. However, the degree of bone loss in patients with PsA has not been well-defined, in part due to the small sample size of most cohorts. Potential factors that contribute to bone loss in patients with PsA include chronic inflammation, concurrent medications, such as methotrexate or glucocorticoid therapy, and prolonged immobilization due to joint dysfunction and severe pain [5, 6].

Osteoprotegerin (OPG) and receptor activator of nuclear factor-κB ligand (RANKL) have been implicated as potential links between T-cell activation, chronic inflammation and bone loss [7]. OPG, a secreted tumour necrosis factor (TNF)-receptor homologue, increases bone density by acting as a decoy receptor for RANKL, an essential regulator of osteoclast biology [8, 9]. Since activated T-cells produce and secrete RANKL, the RANKL/OPG system may play an important role in the pathogenesis of inflammatory bone diseases, including arthritis [10]. In addition to RANKL, TNF-related apoptosis-inducing ligand (TRAIL), an inducer of apoptosis in susceptible cells, has been characterized as a second ligand for OPG [11]. In various studies, alterations of TRAIL and OPG serum levels have been linked to inflammatory or immune- and apoptosis-mediated diseases, including ankylosing spondylitis, systemic lupus erythematosus (SLE), atherosclerosis, allogeneic transplant rejection, chronic hepatitis B and cardiomyopathy [12–19].

In this cross-sectional study, we tested the hypothesis, whether TRAIL and OPG serum concentrations are associated with changes in biochemical markers of bone turnover or bone mineral density (BMD) in a large and well-characterized cohort of patients with PsA.

Patients and methods

Patients and clinical evaluation

We studied 116 patients with PsA, 59 men (mean age 49±13 yrs, range 22–77 yrs) and 57 women (mean age 56±11 yrs, range 19–76 yrs) attending the out-patient clinic of the Department of Internal Medicine, Philipps-University, Marburg, ¹Medical Clinic C, City Hospital, Ludwigshafen and ²Kerckhoff Clinic and Foundation, Department of Rheumatology, Clinical Immunology and Osteology, University of Giessen, Bad Nauheim, Germany.

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of Rheumatology at Kerckhoff Clinic, University of Giessen, Germany. Of the 57 women, 35 (61%) were post-menopausal. All patients fulfilled the diagnostic criteria for PsA defined by the Classification of Psoriatic Arthritis (CASPAR) study [20].

Patients with rheumatoid arthritis, ankylosing spondylitis, Reiter’s syndrome or other diseases affecting bone metabolism were excluded on the basis of a detailed questionnaire, physical examination and a comprehensive laboratory assessment. We specifically excluded patients with alcohol abuse, inflammatory bowel diseases, malnutrition, overt vitamin D deficiency and those taking drugs known to affect bone metabolism. None of the patients had received glucocorticoids or DMARDs for the last 12 months and no patient had a history of long-term (>6 months) glucocorticoid therapy. A total of 89 patients (76.7%) were treated with non-steroidal anti-inflammatory drugs within the last 12 months prior to inclusion into this study. None of the patients received calcium and vitamin D supplementation, and all patients were physically active during the last 12 months.

Measurements were performed after approval by the Ethical Committee of the University of Giessen, and all patients gave their informed consent before participating in the study. Clinical examination was performed by the same experienced rheumatologist to avoid inter-observer variation.

The control group consisted of 90 men without PsA (mean age: 59±9 yrs). This cohort was part of a study to evaluate TRAIL and OPG serum levels in coronary artery disease; only the control cohort with the exclusion of coronary narrowing as assessed by coronary angiography was used [21]. In this control group, 37% had arterial hypertension and 3% diabetes mellitus. Other medical conditions known to impair bone metabolism were excluded by a detailed questionnaire, physical examination and a comprehensive laboratory assessment.

Assessment of bone mineral density

BMD was measured at the lumbar spine (L1–L4, anteroposterior view) and the right femoral neck by dual-energy X-ray absorptiometry (DEXA) using Prodigy Lunar (Milwaukee, WI). The coefficient of variation of repeated measurements was 0.9% for the lumbar spine and 1.6% for the femoral neck. Osteopaenia (T-score between −1.0 and −2.5) and osteoporosis (T-score below −2.5) were defined according to the criteria of the World Health Organization.

Evaluation of laboratory parameters and biochemical markers of bone turnover

All blood samples were taken in the morning after an overnight fasting period. Serum samples were centrifuged and subsequently stored at −80°C prior to analysis. Erythrocyte sedimentation rate (ESR) was determined by the Westergren method, and C-reactive protein (CRP; normal range: <0.5 ng/dl) was measured using a commercial assay (Tina-quant CRP, Roche Diagnostics, Mannheim, Germany). Serum concentrations of thyrotropin, creatinine and calcium were measured using standard routine laboratory methods.

Serum levels of intact parathyroid hormone (PTH, normal range: 10–65 pg/ml), 25-hydroxyvitamin D3 (normal range: 6–42 ng/ml) and 1,25-dihydroxyvitamin D3 (normal range: 20–65 pg/ml) were measured using commercial radioimmunoassays from Nichols Institutes Diagnostics (Wijchen, Netherlands). Serum levels of osteocalcin as a marker of bone formation (normal range: 1.8–6.6 ng/ml) were measured with an immunoassay from Incstar Corporation (Stillwater, MN, USA). Serum cross-laps as a biochemical marker of bone resorption (normal range: 0.1–10 ng/ml) were assessed using an ELISA from Roche.

Measurement of TRAIL and OPG serum concentrations

Serum levels of TRAIL were measured using a sandwich immunoassay from R&D Systems (Minneapolis, MN, USA) with a lower limit of detection of 15.6 pg/ml, and intra-assay and inter-assay coefficients of variance (CV) of 3 and 7%, respectively [17]. OPG serum concentrations were determined using an immunoassay from Immunodiagnostics (Bensheim, Germany) with a lower limit of detection of 0.14 pmol/l and intra-assay and inter-assay CVs of 5 and 8%, respectively [18].

Statistical analysis

Values are presented as mean ± SD and data were not transformed prior to statistical analysis. Statistical evaluation was performed using Student’s t-test for unpaired data or Mann–Whitney U-test, if indicated. Statistical analyses were corrected for multiple testing by the Bonferroni method. Associations between two variables were analysed using linear regression models. A two-tailed type I error (α) of 0.05 was considered significant. Statistical evaluation was performed using standard computer software (SPSS software package, version 13.0, SPSS Inc., Chicago, IL, USA).

Results

Demographic data

The demographic data and clinical findings are summarized in Table 1. The age of the patients ranged from 19 to 76 yrs in women and from 22 to 77 yrs in men. Because of the extended age range, T and Z-scores for the classification of osteopenia and osteoporosis, bone-turnover markers and serum levels of TRAIL and OPG also varied widely.

Bone mineral density

Osteopenia as defined by a T-score of <−1.0 at the lumbar spine or the femoral neck was present in 20 out of 57 women (35.1%) and in 18 out of 59 men (30.5%) with PsA, respectively (Fig. 1). Osteoporosis (as defined by a T-score of <−2.5) was detected in only one woman (1.75%), but in six men with PsA (10.2%), respectively (Fig. 1). None of these patients with osteoporosis (one woman, six men) had received specific treatment for osteoporosis prior to the BMD measurement in our study. Among these seven osteoporotic patients with PsA, T-scores below −2.5 both at the lumbar spine and the femoral neck were detected in three patients. Moreover, T-scores at the lumbar spine were lower than T-scores at the femoral neck in four of seven patients. Notably, osteoporosis was detected in men with PsA as young as 33 and 37 yrs.

Laboratory parameters and biochemical markers of bone metabolism

Serum levels of thyrotropin, intact PTH and calcium were comparable in women and men with PsA and were within normal limits (Table 1). As expected, creatinine serum levels were significantly higher in men compared with women (P < 0.001) due to their larger muscle mass. Markers of systemic inflammation, such as CRP levels and ESR were comparable in women and men with PsA. No gender differences were present for serum concentrations of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3, osteocalcin, and cross-laps which were within normal limits.


Table 1. Demographic data and clinical findings of patients with PsA

<table>
<thead>
<tr>
<th>Measurement (units; normal range)</th>
<th>All patients (n = 116)</th>
<th>Male (n = 59)</th>
<th>Female (n = 57)</th>
<th>(M vs F)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>Mean 52, SD 13</td>
<td>Mean 49, SD 13</td>
<td>Mean 56, SD 11</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>TSH (mU/ml; 0.4–4.0)</td>
<td>1.35, 0.93</td>
<td>1.49, 0.97</td>
<td>1.20, 0.87</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>ESR (mm/h; &lt;10)</td>
<td>16, 11</td>
<td>14, 11</td>
<td>18, 11</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>CRP (ng/dl; &lt;0.5)</td>
<td>0.78, 1.08</td>
<td>0.90, 1.14</td>
<td>0.65, 0.99</td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>Creatinine (mg/dl; &lt;1.0)</td>
<td>0.8, 0.2</td>
<td>0.9, 0.16</td>
<td>0.7, 0.2</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium (mmol/l; 2.1–2.6)</td>
<td>2.4, 0.2</td>
<td>2.4, 0.1</td>
<td>2.4, 0.2</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Lumbar T-score</td>
<td>–0.02, 1.50</td>
<td>–0.27, 1.28</td>
<td>0.25, 1.67</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Lumbar Z-score</td>
<td>0.18, 1.52</td>
<td>–0.39, 1.26</td>
<td>0.77, 1.55</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Femoral T-score</td>
<td>–0.39, 1.17</td>
<td>–0.63, 1.10</td>
<td>–0.14, 1.20</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Femoral Z-score</td>
<td>0.08, 1.07</td>
<td>–0.26, 0.98</td>
<td>0.43, 1.06</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1,25-D3 (pg/ml; 20–65)</td>
<td>41.5, 38.1</td>
<td>43.0, 47.0</td>
<td>40.0, 26.4</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>25-D3 (ng/ml; 6–42)</td>
<td>49.1, 47.0</td>
<td>52.5, 50.2</td>
<td>45.6, 43.6</td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>PTH (pg/ml; 10–65)</td>
<td>35.5, 13.0</td>
<td>36.1, 14.3</td>
<td>34.9, 11.6</td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml; 1.8–6.6)</td>
<td>23.4, 14.5</td>
<td>23.7, 9.7</td>
<td>23.1, 18.3</td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>Cross-laps (ng/ml; 0.1–10)</td>
<td>1.05, 4.63</td>
<td>1.36, 6.22</td>
<td>0.72, 1.96</td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>OPG (pmol/l)</td>
<td>5.88, 2.74</td>
<td>5.09, 2.25</td>
<td>6.70, 2.98</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>TRAIL (pg/ml)</td>
<td>66.1, 45.3</td>
<td>62.3, 25.4</td>
<td>70.1, 59.5</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>OPG-to-TRAIL ratio</td>
<td>0.137, 0.191</td>
<td>0.104, 0.087</td>
<td>0.171, 0.255</td>
<td></td>
<td>0.06</td>
</tr>
</tbody>
</table>

M, male; F, female; TSH, thyroid-stimulating hormone; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; 1,25-D3, 1,25-dihydroxyvitamin D₃; 25-D₃, 25-hydroxyvitamin D₃; PTH, parathyroid hormone; OPG, osteoprotegerin; TRAIL, TNF-related apoptosis-inducing ligand.

FIG. 1. BMD in patients with PsA. Measurement of BMD of men and women with psoriatic arthritis revealed osteopenia in one-third of patients. Osteoporosis was more prevalent in men. Definitions of osteopenia and osteoporosis are based on T-scores as defined by the World Health Organization.

Serum levels of TRAIL and OPG

In patients with PsA, women showed significantly higher OPG serum levels when compared with men (6.70 ± 2.98 vs 5.09 ± 2.25 pmol/l; P < 0.001), whereas TRAIL serum levels were not statistically different between genders (70.1 ± 59.5 pg/ml for women vs 62.3 ± 25.4 pg/ml for men; P = 0.36). However, TRAIL serum levels in the combined cohort of female and male patients were significantly higher compared with a control group consisting of 90 men without PsA (50.0 ± 20.1 pg/ml, P < 0.01). Notably, OPG serum levels in men with PsA (n = 59, 5.09 ± 2.25 pmol/l) were comparable with those found in men without PsA (n = 90, 5.4 ± 2.0 pmol/l, P = 0.38). The OPG-to-TRAIL ratio tended to be higher in women with PsA (0.171 ± 0.255) as compared with men (0.104 ± 0.09, P = 0.06), owing to increased OPG serum levels in women.

To analyse the associations between the two variables, linear regression models were performed (Table 2). Serum levels of TRAIL were not significantly correlated with BMD based on T-scores at the lumbar spine (R = 0.142, P = 0.13) or the proximal femur (R = 0.089, P = 0.34). In addition, serum levels of OPG were not associated with BMD at the lumbar spine (R = 0.046, P = 0.62) and the proximal femur (R = 0.033, P = 0.72). Neither TRAIL nor OPG serum levels were significantly associated with serum levels of cross-laps or osteocalcin (Table 2). There were no significant differences between TRAIL or OPG serum levels in PsA patients with or without osteopenia or osteoporosis.

However, we found a statistically significant association of ESR with OPG serum levels (R = 0.215, P < 0.05), while no associations were found for CRP and OPG serum levels (R = 0.113, P = 0.23). There was a trend that TRAIL serum levels were positively associated with ESR (R = 0.170, P = 0.07), while TRAIL serum levels were significantly related to CRP serum levels (R = 0.201, P < 0.05). No associations were found between CRP and peripheral (R = 0.070, P = 0.46) or axial T-score (R = 0.035, P = 0.71), and between ESR and peripheral (R = 0.042, P = 0.66) or axial T-score values (R = 0.036, P = 0.70). Finally, no significant differences between TRAIL or ESR with osteocalcin levels or cross-laps were found. ESR and CRP levels were not statistically different between women and men with PsA, and were comparable between PsA patients with or without osteopenia and osteoporosis.

Discussion

PsA is a chronic inflammatory process characterized by joint destruction and both local and systemic bone loss [1–5]. Inflammatory cytokines that are produced by immune cells, which stimulate the formation and activation of osteoclasts have been implicated as the mechanistic link between the immune system and bone metabolism [6]. In this study, we evaluated serum concentrations of two cytokines, the TNF superfamily ligand TRAIL and its antagonist OPG, as well as their associations with BMD and biochemical markers of bone metabolism in a cohort of ambulatory patients with PsA.

Clinical assessment revealed a high prevalence of bone loss in patients with PsA. Based on T-scores, one-third of women and men with PsA displayed osteopenia. In addition 10% of men with PsA had a T-score suggestive of osteoporosis, albeit they were middle-aged which is generally a low-risk population. Thus, a high clinical index of suspicion is warranted to detect osteoporosis in a (male) patient with a history of PsA.

TRAIL serum levels, which were found to be similar in women and men, were elevated in patients with PsA as compared with a control male group. Elevated TRAIL serum levels have recently been detected in patients with SLE [13, 15]. In one study [13],
the expression of membrane-associated TRAIL was higher in CD4+CD8+ and activated CD69+CDS+ T-cells in patients with active SLE compared with controls. Similarly, soluble TRAIL serum levels were higher in patients with active SLE and correlated with interferon-α levels, an inducer of TRAIL expression [13]. In another study, 40 patients with SLE were evaluated, of whom 20 had an active disease [15]. Mean serum TRAIL concentrations were elevated in SLE patients, and were higher than in healthy controls or other patients with immune-mediated diseases (rheumatoid arthritis, Wegener’s granulomatosis). Notably, there was no correlation of TRAIL serum levels with leucopaenia, lymphopaenia or SLE disease-activity index [15]. Interestingly, TRAIL serum levels were positively correlated with CRP levels and OPG serum levels with ESR, indicating that the TRAIL/OPG system may be involved in, or may mediate certain aspects of systemic inflammation. In our study, we found that OPG serum levels were comparable between patients with PsA and healthy controls. However, a subgroup analysis revealed that women with PsA had higher OPG serum levels than men with PsA, which is consistent with previous studies (as recently reviewed in [19]), potentially due to the stimulatory effects of estrogens on OPG expression. In a murine arthritis model, TRAIL inhibited inflammation and suppressed synovial proliferation by interfering with cell-cycle progression of immune cells [25]. In addition to cell-cycle arrest [25], induction of apoptosis in synovial cells [26] has also been suggested as an anti-arthritic effect of TRAIL. Thus, elevated TRAIL levels could also be regarded as a compensatory mechanism to preserve joint integrity. Clearly, other cytokines than TRAIL and OPG are also involved in linking inflammation and bone loss in PsA, including interleukin (IL)-1, IL-6, TNF-α and RANKL, the latter of which is also antagonized by the decoy receptor OPG. Notably, specific blockade of these cytokines using infliximab to neutralize TNF-α and an OPG-Fc fusion protein to neutralize RANKL prevented osteoclast formation and bone loss in PsA [7].

Possible limitations of our study include the cross-sectional study design, a potential referral bias and lack of a female control group. Moreover, inflammatory activity as judged from medical treatment and the low mean CRP levels and ESR was generally low in our PsA cohort, which may explain the low R-values of the linear regression analysis. However, there are no specific diagnostic laboratory tests to determine disease severity in PsA. In addition, we measured circulating serum levels of OPG and TRAIL, but not their expression on immune cells or within joint effusions of affected joints. Despite these limitations, we think that clinically important conclusions can be derived from this large, well-characterized cohort of this relatively rare disease.

In summary, osteopaenia is present in one-third of women and men with PsA, while osteoporosis mainly affects men, even at a young age. While TRAIL serum levels are increased in PsA, TRAIL and OPG serum levels are positively correlated with markers of systemic inflammation, but not with BMD or biochemical markers of bone metabolism.

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### Table 2. Associations of OPG and TRAIL serum levels with parameters of bone metabolism and systemic inflammation

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Dependent variable</th>
<th>Equation</th>
<th>R-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPG</td>
<td>Lumbar T-score</td>
<td>$y = -0.180 + 0.025x$</td>
<td>0.046</td>
<td>0.63</td>
</tr>
<tr>
<td>OPG</td>
<td>Femoral T-score</td>
<td>$y = -0.279 - 0.005x$</td>
<td>0.142</td>
<td>0.13</td>
</tr>
<tr>
<td>TRAIL</td>
<td>Lumbar T-score</td>
<td>$y = -0.322 - 0.014x$</td>
<td>0.033</td>
<td>0.72</td>
</tr>
<tr>
<td>TRAIL</td>
<td>Femoral T-score</td>
<td>$y = -0.254 - 0.002x$</td>
<td>0.089</td>
<td>0.34</td>
</tr>
<tr>
<td>OPG</td>
<td>Cross-laps</td>
<td>$y = 0.741 + 0.054x$</td>
<td>0.032</td>
<td>0.74</td>
</tr>
<tr>
<td>TRAIL</td>
<td>Cross-laps</td>
<td>$y = 1.355 + 0.006x$</td>
<td>0.056</td>
<td>0.55</td>
</tr>
<tr>
<td>OPG</td>
<td>Osteocalcin</td>
<td>$y = 25.0 - 0.253x$</td>
<td>0.048</td>
<td>0.61</td>
</tr>
<tr>
<td>TRAIL</td>
<td>Osteocalcin</td>
<td>$y = 23.7 - 0.002x$</td>
<td>0.006</td>
<td>0.95</td>
</tr>
<tr>
<td>OPG</td>
<td>CRP</td>
<td>$y = 0.526 + 0.045x$</td>
<td>0.113</td>
<td>0.23</td>
</tr>
<tr>
<td>TRAIL</td>
<td>CRP</td>
<td>$y = 1.104 - 0.005x$</td>
<td>0.201</td>
<td>0.03</td>
</tr>
<tr>
<td>OPG</td>
<td>ESR</td>
<td>$y = 10.8 + 0.886x$</td>
<td>0.235</td>
<td>0.02</td>
</tr>
<tr>
<td>TRAIL</td>
<td>ESR</td>
<td>$y = 18.8 - 0.043x$</td>
<td>0.170</td>
<td>0.07</td>
</tr>
</tbody>
</table>

OPG, osteoprotegerin; TRAIL, TNF-related apoptosis-inducing ligand; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

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**Rheumatology**

- In psoriatic arthritis, osteopenia is present in one-third of women and men, whereas osteoporosis mainly affects men, even in their 30s.
- Systemic TRAIL levels are increased in patients with psoriatic arthritis, but are not associated with bone mineral density or markers of bone metabolism.
- Systemic TRAIL and OPG levels are associated with markers of systemic inflammation.

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