Clinical study on osteoporosis in ankylosing spondylitis

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssalen (plan 3), Avdelningen för reumatologi och inflammationsforskning, Guldhedsgatan 10 A, Göteborg

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Avhandlingen baseras på följande arbeten:

I. Klingberg E, Lorentzon M, Mellström D, Geijer M, Göthlin J, Hilme E, Hedberg M, Carlsten H, Forsblad-d'Elia H: **Osteoporosis in ankylosing spondylitis – prevalence, risk factors and methods of assessment.** Arthritis Research & Therapy 2012, 14(3):R108

II. Klingberg E, Geijer M, Göthlin J, Mellström D, Lorentzon M, Hilme E, Hedberg M, Carlsten H, Forsblad-d'Elia H: **Vertebral fractures in ankylosing spondylitis are associated with lower bone mineral density in both central and peripheral skeleton.** The Journal of Rheumatology 2012, **39**(10):1987-1995.

III. Klingberg E, Nurkkala M, Carlsten H, Forsblad-d'Elia H: **Biomarkers of bone metabolism in ankylosing spondylitis in relation to osteoproliferation and osteoporosis.** Submitted.

IV. Klingberg E, Lorentzon M, Göthlin J, Mellström D, Geijer M, Ohlsson C, Atkinson EJ, Khosla S, Carlsten H, Forsblad-d'Elia H: **Bone microarchitecture in ankylosing spondylitis and the association with bone mineral density, fractures and syndesmophyte formation.** In manuscript.

V. Klingberg E, Carlsten H, Hilme E, Hedberg M, Forsblad-d'Elia H: **Calprotectin in ankylosing spondylitis – frequently elevated in feces, but normal in serum.** Scandinavian Journal of Gastroenterology 2012, Apr 47(4): 435-44

ABSTRACT
Ankylosing spondylitis (AS) is a disease characterized by chronic inflammation and osteoproliferation in the spine, leading to bony fusion (ankylosis) of the sacroiliacal joints, the growth of bony spurs (syndesmophytes) between the vertebras and impairment of back-mobility. Paradoxically AS patients also have an increased risk of osteoporosis and vertebral fractures.

In this cross-sectional study on 210 included AS patients (New York criteria) from West Sweden we found that osteoporosis and vertebral fractures were common but often not diagnosed or treated. Osteoporosis (WHO definition) was found in 21 % and osteopenia in 44 % of patients 50 years or older and bone mineral density (BMD) below expected range for age was found in 5% of patients younger than 50 years. Totally 42 vertebral fractures were diagnosed in 24 patients (12%). Osteoporosis was associated with old age, long disease duration, advanced chronic AS related changes in the spine, impairment of back- mobility, history of coxitis, glucocorticoid use, elevated inflammatory parameters, low BMI and menopause. Vertebral fractures were associated with old age, long disease duration, advanced chronic AS related changes in the spine, impairment of back-mobility, poor self-estimated general health, smoking, menopause and low BMD.

The osteoproliferation in AS can cause artifactual increase of lumbar BMD when measured in anteroposterior (AP) projection with dual-energy x-ray absorptiometry (DXA). Lumbar BMD can also be measured in the vertebral bodies using lateral projection. Comparing lateral with AP DXA we found that lateral lumbar DXA was more sensitive in detecting low BMD, less affected by the osteoproliferation in AS and more closely associated with vertebral fractures. Combining AP and lateral lumbar DXA also allows for the estimation of volumetric BMD (vBMD).

There is a lack of biomarkers for osteoproliferation and osteoporosis in AS. We analysed serum levels of the following biomarkers for bone metabolism in relation to disease activity, back mobility, osteoproliferation and BMD: Wingless proteins (Wnt-3a, Wnt-5a), Dickkopf-1 (Dkk-1), sclerostin, soluble receptor activator for nuclear factor-κB ligand (sRANKL) and osteoprotegerin (OPG). We found that the AS patients in comparison with healthy controls had significantly higher serum levels of Wnt-3a, but lower serum levels of sclerostin and sRANKL. Elevated serum levels of Wnt-3a were associated with osteoproliferation and impairment of back-mobility, independent of age, suggesting that Wnt-3a could be a marker for the osteoproliferative process. High CRP was associated with lower levels of the Wnt inhibitors Dkk-1 and sclerostin. BMD of femoral neck was negatively correlated with Wnt3a and OPG and positively correlated with sRANKL in the univariate analyses, but positively associated with sclerostin after adjusting for age in multiple regression. Osteoproliferation and impairment of back mobility and function were in addition associated with smoking.

To study peripheral bone microarchitecture in relation to osteoproliferation, fractures and vBMD of the spine 69 male AS patients were randomized to undergo assessment with High Resolution peripheral Quantitative Computed Tomography (HRpQCT) of the ultra-distal radius and tibia and QCT of the lumbar spine. We found strong correlations between trabecular vBMD in lumbar spine and radius and tibia, indicating coupling of trabecular bone loss in axial and peripheral skeleton. Low lumbar vBMD, vertebral fractures and osteoproliferation were in addition associated with deterioration of the bone microarchitecture of the peripheral skeleton. In lumbar spine decreasing trabecular vBMD was associated with increasing cortical vBMD, suggesting that cortical bone is appositioned as part of the osteoproliferative process meanwhile trabecular bone is lost in the vertebral bodies.

AS is closely related to inflammatory bowel disease (IBD) and subclinical intestinal inflammation has been detected in many AS patients. We measured fecal calprotectin, a marker for neutrophil inflammation, to indirectly study the prevalence of gut inflammation in AS. We found elevated levels of fecal calprotectin in 68% of the AS patients, without association with gastrointestinal symptoms. Fecal calprotectin was higher in users of non-steroidal anti-inflammatory drugs (NSAIDs) in a dose dependent manner, but lower in patients treated with methotrexate or TNFα-blockers. No association was found between fecal calprotectin and BMD.

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