Should we look for osteoporosis in patients with rheumatoid arthritis?

Recently, rheumatologists have become more interested in osteoporosis. Obviously, this increased interest is a consequence of progress in diagnostic facilities and in therapeutic options of osteoporosis.

Dual energy x ray absorptiometry (DXA) is now the most commonly used method for measuring bone mineral density (BMD). This technology, (DXA), is crucial for the diagnosis, as osteoporosis is currently defined as a T score of ≤ −2.5 SD, according to the WHO criteria. DXA has become a less expensive diagnostic procedure than five years ago and DXA machines are now widely accessible. Moreover, successful prevention of further bone loss in patients with primary osteoporosis can be offered now with the introduction of new and more potent anti-osteoportic drugs. In postmenopausal women, a decrease in the number of vertebral and hip fractures has been found with the use of alendronate. Studies on the effect on bone of other promising drugs, such as new bisphosphonates and tissue specific oestrogens, are underway.

During the past decade, several authors have formulated guidelines on the prevention of bone loss in patients treated with corticosteroids. In addition, the ACR has recently developed recommendations for the prevention and treatment of osteoporosis in corticosteroid treated patients. In contrast, no consensus or guidelines exist for the prevention and treatment of osteoporosis in patients with rheumatoid arthritis (RA), although osteoporosis frequently occurs in patients with RA. Osteoporosis in RA patients is often related to the use of corticosteroids, but rheumatologists are increasingly aware that bone loss in RA patients may also occur in RA patients without (previous) use of corticosteroids.

The negative effects of RA on bone are illustrated by three types of study, focusing on: (a) markers of bone metabolism; (b) bone mineral density; (c) fracture incidence.

Markers of bone metabolism
There is no unanimity about the levels of markers of bone formation in patients with RA: in some studies alkaline phosphatase and osteocalcin are within the normal range, while others observed increased levels of osteocalcin in patients with active RA, reflecting high bone turnover. In general, markers of bone resorption, for example, urinary excretion of hydroxyproline and pyridinolines, were increased in patients with active RA. Part of the increase in hydroxyproline and pyridinoline excretion may be derived from cartilage and synovium, whereas the increase in deoxypyridinoline is predominantly derived from bone. It is suggested that the increased excretion of these markers in patients with RA is related to the stimulating effect on bone resorption of pro-inflammatory cytokines like interleukin 1 (IL1) and tumour necrosis factor α (TNFα).

Bone mineral density
Changes in the BMD of the appendicular skeleton (for example, the distal radius) reflect the local influence of the arthritic process on bone. RA is not only associated with local, juxta-articular bone loss, but also with generalised bone loss. In cross sectional studies in RA patients, a decrease in BMD of the lumbar spine and hips was found in comparison with healthy controls. In a longitudinal study of early RA patients bone loss in the lumbar spine was greater after one year than in healthy controls (−2.4% versus −0.6%), while the bone loss in the hips was even more impressive (−4.3% versus −0.4%). Bone loss in patients with RA is larger in patients who have a high disease activity and a decreased functional capacity. Data from the placebo arm of the study of Eggelmeijer et al illustrate the relation of bone loss in RA patients with disease activity and functional capacity (table 1).

Fracture incidence
Data on fracture incidence in patients with RA are scarce. The available data suggest an increased relative risk for hip fracture: 1.51 (95% confidence intervals (CI) 1.01, 2.17) and 2.1 (95%CI 1.0, 4.7). After excluding patients with corticosteroid use, the odds ratio is still increased, but not

| Spine | Femoral neck |
|-------|-------------|
| ESR ≤20 mm 1st h | +1.4% | −1.4% |
| ESR >20 mm 1st h | 0.0% | −6.3%** |
| HAQ <1.25 | +1.6% | −3.0% |
| HAQ ≥1.25 | −2.1%*** | −6.6%* |

*p<0.05; **p<0.01; ***p<0.005. (Eggelmeijer et al Arthritis Rheum 1996;39:396–402).
Bone mineral density in RA

Recently, osteoporosis has been redefined as the presence of low BMD (T score < −2.5), based on epidemiological data relating increased fracture incidence to low BMD; the risk of fractures is roughly doubled for each decrease in BMD of 1 SD. The epidemiological data on which the diagnosis is based were largely derived from postmenopausal, white women. Thus, these data may or may not apply to other patient groups. For example, in corticosteroid treated patients, it was observed that BMD was a poor predictor of fracture risk, probably indicating that the use of corticosteroids influences bone quality, and may change fracture thresholds. Nevertheless, measurement of BMD is advocated in patients treated long term with prednisone >7.5 mg/day. In RA patients, data on the relation between fracture rate and BMD are limited, indicating that further research on the relation between low BMD and fracture rate in patients with RA is urgently needed.

In a cross-sectional study by Spector et al, BMD was 4.9% lower in the lumbar spine and 9.9% lower at the hip in RA patients with vertebral fractures compared with those without fractures. Although this difference was not significant, which is probably, at least partly, because of the small number of patients with a vertebral fracture (n=18), it gives some support to the hypothesis that low BMD and fracture rate are related to each other in RA patients.

Measurement of bone density is only useful if it can be followed by effective anti-osteoporotic therapy. Studies showing positive effects on fracture incidence of anti-osteoporotic drugs in patients with RA are not available. Theoretically, anti-resorptive agents would be more beneficial in RA patients with rapid bone turnover—that is, patients with very active disease. Positive effects on BMD of both hormonal replacement therapy and bisphosphonates in patients with moderately active RA have been shown in randomised, double blind, placebo controlled trials. A limitation of these studies is that increase in BMD is their primary end point, and not decrease in fracture rate. As long as data on fracture incidence are not available, it is useful to base clinical decisions or guidelines on studies with BMD as (second best) end point.

Rheumatologists have become aware of the gap between bone density and fracture risk in patients with RA, and the absence of data showing that it is useful to prescribe anti-osteoporotic drugs in high risk RA patients. In daily practice, we find it unethical to withhold anti-osteoporotic drugs from elderly, immobilised RA patients with very active disease. Despite the fact that the relation between (low) BMD and fracture rate has not yet been established in patients with RA, we propose that a low BMD can be an additional argument for prescribing anti-osteoporotic drugs in RA patients.

The question is, to which RA patients a measurement of bone density should be offered. On the one hand, it is possible to measure BMD in every patient with RA, whether the disease is active or in remission. On the other hand, it is also possible to evaluate BMD only in patients with severe RA, for instance those patients with active disease and of low functional capacity. The first, unselective, strategy will undoubtedly lead to overuse of DXA machines and it certainly will not be cost effective. The latter strategy will lead to diagnosing osteoporosis late in the disease, which is not optimal, as it is well known that vertebral osteoporotic deformities are associated with an increased risk of 5 to 12 for further vertebral deformities.

Prophylactic measures are most (cost) effective in high risk patients. In general, the risk for osteoporotic fractures depends on disease related factors, such as disease activity and immobilisation, but also on demographic factors (age and sex) and on other non-disease related risk factors, such as genetic factors (familial osteoporosis), decreased body mass index, early menopause, low calcium intake, and vitamin D deficiency. The use of corticosteroids is also related to osteoporosis, but this is not discussed here, because the use of corticosteroids itself is an indication for bone mass measurement, as described, for example, in the recently developed ACR guidelines.

Criteria to decide the RA patients that should be evaluated for the presence of osteoporosis are currently not available. Guidelines or consensus should be founded on evidence based medicine and supported by the leaders in the field of osteoporosis. It can be expected that, besides age, disease activity, and functional impairment, other factors, such as as genetic factors (familial osteoporosis), decreased body mass index, early menopause, low calcium intake, vitamin D deficiency, and drug treatment (corticosteroids), will probably be incorporated in such a guideline.

In an area in which daily practice seems to call for intervention in RA patients at high risk for osteoporotic fractures, the rheumatologists of Amsterdam have, while awaiting for a widely accepted consensus or guideline, made the following proposal to measure bone density, in RA patients, depending on age, disease activity, and immobilisation.

Arbitrarily, it might be worthwhile to get an impression of BMD in RA patients, if two or more of the following three criteria were present:

(a) high disease activity

As increased bone loss has been shown in RA patients with a mean C reactive protein above 20 mg/l and persistently increased erythrocyte sedimentation rate above 20 mm 1st h, these laboratory values are probably suitable for definition of active RA for this purpose.

(b) (high) age: women > 50 years and men > 60 years;

(c) immobility, defined as a Steinbrocker score > 3 or HAQ score > 1.25.

It is not our (ultimate) goal to defend this proposal: these assumptions are preliminary and arbitrary, as they are limited by the currently available literature. Data on the relation between BMD and fracture rate in RA are inconclusive and intervention studies in patients with RA with fracture rate as end point in RA are lacking.

On the basis of future data on the relation between RA and osteoporosis, it will hopefully be possible to develop a consensus or guideline, which is evidence based, supported by the leaders in the field of osteoporosis, and useful in daily practice for physicians who treat patients with a disease (RA) that is associated with secondary osteoporosis.

So far, as the decrease in BMD is related to high disease activity and immobilisation, prevention of (further) bone loss by the (early) use of aggressive antirheumatic drugs and avoidance of immobilisation (if possible) is essential. This proposal, which advocates the measurement of bone density in a subgroup of RA patients, depending on disease...
activity, age and functional status, may be helpful in daily rheumatological practice, while awaiting a more definite consensus or guideline.

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