Bone mass in rheumatoid arthritis

E.J.J.A. Kroot, R.F.J.M. Laan

Department of Rheumatology, University Medical Center Nijmegen, The Netherlands.

Please address correspondence and reprint request to: Roland F.J.M. Laan, Associate Professor of Rheumatology, University Medical Center Nijmegen, Department of Rheumatology, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.
E-mail: R.Laan@reuma.azn.nl

Clin Exp Rheumatol 2000; 18 (Suppl. 21): S12-S15.

Key words: Bone mass, rheumatoid arthritis, bone mineral density, fractures, disease activity, physical activity, glucocorticoids.

ABSTRACT

Osteoporosis is a common finding in patients with rheumatoid arthritis. Increased rates of bone loss have been observed, especially in the first year of the disease, in patients with active inflammation and low levels of physical activity and in those using glucocorticoids. This bone loss is responsible for increased rates of vertebral and hip fractures.

Introduction

Generalized osteoporosis has been frequently described in patients with rheumatoid arthritis (RA). This may only in part be explained by the high prevalence of both RA and osteoporosis in postmenopausal women. The available data suggest that patients with RA lose bone at increased rates and that they are at increased risk of low bone mass and of osteoporotic fractures when compared to normal subjects. We will first review these data and discuss the possible pathogenetic mechanisms thereafter.

Changes of bone mass in RA

Increased rates of bone loss at both the spine and hip have been documented in longitudinal studies especially in patients with early RA. In patients with a disease duration of more than 6 - 12 months, the differences in rates of bone loss with normal controls have been less pronounced and in general not reaching statistical significance (1-3). Bone loss was particularly increased in patients with active disease or low levels of physical activity, as will be discussed in more detail below.

In the study of Gough *et al*., bone mineral density (BMD) was measured at baseline and after 12 months in 59 female patients with early RA before treatment with corticosteroids or disease-modifying drugs, and in 50 controls matched for menopausal status. Bone loss was greater in RA patients in comparison with controls. Patients with early disease lost significantly more bone at both the spine (mean [SEM] percentage change in BMD from baseline -2.4% [0.5%] versus -0.6% [0.4%], $p < 0.05$) and trochanter (-4.3% [0.8%] versus -0.4% [0.5%], $p < 0.001$). At the lumbar spine high levels of CRP predicted bone loss. In the hip both high scores on the health assessment questionnaire (HAQ), indicating greater physical disability, and high levels of CRP were predictive of bone loss.

In the study by Shenstone *et al*., BMD was measured twice over a 12-month period in 67 non-steroid treated RA patients with disease duration of less than 5 years. No significant changes in BMD, expressed as a percentage of the initial BMD measurement, were found between RA patients and 72 control patients. This study also included 16 patients with a disease duration of less than 6 months. These patients suffered a significantly greater loss of BMD at the femoral neck (mean [SEM] change -3.9% [1.5%]) than the remainder of the cohort (-0.2% [0.7%], $p = 0.02$) and the control subjects (-0.8% [0.6%]). Patients with high disease activity at baseline experienced greater lumbar bone loss. HAQ scores did not correlate with changes in BMD at all (2).

Kroot *et al.* measured BMD twice in 76 RA patients with a mean disease duration of 2.3 years at the first, and 8.9 years at the second BMD measurement. At the first BMD measurement RA patients had a lower BMD in comparison with the reference population (Z-score -0.42). Between both measurements only a small decrease in BMD was observed (-0.28 %/year) and the rate of bone loss was smaller than expected in comparison with age- and sex-matched reference values. The use of prednisone was significantly associated with excessive bone loss in all patients. In a separate analysis, in which only postmenopausal women were included, both increased physical activity and a longer time since menopause were also associated with decreased bone

loss. A high erythrocyte sedimentation rate (ESR) was associated with increased bone loss, but this did not reach statistical significance (3).

Low bone mass in RA

Although the evidence of longitudinal studies points to increased rates of bone loss in patients with early RA only, many cross-sectional studies have documented lower mean bone mass in RA patients in general than in controls. This has been shown in both glucocorticoid treated (4-9) and untreated (6-8, 10) patients.

The prevalence of low bone mass in RA patients is probably more important than a comparison of mean BMD levels between RA patients and controls, and has been studied using different threshold values, involving both T-scores and Z-scores. According to the 1994 World Health Organization definition of osteoporosis, those with a bone mass that is 2.5 standard deviations or more lower than the mean value in young healthy women (T-score ≤ -2.5) are considered to suffer from osteoporosis (11). An alternative approach is the use of Z-scores, which are calculated by comparison with age- and sex-matched controls. By definition, in the normal population 15.9% will have a Z-score ≤ -1 and 2.3% a Z-score ≤ -2.0.

The proportion of RA patients with low bone mass according to these Z-score definitions has been documented in two studies (4, 12). Haugeberg *et al.* studied a representative sample from a population-based register of 394 female RA patients with a mean disease duration of 13 years, using both T-scores and Z-scores. The prevalence of osteoporosis (T-scores ≤ -2.5) was 14.7% (95% CI 11.1 - 18.3) in the femoral neck, 14.7% (95% CI 11.1 - 18.3) in the total hip, and 16.8% (95% CI 13.1 - 20.5) in the spine. The prevalence of reduced bone mass (Z-scores ≤ -1.0) was greater than expected (15.9%) in the femoral neck 27.6% (95% CI 23.1 - 32.1), the total hip 31.6% (95% CI 26.9 - 36.3), and the spine 19.6% (95% CI 15.7 - 23.5) (4). Laan *et al.* examined BMD in 97 patients with recent onset RA and a mean disease duration of 30 months. Low bone mass (Z-score ≤ -1.0) was found in 32.0% (95% CI 22.7 - 41.2) of the patients in the lumbar spine and in 24.2% (95% CI 15.4 - 33.0) in the hip. The results of these two studies are shown in Figure 1. They confirm that low bone mass as defined in comparison with healthy age- and sex-matched controls occurs frequently in patients with RA.

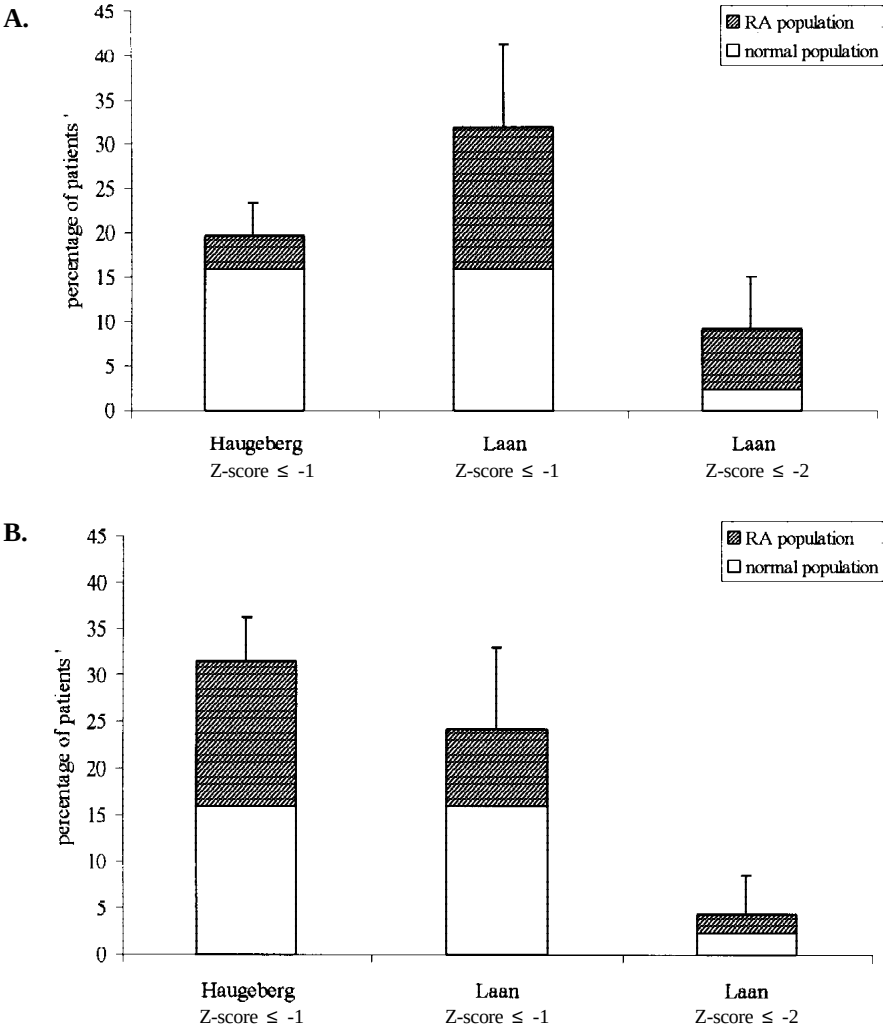

Fig. 1. Expected proportion of RA patients with low bone mineral density compared to expected proportions in the general population.
Percentages of RA patients with decreased Z-scores are shown in the lumbar spine (**A**) and hip (**B**). In the study by Haugeberg, patients with Z-scores of ≤ -1 and in the study by Laan patients with Z-scores of both ≤ -1 and ≤ -2 were studied. 95% CI for the study populations are shown.

Fractures in RA

Low bone mass is generally recognized as a risk factor for fractures, which are the clinically relevant consequence of osteoporosis (13). An increased risk of fracture has been shown in patients with RA both for the spine and the hip (6, 9, 14-16). The relative risk for fractures in RA is about 1.5 - 2.5 higher than in non-RA controls and is most probably even higher after glucocorticoid treatment (15). The relative risk of fractures may be highest for the pelvic region (RR = 2.6), and somewhat lower for the hip (RR = 1.5) (6). Other fractures reported were of the proximal femur, vertebrae, proximal humerus, pelvis and distal forearm (6). Low bone mass is by no means the only risk factor for fractures in RA patients. An increased rate of falls secondary to functional impairment may also result in an increased fracture rate (6, 17).

Mechanisms of low bone mass in RA

Three different disease-dependent mechanisms have been identified that may be responsible for the increased prevalence of low bone mass in RA. These include

high levels of disease activity, reduced physical activity and the use of glucocorticoids. Further potential risk factors for bone loss in RA include treatment with methotrexate or cyclosporin A.

Disease activity

Several cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor are involved in the regulation of osteoclasts (18, 19). The importance of osteoprotegerin ligand and macrophage colony stimulating factor as final effectors in the regulation of osteoclastogenesis has been recognized (20). The effects of pro-inflammatory cytokines on bone cells may explain the observations that patients with active RA are at increased risk of developing osteoporosis (21).

Several studies have now shown that patients with high acute phase responses lose more bone than those with less severe disease activity. Gough *et al.* compared patients with high (> 20 mg/dl) and low (< 20 mg/dl) CRP levels. Patients with active disease lost more bone at the spine and hip than patients with inactive disease (1). Similar results were reported by Laan *et al.* who found a negative association between the mean ESR values in the 6 months preceding the bone mass measurement and bone mass values in the hip. Other indices of disease activity were not associated with low bone mass (12). Finally, Shenstone *et al*. showed larger decreases in spinal bone mass in patients with more active disease at the start of their study (2). The observation that bone loss is most pronounced in the first year after the diagnosis of RA (1, 2, 12) also supports the important role of disease activity in causing bone loss.

Reduced physical activity

A low level of physical activity is a risk factor for low bone mass and fractures (22-24) and there are now reports that exercise training programs have positive effects on bone mass (25). In patients with RA the effect of reduced physical activity has been evaluated mostly using capacity oriented questionnaires such as the HAQ. In the large study by Haugeberg *et al.* a high level of physical disability, as measured with the HAQ, predicted reduced bone mass in the hip but not in the spine (4). The cross-sectional design of this study, however, makes it difficult to separate the effect of reduced physical activity from that of disease activity.

In the longitudinal study by Gough *et al.* greater bone loss was observed in patients with high versus low levels of physical disability, both in the spine and hip (1). Laan *et al*. showed that bone mass was negatively associated with the mean value of the HAQ in the 18 months before the bone mass measurement only at the hip (12). In both of these studies the effect of disability was observed independently of the effect of disease activity. The HAQ may not be the most suitable instrument for evaluating the influence of reduced physical activity on bone mass. In the study by Kroot *et al.* a performance capacity oriented questionnaire was used. Interestingly, they showed that postmenopausal women with higher levels of physical activity had reduced rates of bone loss (3).

Glucocorticoid use

The use of glucocorticoids is associated with increased bone loss and an increased risk of fractures (26, 27). Histologically, reduced bone formation detectable by increased osteoblast and osteocyte apoptosis and areas of necrosis caused by the accumulation of apoptotic osteocytes, also known as aseptic or avascular necrosis, are the most important findings in steroid-induced osteoporosis (21, 28). The effects of glucocorticoids on the number and activity of osteoblasts have been considered the central pathogenetic mechanisms (28). The pathogenesis of glucocorticoid-induced osteoporosis will be discussed in more detail elsewhere in this supplement.

In patients with RA the effects of glucocorticoids on bone mass have long been discussed. In most (4-6, 29) but not all (6, 7, 30, 31) studies the use of glucocorticoids was associated with lower bone mass. Two reasons can be identified for the discrepancies in the literature. First, non-randomized studies are subject to selection bias because RA itself and its concomitant decreased mobility may cause bone loss. Second, the negative effect of glucocorticoids on bone mass may be most pronounced in the initial phase of therapy (27, 29). In a small, but well designed randomized trial, Laan *et*

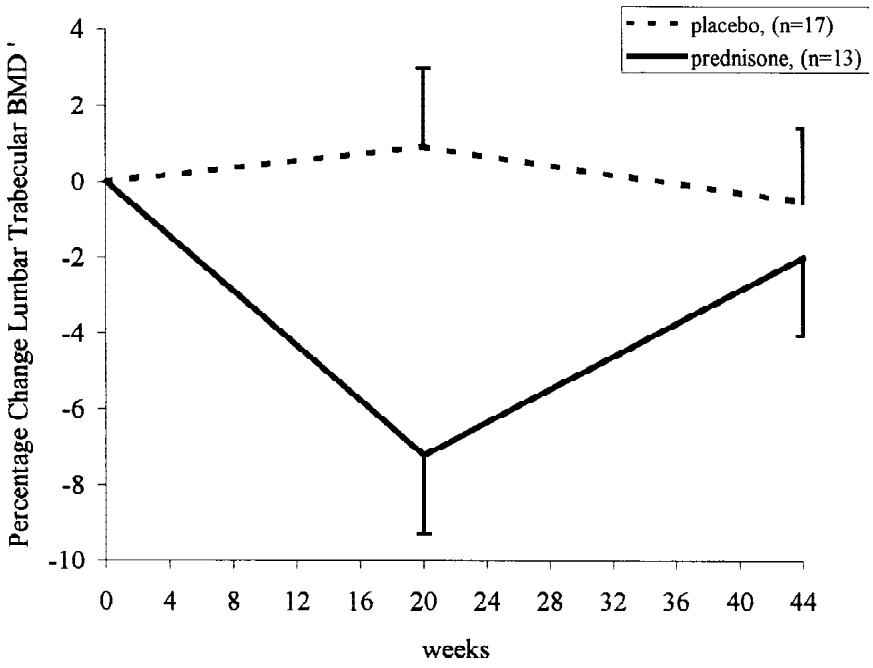

Fig. 2. Mean changes in lumbar and trabecular bone mineral density (BMD) during and after low-dose (10 mg/day) prednisone treatment in a subset of RA patients who did not use prednisone between weeks 20 and 44. The mean change (± SE) in BMD is shown.

Reproduced with permission from: R.F. Laan, P.L. van Riel, L.B. vande Putte, L.J. van Erning, M.A. van't Hof and J.A. Lemmens, "Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. *Ann Intern Med* 1993; 119 (10): 963-8.

al. determined the effects of low-dose oral prednisone (initial dose 10 mg/d; mean dose over 20 weeks 7.5 mg/d) on bone mass. Forty RA patients received intramuscular gold salts and were randomly allocated to receive either prednisone or placebo. Trabecular BMD was measured by quantitative computerised tomography. Rapid trabecular bone loss in the spine was observed in the patients treated with prednisone (mean change -8.2%; 95% CI -12.7% - 3.7%; p = 0.001), despite improvement in disease activity and functional capacity. Interestingly, as shown in Figure 2, an increase in trabecular BMD (mean change 5.3%; 95% CI, 0.7% - 9.9%; p = 0.03) was found between weeks 20 and 44 after the cessation of prednisone (29).

Use of methotrexate and cyclosporin A

Both methotrexate and cyclosporin have been associated with the development of osteoporosis in animal models. The administration of methotrexate has been linked with suppression of osteoblastic activity and the stimulation of osteoclastic activity in rats (32). Cyclosporin induces high turnover osteoporosis in rats (33). Patients treated with cyclosporin after organ transplantation also show rapid bone loss (34). However, these effects cannot be separated easily from the effects of high dose glucocorticoids. Neither methotrexate nor cyclosporin have been shown to cause bone loss in patients with RA.

Conclusion

Patients with RA are at increased risk of developing osteoporosis. The RA patients with the highest risk of bone loss are those with persistently high levels of inflammation, with low levels of physical activity, and those who use glucocorticoids. In general, we recommend bone mass measurements wherever possible to further assess fracture risk in the patient. As will be discussed in other papers in this issue, treatment options to reduce fracture risk are available for patients with low bone mass.

References

1. GOUGH AK, LILLEY J, EYRE S, HOLDER RL, EMERY P: Generalised bone loss in patients with early rheumatoid arthritis. *Lancet* 1994; 344: 23-7.
2. SHENSTONE BD, MAHMOUD A, WOODWARD R *et al*.: Longitudinal bone mineral density changes in early rheumatoid arthritis. *Br J Rheumatol* 1994; 33: 541-5.
3. KROOT EJ, NIEUWENHUIZEN M, VAN RIEL PL, PASKER PC, LAAN RF: Change in bone mineral density (BMD) in patients with recent onset rheumatoid arthritis (RA) during the first decade of the disease. *Ann Rheum Dis* 2000; 59 (Suppl. 1): S182.
4. HAUGEBERG G, UHLIG T, FALCH JA, HALSE JI, KVIEN TK: Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: Results from 394 patients in the Oslo County Rheumatoid Arthritis register. *Arthritis Rheum* 2000; 43: 522-30.
5. LAAN RF, VAN RIEL PL, VAN ERNING LJ, LEMMENS JA, RUIJS SH, VAN DE PUTTE LB: Vertebral osteoporosis in rheumatoid arthritis patients: Effect of low dose prednisone therapy. *Br J Rheumatol* 1992; 31: 91-6.
6. DEODHAR AA, WOOLF AD: Bone mass measurement and bone metabolism in rheumatoid arthritis: A review. *Br J Rheumatol* 1996; 35: 309-22.
7. SAMBROOK PN, EISMAN JA, YEATES MG, POCOCK NA, EBERL S, CHAMPION GD: Osteoporosis in rheumatoid arthritis: Safety of low dose corticosteroids. *Ann Rheum Dis* 1986; 45: 950-3.
8. VERSTRAETEN A, DEQUEKER J: Vertebral and peripheral bone mineral content and fracture incidence in postmenopausal patients with rheumatoid arthritis: Effect of low dose corticosteroids. *Ann Rheum Dis* 1986; 45: 852-7.
9. COOPER C, COUPLAND C, MITCHELL M: Rheumatoid arthritis, corticosteroid therapy and hip fracture. *Ann Rheum Dis* 1995; 54: 49-52.
10. COMPSTON JE, CRAWLEY EO, EVANS C, O'SULLIVAN MM: Spinal trabecular bone mineral content in patients with non-steroid treated rheumatoid arthritis. *Ann Rheum Dis* 1988; 47: 660-4.
11. KANIS JA, MELTON LJ 3rd, CHRISTIANSEN C, JOHNSTON CC, KHALTAEV N: The diagnosis of osteoporosis. *J Bone Miner Res* 1994; 9: 1137-41.
12. LAAN RF, BUIJS WC, VERBEEK AL *et al*.: Bone mineral density in patients with recent onset rheumatoid arthritis: Influence of disease activity and functional capacity. *Ann Rheum Dis* 1993; 52: 21-6.
13. MARSHALL D, JOHNELL O, WEDEL H: Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996; 312: 1254-9.
14. HOOYMAN JR, MELTON LJ 3d, NELSON AM, O'FALLON WM, RIGGS BL: Fractures after rheumatoid arthritis. A population-based study. *Arthritis Rheum* 1984; 27: 1353-61.
15. PEEL NF, MOORE DJ, BARRINGTON NA, BAX DE, EASTELL R: Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis. *Ann Rheum Dis* 1995; 54: 801-6.
16. ALONSO BARTOLOME P, MARTINEZ TABOADA VM, BLANCO R, RODRIGUEZ VALVERDE V: Insufficiency fractures of the tibia and fibula. *Semin Arthritis Rheum* 1999; 28: 413-20.
17. CONSENSUS DEVELOPMENT CONFERENCE: Diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 1993; 94: 646-50.
18. RAISZ LG: Physiology and pathophysiology of bone remodeling. *Clin Chem* 1999: 45:1353-8.
19. MANOLAGAS SC: The role of Il-6 type cytokines and their receptors in bone. *Ann NY Acad Sci* 1998: 840: 194-204.
20. HOFBAUER LC, KHOSLA S, DUNSTAN CR, LACEY DL, BOYLE WJ, RIGGS BL: The roles of osteoprotegrin and osteoprotegrin ligand in the paracrine regulation of bone resorption. *J Bone Miner Res* 2000: 15: 2-12.
21. MANOLAGAS SC: Birth and death of bone cells: Basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. *Endocr Rev* 2000; 21: 115-37.
22. CUMMINGS SR, KELSEY JL, NEVITT MC, O'DOWD KJ: Epidemiology of osteoporosis and osteoporotic fractures. *Epidemiol Rev* 1985; 7: 178-208.
23. SMITH EL, GILLIGAN C: Physical activity effects on bone metabolism. *Calcif Tissue Int* 1991; 49 (Suppl.): S50-4.
24. LAW MR, WALD NJ, MEADE TW: Strategies for prevention of osteoporosis and hip fracture. *BMJ* 1991; 303: 453-9.
25. WOLFF I, VAN CROONENBERG J, KEMPER HC, TWISK JW, KOSTENSE PJ: The effect of exercise training programs on bone mass: A meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporosis International* 1999; 9: 120-8.
26. LUKERT BP, RAISZ LG: Glucocorticoid-induced osteoporosis: Pathogenesis and management. *Ann Intern Med* 1990; 112: 352-64.
27. VAN STAA TP, LEUFKENS HG, ABENHAIM L, BEGAUD B, ZHANG B, COOPER C: Use of oral corticosteroids in the United Kingdom. *QJM* 2000; 93: 105-11.
28. MANOLAGAS SC, WEINSTEIN RS: New developments in the pathogenesis and treatment of steroid-induced osteoporosis. *J Bone Miner Res* 1999; 14: 1061-6.
29. LAAN RF, VAN RIEL PL, VAN DE PUTTE LB, VAN ERNING LJ, VAN'T HOF MA, LEMMENS JA: Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. *Ann Intern Med* 1993; 119: 963-8.
30. SAMBROOK PN, COHEN ML, EISMAN JA, POCOCK NA, CHAMPION GD, YEATES MG: Effects of low dose corticosteroids on bone mass in rheumatoid arthritis: A longitudinal study. *Ann Rheum Dis* 1989; 48: 535-8.
31. SAMBROOK PN, EISMAN JA, CHAMPION GD, YEATES MG, POCOCK NA, EBERL S: Determinants of axial bone loss in rheumatoid arthritis. *Arthritis Rheum* 1987; 30: 721-8.
32. MAY KP, WEST SG, MCDERMOTT MT, HUFFER WE: The effect of low-dose methotrexate on bone metabolism and histomorphometry in rats. *Arthritis Rheum* 1994: 37: 201-6.
33. ROMERO DF, BUCHINSKY FJ, RUCINSKI *et al*.: Rapamycin: A bone sparing immunosuppressant? *J Bone Miner Res* 1995: 10: 760-8.
34. THIEBAUD D, KRIEG MA, GILLARD-BERGUER D, JACQUET AF, GOY JJ, BURCKHARDT P: Cyclosporin induces high bone turnover and may contribute to bone loss after heart transplantation. *Eur J Clin Invest* 1996: 26:549-55.