TRABECULAR BONE DENSITY IN PREMENOPAUSAL RHEUMATOID ARTHRITIS PATIENTS

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Objective. This study was undertaken to compare trabecular bone mineral density (BMD) in premenopausal rheumatoid arthritis (RA) patients and normal age-matched controls.

Method. A protocol was designed to record age, duration of disease, use of corticosteroids (CS) and/or slow-acting anti-rheumatic drug (SAARD) therapy together with duration of such therapy. BMD was measured using the Hologic QDR 1 000 dual energy X-ray absorptiometer. The first four lumbar vertebrae and the left femur were measured in 56 RA patients and 165 controls. Height and weight were measured. Comparisons were made between RA patients and controls, as well as between subgroups of RA patients based on CS therapy.

Results. Patients with RA had significantly lower BMD ($P < 0.05$) at all the sites than the normal controls. The mean duration of RA at the time of study was 60 months (standard deviation 58 months). Thirteen RA patients had used CS in doses less than 10 mg daily for 6 months or longer (mean 19 months), while 25 patients had been on SAARD for an excess of 6 months (mean 23 months). The CS-treated patients had significantly lower BMD than untreated subjects at the femoral neck and inter-trochanteric region ($P < 0.05$), but not at the lumbar spine. However, when compared with normal controls, the CS-treated subgroups had significantly lower BMD at the lumbar spine and all femoral areas. Trochanteric BMD was the best determinant of the RA group, with a sensitivity of 65% and specificity of 77%. The positive predictive value was 16%, while the negative predictive value was 10%. Using Bayes' theorem, the prevalence of osteopenia in RA was found to be 6%.

Conclusion. We conclude that generalised bone loss is a systemic feature of RA and that loss at the spine and femur may be aggravated by CS therapy.

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Generalised bone loss is a recognised feature of rheumatoid arthritis (RA),[1-5] but some recent work has failed to show significant differences in lumbar bone mineral density (BMD) from normal subjects.[6] Results of earlier studies[2-5] are flawed by neglect of an extremely important confounding variable in the form of the menopause. The state of oestrogen deficiency appears to have an overwhelming effect on coupling within the bone metabolic unit, as shown by differences in bone gain between young (< 50 years old) and old RA patients receiving slow-acting anti-rheumatic drugs (SAARD).[7] Oestrogen replacement alone has been shown to stabilise BMD in postmenopausal RA subjects.[8] Guyatt *et al.*[9] have reviewed the flaws in several earlier studies, but many recent studies still include post-menopausal subjects.[10] While it may be possible to 'normalise' for the menopause, the heterogeneous nature of involutional bone loss defies the development of an accurate formula to cater for both rapid and slow losers.[11,12] In addition, osteoporosis is generally defined by the T-score, which is formulated in relation to young normal (premenopausal) subjects at peak bone mass. RA may also be associated with rapid early bone loss followed by a plateau in loss over time, but the confounding effect of the menopause is not known.

The pathogenesis of bone loss in RA patients is likely to be closely linked with the excess osteoclast activators found within the pannus.[13] Tumour necrosis factor (TNF) and interleukin (IL) 1 and 6 are detectable in the serum of RA patients, implicating them in localised and generalised bone loss in RA.[14,15] Mast cell products, including kinins, have also been implicated.[16,17] There is some evidence that SAARD may retard bone loss in RA patients.[7] Recent work has shown a relationship between markers of disease activity and early trabecular bone loss in RA.[18] BMD and skeletal metabolism could potentially be more accurate physiological markers of disease modification in RA than erosion counts or joint space narrowing scores.[19,20]

The effects of low-dose corticosteroid (CS) therapy on bone loss in RA are controversial.[21] Current opinion suggests that a low dose (< 7.5 mg/day) is unlikely to result in accelerated bone loss.[22] There is evidence of recovery of BMD after stopping CS therapy.[10] As several of these studies are based on post-menopausal RA patients they are subject to the same flaws as studies of non-steroid-treated postmenopausal RA patients.[9] There is an increasing tendency to use CS for prolonged periods in RA patients.[23,24] An interesting recent report[25] suggested that in early RA rapid bone loss was greater in those patients receiving prednisone < 5 mg daily than in those receiving > 5 mg daily, confirming the importance of inflammation as a mechanism of bone loss in RA.

Against this background, a study was designed to evaluate trabecular BMD (using dual-energy X-ray absorptiometry (DEXA)) in premenopausal, independently mobile RA patients and to compare these subjects with young normal controls at

peak bone age in order to evaluate the effects of the underlying disease, CS and SAARD therapy in the genesis of probable differences.

MATERIAL AND METHODS

Fifty-six consecutive ambulant female patients under 50 (range 21 - 48) years of age were studied. They were all regularly attending an outpatient arthritis clinic at Groote Schuur Hospital (GSH) over a 36-month period. The protocol was approved by the Ethics and Research Committee at the University of Cape Town (UCT). Age under 50 years, regular menstruation, independent ambulation and disease classification according to the American College of Rheumatology (ACR) revised criteria[26] were the main basis for selection. Males and pregnant females were excluded. Patients were also excluded if they had undergone total hip replacement or had any medical condition likely to interfere with bone metabolism or BMD measurement, such as epilepsy, hyperthyroidism, hyperparathyroidism, amenorrhoea, or scoliosis. Our patients clearly represent a highly specific population of RA subjects, since confounding variables had to be minimised. None of the patients had received calcium supplementation before or during the study. There were 41 coloured, 10 black and 6 white patients in the RA cohort.

A protocol was designed to record age, race, sex, age at onset of disease, duration of disease and criteria for diagnosis of RA. The patients had a complete physical examination by a single observer (AAK). The use of medication, particularly CS and SAARD, was carefully recorded. Functional status was graded according to the ACR classification.[27]

BMD was measured using the Hologic QDR 1 000 densitometer, using DEXA. The lumbar spine was measured from L1 to L4 and the mean lumbar BMD was calculated. The left femur was measured at four different sites (neck, trochanter, inter-trochanter and Ward's triangle). The total femoral BMD was calculated from these values. Radiographs of the hips and vertebrae were not done routinely, unless specifically indicated by symptoms in those areas. The *in vitro* coefficient of variation (cv) of the technique at our institution was 0.5%, using a phantom measured at regular intervals (N = 785) during the 3-year period (1990 - 1992).

One hundred and sixty-five normal female volunteers matched for age (range 22 - 48 years) were studied as controls. All volunteers used for this study were independently mobile, were not on regular medication and had regular menstrual cycles. They were not exposed to calcium supplementation at any point. There were 110 whites, 51 coloureds and 2 blacks among the controls.

The CS-treated group represents subjects who had been receiving continuous therapy for at least 6 months before the study and who were currently on treatment. The daily dose and duration of CS therapy at the time of study were recorded. In general, treated patients received 5 - 10 mg daily. Cumulative CS dose was not calculated. Five SAARDs were used, namely sodium aurothiomalate, D-penicillamine, sulphasalazine, chloroquine and methotrexate. None of our patients was receiving or had received calcium supplements or vitamin D therapy in the course of the study or at any point in the course of the disease.

STATISTICAL METHODS

Statistical tests were performed using the STATISTICA package on an IBM-compatible personal computer. Analysis of variance (ANOVA) was used for univariate comparisons. Multivariate discriminant analysis was used to evaluate the sensitivity and specificity of the measurement of BMD at the various sites in the diagnosis of RA and to predict the CS and SAARD subgroups. The independent variables included BMD at the lumbar spine and femoral sites. Stepwise multiple regression analysis was used to predict lumbar BMD from femoral measurements and total femoral or Ward's BMD from lumbar and femoral measurements in the controls and total RA group as well as the CS and SAARD subgroups, respectively. Age, disease duration, height, weight, daily CS dose and duration of CS therapy (where appropriate) were included as independent variables.

RESULTS

The two groups were comparable with regard to age, height and weight. The mean lumbar BMD was significantly reduced (P = 0.0006) in the RA patients. The BMD was also significantly reduced at all the femoral sites in the RA patients ($P < 0.01$) (Table I). Figs 1 and 2 show the differences between RA and controls graphically for lumbar spine and total hip BMD, respectively, in the form of box and whisker plots. The mean duration of RA was 60 months (standard deviation (SD) 58 months).

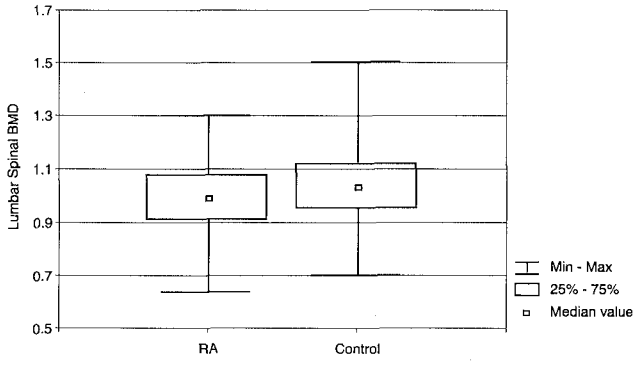

Fig. 1. Box and whisker plots of lumbar bone mineral density showing median and 75% interquartile range in patients with rheumatoid arthritis (RA) and normal controls.

Table I. Comparison of bone mineral density (g/cm²) in patients with rheumatoid arthritis (RA) and normal controls matched for age and sex

Variable	Control (SD)	RA (SD)	*P*-value
Number	165	56	
Age	37 (8)	38 (6)	NS
Lumbar	1.06 (0.12)	0.928 (0.14)	0.0006
Femoral neck	0.859 (0.13)	0.724 (0.13)	0.0004
Trochanter	0.719 (0.102)	0.610 (0.102)	0.0002
Total hip	0.957 (0.13)	0.812 (0.11)	0.0003
Ward's area	0.692 (0.13)	0.593 (0.15)	0.01

SD = standard deviation; NS = not significant.

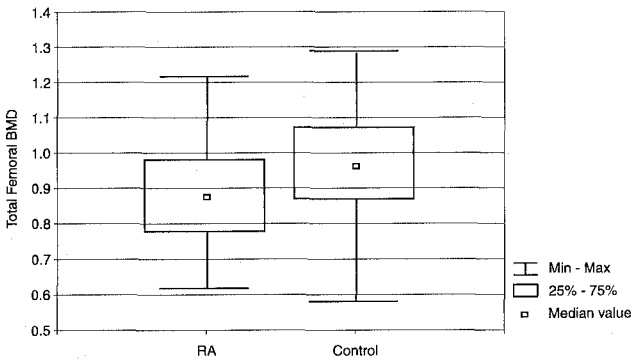

Fig. 2. Box and whisker plots of total femoral bone mineral density showing median and 75% interquartile range in patients with rheumatoid arthritis (RA) and normal controls.

Thirteen patients were receiving CS at the time of study. The CS-treated and non-CS-treated subgroups of patients were comparable for age, height, weight and disease duration. The BMD at the femoral neck ($P = 0.007$) and inter-trochanteric region ($P = 0.05$) were significantly reduced in the CS-treated subgroup. The BMD at the lumbar spine, trochanter, Ward's area and total hip were not significantly lower in the CS-treated subgroup ($P > 0.20$) (Table II). Figs 3 and 4 demonstrate the differences between CS-treated and untreated subgroups graphically for lumbar spine and total hip BMD, respectively, in the form of box and whisker plots.

When the two subgroups of RA patients were compared with the normal controls, the CS-treated subgroup showed significantly lower BMD at the lumbar spine and all femoral sites ($P < 0.01$). However, the subgroup not receiving CS showed significant differences only at the lumbar spine

Table II. Comparison of bone mineral density (g/cm²) at various sites in rheumatoid arthritis (RA) patients based on current therapy with corticosteroids (CS).

Variable	RA patients on CS (SD)	RA patients not on CS (SD)	*P*-value
Number	13	43	
Age	37 (8)	39 (6)	NS
DOD	68 (59)	56 (52)	NS
Lumbar	0.928 (0.14)	1.011 (0.14)	NS
Femoral Neck	0.724 (0.89)	0.834 (0.13)	0.007
Trochanter	0.610 (0.09)	0.658 (0.11)	NS
Inter-trochanter	0.944 (0.14)	1.056 (0.19)	0.05
Total hip	0.812 (0.11)	0.902 (0.15)	NS
Ward's area	0.593 (0.13)	0.659 (0.15)	NS

DOD = duration of disease in months; SD = standard deviation; NS = not significant.

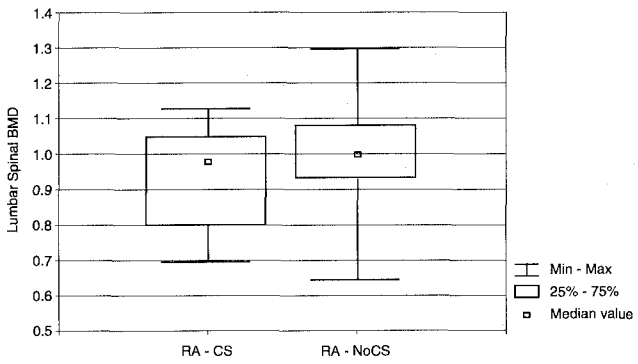

Fig. 3. Box and whisker plots of lumbar bone mineral density showing median and 75% interquartile range in patients with rheumatoid arthritis (RA) receiving corticosteroids (CS) and those not currently receiving CS therapy.

($P = 0.04$), trochanter ($P = 0.0007$), inter-trochanter ($P = 0.03$) and total hip ($P = 0.02$). At Ward's region, the BMD was not significantly lower than normal (Table III). Interestingly, patients in the untreated subgroup were significantly shorter ($P = 0.009$) than the normal controls. The mean duration of CS therapy was 19 (SD 14) months, with a mean daily dose of 5 (SD 5) mg/day. The cumulative CS dose was not calculated. Disease duration did not correlate significantly with BMD at any of the sites (not shown).

Twenty-five patients were receiving SAARD therapy at the time of study. The treated subgroup consisted of patients who

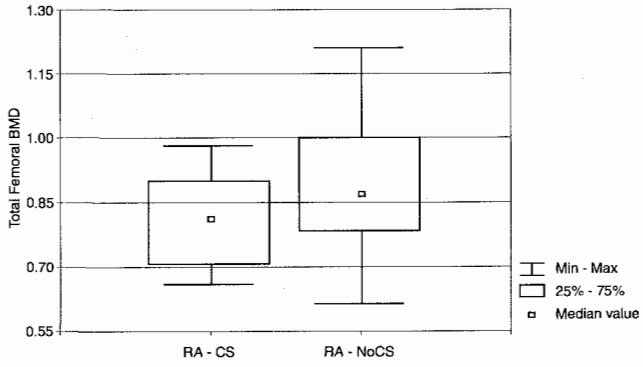

Fig. 4. Box and whisker plots of total femoral bone mineral density showing median and 75% interquartile range in patients with rheumatoid arthritis (RA) receiving corticosteroids (CS) and those not currently receiving CS therapy.

had received the same SAARD for more than 6 months before the study (mean 23 months). The treated and untreated subgroups were comparable for age and body mass index. There were no significant differences between the subgroups with regard to BMD at the lumbar spine or the left femur ($P > 0.20$), despite the longer disease duration in the non-SAARD-treated group. Intention to treat was the method used to define SAARD categories. Four patients were receiving sodium aurothiomalate, 3 D-penicillamine, 4 chloroquine, 5 sulphasalazine and 9 methotrexate. Small sample sizes precluded inferences from intergroup comparisons.

Multiple stepwise discriminant analysis was used to distinguish between the RA patients and the normal controls. The underlying diagnosis was the dependent variable, while age, height, weight, total lumbar and femoral regional BMD measurements were the independent variables. The trochanteric BMD was the best determinant of the RA group, with a sensitivity of 65% and specificity of 77%. The positive predictive value (PPV) was 16%, while the negative predictive value (NPV) was only 10%. Using Bayes' theorem, the prevalence of osteopenia at the trochanter was calculated at 6%. A similar analysis was done to distinguish between CS-treated and untreated subgroups. Femoral neck BMD was the best predictor of the CS-treated subgroup, with a sensitivity of 81% and specificity of 82%. The PPV was 31%, while the NPV was 98%. The prevalence of CS-induced osteopenia was 4%. None of the BMD measurements featured in the discriminant analysis comparing the CS-treated groups with the normal controls. The subgroup of RA patients not being treated with CS was best distinguished from normal controls by a combination of trochanteric and femoral neck BMD. The sensitivity was 67% and specificity 80%. The PPV was 5%, while the NPV was 99%. In addition, none of the independent variables was able to distinguish between the subgroups based on SAARD therapy.

Multiple regression analysis was used to compare the RA patients and normal controls in terms of predicting lumbar BMD from femoral measurements, age, disease duration, height and weight. With regard to lumbar BMD, in the control group, trochanteric and total femoral BMD explained the most variance in lumbar BMD (r^2 47%, $P < 0.05$), while in the RA patients a combination of femoral neck and Ward's BMD explained most of the variance in lumbar BMD (r^2 59%, $P < 0.05$). When trying to predict total femoral BMD we found that in the RA and control group lumbar BMD was not a significant predictor and did not feature in the regression equation.

Table III. Comparison of bone mineral density (g/cm²) in patients with rheumatoid arthritis (RA) based on corticosteroid therapy, and normal controls matched for age and sex

Variable	Control (SD)	RA patients on CS (SD)	*P*-value	RA patients not on CS (SD)	*P*-value
Number	165	13		43	
Age	37 (8)	37 (9)	NS	39 (6)	NS
Lumbar	1.06 (0.12)	0.928 (0.14)	0.0006	1.011 (0.14)	0.04
Femoral neck	0.859 (0.13)	0.724 (0.89)	0.0003	0.834 (0.13)	0.0004
Trochanter	0.719 (0.102)	0.610 (0.09)	0.0002	0.658 (0.11)	0.0007
Inter-trochanter	1.116 (0.16)	0.944 (0.14)	0.03	1.056 (0.19)	0.03
Total hip	0.957 (0.13)	0.812 (0.11)	0.0001	0.902 (0.15)	0.02
Ward's area	0.692 (0.13)	0.593 (0.13)	0.01	0.659 (0.15)	NS

SD = standard deviation; NS = not significant.

The effect of CS on the regression analysis was interesting. In predicting lumbar BMD, Ward's BMD was the best predictor in the CS-treated patients (r^2 56%), as well as the non-treated patients (r^2 63%). When predicting Ward's BMD, femoral neck BMD was the best predictor (r^2 94%) in treated patients, while a combination of lumbar, total femoral and trochanteric BMD was the best predictor (r^2 86%) in the non-treated patients. In the SAARD subgroup, total femoral BMD was the best predictor of lumbar BMD.

Discussion

Virtually every non-invasive method of measuring BMD has been used in RA patients,[1,2,10] yet there are differences of opinion regarding generalised bone loss as a feature of the disease.[28] While researchers have taken cognisance of the importance of excluding RA patients in ACR classes III and IV, they have assumed that it is possible to 'normalise' for the effect of the menopause.[29] Many recent studies still include postmenopausal RA patients,[10,30] in spite of the extensive criticism of the scientific value of such studies by Guyatt *et al.*[9] Normalisation for the menopause is not possible when cross-sectional BMD studies are unable to differentiate between the heterogeneity of rapid and slow losers of bone density during states of oestrogen deficiency.[11,12] We have shown that the beneficial effects of SAARD on metacarpal bone density in RA are negated after 50 years of age.[7] A recent study[28] was unable to demonstrate significant differences in DXA measures of BMD at the lumbar spine and femur between postmenopausal normal controls and age-matched RA patients.[28] The present study is one of the few to evaluate a cohort of young (premenopausal) RA patients in whom DXA measures have been recorded.

Contrary to the results of earlier reports on postmenopausal and perimenopausal RA patients, our data show significant osteopenia at the lumbar spine as well as at different sites within the femur.[6,31] Our patients were all independently mobile and many were actively working. It therefore seems unlikely that immobilisation could sufficiently explain all the differences between the two groups at either site.[10] It was impossible to match the groups for physical activity and the literature is not clear about the minimum exercise required to maintain bone density. It is known that the extremes of physical activity/inactivity (immobilisation as a result of paraplegia, marathon running in males or females) interfere with bone metabolism, but it is not known if the sedentary secretarial female seated all day is likely to lose bone mass.[32] Future research should aim at quantifying physical activity in order to address the role of this confounding variable in the genesis of bone loss, particularly in RA patients. Unfortunately, the health assessment questionnaire (HAQ)[33] and Keitel instrument[34] measure both disability and disease activity, making it difficult to interpret the separate roles of disease activity and disability in the genesis of bone loss in RA using such measurements.[35-37] Fitness measurement may serve as a useful surrogate measure of physical activity.[38] The cohort of RA patients in our study was not strictly matched for ethnicity because of the demographics in the Western Cape. Among South Africans, studies have shown that white and coloured women (Western Cape)[39] and white and black women (Gauteng)[40] have comparable BMD at the lumbar and most femoral sites.

The pathogenesis of osteopenia in RA is likely to be related to a combination of reduced bone formation and increased bone resorption. Kinetic bone studies have, unfortunately, been largely confined to postmenopausal subjects, so that the contributory roles of age and oestrogen deficiency are not clear.[38] The pannus is rich in osteoclast activating factors (OAF) such as TNF, IL 1 and 6, mast cell products, kinins, prostaglandin E (PGE) and osteoclast differentiating factor (ODF).[13,41-43] These may spill over into the circulation, resulting in localised as well as generalised bone loss in RA. Recent work has shown rapid early loss of trabecular bone in patients with persistent elevations in C-reactive protein (CRP).[18] BMD measurement has the potential to be an important marker of arrest of the disease with therapy, but confounding variables must be minimised.[7] The pathogenesis of erosions and osteoporosis in RA is likely to be due to the same mechanisms.[44]

An additional problem in the evaluation of bone loss in RA is the differential degree of bone loss at different skeletal sites of measurement.[45] This was confirmed by the regression and discriminant analyses in this study. Differences are also dependent on whether comparisons are made with normal controls or subgroups of treated and untreated patients. It is possible that different mechanisms, namely physical inactivity and inflammation, operate at the different sites.[10,46] Further research is needed to study these possibilities.

The role of low-dose CS in the genesis of bone loss in RA is similarly confounded by study of postmenopausal patients.[8,10] Our findings confirm those of a recent report[10] which showed that CS have a greater bone-losing effect on the hip than the lumbar spine. This pattern has also been shown in non-steroid-treated RA patients.[6] The authors postulate that this may be due to disability. Our results (despite the small sample) show that the effect of CS is seen at the lumbar spine and left femur, contrary to other reports showing a predominant effect on the lumbar spine.[4,37] The low prevalence of osteoporosis is consistent with other reports.[22] The mechanism of CS-induced osteoporosis in RA is not fully understood and some workers have suggested a protective effect of CS on bone in premenopausal RA patients.[46] This suggestion would be in line with the theoretical possibility that CS have a negative effect on TNF, IL, mast cells and PGE. While CS-induced bone loss has been shown in male RA patients,[47] it was absent in premenopausal systemic lupus erythematosus patients

receiving high-dose CS for periods in excess of 6 months,[48,49] as well as different groups of postmenopausal RA patients.[6,21,28] Clearly, prospective longitudinal observational studies are needed to resolve these controversies. Such studies should preferably be confined to premenopausal subjects and need to compare sites rich in trabecular bone with those rich in cortical bone.

The relationship between disease activity and bone loss in RA is interesting.[25] Some workers have shown a bone-sparing effect of SAARD on bone in RA.[50] Our current data do not support this effect on trabecular bone. This may be due to the fact that our cohort includes patients receiving methotrexate, which can potentially cause osteopenia.[51,52] Larger samples need to be studied to address this question more carefully. Another possible explanation for our apparently contradictory findings in SAARD-treated subjects is the cross-sectional nature of our study and the small size of the treated subgroups. Longitudinal studies may show that SAARD influence the rate of bone loss with time. A recent report[25] showed surprising longitudinal differences in bone loss between RA patients taking CS doses < 5 mg or > 5 mg daily in early disease.[25]

The discriminant analysis showed that the trochanter bears the brunt of the uncoupling within the bone metabolic unit in RA patients. The prevalence of osteopenia of 6% is lower than that reported in studies of cortical bone loss in RA,[53] confirming that the hands show greater bone loss than other skeletal regions.[54] The fact that Ward's area and the femoral neck were the best predictors of variance in lumbar BMD in our cohort of RA patients confirms that trabecular bone is an important target of OAFs in RA. Differences in the results of multiple regression analysis in the RA and control groups indicate a site-specific negative effect of RA on trabecular and cortical bone. The results of the regression analysis suggest that the effect of CS on bone in RA may be an exaggeration of the normal processes. It is therefore not surprising that postmenopausal RA patients taking CS have a higher incidence of fractures due to osteopenia.[55]

This study did not address the role of disease activity in the pathogenesis of bone loss in RA. We are also unable to comment on the relative imbalance between reduced bone formation and increased bone resorption in the apparent uncoupling. Improved biochemical measures of bone resorption such as urinary hydroxy pyridinoline cross-links may be more sensitive in RA patients than hydroxy-proline measurement,[56] and this needs to be studied in premenopausal RA females. Osteocalcin and alkaline phosphatase are not useful measures of bone formation in RA because they are influenced by disease activity and CS therapy respectively.[57,58] Newer techniques of measuring skeletal dynamics may have greater value in RA.[19,20] Bone biopsy following tetracycline labelling may prove to be the most useful method of assessing bone kinetics in RA. These would need to be done in patients with early disease who are not menopausal. Current evidence from bone biopsy in RA suggests that the bone is metabolically inactive in this disease.[59]

We conclude that RA causes significant vertebral and femoral bone loss in young patients, with a prevalence of osteopenia of 6%. CS exert their major effect at the femur rather than at the lumbar spine, although both sites are affected. There was no apparent protective effect from SAARD therapy on trabecular bone in this cross-sectional analysis of relatively few patients. The pathogenesis and prevention of bone loss in RA needs further longitudinal studies in young (premenopausal) patients with early disease.

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NUTRITIONAL STATUS OF RENAL TRANSPLANT PATIENTS

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Objective. To assess the effect of renal transplantation on the nutritional status of patients.

Design. Prospective descriptive study.

Setting. Renal Transplant Clinic at Tygerberg Hospital, Western Cape.

Subjects. Fifty-eight renal transplant patients from Tygerberg Hospital were enrolled in the study. The sample was divided into two groups of 29 patients each: group 1, less than 28 months post-transplant; and group 2, more than 28 months post-transplant.

Outcome measures. Nutritional status assessment comprised biochemical evaluation, a dietary history, anthropometric measurements and a clinical examination.

Results. Serum vitamin B_6 levels were below normal in 56% of patients from group 1 and 59% from group 2. Vitamin B_6 intake, however, was insufficient in only 14% of patients from group 1 and 10% from group 2. Serum vitamin C levels were below normal in 7% of patients from group 1 and 24% from group 2, while vitamin C intake was insufficient in 21% and 14% of patients from groups 1 and 2 respectively. Serum magnesium levels were below normal in 55% of patients from group 1, and in 28% from group 2. Serum albumin and cholesterol levels increased significantly during the post-transplant period in the total sample ($P = 0.0001$). There was also a significant increase in body mass index ($P = 0.0001$) during the post-transplant period.

Conclusions. Several nutritional abnormalities were observed, which primarily reflect the side-effects of immunosuppressive therapy. The causes, consequences and treatment of the vitamin B_6 and vitamin C deficiencies in renal transplant recipients need further investigation.

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