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A prospective study of bone loss and turnover after allogeneic bone marrow transplantation: effect of calcium supplementation with or without calcitonin

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Summary:

Transplantation of solid organs including heart, kidney, and liver is associated with rapid bone loss and increased rate of fracture; data on bone marrow transplantation recipients (BMT) are scarce. The purpose of the present study was to examine the magnitude, timing, and mechanism of bone loss following allogeneic BMT, and to study whether bone loss can be prevented by calcium with or without calcitonin. Sixty-nine patients undergoing allogeneic BMT for malignant blood diseases were enrolled into the study. Forty-four (22 women, 22 men) completed 6 months, and 36 patients 1 year follow-up. They were randomized to receive either no additional treatment ($n = 22$), or oral calcium 1 g twice daily for 12 months ($n = 12$) or the same dose of calcium plus intranasal calcitonin 400 IU/day for the first month and then 200 IU/day for 11 months ($n = 10$). Bone mineral density (BMD) at the lumbar spine and three femoral sites (femoral neck, trochanter, Ward's triangle) was measured by dual-energy X-ray absorptiometry (DXA). Bone turnover rate was followed with markers of bone formation and resorption (serum bone-specific alkaline phosphatase (B-ALP), type I procollagen carboxyterminal (PICP) and aminoterminal propeptide (PINP), serum type I collagen carboxyterminal telopeptide (ICTP)). Serum testosterone was assayed in men. Calcium with or without calcitonin had no effect on bone loss or bone markers; consequently the three study groups were combined. During the first 6 post-transplant months BMD decreased by 5.7% in the lumbar spine and by 6.9% to 8.7% in the three femoral sites ($P < 0.0001$ for all); no significant further decline occured between 6 and 12 months. Four out of 25 assessable patients experienced vertebral compression fractures. Markers of bone formation reduced: B-ALP by 20% at 3 weeks ($P = 0.027$), PICP by 40% ($P < 0.0001$) and PINP by 63% at 6 weeks ($P < 0.0001$), with a return to baseline by 6 months. The marker of bone resorption, serum ICTP was above normal throughout the whole observation period, with a peak at 6 weeks (77% above baseline, $P < 0.0001$). In male patients serum testosterone decreased reaching a nadir (57% below baseline) at 6 weeks ($P = 0.0003$). In conclusion, significant bone loss occurs after BMT. It results from imbalance between reduced bone formation and increased bone resorption; hypogonadism may be a contributing factor in men. Bone loss can not be prevented by calcium with or without calcitonin.

Keywords: bone marrow transplant; osteoporosis; bone markers; calcium; calcitonin

Allogeneic bone marrow transplantation (BMT) has become a successful form of therapy for a number of malignant and non-malignant hematological disorders. As the majority of BMT patients become long-term survivors it is important to take into account possible late side-effects of treatment. One important target organ of adverse effects of organ transplantations is the bone. It has been shown that recipients of heart, kidney, lung, and liver transplants have an increased risk of osteoporosis.[1] Several factors may increase risk of osteoporosis also in BMT recipients.[2] Different cytokines including interleukin-1 and interleukin-6 are associated with induction of bone resorption and development of osteoporosis.[3] These cytokines are active in malignant hematologic diseases and in associated diseases such as infections. Immobilization acutely increases bone resorption. As a part of conditioning therapy BMT recipients receive total body irradiation which induces amennorhea and hypoestrogenism in women; in men testosterone production remained unaffected in one study.[2] Cranial irradiation may impair the production of growth hormone from the pituitary.[4] Before BMT, patients with malignant blood diseases have received cytotoxic drugs which may affect the bone state.[5] After BMT the most harmful drugs for the bone are corticosteroids and cyclosporine used for prophylaxis and treatment of graft-versus-host disease (GVHD).[5]

Prevalence of osteoporosis among bone marrow transplant recipients has been studied only in two cross-sectional studies;[2,6] no longitudinal study of bone mass changes after transplantation is available. In the only study concerning treatment of BMT-associated osteoporosis, estrogen

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replacement therapy (HRT) increased bone mass in 13 women who started treatment on average 13 months after BMT.[7]

The present study is the first prospective one to describe changes in bone mass following BMT. During a 1 year follow-up, markers of bone formation and resorption were also assessed to study the mechanism underlying bone loss in bone marrow transplant recipients. We also assessed whether bone loss after BMT could be prevented by calcium with or without calcitonin.

Patients and methods

Patients

Sixty-one adult patients who received an allogeneic BMT were randomized to receive no additional treatment (group I), calcium (group II), or calcium and calcitonin (group III). Informed consent was obtained before randomization. Twenty-five of the patients discontinued the study earlier than 6 months after BMT. The reason for the drop-out was death in nine patients, relapse and new cytotoxic treatment in four patients, cessation of all less necessary medication in a critical and complicated situation in two patients and nausea caused by the medication in 10 patients. Because of the large number of drop-outs, eight participants in an earlier pilot study in which only bone mineral density (BMD) was followed, were included in group I. Patients received bone marrow from an HLA-identical sibling apart from three cases who had a matched, unrelated donor. Patients were conditioned with cyclophosphamide (CY) 60 mg/kg body weight (BW) intravenously on 2 consecutive days, and total body irradiation 12 Gy (lungs 10 Gy) in six fractions of 2 Gy over 5 days; three patients received busulphan 4 mg/kg BW daily for 4 days and then CY as above.

Acute GVHD prophylaxis consisted of cyclosporin A (CsA), a short course of methotrexate, and methylprednisolone (MP). CsA was started the day before BMT at a dose of 3 mg/kg BW intravenously daily, switched 2 to 3 weeks later to an oral dose of 3–4 mg/kg BW daily, continued for 1 year after BMT. Thereafter, CsA was tapered off over a couple of months. Methotrexate was given intravenously 15 mg/m^2 on day +1 after BMT, and 10 mg/m^2 on days +3, +6, and +11 after BMT. MP was started orally 14 days after BMT at a dose of 0.5 mg/ kg BW for a week. The dose was doubled for 2 weeks, and thereafter halved every third week and stopped by day +110 after BMT.

Acute GVHD was defined and graded according to Thomas *et al*[8] and treated with MP starting with a dose of 10 mg/kg BW. The daily dose of MP was halved every third day until it was approximately 1 mg/kg BW, and thereafter tapered off individually. Chronic GVHD was defined according to Shulman *et al*[9] and treated with a low daily dose of MP alone or in combination with CsA or thalidomide.

Due to menopausal symptoms estrogen replacement therapy was started for 20 women during the study, on average 171 (range 40–319) days after BMT.

Study design

For prevention of bone loss the patients were randomized to receive either no additional treatment (group 1, $n = 22$), or oral calcium (Mega-Calcium; Sandoz, Basel, Switzerland; calcium lactate gluconate 5.23 g, calcium carbonate 0.8 g) 1 g twice daily for 12 months (group 2, $n = 12$) or the same dose calcium plus intranasal calcitonin (Miacalcic; Sandoz) 400 IU/day for the first month and then 200 IU/day for 11 months (group 3, $n = 10$). The study was approved by the Ethical Committee of the Third Department of Medicine, University of Helsinki.

BMD measurement

BMD of the lumbar spine (lumbar vertebrae L1–L4) and of the three femoral sites (femoral neck, trochanter, Ward's triangle) was measured by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR-1000 densitometer (Hologic, Waltham, MA, USA) before and 6 and 12 months after BMT. Precision of the method (coefficient of variation, CV) was 0.9% at the lumbar spine and 1.2% at the femoral neck. X-ray of the spine was taken at the beginning and the end of the 1 year follow-up.

Assays

Blood was sampled for the determination of serum ionized calcium, phosphate, magnesium, creatinine, bone-specific alkaline phosphatase (B-ALP), type I procollagen carboxyterminal (PICP) and aminoterminal (PINP) propeptide, type I collagen carboxyterminal telopeptide (ICTP), and testosterone in men before and 3 weeks, 6 weeks, 3 months, 6 months, and 12 months after BMT.

PICP, PINP,[10] and ICTP were determined by RIA kits from Orion Diagnostica, Oulunsalo, Finland. The intra-assay and interassay CVs for these assays ranged from 2 to 9%. ALP isoenzymes were determined using a kit from Boehringer Mannheim, Mannheim, Germany, in which bone-specific isoenzyme is precipitated by lectin, and bone ALP activity is calculated from total and residual ALP activity. The intra-assay and inter-assay CVs for the assay were 4% and 5%, respectively. Serum testosterone was assayed by an automated luminoimmunoassay (Chiron Diagnostics, Medfield, USA) with intra- and interassay CVs ranging from 4 to 7%. For determination of serum ionized calcium, blood samples were centrifuged immediately after being drawn, and the serum analyzed with an ion-selective analyzer (Microlyte, Kone, Finland) within a few hours of blood collection (intra-assay CV 1.6%). The serum magnesium, phosphate, and creatinine were determined by routine methods.

Statistics

Statistical analyses were performed by analysis of variance for repeated measures. SAS/MIXED procedure was used because it allows missing values in the data. Therefore, all patients could be included in analyses. Some secondary analyses were executed without outliers, but they did not have any influence on statistical conclusions. Covariance

structure was chosen on the basis of −2 log likelihood tests. Normality assumption was checked using residuals. The assumption was not met in the case of PINP, PICP, ICTP, B-ALP, and for those variables natural logarithm transformation was used. If overall tests showed a statistically significant result, pairwise comparisons were made by linear contrasts. The significance level used in overall tests as well as in linear contrasts was 0.05. All statistical analyses were performed as two-sided and using SAS System.

Results

Characteristics for the patients followed for 6 months or longer in different study groups are presented in Table 1. The groups were of similar age, but differed with respect to female preponderance in group 2. The duration of amenorrhea before BMT was shortest in women in group 3. The interval between BMT and start of HRT did not differ between the women in the study groups. At baseline, the BMD in the femoral neck was higher in group 3 than in group 1 ($P = 0.012$) and in the trochanter higher in group 3 than in the other two groups ($P < 0.0001$). In all the study groups the major amount of methylprednisolone was given during the first 6 months after BMT, whereas the cumulative dose of cyclosporin A at 12 months was nearly double that at 6 months (Table 1). Forty-four patients completed the 6 months' follow-up; thereafter one, three and four patients died in the three study groups, respectively.

BMD and vertebral fractures

Mean bone loss at the lumbar spine calculated as per cent change from baseline varied in the study groups from 3.9% to 6.8% at 6 months and 1.2% to 4.0% at 12 months ($P < 0.0001$ for time-effect) (Figure 1a). At the femoral neck, bone loss in the three study groups varied from 6.3% to 7.5% at 6 months, and from 6.1% to 8.6% at 12 months ($P < 0.0001$ for time-effect, Figure 1b). At the trochanter and the Ward's triangle the respective changes were −7.0% to −9.0% and −6.5% to −10.5% at 6 months and −6.0% to −10.9% and −8.0% to −12.8% at 12 months ($P <$

Table 1 Characteristics (mean (s.d.) or median with range) of the patients

	Control	*Calcium*	*Ca + Calcitonin*
No.	22	12	10
Age (years)	40 (10)	40 (8)	41 (12)
F/M	10/12	9/3	4/6
Primary disease			
AML	10	5	2
ALL	4	1	1
CML	7	2	6
MDS	1	3	1
Burkitt's lymphoma		1	
Conditioning regimen			
CY + TBI	19	12	9
CY + Bu	3		1
Weight (kg)	66 (13)	72 (16)	79 (13)
Height (cm)	170 (7)	167 (7)	175 (5)
Acute GVHD	9	7	5
grade II–IV	6	3	3
Chronic GVHD	11	5	6
extensive	4	2	0
Duration of amenorrhea (days)			
before BMT	120 (0–274)	66 (0–334)	0 (0–114)
after BMT	146 (73—319)	204 (108–365)	170 (40–202)
Baseline BMD (g/cm^2)			
lumbar spine	0.975 (0.150)	1.022 (0.155)	1.087 (0.164)
femoral neck	0.883 (0.141)	0.929 (0.134	1.014 (0.096)[a]
trochanter	0.736 (0.103)	0.731 (0.071)	0.875 (0.111)[b]
Ward's triangle	0.695 (0.162)	0.752 (0.192)	0.758 (0.097)
Cumulative dose of methylprednisolone (g)			
at 6 months	3.6 (0.5)	5.5 (0.7)	5.1 (0.8)
at 12 months	4.4 (0.6)	5.8 (0.8)	5.9 (0.8)
Cumulative dose of cyclosporin A (g)			
at 6 months	38.2 (4.0)	40.4 (5.3)	46.2 (5.8)
at 12 months	62.1 (4.3)	68.1 (5.7)	77.2 (7.0)

AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myelogenous leukemia; MDS = myelodysplastic syndrome; Cy = cyclophosphamide; TBI = total body irradiation; Bu = busulphan; GVHD = graft-versus-host disease; BMT = bone marrow transplantation; BMD = bone mineral density.
[a]$P = 0.012$ for difference from group 1.
[b]$P = 0.0001$ for differences from the other two groups.

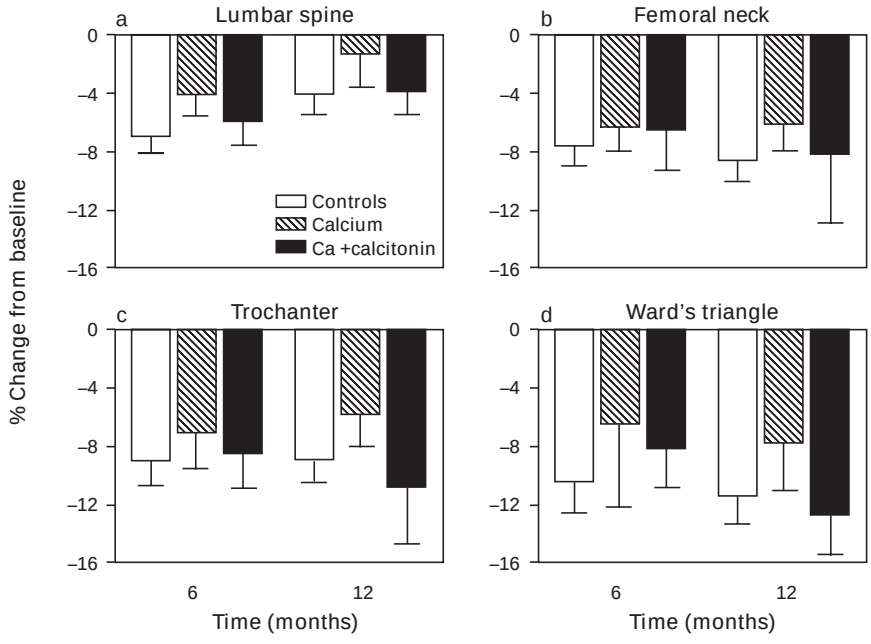

Figure 1 Bone loss after bone marrow transplantation in the three study groups. Changes in BMD (mean and s.e.m.) as per cent from baseline. (**a**) Lumbar spine; (**b**) femoral neck; (**c**) trochanter; (**d**) Ward's triangle. $P < 0.0001$ for time-effect at all measurement sites in all study groups.

0.0001 for time-effect, Figures 1c and d). Although the changes appeared to be smallest in the calcium group, no statistically significant differences were found between the groups at any of the four measurement sites ($P = 0.68$–0.95 for treatment × time-point). Consequently, to study the effect of calcium the two treatment groups were combined and compared with the control group with respect to the changes in BMD at the four measurement sites; no statistically significant differences were found (data not shown). Finally, all the three study groups were combined to study the changes in BMD as a function of time. As shown in Figure 2 all the bone loss at the lumbar spine occurred between 0 and 6 months after BMT which was the case also for the trochanter area. Some further bone loss seemed to take place at the femoral neck ($P = 0.30$) and at the Ward's triangle ($P = 0.24$) between 6–12 months (Figure 2).

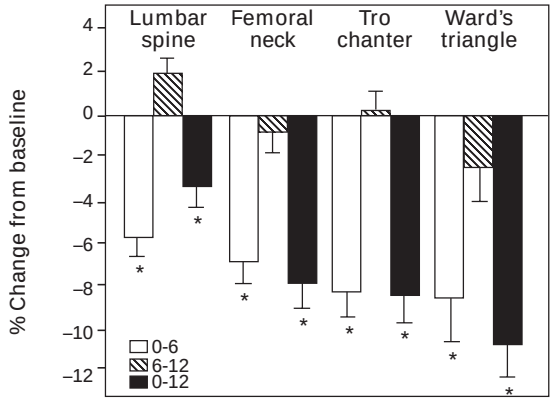

Figure 2 Bone loss in the combined study population. Changes in BMD (mean and s.e.m.) as per cent from baseline between 0 and 6 months, 6 and 12 months, and 0 and 12 months after bone marrow transplantation. * $P < 0.0001$ for changes from baseline.

Table 2 shows the number of the patients who fullfilled the WHO criteria[11] for osteopenia and osteoporosis at different stages of the study. Before BMT 39% of the patients had osteopenia at least in the lumbar spine and 25% had it in the femoral neck. By the end of the study this percentage more than doubled at the femoral neck (58%) and slightly increased at the lumbar spine (47%).

Out of 25 assessable patients two experienced a single vertebral compression fracture, and two had multiple fractures by the end of the follow-up. These four patients were in the control and calcium groups, two in each.

Markers of bone turnover

During the whole study period there were no statistically significant differences between the study groups in any of the bone markers measured ($P = 0.20$–0.98 for treatment × time-point; data not shown). Consequently, all three study groups were combined to study the changes in bone markers as a function of time. All the three markers of bone formation B-ALP, PICP, and PINP decreased 3 week to 3 months after BMT, the maximum reductions of means

Table 2 Number of patients (% of the assessable patients) in the whole study group fulfilling the WHO criteria for osteopenia and osteoporosis at each time point

	Lumbar spine			*Femoral neck*		
Time (months)	0	6	12	0	6	12
Osteopenia	15	17	16	11	17	20
Osteoporosis	2	3	1	0	1	1
Total	17 (39)	20 (50)	17 (47)	11 (25)	18 (45)	21 (58)

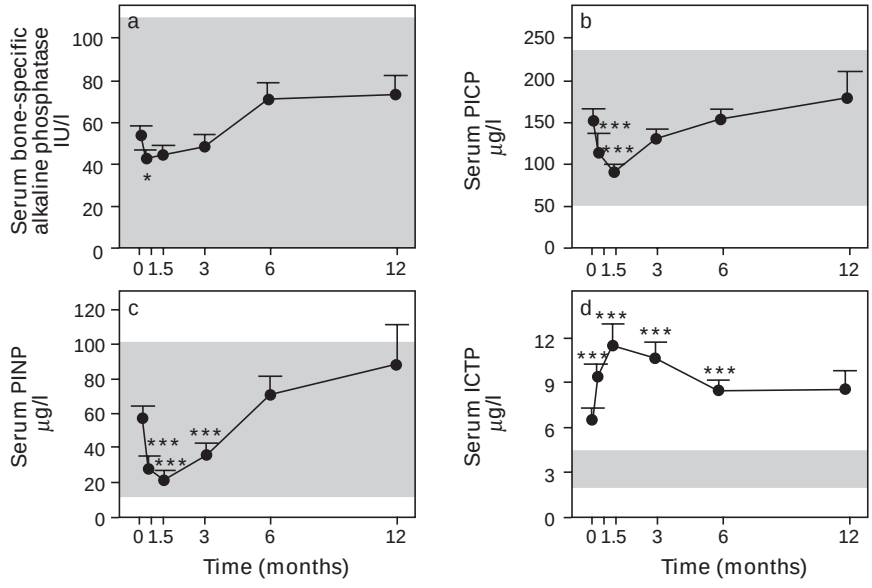

Figure 3 Markers of bone turnover (mean and s.e.m.) in the combined study population. (**a**) Serum bone-specific alkaline phosphatase; (**b**) serum PICP; (**c**) serum PINP; (**d**) serum ICTP. *$P < 0.05$, ***$P < 0.001$ for differences from baseline. Shaded area represents the normal range.

being 20% in B-ALP at 3 weeks ($P = 0.027$), 40% in PICP at 6 weeks ($P < 0.0001$), and 63% in PINP at 6 weeks ($P < 0.0001$). Thereafter, all the markers recovered back to baseline by 6 months, and at 12 months they tended to be even higher than at baseline (Figure 3a–c). The marker of bone resorption, serum ICTP, was above the normal range throughout the whole observation period. After BMT it further increased reaching its maximum (+77% above baseline) at 6 weeks ($P < 0.0001$). Thereafter, it declined but was still above the normal range at the end of the study (Figure 3d).

Other biochemical measurements

In all study group men, the mean serum testosterone level decreased, reaching its nadir (57% below baseline) at 6 weeks ($P = 0.0003$); it recovered back to baseline by 6 months (Figure 4). No significant changes were observed in serum ionized calcium or phosphate (data not shown). In the whole study group, mean serum magnesium level dropped from 0.87 (0.02 s.e.m.) mmol/l at baseline to 0.69 (0.02) mmol/l at 3 weeks after BMT ($P < 0.0001$ for time-effect). Mean serum creatinine level increased from 3 months onwards ($P = 0.015$ for time-effect) (87 (3) μmol/l at 3 months; 100 (4) μmol/l at 12 months).

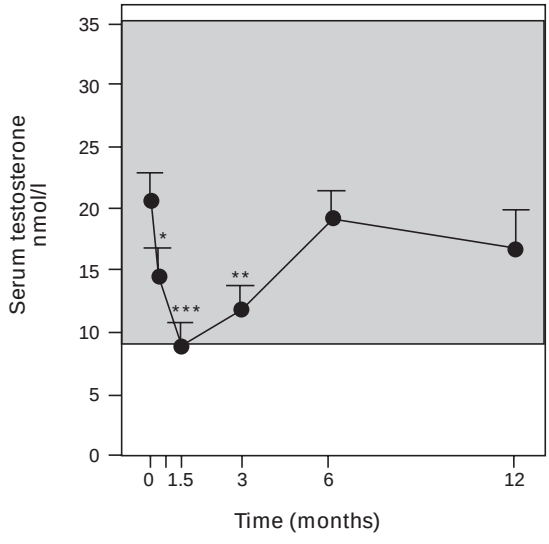

Figure 4 Serum concentration of testosterone (mean and s.e.m.) in male patients of the combined study population. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ for differences from baseline. Shaded area represents the normal range.

Discussion

In this first prospective study of the effects of bone marrow transplantation on bone mass we demonstrated that depending on the measurement site, the cumulative bone loss in transplant recipients varied from 5.7% to 8.7% in 6 months and from 3.3% to 10.8% in 12 months. Bone marker studies implied that bone loss was a consequence of imbalance between reduced bone formation and enhanced bone resorption. Bone loss was not prevented by calcium with or without calcitonin. Finally, our results suggest that in male patients also hypogonadism should be taken into account as a possible osteoporosis-promoting factor.

BMT procedures are associated with considerable morbidity and mortality which make this kind of study difficult to accomplish. In the present study such problems were reflected in a high drop-out rate; 25 patients were withdrawn from the trial before 6 months and eight patients were lost due to death before 12 months. Partly due to this high drop-out frequency the study groups were not well matched with respect to the gender distribution. Some bias was also caused by the protocol violation of starting estro-

gen replacement therapy for 20 out of 22 female participants during the study. In most cases severe menopausal symptoms made this necessary. Nevertheless, start of treatment did not happen early; in one woman within 0–60 days, in four women within 61–120 days, in five women within 121–180 days, and in 10 women after 6 months. The female preponderance and start of estrogen replacement therapy (for two of nine women before 6 months) may explain the fact that in the calcium group bone loss seemed to be smallest at 12 months, even though no statistically significant differences were found. Despite the bias associated with estrogen therapy, we still consider it valid to conclude that bone loss after BMT can not be prevented by calcium with or without calcitonin. Naturally, it is possible that small benefits might have been revealed by a greater number of patients in the study groups, but clinically significant effects appear very unlikely.

Keeping in line with findings made in cardiac transplant recipients,[12] the most bone loss occurred during the first 6 months, after which there was no further decline at the lumbar spine and trochanter; the further small reductions in the femoral neck and the Ward's triangle were not statistically significant. In fact, at the lumbar spine the bone state seemed to recover during the latter half of the study. Due to BMT-induced bone loss the proportion of osteopenic patients grew from 39% to 50% at the lumbar spine, and from 25% to 45% at the femoral neck in 6 months; at the end of the study 58% of the patients had osteopenia at least in the femoral neck. In a very recent cross-sectional study, 51% of the patients fulfilled the BMD criteria of osteopenia at least in the lumbar spine 3 years after BMT.[6] Note that the majority of our patients had a reduced bone mass even at the beginning of the study. The basic hematologic malignancy together with its treatment offer a conceivable explanation for the finding. Importantly, four patients (9% of the whole study group, 16% of the assessable patients) developed vertebral compression fractures during 1 year follow-up.

There is no study available concerning prevalence of vertebral fractures in bone marrow transplant recipients. In cardiac transplant recipients prevalence has varied from 18 to 50%,[13] and after liver transplantation the fracture rate may be even higher.[14] A fracture rate of 9–16% in the present study seems to be lower than in association with other organ transplants. Some factors may argue for milder bone disease in bone marrow transplant recipients. Patients are generally younger, and duration of the basic disease is shorter before bone marrow than other organ transplants, possibly resulting in a better pretransplant bone state than, for example, in cardiac transplant recipients.[15] Finally, unlike transplant recipients of solid organs, recipients of hemopoietic transplants do not need lifelong immunosuppression, and cyclosporin A can be stopped.

The major part of the bone loss occurred in the first 6 months when bone markers showed suppressed bone formation (PINP, PICP, B-ALP) and increased bone resorption (ICTP). As to the markers of bone formation, the clearest changes were observed in the most novel one, serum type I procollagen aminoterminal propeptide (PINP), which holds great promise as a measure of bone turnover.[10] Our results are exactly the same as those of Carlson *et al*[16] obtained during the first 12 weeks after BMT. As markers of bone formation they measured serum osteocalcin and B-ALP, and bone resorption was reflected by ICTP. Furthermore, in cardiac transplant recipients serum osteocalcin decreased and the marker of bone resorption, urinary deoxypyridinoline, increased 1 to 3 months after transplantation.[12] It is noteworthy that a marker of bone resorption, serum ICTP was above the normal range even before the study and then throughout the whole observation period. Serum ICTP has been considered too insensitive to measure small changes of bone turnover in patients with primary osteoporosis but it has worked much better as a reflector of profound changes in bone resorption in diseases, such as malignancies.[17]

Since glucocorticoids suppress bone formation and increase bone resorption,[18] they primarily appear to be responsible for the observed uncoupling of reduced bone formation and increased resorption. Note that the uncoupling and most rapid bone loss coincided with the maximum administration of corticosteroids. As established both in rats[19] and in humans,[20] cyclosporin A causes high turnover bone loss with both increased resorption and enhanced formation. Thus, from the sixth month onwards the bone marker findings fitted to be primarily due to the effect of cyclosporin A; bone resorption was accelerated and the markers of bone formation tended to rise even above the baseline level. It is noteworthy that if further decline in BMD occurred from 6 months onwards, it was restricted to the upper femur, which contains more cortical bone than the lumbar spine. In contrast to corticosteroids which mainly affect trabecular bone, cortical bone does not escape the effects of cyclosporin A.[5] It is noteworthy, that in 29 patients after autologous bone marrow/blood-derived progenitor cell transplantation, osteopenia and osteoporosis were not found at all, possibly due to the fact that corticosteroids were used only for a comparably short period of time, and cyclosporin A was not administered at all.[21]

At the time of the maximum bone loss most of the female patients were not receiving estrogen replacement and male patients showed lowered levels of serum testosterone. Thus, hypogonadism in both sexes may well have contributed to bone loss. Although initiation of estrogen therapy has been recommended for women after organ transplantation, men may also need sex hormone replacement therapy; administration of both corticosteroids[22] and cyclosporin A[23] has been associated with decreases in serum testosterone levels.

In the present study calcitonin appeared to be ineffective in preventing BMT-associated bone loss in doses which have been recommended for treatment of osteoporosis.[24] In smaller doses of 100 IU daily intranasally, calcitonin was less effective than 25 hydroxycholecalciferol in preventing bone loss in cardiac transplant recipients but there was no untreated control group in the study.[25] On an average of 17 months after liver transplantation 40 patients were enrolled to receive either calcitonin 40 IU daily intramuscularly or sodium etidronate 400 mg orally for 15 days every 3 months for 1 year. Treatment increased vertebral BMD 6.4% and 8.2%, but no untreated control group was included in the study.[26] In the only study available of treatment of BMT-associated osteoporosis, HRT for 1 year

increased bone mass by 5% in 13 women, who started the treatment an average of 13 months after BMT.[7]

Our study implies that bone loss is a clinically significant problem after BMT not resolved by calcium or calcitonin alone, but requiring additional measures. Doses of immunosuppressive therapy should be kept as low as possible. Patients should be instructed to resume weight-bearing exercise, the beneficial effect of which has been emphasized in cardiac transplant recipients.[27] Since most bone loss takes place in the first 6 months post-transplant and since at least transdermal HRT is also safe for transplant recipients, estrogen therapy should be initiated shortly after BMT. Our results also emphasize the need for testosterone replacement therapy in male patients, who often show at least a temporary decrease in serum testosterone levels. Additional treatment such as biologically active vitamin D preparations or new effective bisphosphonates require testing in further studies. The former has been of benefit in patients receiving corticosteroid treatment[28] in association with organ transplants[29] and a preliminary report confirms benefits provided by bisphosphonates in organ transplant recipients.[30]

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