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Reduction of Bone Mass in Women after Bone Marrow Transplantation

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Abstract. Osteoporosis is a common disease among patients undergoing transplantation. Its prevalence and complications have been well described in solid organ recipients, especially kidney, liver, and heart. However, studies in bone marrow transplantation (BMT) are scarce. Among the mechanisms invoked in the pathogenesis of BMT osteoporosis are the baseline disease, the use of immunosuppressive drugs and, more remarkably, secondary hypogonadism. We present a study of 27 women who underwent BMT, all of them suffering ovarian failure. We studied different biochemical markers of bone formation/resorption and also evaluated the presence of osteopenia/osteoporosis by dual energy X-ray absorptiometry (DXA) of the lumbar spine. Osteopenia was observed in nine patients (33%) and osteoporosis in another five (18%), according to the World Health Organization criteria. We also detected a subgroup showing elevation of several bone turnover biochemical markers, indicating high osseous remodeling. A remarkable increase in urine hydroxyproline/creatinine was detected in 95% of cases, although an explanation is lacking. We outline a reasonable therapeutic approach for osteoporosis in BMT emphasizing the need to monitor these patients after transplantation.

Key words: Bone mineral density — Bone marrow transplantation — Menopause — Osteopenia — Osteoporosis.

Transplantation procedures have improved notably in recent decades, resulting in a great increase in life expectancy of the recipients. Thereby, we should look to prevention of long-term complications. Metabolic bone diseases are usually detected among these late complications, appearing either as aseptic bone necrosis, mainly related to renal and bone marrow transplants [1, 2], or as diffuse loss of bone mass [3, 4]. Risk factors for osteoporosis in transplanted patients depend either on host status (nutritional, exertional), on the system organ transplanted, as well as on the immunosuppresive treatment [3–5].

Osteoporosis has been well documented as a complication of renal [6, 7], hepatic [8–10], and to a lesser extent, cardiac transplants [11–13]. However, references to osteoporosis after bone marrow transplantation (BMT) are scarce [14]. Bone disease following BMT shows striking differences as compared with other organ transplants: the recipient is usually younger and the time elapsing from diagnosis to BMT currently does not exceed 1 or 2 years. Therefore, these patients seldom suffer from prolonged bedrest or poor nutrition. Finally, many undergo radiotherapy as part of the preparative regimen for the BMT. Due to the systemic nature of the primary processes, they are radiated without a gonad shield, which produces long-term, frequently permanent amenorrhea in women. Moreover, total body radiation causes a decrease in growth hormone (GH) secretion [15, 16]. Both estrogen and GH deficiencies are known to exert a negative effect on bone metabolism. Regarding the use of drugs producing bone loss in BMT, immunosuppressives are used only in minimum effective doses for short periods of time, and glucocorticoids are restricted to certain leukemia and to the graft-versus-host disease (GVHD). Altogether, the principal factors involved in BMT-induced osteoporosis are age, use of radiotherapy and, to a lesser extent, the use of drugs [3].

Since our hospital is a reference center for BMT, we decided to conduct a cooperative and prospective study between the Departments of Haematology and Rheumatology. The aim of our study was to analyze bone mineral density (BMD) and laboratory markers of bone metabolism in a group of women who underwent BMT.

Subjects and Methods

The study included 27 Caucasian women, aged 16–49 years (31.3 ± 9.9 years mean ± SD) without previous bone disease, who received a bone marrow transplant. Fourteen were allogeneic and 13 were autologous. Conditions leading to the BMT were as follows: 10 suffered acute nonlymphoblastic leukemia (ANL), 8 chronic myeloid leukemia (CML), 3 acute lymphoblastic leukemia (ALL), 2 nonHodgkin's lymphoma (NHL), 2 Hodgkin's disease (HL), 1 aplastic anemia (AA), and 1 refractary anemia with excess of blasts (RAEB). The design of the study was conducted in a cross-sectional fashion.

Pretransplant conditioning regimens used were (1) busulphan and cyclophosphamide in ANL and CML; (2) cyclophosphamide and total-body or nodal irradiation in ALL and AA, with a cumulative dose of 12 Gy in six sessions and 7 Gy in two sessions, respectively; (3) steroids were used in ALL as part of the treatment for remission induction. GVHD in allogeneic transplants was prevented with short-term methotrexate (MTX) and cyclosporine A (CsA) that was tapered from the sixth month if there was no evidence of GVHD. If GVHD appeared, steroids were added and

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Table 1. Results and normal values of biochemical parameters analyzed

Parameters	Mean ± SD (range)	Normal ranges
Blood		
Calcium (mg/dl)	9.39 ± 0.41 (8.7–10.1)	8.8–10
Phosphorus (mg/dl)	3.74 ± 0.49 (2.6–4.5)	2.5–4.5
Osteocalcin (ng/ml)	4.87 ± 2.2 (1.5–9)	2–5
$1,25(OH)_2D_3$ (pg/ml)	44.4 ± 13.6 (25–70.3)	18–62
i-PTH (pg/ml)	49.4 ± 34.4 (21–170)	10–65
Estradiol (pg/ml)	13.81 ± 9.64 (10–54)	<25[a]
FSH (IU/liter)	99.7 ± 45.4 (10–174)	2–22
LH (IU/liter)	34.5 ± 17.4 (4.6–66)	0.66–24
TRAP (IU/liter)	9.33 ± 3.22 (5–16)	4.7–11.5
ICTP (ng/ml)	5.69 ± 1.98 (3.7–9.4)	1.8–5
PICP (ng/ml)	170.7 ± 55.8 (97–269)	50–170
Urine		
Calcium/Creatinine	0.13 ± 0.07 (0.02–0.26)	0.06–0.19
hp/Creatinine	0.05 ± 0.02 (0.016–0.12)	<0.022

[a] Postmenopausal Women

CsA treatment was prolonged. Fourteen patients received CsA and seven needed glucocorticoids for treatment of ALL and/or GVHD.

Biochemical Markers

Renal function together with calcium, phosphorus, and magnesium determinations in blood and urine were performed in all cases (n = 27) (Shimadzu autoanalyzer, Shimadzu Corp., Tokyo, Japan). Serum estradiol levels [radioimmunoassay (RIA) Clinical Assays, Sorin Biomedica Diag., Saluggia, Vercelli, Italy], follicle-stimulating hormone (FSH), and luteinizing hormone (LH) [enzymoimmunoassay (EIA) (Tosoh Corp., Eurogenetics, Tessenderlo, Belgium)] were analyzed as parameters of gonadal function (n = 27). The following serum markers of bone metabolism were investigated: total alkaline phosphatase (TAP, colorimetric method) (n = 27), osteocalcin bone Gla-protein (BGP), [RIA, Incstar Corpil., Stillwater, MN, USA)] (n = 20), procollagen type I carboxy-terminal propeptide [(PICP), (RIA, Orion Diagnostica, Espoo, Finland) (n = 19), tartrate-resistant acid phosphatase (TRAP, colorimetric method) (n = 15), telopeptide carboxyterminal propeptide of type I collagen [(ICTP), (RIA, Orion Diagnostica, Espoo, Finland)] (n = 19), intact parathyroid hormone levels [(i-PTH), immunoradiometric assay (IRMA, Nichols Inst., San Juan Capistrano, CA, USA)] (n = 27), and levels of $1,25(OH)_2D_3$ [radioreceptor assay (RRA, Nichols Inst., San Juan Capistrano, CA, USA)] (n = 27). Hydroxyproline (hp) was measured in 24-hour urine (hp, spectrophotometry) (n = 22). Table 1 shows the normal value ranges for the different biochemical parameters in blood and urine. Sensitivities of the different tests used are as follows: serum estradiol, 5.2 pg/ml; FSH, 0.37 IU/liter; LH, 0.5 IU/liter; BGP, 0.2 ng/ml; PICP, 1.2 ng/ml; TRAP, 1 IU/liter; ICTP, 0.5 ng/ml; i-PTH, 1 pg/ml; $1,25(OH)_2D_3$, 3 pg/ml. The intraassay coefficients of variation (CV) are as follows: serum estradiol, 7%; FSH, 3%; LH, 5%; PICP, 3%; TRAP, 5%; ICTP, 4%; i-PTH, 3%; $1,25(OH)_2D_3$, 10%. The interassay CVs for each of these assays are as follows: serum estradiol, 14%; FSH, 5%; LH, 8%; PICP, 6%; ICTP, 5%; i-PTH, 6%; $1,25(OH)_2D_3$, 14%.

Bone Densitometry

BMD measurements were performed in all patients at the lumbar spine by the time of their inclusion in the study. Dual energy x-ray absorptiometry (DXA) with an Hologic QDR-1000™ densitometer (Hologic Inc., Waltham, MA, USA) was used. In our experience, by using an anthropomorphic phantom, the *in vitro* CV is 0.41% (n = 540), with an *in vivo* CV of 1% for lumbar spine (L_2–L_4). BMD measurements are expressed in g/cm^2, and were compared with both a control Spanish population matched in age and sex (Z score) and with a normal population of 35-year-old women (bone mass peak or T score) [17]. Both Z and T scores are statistical transformations expressing the number of standard deviations (SDs) of a particular value from the average ($\bar{x}$). Results are expressed as X ± SD and they are always referred to T score in order to fit with the criteria of osteopenia and osteoporosis by Kanis et al. [18]. According to these criteria, osteopenia is defined when BMD is more than −1 SD below the T score, and osteoporosis when more than −2.5 SD below the T score.

Statistical Analysis

The relative effect of various possible influences on axial bone density was analyzed individually calculating Pearson's correlation coefficient. Means of biochemical bone markers between normal and osteopenic/osteoporotic groups were compared using the Student's *t*-test. The variables included were age, body mass index (kg/m^2), time since transplantation and menopause, and all the studied biochemical indices of bone metabolism. All statistical calculations were made using the SPSS package (SPSS Inc, Chicago, IL).

Results

The average time between the BMT and the inclusion of the patients in the study was 33.6 ± 34.5 months (range: 7–158 months). At inclusion, all patients presented amenorrhea lasting 35.4 ± 36.1 months (range: 10–168 months). Most of them were on a normal or low calcium diet, and only one patient was undergoing sex hormone replacement.

Renal function was normal in all patients (creatinine < 115 μmol/liter). Serum levels of calcium, phosphorus, and magnesium were also normal. Serum TAP was elevated in 7 cases, reflecting hepatic disease by GVHD. Serum BGP and PICP were elevated in 6 and 10 patients, respectively, indicating an increase in bone formation. In 2 cases, serum levels of $1,25(OH)_2D_3$ appeared elevated. An increase in serum i-PTH values was detected in 2 patients, being in the upper normal limit in a 3rd patient. PTH values were normalized by treatment with calcium and vitamin D. All patients, with the exception of those on sexual hormone replacement therapy, had biochemical evidence of ovarian failure, showing low levels of serum estradiol (<25 pg/ml) and high levels of FSH (>22 IU/liter) and LH (>24 IU/liter). Serum TRAP was elevated in 4 cases, and ICTP in 8 cases. Urine calcium was raised in 5 cases (calcium/creatinine ≥0.20). A high level of hydroxyprolinuria was remarkable, with hp/creatinine ratio >0.022 in 21 of the 22 patients tested. The different parameters analyzed are shown in Table 1.

Average BMD in lumbar spine from L_2 to L_4 was 0.960 ± 0.106 g/cm^2; T score was −1.15 ± 1.38. The individual T score values of the study population are shown in Figure 1. According to Kanis et al.'s criteria [18], 9 of our patients (33%) had densitometric evidence of osteopenia and another 5 (18%) had osteoporosis (Table 2). Z score could not be calculated in 3 patients younger than 20 years, which is the minimum age for the reference population [17]. They all received oral calcium supplements (500–1000 mg/day) for 1 year, and 11 were given hormone replacement therapy. No vertebral collapses or peripheral fractures were observed after a 1-year follow-up.

With respect to analyzed variables, body mass index was the only independent variable correlated with lumbar density ($r = 0.46$, $P = 0.016$). There was no relationship between BMD and the other analyzed variables. No signifi-

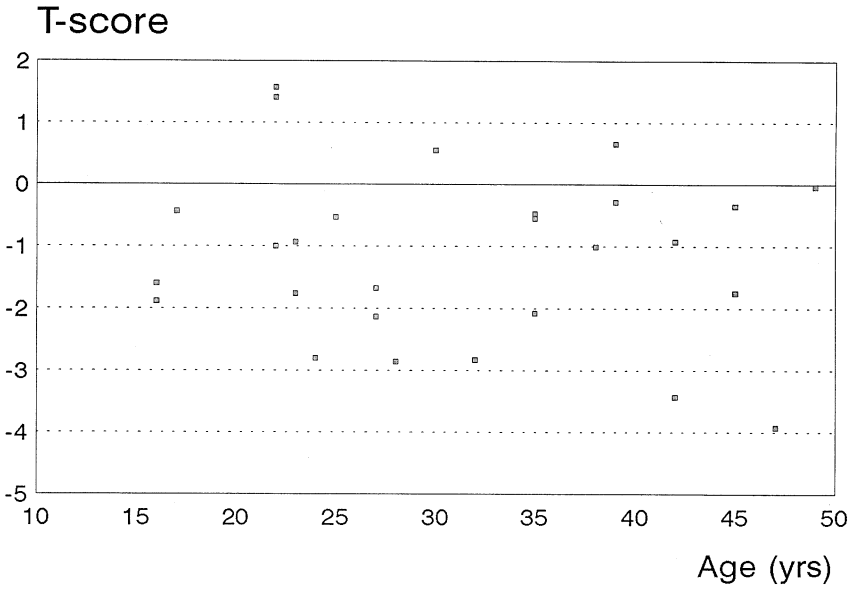

Fig. 1. Individual T-score values and age (years) of the patients in our study population.

Table 2. BMD in BMT: distribution of cases with respect to T score (Kanis criteria)

T ≥ 0 (normal)	n = 4
T between 0 and −1 SD (normal)	n = 9
T between −1 and −2.5 SD (osteopenia)	n = 9 (33%)
T < −2.5 SD (osteoporosis)	n = 5 (18%)

cant differences were found in the biochemical parameters of bone metabolism between normal and osteopenic/ osteoporotic groups (Table 3).

Discussion

Several reviews regarding bone complications in transplanted patients have appeared [1–4]. Most of these works refer to renal and hepatic recipients [6–10] and more recently to cardiac transplants [11–13], whereas references to BMT remain scarce [14]. Therefore, the aim of our study was to elucidate the eventual action of BMT on bone mass.

In our study, we found a slight reduction in bone mineral content of the lumbar spine in more than half of the women who previously underwent a BMT. BMD in 14 out of our 27 patients (51.8%) was lower than −1 SD with respect to bone mass peak (T score). This reduction led us to diagnose 33% of our patients as osteopenic and 18% as osteoporotic according to Kanis et al. [18], which is especially relevant considering the young age of our patients. It is now known that small reductions in BMD increase the risk of fracture. In this sense, it has been estimated that every SD below T index approximately doubles the risk of fracture [19, 20]. Although we did not detect vertebral or peripheral fractures in our series, we believe that women treated with BMT represent a high risk population for bone fragility and fractures if prompt preventive treatment is not established.

Pathogenic mechanisms for osteopenia in transplanted patients are shown in Table 4. Regarding bone loss after BMT, immunosuppressive therapy and ovarian failure are the principal factors.

The drugs more frequently used in BMT are glucocorticoids (GC), CsA and MTX. The deleterious effect of GC on bone, as is well known, is reduction of bone formation and increase in resorption [5]. For CsA a controversial effect on bone has been described. Thus, CsA produces inhibition of bone resorption *in vitro* [21, 22], and induces osteopenia *in vivo* [23]. The combination of GC and CsA appears to be more protective for bone, due perhaps to the reduction in the doses of each individual drug [24, 25]. MTX also seems to exert a slight negative effect on bone [26]. Nevertheless, the role played by these three drugs in BMT-induced bone loss should not be very important, since at the present time they are used at minimum effective doses and only for short periods of time.

In our opinion, of greater importance is the permanent ovarian failure secondary to radiotherapy and also to some of the drugs used. In this and previous works, lasting amenorrhea complicates all cases. In this sense, Kelly et al. [14] demonstrated similar decreases in BMD in patients after BMT and in postmenopausal women matched in age and duration of amenorrhea. As stated, all patients in our series were amenorrheic and only one was receiving hormone replacement therapy at inclusion time.

With respect to biochemical markers of bone metabolism, our findings are summarized as follows. Serum PTH and $1,25(OH)_2D_3$ levels were elevated only as exceptions. The transient increase of i-PTH detected in 3 patients, in the absence of renal failure, possibly reflects the presence of secondary hyperparathyroidism related to GC use. Serum BGP levels were elevated in 6 out of 20 cases analyzed, reflecting an increase in bone formation. High serum PICP in 10 out of 19 cases (52%) is also a finding in this line.

Regarding bone resorption markers, we found an increase in urinary calcium/creatinine ratio in 5 cases, serum TRAP was elevated in 4 out of 15, and ICTP in 8 out of 19 (42%). These results also indicate an accelerated bone turnover. These findings, together with those of formation markers, suggest that at least part of the population studied had high turnover bone metabolism. We want to emphasize the elevation of hp/creatininuria ratio found in 21 out of 22 patients (95%). Nonetheless, it did not completely correlate with the other resorption parameters, compeling us to be

Table 3. Results of analyzed variables according to the lumbar spine T-score

	Lumbar spine T-score > −1 mean ± SD (n = 13)	Lumbar spine T-score ≤ −1 mean ± SD (n = 14)	*P*
Age (years)	32.53 ± 10.12	30.14 ± 10.05	NS
BMI (kg/m^2)	27.53 ± 6.91	25.42 ± 3.89	NS
Transplantation (months)	29.69 ± 31.71	36 ± 38.98	NS
Menopause (months)	29.23 ± 30.49	41.14 ± 41.06	NS
Ca (mg/dl)	9.23 ± 0.42	9.55 ± 0.33	0.045
P (mg/dl)	3.70 ± 0.48	3.77 ± 0.51	NS
TAP (IU/liter)	293.07 ± 211.22	236.33 ± 71.92	NS
BGP (ng/ml)	5.20 ± 2.34	4.25 ± 2.02	NS
1,25 $(OH)_2$ D_3 (pg/ml)	44.09 ± 12.80	45.45 ± 18.05	NS
i-PTH (pg/ml)	47.79 ± 26.05	41.64 ± 8.17	NS
TRAP (IU/liter)	9.55 ± 3.90	9 ± 2.09	NS
ICTP (ng/ml)	5.42 ± 1.86	6.28 ± 2.29	NS
PICP (mg/ml)	173.84 ± 52.27	164 ± 67.73	NS
Ca/creatinine	0.13 ± 0.07	0.13 ± 0.06	NS
Hp/creatinine	0.04 ± 0.01	0.04 ± 0.03	NS

Hp = hydroxyproline
Results are expressed as $\bar{x}$ ± SD

Table 4. Risk factors for osteopenia in transplantations

Host-derived factors
Age/Menopausal status
Family trends
Cigarette smoking
Alcohol abuse
Immobilization/Inactivity
Poor nutritional status
Hypercatabolism
Parallel diseases
Specific organ-related factors
Uremia
Secondary hyperparathyroidism
Aluminum deposition
Vitamin D altered metabolism
Hyperbilirubinemia
Secondary hypogonadism
Diabetes
Hemochromatosis
Treatment-derived factors
Glucocorticoids
Cyclosporine
Radiotherapy
Methotrexate
Azathioprine (?)
Parenteral nutrition
Loop diuretic therapy
Anticoagulants

cautious in the interpretation. This finding is probably not so relevant because urinary hp is notoriously aspecific as resorption bone marker. Perhaps urine hp elevation traduces nonosseous collagen degradation.

When we analyzed values of BMD and markers of bone turnover, we did not find significative differences in biochemical parameters between normal and osteopenic/osteoporotic groups. With respect to the variables studied, body mass index was the only independent variable correlated with lumbar density.

In summary, our results confirm a decreased bone mass in women undergoing BMT, with densitometric evidence of osteopenia or osteoporosis detected in more than half of the patients studied (52%). As indicated, a part of our population shows markers of high turnover bone metabolism. An initial bone mass assessment is recommended and a second one soon after the BMT to all transplanted women, plus periodic biochemical and densitometric monitoring in populations at risk. Hormone replacement treatment or other alternative prevention therapy should promptly be established. In this sense, calcitonin and bisphosphonates have recently been used with some success in patients after liver transplantation [27]. Other experimental therapies are yet to be validated [28–30].

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