Calcif Tissue Int (1995) 57:15–19

Calcified
Tissue
International

Calcitonin and Bisphosphonates Treatment in Bone Loss After Liver Transplantation

M. A. Valero,[1] C. Loinaz,[2] L. Larrodera,[3] M. Leon,[1] E. Moreno,[2] F. Hawkins[1]

[1]Service of Endocrinology, University Hospital, 12 de Octubre, Ctra. de Andalucia Km 5.4, 28041 Madrid, Spain
[2]Department of Surgery, University Hospital, 12 de Octubre, Madrid, Spain
[3]Service of Biochemistry, University Hospital, 12 de Octubre, Madrid, Spain

Received: 9 November 1994 / Accepted: 9 January 1995

Abstract. Osteopenia is a major complication of orthotopic liver transplantation (OLT). However, no effective therapy for bone disease has been defined. We have studied vertebral bone mineral density (VMD) and fasting serum markers of bone formation [bone gla protein (BGP), procollagen I carboxyterminal peptide (PICP)] and metabolism (serum Ca, P, intact parathyroid hormone (iPTH), $25OHD_3$ and $1,25(OH)_2D_3$) in 120 patents after OLT. VMD was measured by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR 1000 densitometer on two occasions, 12 months apart. Patients with OLT had a VBD significantly lower compared with age- and sexed-matched Spanish controls ($P < 0.05$). Prevalence of osteoporosis (Z score below -2 SD) was 35.8%. Serum BGP (8.6 ± 0.7 ng/ml) and PICP (222.9 ± 81.9 ng/dl) were higher than those of controls. However, serum calcium, phosphorus, iPTH, $25OHD_3$, and $1,25(OH)_2D_3$ were within normal range. Patients with osteoporosis were randomly treated with 40 IU/day of calcitonin i.m. (Diatin, Ferrer Int. Laboratories) (n = 17) or 400 mg p.o., 15 days every 3 months, of sodium ethiodronate (Difosfen, Rubio Laboratories) (n = 23). All patients received 500 mg/12 hours of elemental calcium p.o. After 12 months of treatment, a significant increment of vertebral mineral density (VMD) was observed (6.4% and 8.2%, respectively). Serum BGP and PICP values remained elevated without a difference between the two drugs. Our results indicate that antiresorptive drugs may be of benefit in the high turnover osteoporosis of OLT recipients.

Bone loss is recognized as a frequent complication in patients with orthotopic liver transplantation (OLT). Severe bone loss increases susceptibility to atraumatic bone fractures and avascular necrosis in this population [1–4]. Several factors that contribute to bone disease in these patients have been suggested, such as previous chronic liver disease [5], parenteral nutrition [6], immobilization [7], and use of glucocorticoids [8]. In relation to cyclosporine A, Stewart and Stern [9] showed *in vitro* that this drug inhibits resorption, but Moskowitz et al. [10] demonstrated high turnover remodeling and excess resorption in rats. It is still unknown the extent to which the experimental data in rats apply to patients because cyclosporine is rarely used as the sole immunosuppressive agent, among other reasons [11].

Correspondence to: F. Hawkins

In OLT recipients, bone metabolism is complex and poorly understood so that no specific effective therapy exists. No therapeutic controlled studies on the bone loss in these patients have yet been performed. We speculated that therapy with calcitonin and bisphosphonates, two antiresorptive drugs, might decrease bone loss.

The aims of this study were to determine the prevalence and annual rate of bone loss in patients with OLT and the efficacy of calcitonin and bisphosphonates in the therapy for osteoporosis in patients with different chronic liver diseases undergoing OLT.

Subjects and Methods

Between 1986 and 1991, 196 patients underwent OLT at our Surgical Department. Of these, 42 women and 78 men were volunteerly enrolled in this study. Exclusion criteria were age lower than 18, short survival, and residence at long distance that precluded the participation in the study. Mean age for women was 45.4 ± 12.8 years and 47.7 ± 10.4 years for men (mean ± SD). Seventeen women were postmenopausal (12 months of spontaneous amenorrhea). Men did not refer to symptoms of hypogonadism and therefore a biochemical evaluation of this potential deficit was not performed. All patients were fully ambulatory and none were taking any drug known to interfere with calcium metabolism before OLT. Before transplantation, X-ray vertebral osteoporosis, defined by established criteria [12], was evident in 10% of patients. All had undergone OLT for the following liver diseases: alcoholic liver disease 39 patients, viral liver disease 28, cryptogenic cirrhosis 15, primary biliary cirrhosis 12, fulminant hepatitis 9, and miscellaneous liver diseases 17. After OLT, all patients were given cyclosporine A 2 mg/kg/day after 36 hours posttransplantation, maintaining levels (measured by radioimmunoassay) between 100 and 300 ng/ml; prednisone 500 mg i.v. for induction, repeated at 6 hours, slowly reduced to 0.3 mg/kg/day p.o.; and azathioprine 2 mg/kg/day i.v. and 1 mg/kg/day p.o. for 3 months.

Mean follow-up was 17 months (range 1–74 months) from when patients first enrolled in this study. At the start of the study, fasting serum samples were obtained. Serum concentrations of total calcium, phosphorus, alkaline phosphatase, total proteins, albumin, creatinine, glucose, GOT, GPT, glytamyl transferase, lactate dehydrogenase, and total bilirubin were determined by an automated technique (DAX 72). Fasting serum levels of intact parathyroid hormone (iPTH) [radioimmunoassay (RIA), Nichols Lab], $25OHD_3$ and $1,25(OH)_2D_3$ (RIA, Incstar Corp), procollagen type I carboxyterminal peptide (PICP) (RIA, Orion Diagnostica), and bone gla protein (BGP) (RIA, Henning Lab) were also assessed. Vertebral mineral density (VMD) was measured by dual X-ray energy absorptiometry (DXA) with a Hologic QDR 1000/w densitometer. The precision of this technique in our hands is 1.3% *in vivo* and 0.3% *in vitro*. The results of VMD (L_2-L_4) were expressed as grams of hydroxyapatite

Table 1. Serum biochemical values in all patients before and after liver transplantation (X ± SD)

	Before	1[a] DXA	2[a] DXA	Normal range
Glucose (mg/dl)	108.1 ± 40.4	102.2 ± 67.8	94.7 ± 20.7	70–110
Creatinine (mg/dl)	1.0 ± 0.8	1.2 ± 0.4	1.3 ± 0.3	0.7–1.1
Total proteins (g/dl)	6.6 ± 1.0	6.7 ± 0.7	7.1 ± 0.7	6.3–8.0
Albumin (g/dl)	3.3 ± 0.6[b]	3.7 ± 0.5[b]	4.6 ± 0.3[b]	3.2–5.5
GOT (UI/liter)	262.3 ± 602.5[b]	77.0 ± 120.6[b]	56.8 ± 75.7[b]	5–45
GPT (UI/liter)	275.8 ± 694.8[b]	124.7 ± 145.9[b]	82.5 ± 12.8	5–45
GGT (UI/liter)	178.9 ± 277.4	240.3 ± 407.3	131.7 ± 193.3	3–52
LDH (UI/liter)	346.1 ± 609.2[b]	169.3 ± 138.2[b]	150.2 ± 38.2[b]	90–230
Alkaline phosphatase (UI/liter)	341.3 ± 490.8[b]	216.7 ± 289.1[b]	143.9 ± 132.5[b]	30–115
Calcium (mg/dl)	8.8 ± 0.7	8.8 ± 0.5	9.0 ± 0.5	8.4–10.2
Phosphorus (mg/dl)	3.6 ± 0.7	3.6 ± 0.5	3.6 ± 0.4	2.3–4.6
Osteocalcin (ng/ml)	—	8.6 ± 5.7	10.2 ± 5.9	4.5–6.5
PICP (ng/dl)	—	222.9 ± 81.4	—	40–166
PTH (pg/ml)	—	39.3 ± 22.2	46.6 ± 5.9	3–50
25OH vitamin D (ng/ml)	—	14.4 ± 9.7	—	4–35
1,25OH vitamin D (ng/dl)	—	27.3 ± 15.1	—	11–51

1[a] DXA = first bone study; 2[a] DXA = second bone study
[b] $P < 0.05$

divided by the projected area in square centimeters. The patient's Z score was calculated as p − m/SD (p = measured patient value, m = mean value for sex and age-matched controls, and SD = standard deviation of the mean value for sex- and age-matched controls).

The sex- and age-matched healthy control group for the bone mass study included 117 premenopausal women, 115 postmenopausal women, and 1136 men. They had no evidence of bone disease and were not taking therapy known to influence calcium metabolism [13]. Transplant patients with Z scores lower than −2 SD were considered to have osteoporosis [14]. Immediately after the first DXA study, those patients were randomly assigned to be treated with salmon calcitonin or bisphosphonates for 12 months. Patients in the calcitonin group were given 40 units of synthetic salmon calcitonin i.m. daily. The other group received disodium ethidronate 400 mg/day p.o., 15 days every 3 months. All patients received 500 mg/12 hours of elemental calcium p.o., contained in tablets of calcium gluconate-lactate (2.94 g) and calcium carbonate (0.3 g).

Serum and bone density measurements were made at the beginning of the study and after 12 months. Annual variation of VMD was calculated as follows: % variation = $VMD_2 - VMD_1/VMD_1 \times 100$, where VMD_1 and VMD_2 were VMD measured on two occasions, separated by 12 months.

Statistical Analysis

Data are presented as mean ± SD. Comparison between groups was performed with Fischer's *t* test. Lineal regression analysis was used to assess association between numeric variables. A *P* value of less than 0.05 was considered significant.

Results

In all the patients, glucose, creatinine, total protein, calcium, and phosphorus were within normal range before and after OLT. Hepatic function and albumin improved after transplantation (Table 1). Mean serum alkaline phosphatase concentration decreased gradually, but this value was still above the normal limit. Serum BGP and PICP were above the upper normal range—8.6 ± 5.7 ng/ml and 222.9 ± 81.4 ng/dl, respectively. Serum iPTH (39.3 ± 22.2 pg/ml), $25OHD_3$ (14.4 ± 9.7 ng/ml), and $1,25(OH)_2D_3$ (27.3 ± 15.1 pg/ml), were well within the normal range.

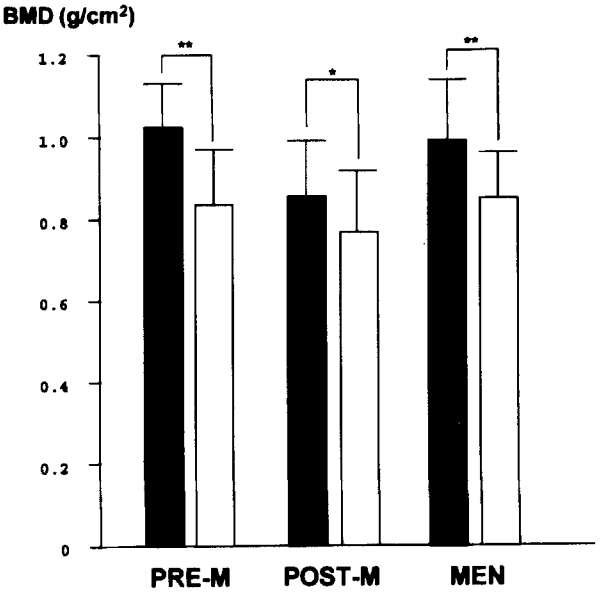

Fig. 1. VMD in patients with OLT. Men and pre- and postmenopausal women had lower VMD values than those of age- and sex-matched controls (*$P < 0.05$ and ** $P > 0.001$).

The daily doses of immunosuppressive therapy were reduced during the study. At the start of the study the mean daily dose of prednisone, cyclosporine, and azathioprine was 13.3 ± 8.6 mg/24 hours, 150 ± 120 mg/24 hours and 38.4 ± 49.9 mg/24 hours, respectively. The cumulative doses were 5.1 ± 6.3 g for prednisone, 5382.1 ± 4990.0 g for cyclosporine and 8.6 ± 17.5 g for azathioprine. Sixty-eight patients (57.1%) had presented episodes of acute rejection which were treated with high doses of prednisone.

The mean VMD was 0.837 ± 0.124 g/cm² (Z = −1.63 ±

Table 2. VMD and annual variation following liver transplantation according to different types of liver disease in the whole group and in patients without antiresorptive treatment (X ± SD)

Liver disease (n)	VMD (g/cm²) Basal total group	Basal NTG	After NTG	Annual variation (%)
Primary biliary cirrhosis (12)	0.788 ± 0.174	0.936 ± 0.159	0.922 ± 0.123	−3.2 ± 6.5
Viral cirrhosis (28)	0.807 ± 0.105	0.855 ± 0.103	0.811 ± 0.096	−2.4 ± 9.6
Fulminant hepatitis (9)	0.834 ± 0.173	0.934 ± 0.067	0.942 ± 0.138	+0.6 ± 5.0
Alcoholic liver disease (39)	0.840 ± 0.113	0.905 ± 0.096	0.895 ± 0.123	−3.4 ± 7.2
Cryptogenic cirrhosis (15)	0.884 ± 0.112	0.927 ± 0.113	0.890 ± 0.116	−2.0 ± 6.3
Miscellaneous (17)	0.860 ± 0.104	0.893 ± 0.084	0.854 ± 0.082	−3.9 ± 6.0
All types of disease (120)	0.837 ± 0.124	0.906 ± 0.100	0.880 ± 0.111	−3.4 ± 6.1

No significant differences
NTG = Nontreated group

1.1). VMD values were significantly different between controls and patients with OLT (Fig. 1). Premenopausal women with OLT had lower bone density than men (VMD = 0.839 ± 0.131 g/cm², Z = −1.61 ± 1.12 versus VMD = 0.854 ± 0.110 g/cm², Z = −1.71 ± 1.07). Postmenopausal women had the lowest bone density (VMD = 0.772 ± 0.147 g/cm², Z = −1.23 ± 1.26). Mean VMD was lower in primary biliary cirrhosis ($P < 0.05$) compared with the other etiologies pre-OLT, but annual variation was similar for all liver diseases (Table 2). VMD did not correlate with age, time of follow-up, cumulative total doses of immunosuppressant drugs received, or with biochemical parameters, except serum BGP ($r = -0.23$, $P < 0.05$) (Fig. 2). In nontreated patients, the annual rate of bone loss was 3.4% in spinal trabecular bone. Forty-three patients (35.8%), 17 women and 26 men, had densitometric evidence of osteoporosis (VMD = 0.725 ± 0.078 g/cm², Z = −2.74 ± 0.56). These patients (17 with calcitonin and 23 with bisphosphonates) received specific treatment for osteoporosis for 12 months. Clinical data for these patients are shown in Table 3. The demographic and anthropometric data were homogeneous for both groups, except for age: patients on calcitonin treatment were significantly older. However, this difference did not interfere with our findings, because the patients were compared with themselves and the VMD results were adjusted for age in each case.

After 12 months of participation in the study, VMD had significantly increased in the two groups. The mean difference in bone mass change between the two groups at 12 months was not statistically different. Biochemical data of the treated population at the end of the study are summarized in Table 4. No differences in serum biochemical markers were observed between the two groups. Serum calcium, phosphorus, alkaline phosphatase, and iPTH were within normal range. However, serum BGP levels were higher than normal.

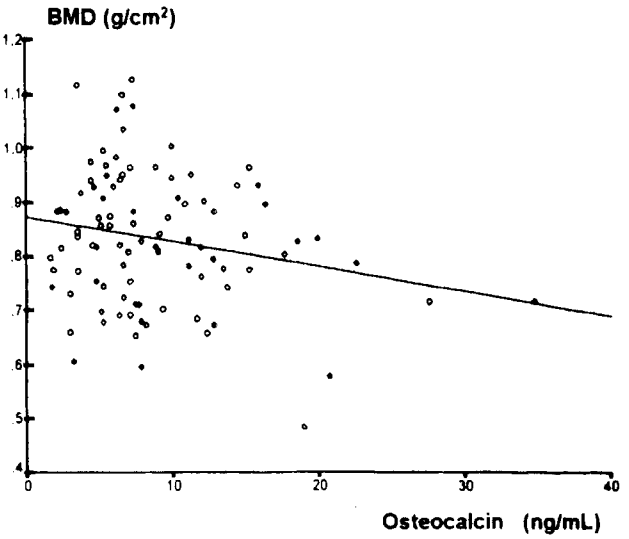

Fig. 2. Inverse correlation of VMD and BGP in patients with OLT ($r = -0.23$, $P < 0.05$).

Table 3. Clinical data in treated groups (X ± SD)

	Calcitonin (n = 17)	Bisphosphonates (n = 23)
Age (yrs)	52.1 ± 6.2	40.4 ± 12.8
Sex (men/women)	10/7	16/7
Menopausal (pre/pos)	4/3	6/1
Weight (kg)	62.6 ± 11.4	65.5 ± 13.0
BMI (kg/m²)	23.0 ± 3.8	23.5 ± 4.8
VMD_1 (g/cm²)	0.698 ± 0.060	0.749 ± 0.067
VMD_2 (g/cm²)	0.746 ± 0.080	0.816 ± 0.091
Annual variation (%)	+6.4	+8.2

BMI = body mass index; VMD_1 = vertebral mineral density measured before treatment; VMD_2 = vertebral mineral density measured after treatment

Discussion

Although bone disease has been recognized to occur with chronic liver disease [5, 15, 16], the clinical significance of osteoporosis in OLT patients has only recently been studied. There are several reasons for the increasing importance of osteopenia after OLT, such as more effective immunosuppressive therapy and improvement in surgical techniques that have reduced the mortality rate post-OLT. On the other hand, in recent years, the rate of bone loss can be determined by precise methods, and may also be evaluated by biochemical markers of bone turnover.

Using DXA, a technique that measures smaller changes in bone mass than other procedures [17], we have shown that there is a high prevalence of bone disease in patients undergoing OLT. Primary biliary cirrhosis is associated with lower VMD [5, 7]. However, annual bone loss was similar in all the different liver diseases.

Table 4. Serum biochemical data in OLT patients with and without antiresorptive treatment (X ± SD)

	Nontreated (n = 77)		Calcitonin (n = 17)		Bisphosphonates (n = 23)	
	Before	After	Before	After	Before	After
Calcium (mg/dl)	8.7 ± 0.6	8.9 ± 0.7	8.2 ± 1.1	8.7 ± 0.6	8.2 ± 0.8	8.9 ± 0.9
Alkaline phosphatase (UI/liter)	239 ± 208	155 ± 160	200 ± 180	147 ± 105	209 ± 111	113 ± 48
Osteocalcin (ng/dl)	10.0 ± 7.4	9.6 ± 6.0	8.9 ± 6.6	10.4 ± 6.1	10.8 ± 8.4	9.5 ± 5.2
PTH (pg/ml)	42.5 ± 22.0	38.3 ± 17.9	43.5 ± 27.2	46.8 ± 21.2	43.1 ± 12.2	41.3 ± 17.2

No significant differences

In agreement with McDonall et al. [3], we have found differences of VMD among controls and men or women post-OLT. In their paper, bone mass was correlated with age but not with any biochemical variable. However, Eastell et al. [1] have found an inverse correlation between bone mass and bilirubin concentration and a direct relationship with serum albumin, but r values (−0.36 and 0.20, respectively) were very small. In our study, we could not demonstrate a relationship between VMB and age or biochemical parameters. Probably multifactorial causes and drugs received can explain these different findings. Also, small numbers of patients were enrolled in these studies.

The annual rate of bone loss in healthy controls is around 1–2% [18]. However, the annual rate of bone loss in patients treated with glucocorticoids can reach up to 10% [8]. In patients undergoing OLT, an accelerated rate of bone loss has been shown in the first 3–6 months after transplantation [2, 3, 19], although some patients followed after OLT actually showed improvement in VMD. In our nontreated patients, the rate of bone loss was −3.4%, but we have not found a relationship between VMD and time after transplantation. This loss had not stopped 12 months after the transplantation in those patients in which DXA studies were done just after OLT. As we did not perform DXA studies at 180 days after OLT like other authors [2, 3, 20], we cannot rule out the presence of an accelerated bone loss in our patients in the first months that was subsequently slowed. Eastell et al. [1] concluded that the most likely explanation for the recovery in bone density is that bone mass is increased when initial high dose steroid is decreased. However, in our study and in others [2, 3, 21], bone loss is not correlated with the dose of immunosuppressants or with the number of rejections that require additional steroid therapy.

Increased bone turnover has been found, assessed biochemically, by high BGP serum levels [3, 4, 22], as well as by histomorphometry [3]. Our findings are in agreement: mean serum BGP and PICP values were above the normal range. Although serum BGP and PICP concentrations are increased in renal failure [23, 24], this does not explain our results, as creatinine clearance was normal in our patients. Also, a direct correlation was found between BGP and VMD. High BGP levels could be expected if we consider that previous liver disease and steroid treatment cause low bone formation. However, hepatic disturbances are corrected and steroids are progressively decreased after OLT. In this situation, it is possible that the high levels of BGP reflect an increase of bone turnover secondary to cyclosporine, as Kelly et al. [25] have previously suggested. Similar effects of glucocorticoids and cyclosporine on BGP have been found in heart transplantation [26, 27].

McDonall et al. [3] have shown no histological evidence of osteomalacia, although some of their patients had low levels of serum $25(OH)_2D_3$, with normal serum calcium and iPTH. We found that serum calcium, phosphorus, $25OHD_3$, $1,25(OH)_2D_3$, and iPTH were within the normal range. As with Hay et al. [21], we were unable to demonstrate any relationship between vitamin D and PTH or VMD. No controlled studies of treatment on bone disease of OLT have been previously performed. Treatment with calcitonin [28, 29] or bisphosphonates [30, 31] produces a significant increase in lumbar bone density in postmenopausal and steroid-induced osteoporosis. In patients with chronic liver diseases in whom increased bone resorption is exacerbated by posttransplantation glucocorticoid therapy, the use of antiresorptive drugs seems attractive. One of the more relevant findings of our study is the improvement of VMD, when osteoporotic OLT patients are treated with those agents. In effect, we observed a significant increase in bone mass of 6.4% and 8.2% in patients treated with calcitonin and bisphosphonates, respectively, compared with the nonosteoporotic group without treatment, whose bone loss was 3.4%. After 12 months of treatment, no significant differences in biochemical bone markers were found between patients treated with antiresorptive drugs. Serum BGP concentrations remained above the upper limit in all the groups.

In summary, patients undergoing liver transplantation have an increased risk for bone disease. Biochemical markers of bone remodeling suggest an increase of bone turnover. Our findings suggest that antiresorptive drugs may be effective in the treatment or prevention of osteoporosis in liver transplant recipients.

Acknowledgments. This work was supported by a research grant from the Spanish Science and Technology Commission (ref IN90010).

References

1. Eastell R, Dickson R, Hodgson SF, Wiesner RH, Porayko MK, Wahner HW, et al (1991) Rates of vertebral bone loss before and after liver transplantation in women with primary biliary cirrhosis. Hepatology 14:296–300
2. Porayko MK, Wiesner RH, Hay JE, Krom RAF, Dickson ER, Beaver S, et al (1991) Bone disease in liver transplant recipients: incidence, timing and risk factors. Trans Proc 23:1462–1465
3. McDonall JA, Dunstan CR, Dilworth P, Sherbon K, Sheil AG, Evans RA, et al (1991) Bone loss after liver transplantation. Hepatology 14:613–619
4. Hawkins FG, Leon M, López MB, Valero MA, Larrodera L, García I, et al (1994) Bone loss and turnover in patients with liver transplantation. Hepato-Gastroenterol 41:158–161
5. Diamond TH, Stiel D, Lunzer H, McDowall D, Eckstein RP, Posen S (1989) Hepatic osteodystrophy: static and dynamic bone histomorphometry and serum bone Gla-protein in 80 patients with chronic liver disease. Gastroenterology 96:213–221

6. Saitta JC, Ott SM, Sherrard DJ, Walden CE, Lipkin EW (1993) Metabolic bone disease in adults receiving long-term parenteral nutrition: longitudinal study with regional densitometry and bone biopsy. JPEN 17:214–219
7. Stewart AF, Adler M, Byers CM, Segre GV, Broadus AE (1982) Calcium homeostasis in immobilization: an example of resorptive hypercalciuria. N Engl J Med 306:1136–1140
8. Lukert BP, Raisz LG (1990) Glucocorticoid-induced osteoporosis: pathogenesis and management. Ann Intern Med 112:355–364
9. Stewart PJ, Stern PH (1989) Cyclosporine: correlation of immunosuppressive activity and inhibition of bone resorption. Calcif Tissue Int 45:222–226
10. Moskowitz C, Epstein S, Fallon M, Ismail F, Thomas S (1988) Cyclosporin-A in vivo produces severe osteopenia in the rat: effect of dose and duration of administration. Endocrinology 123:2571–2577
11. Shane E, Epstein S (1994) Immunosuppressive therapy and the skeleton. Trends Endocrinol Metab 5:169–175
12. Eastell R, Cedel SL, Wahner HW, Riggs BL, Melton LJ (1991) Classification of vertebral fractures. J Bone Miner Res 6:207–215
13. Diaz Curiel M, Castro N (1992) On behalf of the proyecto multicétrico de investigación, Madrid 1992. Bone mineral density in the Spanish population measured by dual X-ray absorptiometry (DEXA).
14. Compton JE, Evans WD, Crawley EO, Evans C (1988) Bone mineral content in normal UK subjects. Br J Radiol 61:631–636
15. Diamond T, Stiel D, Lunzer M, Wilkinson M, Roche J, Posen S (1990) Osteoporosis and skeletal fractures in chronic liver disease. Gut 31:82–87
16. Bonkovsky HL, Hawkins M, Stenberg K, Hersh T, Galambos JT, Henderson JM, et al (1990) Prevalence and prediction of osteopenia in chronic liver disease. Hepatology 12:272–280
17. Lai KC, Goodsitt MM, Murano R, Chesnut H III (1992) A comparison of two dual-energy X-ray absorptiometry systems for spinal bone mineral measurement. Calcif Tissue Int 50:203–208
18. Riggs BL, Wahner HW, Melton LJ, Richelson LS, Jud HL, Offord KP (1986) Rates of bone loss in the axial and appendicular skeletons of women: evidence of substantial vertebral bone loss prior to menopause. J Clin Invest 77:1487–1491
19. Hay JE (1993) Bone disease in liver transplant recipients. Gastroenterol Clin North Am 22:337–000
20. Shane E, Rivas MC, Silverberg SJ, et al (1993) Osteoporosis after cardiac transplantation. Am J Med 94:257–264
21. Hay JE, Dickson ER, Weisner RH, Kron RAF (1990) Long-term effect of orthotopic liver transplantation on the osteopenia of primary biliary cirrhosis (abstract). Hepatology 12:838
22. Watson RGP, Coulton L, Krain JA (1990) Circulating osteocalcin in primary cirrhosis following liver transplantation and during treatment with cyclosporin. J Hepatol 11:354–358
23. Delmas PD, Wilson DM, Mann KG (1983) Effect of renal function on plasma levels of bone Gla-protein. J Clin Endocrinol Metab 57:1928–1930
24. Coen G, Mazzaferro S, Ballanti P, et al (1992) procollagen type I C-terminal extension peptide in predialysis chronic renal failure. Am J Nephrol 12:246–251
25. Kelly PJ, Sambrook PN, Esiman JA (1989) Potential protection by cyclosporin against glucocorticoid effects on bone. Lancet 2:1388
26. Sambrook PN, Kelly PJ, Keogh AN, et al (1994) Bone loss after heart transplantation: a prospective study. J Heart Lung Transplant 13:116–121
27. Thiebaud D, Krieg MA, Gillard D, Goy JJ, Burckhardt P (1994) Cyclosporine maintains high-bone turnover with cortical bone loss after heart transplantation. J Bone Miner Res 9:S387
28. Mazzuoli GF, Posseri M, Gennari C, Minisola S, Antonelli R, Valtorta C (1986) Effect of salmon calcitonin in postmenopausal osteoporosis: a controlled double-blind clinical study. Calcif Tissue Int 38:3–8
29. Sambrook P, Birminghan J, Kelly P, Kempler S (1993) Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol and calcitonin. N Engl J Med 328:1747–1752
30. Reid IR, King AR, Alexander LJ, Ibberston HK (1988) Prevention of steroid-induced osteoporosis with (3-amino-1-hydroxpropyllidine)-1,1-bisphosphonate (APD). Lancet 1:143–146
31. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH (1990) Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in postmenopausal osteoporosis. N Engl J Med 322:1265–1271