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Effect of HMG-CoA Reductase Inhibitors on Bone Mineral Density in Renal Transplantation

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Abstract
Recent studies in non-transplanted patients have suggested that HMG-CoA reductase inhibitors (statins) can increase the bone mineral density (BMD). The study objective was to determine if renal transplant patients on statins were more likely to retain a higher bone mineral density and lower risk of osteoporosis than patients not taking these drugs. In this case-control study, 23 transplanted patients on statins for 2.6 ± 0.2 years (10 male, 13 female, mean age ± SEM 43.6 ± 2.0 years) and 30 patients (10 male, 20 female, mean age 43.2 ± 1.3 years) who did not take statins were evaluated. All patients had serum Cr £2 mg/dl (1.37 ± 0.06) and serum Ca £5.5 meq/l (5.09 ± 0.05). Both groups were given similar dosages of corticosteroids and calcineurin inhibitors, and have not different BMI (26.3 ± 0.9 vs. 24.8 ± 0.7 Kg/m2, p=NS). Comparison of these two groups showed a higher BMD of the spine in patients taking statins (Norland, L2-L4: 0.925 ± 0.034 g/cm2 vs. 0.757 ± 0.025 g/cm2, p=.00016). When men and women were compared separately between the two groups, those on statins had also higher BMD of the spine (p=.0151 and p=.0029, respectively). The mean difference was 0.022 g/cm2, about 5.6% higher BMD. The risk of osteoporosis (defined as a T-score £-2.5) in patients who received statins was approximately half (-1.48 ± 0.26 vs. -2.79 ± 0.19, p=.00011, OR .55, 95% CI 0.15-1.93). In conclusion, the above findings suggest that statins seem to decrease osteoporosis risk in renal transplant recipients.

Introduction
Most patients undergoing kidney transplantation already have some degree of renal osteodystrophy, a general term encompassing all histological derangements of bone that may occur in uremic patients such as hyperparathyroidism (with or without osteitis fibrosa), osteomalacia, osteosclerosis and adynamic bone disease. In some patients more than one of these conditions may be present at the same time. After successful renal transplantation some improvement of hyperparathryroidism, aluminum-related bone disease and amyloidosis may occur, but the introduction of immunosuppressive agents, particularly corticosteroids, expose the patients to the risk of new bone complications, such as osteoporosis and osteonecrosis, as well as muscle and joint complications[1].
As a general rule, patients at risk of osteoporosis should be active physically, discontinue those life-style habits (tobacco and alcohol) that are risk factors for osteoporosis, and adapt a diet adequate in calcium, proteins, and vitamins.
Vitamin D therapy may be theoretically indicated; as calcitriol may increase calcium absorption may also stimulate the function of osteoblasts. However, the precise mechanism by which vitamin D may prevent bone loss in this setting is unknown.
Calcitonin is a specific inhibitor of bone resorption. Eel and salmon calcitonin have the highest activity/weight ratio. Pig and human calcitonins have a weaker effect. Blood calcium levels modulate secretion of endogenous calcitonin. Calcitonin inhibits bone resorption and thereby lowers plasma calcium.
Bisphosponates bind preferentially to bones with high turnover rates, such as trabecular bone. These agents oppose the increased bone resorption caused by corticosteroids by inhibiting osteoclast activity and by reducing the number of osteoclasts. Osteoclast survival may be decreased by destruction when contact is made with bone containing bisphosponate or by apoptosis. As a consequence fewer osteoclasts are recruited to bone remodeling sites and differentiation of osteoclast precursor is impaired. The number of trabecular perforations, which are the cause of reduced bone strength, is decreased.
Estrogen therapy effectively prevents bone loss in postmenopausal women. Although no studies regarding the effects of hormone replacement therapy in organ transplant recipients have been published, it is rational to give estrogen replacement therapy both to premenopausal women with amenorrhea and to postmenopausal women, before and after transplantation, if no contraindication exists.
Recent studies in non-transplanted patients have suggested that 3-hydroxy-3-methylglutaryl A (HMG-CoA) reductase inhibitors (statins), lipid-lowering agents, can increase the bone mineral density, and can improve the fracture risk profile [2-7]. The data suggest that statins have similar effects on bone turnover as nitrogen-containing bisphosphonates. Both drugs interfere with the same metabolic pathway. Both exert their activity in the mevalonate pathway leading to cholesterol synthesis and to protein prenylation, i.e. adding a lipid chain to transpeptidases in the cell (osteoclast) membrane [11]. Statins interfere with HMG-CoA reductase early in this pathway, decreasing the formation of mevalonate. Nitrogen-containing bisphosphonates inhibit the enzyme

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farnesyl-pyrophosphate synthase, thereby decreasing the formation of farnesylpyrophosphate, which is a later step in this pathway. As both types of drugs interact in the same pathway, similarities in the therapeutic effects might be expected. Indeed, the nitrogen-containing bixsphosphonate neridrenate was reported to cause a modest decrease of serum low-density lipoprotein cholesterol [8-12]. This may be expected when considering the different metabolism of the two types of drugs. Statins are absorbed in the intestine and exert their effect for the greater part in the liver. Bisphosphonates are absorbed in the intestine for about 1% of the dose and about half of the absorbed fraction immediately adheres to the skeleton on sites of bone resorption while the other half is excreted in the urine. One should not expect a great cross-reactivity. However, it is also reassuring that statins do not have a negative effect on the skeleton. Some statins have been shown to stimulate bone formation by osteoblasts in vitro [13]. More recently, epidemiological data suggested that statins increase BMD and decrease fracture risk. Postmenopausal women on statins had higher BMD than aged-matched controls after adjustment for age, height, weight and oestrogen use [14]. Another case-control study in Medicare patients with hip fractures and age- and sex-matched controls showed a decrease of hip fracture risk in statin users [15]. Current use and long-term use were associated with the highest protection (adjusted odds ratios 0.29, 95% CI 0.17-0.82, respectively). In another case control study in six health-maintenance organizations [16], statin users (≥13 dispensings) and a lower risk for osteoporotic fractures than controls (adjusted OR 0.48, 95% CI 0.27-0.83). However, the General Practice Research Database in the UK gave discordant results [17]. More than 80000 patients with various fractures were matched with a similar number of controls. There was no protective effect, neither with long duration, high (cumulative) dose, different types of statin, nor according to different fracture types.

Table 1. Patient characteristics. (Note.-Values are (%) of patients or mean ± SEM for each group. NS=non significant)

	Patients taking statins (n=23)	Patients not taking statins (n=30)	p Value
Male gender (%)	43.5	50.0	NS
Age (years)	43.6 ± 2.0	43.2 ± 1.3	NS
Time post transplant (years)	8.3 ± 1.0	6.4 ± 1.1	NS
Living donation (%)	26.1	57.1	
Time on statins (years)	2.6 ± 0.2	–	0.001
Serum creatinine (mg/dl)	1.4 ± 0.1	1.5 ± 0.1	NS
Serum calcium (meq/l)	5.07 ± 0.03	5.06 ± 0.08	NS
Serum iPTH (ng/ml)	70.4 ± 9.2	82.8 ± 13.5	NS
BMI (kg/m2)	26.3 ± 0.9	24.8 ± 0.7	NS

Another possible working mechanism of statins on bone metabolism was considered in a cross-sectional study in 140 postmenopausal women who had been treated with a statin for a median period of 4 years [18]. These patients were compared with 140 age- and sex-matched control subjects recruited as a random sample from the general population. They observed lower plasma concentrations of osteocalcin and bone-specific alkaline phosphatase, two markers of bone formation, and of C-terminal telopeptide of type 1 collagen, a marker of bone resorption, in the statin users than in the control subjects. Plasma parathyroid hormone levels were higher in the statin users than in the controls. BMD at the lumbar spine, hip, forearm and total body was similar in both groups. They concluded that statins decreased bone turnover, but did not have a positive effect on bone mass. These data are intriguing [19, 20].

The study objective was to evaluate if renal transplant patients on statins were more likely to retain a higher bone mineral density and lower risk of osteoporosis than patients not taking these drugs.

Patients and methods

Twenty-three renal transplant patients on statins (fluvastatin, pravastatin or atorvastatin) for 2.6 ± 0.2 years and 30 patients who did not take statins were evaluated (Table 1). All patients had serum creatinine ≤2.0 mg/dl (mean ± SEM 1.37 ± 0.06 mg/dl) and serum calcium ≤ 5.5 meq/l (5.09 ± 0.05 meq/l), and have no difference in body mass index (26.3 ± 0.9 vs. 24.8 ± 0.7 kg/m^2, p=NS). All patients were on triple immunosuppressive therapy with azathioprine (1.01 ± 0.07 mg/k/day), or mycophenolate mofetil (1.77 ± 0.11 g/day), cyclosporine (Sandimmun Neoral® 2.91 ± 0.12 mg/kg/day), and methylprednisolone (4.55 ± 0.36 mg/day). No patient had changed the immunosuppressive regimen for the last 3 years. The mean cyclosporine trough levels were 153 ± 6 ng/ml. The bone mineral density of the spine by DEXA was measured before and after the statins use. No patients were taking during the observation period calcium supplements, vitamin D, calcitonin, bisphosphonates or hormone replacement therapy. The risk of osteoporosis, T-score <-2.5 below of peak bone mass and –Z-score <-2.5 below the average bone mineral density of a group of age- and sex-matched controls, was considered in all the study patients. Values were expressed as mean ± SEM. The data were analyzed using parametric statistics. P values less than 0.05 were considered to be significant.

Results

Patient characteristics at the initiation of statin therapy are shown in Tables 1 and 2.

Table 2. The doses of immunosuppressive drugs and the cyclosporine trough levels between the two groups. (NS=non significant)

	AZA/MMF + CsA + MP: 17 MMF + MP: 4 CsA + MP: 2	AZA/MMF + CsA + MP: 16 MMF + MP: 1 CsA + MP: 1 MMF + CsA: 12	p Value
Azathioprine dose (mg/kg/day)	1.01 + 0.09	1.06 + 0.11	NS
Mycophenolate mofetil dose (g/day)	1.79 + 0.10	1.75 + 0.19	NS
Cyclosporine dose (mg/kg/day)	2.82 + 0.17	3.04 + 0.18	NS
Methylprednisolone dose (mg/day)	4.23 + 0.32	4.94 + 0.71	NS
Cyclosporine trough levels (ng/ml)	162 + 7	143 + 10	NS

Table 3. The mean DEXA-BMD of the spine, T-score and Z-score, and the frequency of T-score <–2.5 between the two groups.

	Patients taking statins (n=23)	Patients not taking statins (n=30)	p Value
DEXA-BMD of the spine (Norland, g/m^2)	0.925 ± 0.034	0.757 ± 0.025	0.00016
T-score	-1.478 ± 1.239	-2.797 ± 0.192	0.00011
Z-score	-0.807 ± 0.273	-2.797 ± 0.165	0.0000001
T-score ≤-2.5	78.3	66.7	NS

Note.-Values are (%) of patients or mean ± SEM for each group. NS=non significant

Table 4. The mean DEXA-BMD of the spine, T-score, and Z-score according to the gender between the two groups.

	Patients taking statins (n=23)	Patients not taking statins (n=30)	p Value
DEXA-BMD of the spine (g/m^2)			
Male	0.989 ± 0.064	0.811 ± 0.039	0.0151
Female	0.876 ± 0.029	0.730 ± 0.139	0.0029
T-score			
Male	-1.61 + 0.31	-2.38 + 0.35	NS
Female	-1.71 + 0.27	-2.95 + 0.24	0.0022
Z-score			
Male	-1.50 + 0.30	-2.05 + 0.28	NS
Female	-1.18 + 0.19	-1.98 + 0.21	0.012

Comparison of the two groups showed a higher BMD of the spine in patients taking statins than those who did not take statins (Norland, L2-L4: 0.925 ± 0.034 g/cm2 vs. 0.757 ± 0.025 g/cm2, p=.00016). The mean difference was 0.022 g/cm2, about 5.6% higher BMD. When men and women were compared separately between the two groups, those on statins had also higher BMD of the spine (p=.0151, and p=.0029, respectively). The risk of osteoporosis (defined as a T-score £-2.5) in patients who received statins was approximately half (-1.48 ± 0.26 vs. -2.79 ± 0.19, p=.00011, OR .55, 95% CI 0.15-1.93).

Conclusions

The above findings suggest that statins seem to decrease osteoporosis risk in renal transplant recipients.

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