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Metabolic Bone Disease in Chronic Renal Failure

II. Renal Transplant Patients

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Trabecular vertebral bone of renal transplant patients was quantitatively compared with bone from normal individuals and dialyzed and nondialyzed patients with chronic renal failure reported in detail in an earlier study. Long- and short-term transplant patients have increased bone resorption and mineralization defects similar to renal osteodystrophy in dialyzed and nondialyzed patients. However, in transplant patients the magnitude of resorption is greater, and bone volume tends to decrease rather than increase. Resorptive activity in transplant patients is maximal during the first year after transplantation. Bone volume decreases continuously for at least 96 months after transplantation. Only decreased bone volume correlated with success or failure of the renal transplant. Morphologic findings in this study correlate with other clinical and morphologic data to suggest that reduction in bone volume in transplant patients results from a combination of persistent hyperparathyroidism and suppression of bone formation by steroid therapy. (Am J Pathol 78:385–400, 1975).

A PREVIOUS STUDY from this institution substantiated the results of earlier papers which showed that persistent metabolic bone disease closely resembling conventional renal osteodystrophy remains a significant obstacle to complete rehabilitation of patients with chronic renal failure treated by maintenance hemodialysis.[1] The study showed that bone disease in dialysis patients did not improve significantly between 1966 and 1972.

Persistent metabolic bone disease in patients with chronic renal failure treated by renal transplantation is a less severe clinical problem.[2] Some transplant patients, however, have debilitative bone disease [3,4] which is explainable in part by lesions characteristic of conventional renal osteodystrophy and dialysis bone disease.[2,4]

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No systematic histomorphologic study defining the relationship of transplant bone disease to metabolic bone disease in dialyzed and non-dialyzed patients has been reported. Most of the studies of bone disease in transplant patients have focused on aseptic necrosis and steroid-induced osteoporosis [3–6] without first defining the relationship between these diseases and renal osteodystrophy and dialysis bone disease. The relationship is significant since most patients receiving transplants will have some form of renal osteodystrophy [2] and many will have been treated by maintenance dialysis. In addition, some workers feel that aseptic necrosis can result from fractures in bones weakened by osteoporosis.[7] It is appropriate to ask, therefore, whether the osteoporosis seen in transplant patients is similar to other forms of osteoporosis, or whether it is more closely related to lesions of renal osteodystrophy and dialysis bone disease.

Preliminary studies from Hammersmith Hospital have indicated that bone lesions characteristic of renal osteodystrophy regress after renal transplantation, with the most marked improvement in patients with better than average renal function.[8] Histologic improvement was said to continue, providing renal function did not deteriorate. The bones of some patients, however, were adversely affected by steroids.

In contrast, preliminary studies from this institution showed severe resorptive bone lesions in 6 long-term transplant patients with good renal function but with clinical evidence of hyperparathyroidism.[9] The bone lesions were thought to represent persistent osteitis fibrosa modified by steroid therapy. The findings and conclusions are compatible with other clinical studies indicating that hyperparathyroidism frequently persists in both short-term [2] and long-term [10] transplant patients.

Since the results cited above suggested that reduced bone volume (osteoporosis) in transplant patients was related to persistence of one form of renal osteodystrophy, secondary hyperparathyroidism, it seemed appropriate to determine whether other lesions characteristic of renal osteodystrophy persist in transplant patients. The study reported here was designed to answer that question, to provide further information about the pathogenesis of osteoporosis in renal transplant patients, and to provide further data about the relationship between success or failure of renal transplants and the severity and types of metabolic bone lesions.

Materials and Methods

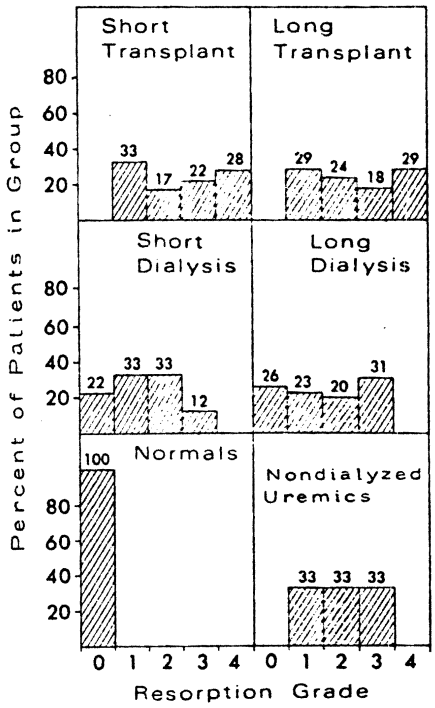
Sections of trabecular vertebral bone obtained at autopsy from 18 short-term (<6 months) and 17 long-term (>6 months) transplant patients were processed for microscopic examination by methods previously described.[1] Data obtained by a modification of Garner and Ball's point-counting method [11] was used to calculate

the relative total bone volume (BV), calcified bone volume (Ca^{++} BV), osteoid index (OI), resorption volume (RV), resorptive index (RI) and volume to surface ratio (V:S) of all sections by formulae given in the previous publication.[1] Semiquantitative resorption grades from 0 to 4 were also assigned to each section using histologic criteria previously defined.[1] To facilitate comparison between bone from transplant patients and that from dialyzed and nondialyzed patients, some of the data in the preceding publication is reported here. Statistical methods have been described previously.[1]

Results

Resorptive Activity and Distortion of Trabecular Architecture

All transplant patients had increased resorptive activity as judged by semiquantitative grading (Text-figure 1). There was no significant difference in the percentage of individuals with Grade 1 to 4 resorption between long- and short-term transplant patients. The most significant difference between transplant patients and dialyzed and nondialyzed patients was the exclusive occurrence of Grade 4 lesions in the transplant group. These lesions were characterized by extreme loss of volume in the majority of trabeculae by a process of internal tunneling resorption as illustrated in Figure 1. The lesions were distinguished from similarly extensive tunneling resorption in primary hyperparathyroidism



TEXT-FIG 1—Distribution of individuals with different resorptive grades in groups of long- and short-term transplant patients compared with dialyzed and nondialyzed uremics and control patients. Bar graphs illustrate the percentage of individuals in each group with a specific resorption grade.

by their lack of significant marrow fibrosis and relative lack of secondary bone formation; they were distinguished from tunneling resorption seen in secondary hyperparathyroidism of dialyzed and nondialyzed patients because in those individuals marrow fibrosis and bone formation was more prominent, the proportion of resorptive space to total trabecular volume (RI) was less, and the ratio of trabecular volume to trabecular surface (V:S ratio) was greater (see below).

The relative intratrabecular volume resulting from bone resorption (resorption volume) was markedly increased in transplant patients (Table 1). The mean resorptive volume of all transplant patients was significantly greater than that of normal individuals ($P < .005$) and was slightly greater than the mean of nondialyzed and dialyzed patients. The mean resorption volume of short-term transplant patients was almost two times greater than the means of nondialyzed and dialyzed patients and of long-term transplant patients ($P < .005$).

The ratio of intratrabecular resorption volume to total bone volume (resorptive index) was also greater in the transplant group than it was in the nondialyzed and dialyzed groups (Table 1). However, there was little difference in mean resorptive indices (RI) between long- and short-term transplant patients.

The volume to surface ratio (V:S) measured both resorptive activity and degree of trabecular distortion. V:S ratio of short-term transplant patients was similar to that of dialyzed patients. The mean V:S ratio of long-term transplant patients, however, was approximately one-half that of the other renal disease groups (Table 1).

The percentages of individuals in each renal disease group with specified deviations from normal mean values of RI and V:S are illustrated in Text-figure 2. The overall distribution of RI values was similar in both of the transplant groups and the long-term dialysis patients. The distribution of V:S ratios in short-term transplant patients was also similar to the distribution in long-term dialysis patients. However, the distribution with respect to this parameter in the long-term transplant group was markedly different from any other group; most of the individuals fell in the range from one-fifth to three-fifths normal.

Changes in Bone Volume

Mean values for bone volume of the total transplant group or of the short-term transplant group did not differ significantly from normal or from the dialyzed or nondialyzed uremic groups (Table 1). However, the mean value of the long-term transplant group was significantly lower than all other groups ($P < .005$). The distribution of individuals

Table 1—Quantitative Parameters of Bone Histology in Long- and Short-Term Transplant Patients Compared to Dialyzed and Nondialyzed Uremics and Normal Controls (Mean Values ± 1 SD)

Patient group	Number of individuals	Age (yrs)	RV × 10^{-2}	RI × 10^{-2}	V:S	BV × 10^{-2}	Ca^{++} BV × 10^{-2}	OI × 10^{-2}
Transplanted uremics								
Total	35	24	6.7 ± 11.1	5.1 ± 7.2	3.8 ± 2.0	12.3 ± 4.6	11.9 ± 4.6	3.4 ± 4.6
Short term	18	26	9.1 ± 16.0	5.8 ± 8.4	5.1 ± 1.6	14.5 ± 5.0	14.1 ± 4.9	3.0 ± 3.9
Long term	17	23	4.3 ± 6.5	4.4 ± 6.1	2.3 ± 1.0	9.9 ± 2.8	9.6 ± 2.8	3.8 ± 5.2
Normals	20	36	0.2 ± 0.4	0.1 ± 0.3	7.8 ± 1.4	13.0 ± 2.4	12.9 ± 2.3	0.4 ± 0.4
Conservatively treated uremics	15	46	4.2 ± 9.9	1.9 ± 3.3	7.1 ± 2.2	14.0 ± 6.4	13.3 ± 6.2	1.9 ± 2.5
Dialyzed uremics								
Total	44	39	4.1 ± 6.7	2.9 ± 4.0	4.8 ± 1.4	13.7 ± 6.1	12.7 ± 6.0	7.6 ± 7.8
Short term	9	39	0.9 ± 1.8	0.6 ± 1.3	5.8 ± 1.4	15.6 ± 10.6	15.1 ± 10.6	3.4 ± 3.2
Long Term	35	39	4.9 ± 7.0	3.5 ± 4.3	4.6 ± 1.4	13.3 ± 4.4	12.1 ± 4.2	8.7 ± 8.3

icantly less than the mean for long-term dialysis patients ($P < .005$). The distribution of individuals with specified ranges of osteoid index was approximately the same in long- and short-term transplant groups, both of which were comparable to short-term dialysis patients.

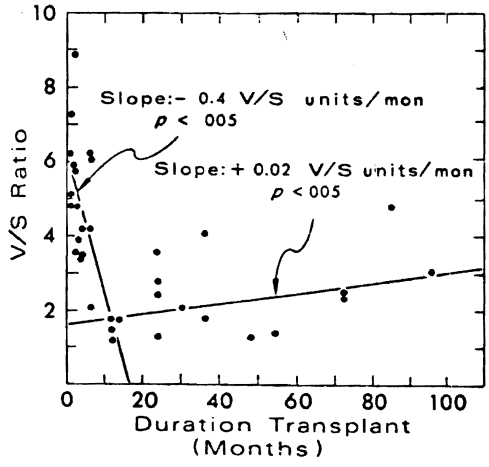
Interrelationships Among Different Indices of Bone Histology and the Duration of Transplantation

There was no statistically significant relationship between osteoid index and any other index of bone histology, or between osteoid index and duration of transplantation. Stated differently, both the osteoid and the calcified bone volumes changed in the same way as the total bone volume changed.

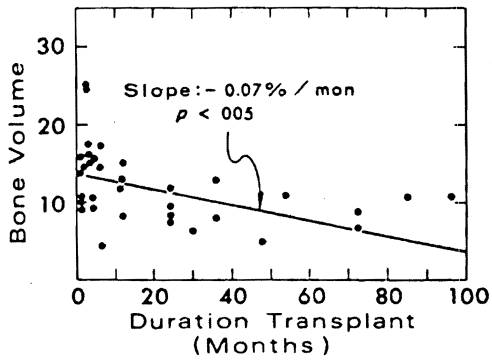
As noted previously, the absolute amount of resorptive volume was maximal in short-term transplant patients and was somewhat decreased in long-term transplant patients. The resorptive index was approximately the same in long- and short-term transplant patients. There was, however, no statistically significant linear correlation between these two indices and duration of transplantation.

There was no linear correlation between V:S ratio and duration of transplantation for the entire transplant group (0.2 to 96 months). However, from 0.2 to 12 months there was a significant ($P < .005$) decrease in V:S ratio, and from 12 to 96 months an equally significant but markedly less steep increase in the V:S ratio (Text-figure 3).

As noted above, bone volume in long-term transplant patients tended to be lower than the bone volume in short-term transplant patients. There was a statistically significant decrease in bone volume from 0.2 to 96 months (Text-figure 4).



TEXT-FIG 3—Regression analysis of V:S ratio as a function of transplant duration. There is a strong negative slope between 0 to 13 months (− 0.38 V:S units/mon, $P < .005$) and a slight positive slope from 12 to 96 months (+ .017 V:S units/mon, $P < .005$).



TEXT-FIG 4—Regression analysis of total bone volume as a function of transplant duration. There is a slight negative slope (− 0.07%/mon, $P <$ .005).

Relationship Between Transplant Rejection and Quantitative Bone Histology

Tables 2 and 3 compare indices of bone histology in transplant patients with good and bad renal function. Individuals in Group A had no clinical evidence of rejection or had rejection of less than 2 months. Individuals in Group B had clinical evidence of rejection during the entire period of transplantation. The osteoid index, resorptive volume, and volume to surface ratio of the transplant patients with good renal function did not differ significantly from those of patients with poor renal function following transplantation. The duration of transplantation for 8 of the 10 patients with good renal function was 4 months or less. The only significant difference in bone histology between the two groups was a decrease in bone volume in the patients with rejection (P .05 to .025). Individuals in Group C all had long-term transplants, but there were marked differences in the duration of rejection between individuals with the same total transplant duration. There were no consistent differences in any of the quantitative indices of bone histology between such individuals.

Discussion

The results of this study do not fully support the experience of Hammersmith Hospital.[8] Both long- and short-term transplant patients at this institution have many of the features of renal osteodystrophy. As a group, transplant patients have more severe bone resorption than either nondialyzed or dialyzed patients. They also have mineralization defects which in terms of relative incidence and severity are more severe than those of nondialyzed patients, about the same as those of short-term dialysis patients, and less severe than those of long-term dialysis patients.

Metabolic bone disease in transplant patients here differs from that

Table 2— Quantitative Bone Histology and Transplant Function

Case No.	Total transplant duration (mons)	Months good function	Months rejection	OI	RV	BV	V:S	RG*
Transplant patients with 0 to 2 months rejection (Group A)								
72-235	0.1	0.1	0	.017	.000	.159	6.2	1
69-228	1.0	1.0	0	.014	.000	.138	7.3	1
69-79	2.0	1.0	1	.019	.006	.245	5.9	2
69-2	2.0	2.0	0	.003	.001	.247	9.0	1
72-282	2.0	2.0	0	.009	.003	.145	5.9	2
72-24	3.0	2.75	.25	.088	.056	.176	3.5	3
71-282	3.0	3.0	0	.012	.000	.106	3.9	1
71-214	4.0	4.0	0	.031	.019	.158	4.2	4
72-166	12.0	10.0	2	.000	.000	.078	1.9	1
70-52	12.0	11.0	1	.032	.023	.153	1.5	4
				.023 ± .025	.011 ± .018	.161 ± .053	4.9 ± 2.4	
Transplant patients with no normal function (Group B)								
69-387	0.2	0	0.2	.003	.001	.106	5.1	3
70-212	1.0	0	1	.024	.000	.098	4.8	1
71-272	2.0	0	2	.021	.013	.110	3.6	4
69-373	3.0	0	3	.004	.037	.163	4.8	4
69-380	6.0	0	6	.016	.001	.148	6.2	3
71-356	6.0	0	6	.037	.001	.045	2.1	4
69-401	12.0	0	12	.038	.003	.130	1.7	4
71-254	12.0	0	12	.022	.003	.119	1.2	1
69-255	24.0	0	24	.000	.002	.097	3.6	3
				.018 ± .014	.007 ± .011	.133 ± .034	3.7 ± 1.7	

* Resorptive grade.

Table 3—Quantitative Bone Histology and Transplant Function in Long-Term Transplants (Group C)

Case No.	Total transplant duration (mon)	Poor function	Good function	OI	RV	BV	V:S	RG*
69-401	12	12	0	.038	.003	.130	1.7	4
70-52	12	1	11	.032	.023	.153	1.5	4
71-254	12	12	0	.022	.003	.119	1.2	1
72-166	12	2	10	.000	.000	.078	1.9	1
69-255	24	24	0	.000	.002	.097	3.6	3
69-265	24	12	12	.004	.000	.089	2.4	2
69-283	24	6	18	.046	.008	.078	1.3	4
72-87	24	12	12	.013	.000	.126	2.8	2
72-232	36	12	24	.000	.003	.132	4.1	2
72-235	36	12	24	.072	.001	.082	1.8	2
60-351	48	12	36	.125	.008	.050	1.3	4
72-254	54	24	30	.042	.025	.109	1.4	4
69-111	72	12	60	.199	.000	.090	2.5	3

* Resorptive grade.

seen in dialyzed and nondialyzed uremics in one important aspect: Transplant patients do not have increased bone volume but rather a very strong tendency toward a decreased bone volume. The opposite situation tends to prevail in the other two groups.

According to these data, none of these abnormalities in bone except bone volume are influenced by success or failure of the renal transplants. This is a generalization that must be documented in carefully controlled prospective studies in which detailed analysis of renal function are correlated with bone changes determined by kinetic studies on serial bone biopsies.

Reduced bone volume, increased resorption volumes and decreased volume:surface ratios are the most significant abnormalities in bone of transplant patients. From a morphologic standpoint, bone of transplant patients with the most severe reductions in volume is quite unlike bone seen in other forms of metabolic bone disease. The most striking feature of trabecular bone in these transplant patients is the extent to which tunneling resorption has hollowed out the bone trabeculae and decreased the V:S ratio while markedly increasing the resorptive volume. It is apparent that, for a given decrease in trabecular volume, tunneling resorption will result in at least twice the increase in trabecular surface that resorption from a single surface could produce. Morphologically, this type of tunneling resorption of trabecular bone is similar to cortical bone remodeling units described by La Croix.[12]

Accordingly, spaces formed in trabecular bone by tunneling resorption would be expected to fill in with new bone, once the resorptive phase of remodeling were complete.[12]

Tunneling resorption is a characteristic feature of primary hyperparathyroidism[13] and secondary hyperparathyroidism in renal osteodystrophy.[14,15] In primary hyperparathyroidism, the spaces are filled with fibrous marrow in early stages, and there is a moderate amount of new bone formation in later stages. Total skeletal volume is markedly reduced.[13] In short- or long-standing renal osteodystrophy in dialyzed and nondialyzed patients, intratrabecular spaces occur, but they contain both osteoclasts (resorptive phase) and osteoblasts (bone-forming phase), and the total trabecular bone volume is characteristically normal or increased.[1]

Less severe tunneling resorption is also seen in osteoporosis associated with hyperthyroidism, again with both osteoblasts and osteoclasts within the spaces.[16,17] In the resorptive phase of disuse osteoporosis, similar tunneling resorption of trabeculae is seen. This is followed by renewed bone formation within the resorptive spaces once the bone is remobilized.[17] Increased resorptive activity of any kind is said to be rare in senile and idiopathic osteoporosis,[18] although in our experience it is possible to see mild degrees of increased resorption, including occasional small resorption tunnels containing either osteoclasts or osteoblasts, in these conditions also. In steroid-induced osteoporosis, resorptive spaces are rarely seen.[19] In this condition the smooth trabeculae are covered by normal-appearing osteoblasts. Thus, in comparison to other conditions characterized by reduced bone volume and volume:surface ratios, severely affected bone in transplant patients has a markedly increased resorption volume in proportion to trabecular volume, there is no marrow fibrosis, and the osteoblastic phase of the remodeling process must be partially suppressed since bone volume falls. In most of the patients, some bone formation can be shown by the frequent occurrence of osteoid seams and elevated osteoid indices. However, unlike the situation in dialyzed and nondialyzed patients, the osteoid seams are quite thin. The elevations of osteoid index in transplant patients thus seem to represent a mineralization defect which is exaggerated by the markedly reduced bone volume characteristic of these patients.

The data of this study indicate that the critical period is the first year after transplantation. Resorption volume is maximal during the first 6 months following renal transplantation. The V:S ratio falls sharply during the first year. The bone volume begins to fall during the first year and declines progressively for as long as 96 months. During the first year

after transplantation, hypercalcemia is frequent and is associated with parathyroid hyperplasia.[10] These clinical and biochemical studies support the morphologic data presented here and suggest that parathormone-induced bone resorption is a primary cause of declining bone volumes in transplant patients. Studies of bone volume changes in long-term dialysis patients suggested that lower serum phosphate levels might contribute to a reduced bone volume, either through loss of suppression of parathormone-induced bone resorption or by loss of stimulation to bone formation.[1] In the present study patients with poor renal function (and presumably higher serum phosphate levels) had somewhat lower bone volumes. These results might be explained by increased steroid-induced suppression of the synthetic phase of bone remodeling,[20,21] since the patients with rejection receive higher doses of steroids.

Similar mechanisms presumably explain the slow recovery of V:S ratios and the continuing decline of bone volume in long-term transplant patients. Grade 4 resorptive lesions persist in these patients, as does clinical evidence for hyperparathyroidism.[10] The continued use of steroids could be anticipated to perpetuate suppression of bone formation which in the face of continued excessive resorption would result in a declining bone volume. Prospective studies correlating steroid dosage, renal function, serum mineral levels, and parathormone levels with serial quantitative bone biopsies or densitometric studies are needed to resolve these questions.

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