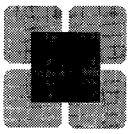

Chemical and histological features of men with osteoporosis

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■ Six men (average age, 42) underwent evaluation for idiopathic osteoporosis. Standard measurements of serum and urine were studied. Lumbar skeletal mineral density was measured by dual-photon absorptiometry. Skeletal biopsies of the iliac crest were obtained after double-labeling with tetracycline. Average renal cyclic adenosine monophosphate and urinary calcium values were elevated. Lumbar spinal density was 72% of age-matched norms, and histomorphometric analyses of bone revealed decreased trabecular bone volume and formation rate and increased trabecular osteoid area, osteoclast number, and calcification rate. The results suggest that idiopathic osteoporosis in these men is associated with increased parathyroid hormone secretion as assessed by increased renal cyclic adenosine monophosphate and high skeletal remodeling activity.

□ INDEX TERMS: OSTEOPOROSIS; MALE; BONE REMODELING; PARATHYROID HORMONES; ADENOSINE CYCLIC MONOPHOSPHATE
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OUR UNDERSTANDING of osteoporosis in men is limited compared with our understanding of osteoporosis in women.[1] Primary osteoporosis is unusual in men; secondary causes are more frequent. Recent data suggest that changes in vitamin D and parathyroid hormone may cause primary osteoporosis in older men[2]; however, there is no consistent explanation for osteoporosis occurring in young men. Secondary conditions that may be associated with, or cause, osteoporosis in the young population include hypercalciuria, hypogonadism, alcoholism, genetic abnormalities, and malignancy[3–6]; however, most cases of osteoporosis in men are idiopathic. To investigate the cause of osteoporosis in men, this retrospective study evaluated serum biochemistry and skeletal histology in six patients.

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METHODS

Data were obtained from the records of six men (ages 34 to 50) with chronic back pain who were evaluated for osteoporosis. They had roentgenographic evidence of vertebral fractures, osteoporosis, or both. They had no history of gastrointestinal, renal, or endocrine diseases. Two patients had lactose intolerance (patients 3 and 4), two had a history of alcohol and drug use (patients 1 and 3), one had smoked cigarettes for more than 30 years (patient 4), and another had an unsubstantiated history of renal colic (patient 2).

Routine laboratory assays were used to measure serum and urine markers of calcium metabolism. Serum calcifediol (25-dihydroxyvitamin D) and calcitriol (1,25-dihydroxyvitamin D) were measured by radioimmunoassay (Nichols Laboratory, San Diego, Calif). Nephrogenous cyclic adenosine monophosphate (AMP), calculated from the analyses of plasma and urine nucleotides,[7] was used to assess parathyroid hormone secretion. Normal values of cyclic AMP were less than 2.8 nmol/dL of glomerular filtrate. Lumbar spinal mineral density was measured by dual-photon

TABLE 1
OSTEOPOROSIS IN MEN: SERUM CHEMICAL AND HORMONE VALUES

Patient No.	Age (yrs)	Weight (kg)	Calcium (mg/dL)	Phosphorus (mg/dL)	Creatinine (mg/dL)	Alkaline phosphatase (IU/L)	Albumin (g/dL)	Calcifediol (ng/mL)	Calcitriol (pg/mL)	Thyroxine (µg/mL)	Testosterone (ng/mL)
1	34	73	9.7	4.1	0.9	40	4.8	41	47	-	402
2	46	92	9.4	3.9	0.9	61	4.6	-	-	-	-
3	34	83	9.7	4.5	1.3	54	4.3	-	65	-	509
4	50	68	9.7	3.5	0.8	59	4.3	28	35	10.2	416
5	40	78	9.8	4.3	0.7	72	4.9	23	53	10.3	403
6	50	74	9.6	3.6	1.2	61	4.5	35	46	9.8	393
Mean ± SD*			9.6 ± 0.1	3.9 ± 0.3	0.96 ± 0.23	58 ± 10	4.5 ± 0.2	32 ± 8	49 ± 10	10.1 ± 0 .2	424 ± 48
Reference normal ± 2 SD			8.5–10.5	2.5–4.5	0.7–1.4	20–120	3.5–5.0	9–52	37–69	5.2–11.3	200–1,000

*Standard deviation

absorptiometry using a gadolinium source (Lunar Radiation Model DP3). The resulting values represent area density expressed in grams per centimeter squared (g/cm^2).

Iliac crest biopsies were obtained from the standard location, 2 cm posteroinferior to the anterosuperior iliac spine. The transverse sample containing both outer and inner cortical tables of the pelvis encompassing the trabecular bone was obtained using an 8-mm trocar, sleeve, and biopsy needle. The biopsy was fixed in 70% alcohol and processed for nondecalcified section using a Jung microtome. Sections were stained with hematoxylin and eosin, Goldner's trichrome, and toluidine blue. Selected parameters of bone remodeling were quantitated using a digitizing pad and microcomputer with image-analysis software (R & M Biometrics, Nashville, Tenn). These parameters included trabecular bone volume, trabecular osteophyte surface, trabecular osteoid area, osteoclasts per millimeter of trabecular surface, calcification rate, and bone formation rate.[8] Data were represented as the mean plus or minus one standard deviation.

TABLE 2
OSTEOPOROSIS IN MEN: URINARY VALUES

Patient	Cortisol (µg/day)	Calcium (mg/day)	Renal cyclic adenosine monophosphate (nmol/dLof glomerular filtrate)
1	70	201	5.0
2	68	324	3.2
3	40	342	2.7
4	68	202	4.1
5	121*	397	2.1
6	82	314	3.0
Mean ± SD†	74 ± 26	296 ± 79	3.4 ± 3.0
Reference normal ± 2 SD	20–110	<300	0–2.8

*Dexamethasone suppression test and repeated urinary cortisol were normal
†Standard deviation

RESULTS

Serum biochemical and hormonal values were normal (*Table 1*); however, testosterone levels were low-normal. Four patients were hypercalciuric (urinary calcium >300 mg/day) (*Table 2*). Five patients had high-normal or increased renal cyclic AMP. The group average was 22% greater than the upper 95% confidence interval; however, not every patient had elevated values.

Bone mineral density varied widely; mean bone mineral density was about 30% less than that of age-matched normal patients (*Table 3*). Histomorphometric data showed a decreased trabecular bone volume and bone formation rate (*Table 3*). Trabecular osteoid volume was increased in four patients. The average osteoclast number was increased but this value was skewed from the small number of observations and the large increases noted in patients 4 and 6 (*Table 3*). These histological changes were compatible with a high rate of remodeling activity.

DISCUSSION

In these patients, renal cyclic AMP and urinary calcium were either increased or unusual for the clini-

TABLE 3
OSTEOPOROSIS IN MEN: BONE DENSITY AND HISTOLOGY

Patient	Density (g/cm^2)	Percent of density in age-matched normal patients	Trabecular bone volume*	Trabecular osteoid volume†	Osteoclasts/mm of trabecular bone perimeter	Calcification rate‡ (μ/day)	Bone formation rate§ (μ/day)
1	0.82	68	-	-	-	-	-
2	0.94	79	10.2%	4.6%	0.03	0.72	0.02
3	0.84	70	19.8%	1.9%	-	0.87	0.04
4	0.81	59	11.4%	2.5%	0.12	0.59	0.21
5	0.79	67	10.4%	3.3%	-	-	-
6	1.0	89	15.6%	4.4%	0.09	0.72	0.15
Mean (SD)‖	0.86 (0.08)	72 (10)	13.4%(4.2%)	3.3%(1.1%)	0.08(0.04)	0.72(0.11)	0.10(0.09)
Norms[29]	-	-	22%(4%)	1.9%(0.04%)	0.03(0.01)	0.64(0.01)	0.48(0.19)

*Proportion of medullary cavity occupied by mineralized and osteoid trabecular bone
†Proportion of osteoid and mineralized trabecular bone consisting of osteoid bone
‡Average distance between all tetracycline double labels divided by the time between administration of labels
§Calcification rate multiplied by the trabecular bone surface covered by tetracycline
‖Standard deviation

cal setting; however, the causal relationship between these measurements and the histomorphometric changes of the biopsy is unclear.

Several problems arise in the interpretation of the data: the study group is small, the data are heterogeneous, and it is uncertain whether these changes are sufficiently long-standing to cause osteoporosis or merely reflect a short-term physiologic change without causal significance. However, the observations afford an opportunity to speculate about the significance of these chemical changes on osteoporosis and the relation of aspects of the medical histories and skeletal function.

Renal cyclic AMP, rather than the parathyroid hormone assay, was used to measure biologically active parathyroid hormone. Technical problems with the parathyroid hormone assay and metabolism of the hormone to a variety of smaller fragments make the usual C-terminal and N-terminal assays less reliable than measurements of renal cyclic AP.[9-12] Cyclic AMP is a marker for biologically active intact parathyroid hormone; increased levels directly reflect serum hormone concentrations and obviate the problems encountered with the hormonal assays.[7] The new immunoradiometric assay (IRMA) for intact parathyroid hormone, which also overcomes these difficulties, was not available when these patients were evaluated.[13]

Four of our patients with hypercalciuria are reminiscent of osteoporotic men described by Perry and colleagues.[3] Their patients were hypercalciuric (average daily output 473 mg), consumed a diet uncontrolled for calcium, had normal serum parathyroid hormone levels, and had a high state of bone remodeling. Hypercalciuria in the presence of normal parathyroid hormone suggests hyperabsorptive hypercalciuria. This condition does not increase urinary hydroxyproline, osteoclastic activity, or bone turnover[14]; however, it decreases bone matrix and mineralization.[15] In four of our patients, renal cyclic AMP was high-normal (2.75 nmol/dL) and urinary calcium was increased (average value 374 mg). Together, these findings indicated a renal calcium leak (renal hypercalciuria). In two patients renal cyclic AMP was high (average 4.5 nmol/dL of glomerular filtrate) and daily urinary calcium was lower than in the other patients (mean 201 mg). These two patients lowered the average renal cyclic AMP to 1.1 nmol/dL of glomerular filtrate after calcium supplementation. These findings suggested secondary hyperparathyroidism from dietary deficiency.

Studies show that parathyroid hormone increases the remodeling rate of bone. Depending on the concentration, the effect can be bone loss or gain.[16,17] Renal leak calciuria and its secondary hyperparathyroid state are associated with osteopenia[18]; four of our patients may have developed osteoporosis as a result of this abnormality. The two other patients had secondary hyperparathyroidism from calcium deficiency that reversed after supplementation of the diet with calcium. Chronic calcium deficiency is considered a cause of osteoporosis by some[19] but not all investigators.[20]

Alcohol abuse and lactose intolerance were recognized in a few patients; these conditions have implications for osteoporosis. Ethanol impairs osteoblastic activity and decreases bone formation.[21,22] Experimental diets that contain 30% total calories from ethanol decrease osteoblastic function in rats.[22] A comparable

situation in human subjects is the daily consumption of 600 to 700 calories from alcohol or 9 to 10 oz of 80-proof whiskey or its equivalent.[23] The key factor for the male osteoporotic patient is how much and how long he abused alcohol. Lactose intolerance occurs frequently in women with primary osteoporosis, but its occurrence in men is unclear.[24] Some data attribute osteoporosis to a lifelong avoidance of dairy products[24,25] rather than to a malabsorption of calcium.[26]

The heterogeneity of our patients makes it difficult to determine an unequivocal reason for their skeletal disease. Diagnosing a cause for osteoporosis in men is more complex than for women because in men secondary causes must be sought. Hence, laboratory evaluation is important and should include serum calcium, phosphorus, alkaline phosphatase, kidney and liver function, and the complete blood profile, and any abnormalities must be evaluated. Thyroid, gonadal, parathyroid, and adrenal functions should be measured. Hypercalciuria should be sought, since this is treatable with thiazide diuretics, which suppress excessive urinary calcium and increase bone density.[27,28]

Therapy of the disease must include removal of the secondary causes. Where primary disease is found, the approach includes good nutrition (adequate calcium), exercise, and the empirical use of drugs in much the same fashion as needed to treat primary osteoporosis in women (with the substitution of male hormones for female hormones).[29]

In summary, we have described a heterogeneous group of osteoporotic men who had inappropriate levels of renal cyclic AMP and urinary calcium, and bone biopsies that showed a high remodeling state. We postulate that increased parathyroid hormone levels promoted a chronic high remodeling state that eventually led to osteoporosis.

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