0021-972X/00/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 85, No. 3
Printed in U.S.A.

Effect of Vitamin D Nutrition on Parathyroid Adenoma Weight: Pathogenetic and Clinical Implications*

D. SUDHAKER RAO, M. HONASOGE, GEORGE W. DIVINE, EVELYN R. PHILLIPS, MIN W. LEE, MOHAMMED R. ANSARI, GARY B. TALPOS, AND A. MICHAEL PARFITT

Division of Bone and Mineral Metabolism, Department of Medicine (D.S.R., M.H., E.R.P.), Departments of Biostatistics (G.W.D.), Pathology (M.W.L.), and Surgery (M.R.A., G.B.T.), Henry Ford Health System, Detroit, Michigan 48202; and Division of Endocrinology and Center for Osteoporosis and Metabolic Bone Disease, University of Arkansas for Medical Sciences (A.M.P.), Little Rock, Arkansas 72205

ABSTRACT

In primary hyperparathyroidism, adenoma size is a major determinant of disease severity and manner of presentation, but the reason for the large variation in size (>100-fold) is unknown. One factor could be the level of vitamin D nutrition, because in India, where vitamin D deficiency is endemic, adenomas are larger and the disease more severe than in the U.S. Accordingly, we determined the relationship between vitamin D nutrition, as measured by serum levels of 25-hydroxyvitamin D (25OHD), and parathyroid gland weight, expressed on a logarithmic scale, in 148 U.S. patients with primary hyperparathyroidism.

A significant inverse relationship was found between log gland weight as dependent variable and serum 25OHD as independent variable ($r = -0.365$; $P < 0.0001$). The only other influence on gland weight was a weak inverse correlation with age. Log gland weight as an independent variable was significantly related to adjusted calcium, PTH, and alkaline phosphatase (AP) as dependent variables. In 51 patients with serum 25OHD levels less than 15 ng/mL, gland weight, PTH, AP, and adjusted calcium were each significantly higher than in 97 patients with 25OHD levels of 15 ng/mL or more, but 1,25-dihydroxyvitamin D levels were similarly increased in both groups. In the former group the response of adjusted calcium to PTH was blunted, and the response of AP was enhanced, based on significant differences in regression slopes ($P = 0.0004$ and 0.0022, respectively).

Suboptimal vitamin D nutrition stimulates parathyroid adenoma growth by a mechanism unrelated to hypocalcemia or 1,25-dihydroxyvitamin D deficiency and reduces the calcemic response to PTH, so that a higher PTH level and more parathyroid cells are needed to raise the patient's serum calcium to the level corresponding to the increased set-point that is characteristic of the disease. Improved vitamin D nutrition in the population is partly, perhaps largely, responsible for the historical changes in disease severity and manner of presentation that have occurred over the last 50 yr. (*J Clin Endocrinol Metab* **85:** 1054–1058, 2000)

SINCE THE classic descriptions of the disease by Fuller Albright more than half a century ago (1), two major changes have taken place in the clinical expression of primary hyperparathyroidism. First, there has been both a rise and a fall in the apparent incidence of the disease (2, 3), and second, there has been a substantial shift in its clinical pattern of presentation (4–6). A 10-fold increase in the incidence of the disease occurred after its association with nephrolithiasis was established in 1934 (6), and a further 4-fold increase in apparent incidence was observed in the early 1970s when routine biochemical screening was introduced in the U.S. (2). Since then, there has been a 3-fold decline in incidence (3), ascribed to factors such as increasing use of hormone replacement therapy in postmenopausal women (3), abandoning the therapeutic use of head and neck radiation (3), and improvement in vitamin D nutrition in the population (3, 7, 8). However, no systematic studies have been performed to either confirm or refute these possibilities.

The introduction of biochemical screening led to a large increase in the proportion of asymptomatic patients (5, 9, 10) and a corresponding reduction in the proportion of patients with nephrolithiasis and osteitis fibrosa, the specific bone disease of hyperparathyroidism (6). This dilution effect also contributed to the striking reduction in mean tumor weight over the last 50 yr (6), but there may have been an absolute reduction in the number of very large tumors and a consequent absolute reduction in the number of patients with osteitis fibrosa (7, 11). We previously reported that poorer vitamin D and calcium nutrition in India than in the U.S. could account for the persistence of both large tumors and osteitis fibrosa in India (8). We now report a significant inverse relationship between vitamin D nutrition and parathyroid tumor weight within the U.S. that may be partly responsible for the changes in disease presentation previously described.

Received August 5, 1999. Revision received November 4, 1999. Accepted November 22, 1999.

Address all correspondence and requests for reprints to: Dr. D. Sudhaker Rao, Division of Bone and Mineral Metabolism, Henry Ford Health System, 2799 West Grand Boulevard, K-16, E-1607, Detroit, Michigan 48202-2689. E-mail: danrao50@hotmail.com.

* This work was supported in part by NIH Grants RO1-DK-43858, P01-AG-13918, and RO1-AR-43003.

Subjects and Methods

Patients

All patients with primary hyperparathyroidism who were cured by removal of a single adenoma of known weight from 1992–1997, retrieved

through the computerized medical record system of the Henry Ford Health System, were considered for inclusion in the study. We excluded patients referred directly for surgery, because the preoperative biochemical measurements were not performed either at Henry Ford Health System Laboratory or in the Bone and Mineral Research Laboratory. We also excluded patients with serum creatinine levels above 1.5 mg/dL and those with multiple endocrine neoplasia, multiglandular disease, or tumors weighing less than 100 mg. In addition, 1 patient each was excluded because of concomitant Paget's disease of bone, therapy with lithium, or parathyroid carcinoma. Three patients of Asian Indian ethnicity were also excluded. Two hundred and thirty-seven patients remained, in 148 of whom serum levels of 25-hydroxyvitamin D (25OHD) were available, forming the primary study group. Their characteristics are compared in Table 1 with the remainder of the 237 patients in whom 25OHD levels were not available. The patients excluded had a lower proportion of women and were younger; the reasons for these differences were not evident. The proportions of women and African Americans were generally similar to those in other studies of primary hyperparathyroidism reported from our institution (5, 9, 10).

Laboratory methods

Serum levels of total calcium (Ca; reference range, 8.2–10.0 mg/dL), phosphate (P; reference range, 2.5–4.5 mg/dL), alkaline phosphatase (AP; reference range, 0–120 IU/L), creatinine (reference range, 0.6–1.5 mg/dL), total protein, and albumin were measured in the hospital laboratory by standard methods using a Hitachi-747 autoanalyzer (Hitachi, Hialeah, FL). Serum Ca was adjusted for serum albumin (12). Serum ionized Ca was measured by a Nova-6 ion-specific electrode (reference range, 1.0–1.35 mmol/L). Serum intact PTH (reference range, 10–65 pg/mL) was measured by immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA). Serum 25OHD was measured by RIA (INCSTAR Corp., Stillwater, MN; reference range, 15–60 ng/mL), and serum 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D] by radioreceptor assay using kits from Nichols Institute Diagnostics (reference range, 20–75 pg/mL).

Statistical methods

Unpaired *t* tests were used to compare the groups, and ANOVA was used to examine the effects of age and sex. Linear regression was used to examine the relationships between variables. Parathyroid gland weight is log normally distributed (6) and therefore was expressed on a logarithmic scale.

Results

The excluded patients had a higher serum creatinine level, but otherwise the included and excluded patients did not differ significantly in biochemical characteristics or parathyroid gland weight (Table 2). The mean (±SD) serum level of 25OHD for the entire study group was 18.8 ± 9.4 ng/mL (range, 1–52 ng/mL), and the geometric mean weight of the resected parathyroid gland was 0.743 g (geometric SD, 2.71 g; range, 0.10–8.7 g), with a significant inverse correlation between them ($r = -0.365$; $P < 0.0001$; Fig. 1 and Table 3). There was a weak direct correlation between parathyroid gland weight and serum 1,25-$(OH)_2$D, and a weak inverse correlation between gland weight and age, but no relationship with serum creatinine (Table 3). There were the expected significant direct relationships between parathyroid gland weight and serum levels of PTH, adjusted Ca, and AP (6) (Table 3).

The study group was divided into those with and without vitamin D insufficiency (serum 25OHD, <15 ng/mL) (13–15). The mean parathyroid gland weight and, as a result, the mean serum levels of PTH, AP, and adjusted Ca were all significantly higher in patients with vitamin D insufficiency, and plasma phosphate was lower (Table 4). However, there was no significant difference in serum 1,25-$(OH)_2$D levels between the two groups.

The effects of PTH in these two groups are compared in Table 5. Based on highly significant differences in regression slopes, vitamin D insufficiency blunted the calcemic response to PTH, but exaggerated its effect on AP.

TABLE 1. Demographic characteristics of the patient population (n = 237)

Characteristic	Study patients [no. (%)]	Excluded patients [no. (%)]
Total no.	148 (100)	89 (100)
Men	24 (16)	27 (30)[a]
Women	124 (84)	62 (70)[a]
African-Americans	57 (39)	26 (29)
Caucasians	91 (61)	63 (71)
Age (yr ± SD)	62 ± 12	55 ± 13[b]

[a] $P = 0.0165$.
[b] $P < 0.0001$.

TABLE 2. Biochemical findings in patients with primary hyperparathyroidism

Measurement	Study patients (n = 148)		Excluded patients (mean ± SD)
	Mean ± SD	Range	
Adjusted calcium (mg/dL)	10.8 ± 0.70	10.0–13.1	10.9 ± 0.78
Ionized calcium (mmol/L)[a]	1.35 ± 0.40	1.20–1.93	1.48 ± 0.13
Phosphate (mg/dL)	2.82 ± 0.49	1.60–4.20	2.78 ± 0.54
Creatinine (mg/dL)	0.93 ± 0.22	0.50–1.50	1.06 ± 0.21[b]
25OHD (ng/mL)	18.8 ± 9.4	1.00–52.0	NP
1,25-$(OH)_2$D (pg/mL)[c]	61.8 ± 18.1	26.0–128	NP
Alkaline phosphatase (IU/L)	121 ± 79	44.0–725	120 ± 57
PTH (pg/mL)	128 ± 130	37.0–1256	117 ± 72
Parathyroid gland wt (g)	1.27 ± 1.61	0.10–8.69	1.47 ± 1.72
Parathyroid gland wt (g)[c]	0.743 (2.71)		0.863 (2.89)

NP, Not performed (exclusion criterion).
[a] n = 78.
[b] $P < 0.0001$.
[c] n = 80.
[c] Geometric mean and (geometric or multiplicative SD).

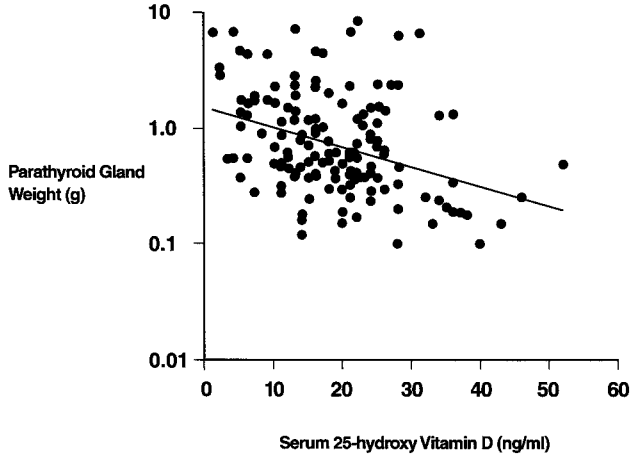

FIG. 1. Significant inverse relationship ($r = -0.365$; $P < 0.0001$) between parathyroid gland weight (logarithmic scale) and an index of vitamin D nutrition (serum 25OHD) in 148 patients with primary hyperparathyroidism. Regression parameters are given in Table 3.

TABLE 3. Linear relationships between log parathyroid gland mass (PGM) and other variables in patients with primary hyperparathyroidism

Variable	Intercept	Slope	r	*P*
Log PGM as dependent variable				
Age	0.229	−0.0058	−0.166	0.043
25OHD	0.187	−0.0168	−0.365	<0.0001
1,25-$(OH)_2D$[a]	−0.404	0.0046	0.190	0.091
Creatinine	−0.253	0.129	0.089	0.283
Log PGM as independent variable				
Adjusted calcium	10.8	0.621	0.354	<0.0001
PTH (pg/mL)	144.9	140.2	0.467	<0.0001
Alkaline phosphatase	125.6	36.1	0.198	0.016

[a] n = 80.

TABLE 4. Comparison of biochemical findings in patient with low and normal serum 25OHD levels

Measurement	25OHD <15 ng/mL	25OHD ≥15 ng/mL	*P*
No. of patients	51	97	
Age (yr)	62 ± 14	62 ± 12	NS
25OHD (ng/mL)	9.29 ± 3.79	23.8 ± 7.34	[a]
1,25-$(OH)_2D$ (pg/mL)	63.5 ± 21.9	60.7 ± 15.5	NS
Parathyroid gland wt (g)	1.66 ± 1.75	1.07 ± 1.53	0.035
Parathyroid gland wt (g)[b]	1.05 (2.69)	0.62 (2.61)	0.002
PTH (pg/mL)	172 ± 192	104 ± 71	0.002
Alkaline phosphatase (IU/L)	141 ± 113	110 ± 51	0.023
Adjusted calcium (mg/dL)	11.0 ± 0.80	10.7 ± 0.63	0.048
Ionized calcium (mmol/L)	1.48 ± 0.16	1.44 ± 0.10	NS
Phosphate (mg/dL)	2.73 ± 0.58	2.87 ± 0.43	0.017

[a] Criterion for separation.
[b] Geometric mean (geometric or multiplicative SD).

Discussion

In a large series of patients with primary hyperparathyroidism, most of whom were asymptomatic and had mild disease, we found for the first time a significant inverse relationship between serum 25OHD, the best available index of vitamin D nutrition (13–15), and gland weight, the best available index of parathyroid tumor cell number (6). We also confirmed earlier reports (16, 17) that parathyroid tumor weight is a significant determinant of disease severity, as reflected by serum levels of PTH, Ca, and AP. One possible explanation for our data is that hyperparathyroidism in some way compromises vitamin D nutrition (7, 18). PTH stimulates the renal 1α-hydroxylase, and it was suggested that increased 1,25-$(OH)_2D$ biosynthesis could accelerate the consumption of 25OHD as substrate (19), but this suggestion is inconsistent with the wastefulness of vitamin D metabolism. Only about 10% of daily calciferol supply is ordinarily used for 1,25-$(OH)_2D$ production (20). A more plausible possibility is that an increased serum level of 1,25-$(OH)_2D$ accelerates 25OHD catabolism (21), but we found no inverse correlation between serum levels of 1,25-$(OH)_2D$ and 25OHD. Consequently, we believe that parathyroid weight is the dependent and 25OHD the independent variable, not the other way around.

It has been known for many years that severe and advanced vitamin D deficiency, as can occur in the United Kingdom because milk is not fortified (22) or in India because of malnutrition (23), is associated with very severe hyperparathyroidism. Such patients have either subnormal levels of 1,25-$(OH)_2D$ (7, 24) or hypocalcemia (25, 26), the major signals for parathyroid hyperplasia in secondary hyperparathyroidism (6). In early or mild vitamin D depletion, 1,25-$(OH)_2D$ levels are normal or even increased (21), and our data indicate that suboptimal vitamin D nutrition promotes cell proliferation in parathyroid adenomas by some mechanism other than 1,25-$(OH)_2D$ deficiency or hypocalcemia. This effect on growth of an existing adenoma must be distinguished from the mutagenic effect of increased parathyroid cell proliferation secondary to prolonged vitamin D deficiency, a phenomenon referred to as tertiary hyperparathyroidism (6). 1,25-$(OH)_2D$ exerts receptor-mediated inhibitory effects on both hormone secretion and cell proliferation in parathyroid cells (6, 27). 25OHD is present in blood in a much higher total concentration than 1,25-$(OH)_2D$ and binds to 1,25-$(OH)_2D$ receptors, although with very low affinity. However, calculation of free concentrations makes it unlikely that 25OHD can be an effective agonist for 1,25-$(OH)_2D$ receptors in the parathyroid gland (28). 25OHD can serve as a substrate for extrarenal production of 1,25-$(OH)_2D$ in intestinal and bone cells (20), but there is no evidence for such a mechanism in parathyroid cells.

As no direct effect of 25OHD on parathyroid growth seems plausible, an indirect effect must be considered. An important feature of primary hyperparathyroidism discovered as a result of biochemical screening, as were most patients in the present study, is lack of progression after the diagnosis was made (9.10). The stability of the clinical course of the disease can rarely be observed directly in patients subjected to surgical treatment, but our study patients differed in no way from others who have been followed uneventfully without surgery for many years (9, 10). The most reasonable explanation for prolonged stability of plasma Ca is cessation of net tumor growth. After rapid clonal expansion from a single altered cell, tumor growth slows down progressively as an asymptotic value is approached (29), most likely because growth is driven by an increase in the secretory set-point (30). Whether this is a primary abnormality (30) or is secondary to one of the many potentially growth-promoting mutations that have been found (31), growth would slow down and eventually stop once there is a sufficient number of parathyroid cells and a sufficient increase in PTH to raise plasma Ca to the new set-point (30). If diminished local production of 1,25-$(OH)_2D$ as a result of substrate deficiency (20) rendered bone cells less responsive to the calcemic effect of PTH, a larger number of parathyroid cells would be needed to reach the new set-point, a mechanism analogous to that which operates in chronic renal failure (6).

TABLE 5. Effect of vitamin D nutrition on responses to PTH in patients with primary hyperparathyroidism

Dependent variable	25OHD[a]	Intercept	Slope	r	P^b
Adjusted calcium (mg/dL)	Normal	10.2	0.0049[c]	0.554	<0.0001
	Low	10.8	0.0012	0.293	0.037
Alkaline phosphatase (IU/L)	Normal	102	0.082[d]	0.125	0.260
	Low	72	0.402	0.681	<0.0001

[a] Defined in Table 4.
[b] For regression slope.
[c] For difference in slopes, $P = 0.0004$.
[d] For difference in slopes, $P = 0.0022$.

Whatever the explanation for the stimulatory effect of 25OHD deficiency on adenoma growth, this relationship is relevant to the historical changes in disease frequency, severity, and course that were mentioned earlier. There has been substantial improvement of the level of vitamin D nutrition in the U.S. since the 1920s, when rickets was common. In rough chronological order, lessening of atmospheric pollution, fortification of milk with vitamin D beginning in 1933 (the single most important factor), greater participation in outdoor activity, and wider use of multivitamin supplements have led to a substantial fall in the incidence of rickets (32), presumably because both maternal and infantile stores of vitamin D have increased. Based on the relationship we have demonstrated, this would have led to a greater reduction in adenoma weight and disease severity than could be accounted for by the dilution effects of case findings among patients with nephrolithiasis or routine biochemical screening. Further evidence for this interpretation is that the historical changes observed in the West have not occurred in India, where vitamin D deficiency remains endemic (23). Sun exposure and vitamin use may have progressed further since 1980 (7), and the prescription of vitamin D for prevention of bone loss has increased considerably in the last 15 yr. This may have contributed to the recent fall in apparent incidence (3), because adenomas with a small increase in set-point could remain too small for detection provided vitamin D stores were sufficient.

Our results are also relevant to the management of primary hyperparathyroidism. In a patient from whom surgery is withheld for any reason, limiting dietary intake of vitamin D and Ca are often advised in the hope of minimizing the hypercalcemia. However, moderate restriction of vitamin D intake will not reduce plasma Ca, but will lead to increased PTH secretion, higher bone turnover, and greater acceleration of cortical bone loss (9, 11). Patients with primary hyperparathyroidism need at least as much vitamin D as normal subjects and possibly more, especially because, for a variety of reasons, vitamin D deficiency is becoming more common again (33). Similar observations apply to calcium. Restricting dietary calcium intake can lead to a substantial fall in urinary calcium excretion but to only a trivial fall in plasma calcium, accompanied by increased bone resorption (34), and an increased risk of developing osteitis fibrosa (1, 8). Cessation of calcium intake is sensible in a patient with severe hypercalcemia being prepared for surgery, but has no place in long term conservative management (35, 36).

Acknowledgments

We thank Mrs. Nayana Parikh, Ms. Julie Durr, Ms. Charlotte Jarvis, and Mr. John Hill for measurements of PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D, and Ms. Melber Jones for helping with the preparation of the manuscript. We are indebted to many physicians, both within and outside the Henry Ford Health System, who referred patients to our division without whose help the study would not have been accomplished.

References

1. **Albright F, Reifenstein EC.** 1948 The parathyroid glands and metabolic bone disease: selected studies. Baltimore: Williams & Wilkins.
2. **Heath H, Kennedy MA.** 1980 Primary hyperparathyroidism: incidence, morbidity, and potential economic impact in a community. N Engl J Med. 302:189–193.
3. **Wermers RA, Khosla S, Atkinson EKJ, Hodgson SF, O'Fallon WM, Melton LJ.** 1997 The rise and fall of primary hyperparathyroidism: a population-based study in Rochester, Minnesota, 1965–1992. Ann Intern Med. 126:433–440.
4. **Mundy GR, Cove DH, Fisken R.** 1980 Primary hyperparathyroidism: changes in the pattern of clinical presentation. Lancet. i:7–1320.
5. **Rao DS.** 1985 Primary hyperparathyroidism: changing patters in presentation and treatment decisions in the eighties. Henry Ford Hosp Med. J 33:194–197.
6. **Parfitt AM.** 1994 Parathyroid growth: normal and abnormal. In: Bilezikian JP, Levine MA, Marcus R, eds. The parathyroids: basic and clinical concepts. New York: Raven Press; 373–405.
7. **Kleeman CR, Norris K, Coburn JW.** 1987 Is the clinical expression of primary hyperparathyroidism a function of the long-term vitamin D status of the patient? Miner Electrolyte Metab. 13:305–310.
8. **Rao, DS, Phillips E, Honasoge M, Mithal A, Mishra SC, Sing AK, et al.** 1997 Role of vitamin D nutrition in primary hyperparathyroidism: effect on parathyroid gland mass and on bone. In: Norman AW, Boullion R, Thomasset M, eds. Vitamin D: chemistry, biology, and clinical applications of the steroid hormone. Riverside: University of California; 723–724.
9. **Rao DS, Wilson RJ, Kleerekoper M, Parfitt AM.** 1988 Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism: evidence for biphasic disease course. J Clin Endocrinol Metab. 67:1294–1298.
10. **Parfitt AM, Rao D., Kleerekoper M.** 1991 Asymptomatic primary hyperparathyroidism discovered by multichannel biochemical screening: clinical course and considerations bearing on the need for surgical intervention. J Bone Miner Res. 6:S97–S101.
11. **Silverberg SJ, Shane E, De La Cruz L, et al.** 1989 Skeletal disease in primary hyperparathyroidism. J Bone Miner Res. 4:283–291.
12. **Parfitt AM, Podenphant J, Villanueva AR, Frame B.** 195 Metabolic bone disease with and without osteomalacia after intestinal bypass surgery: a bone histomorphometric study. Bone. 6:211–220.
13. **Gloth FM, Gundberg CM, Hollis BW, Haddad JGJ, Tobin JD.** 1995 Vitamin D deficiency in homebound elderly persons. JAMA. 274:1683–1686.
14. **Malabanan A, Veronikis IE, Holick FM.** 1998 Redefining vitamin D insufficiency. Lancet. 351:805–806.
15. **Van der Wielen RPJ, Lowik MRH, van der Berg H, et al.** 1995 Serum vitamin D concentrations among elderly people in Europe. Lancet. 346:200–210.
16. **Lloyd HM.** 1968 Primary hyperparathyroidism: an analysis of the role of the parathyroid tumor. Medicine. 47:53–71.
17. **Locchi F, Tommasi M. Brandi ML, Tonelli F, Meldolesi U.** 1997 A controversial problem: is there a relationship between parathyroid hormone level and parathyroid size in primary hyperparathryoidism. Int J Biol Markers. 12:106–111.
18. **Woodhouse, NJY, Doyle FH, Joplin GF.** 1971 Vitamin-D deficiency, and primary hyperparathyroidism. Lancet. i:283–287.
19. **Mawer, EB, Backhouse J, Hill LP, Lumb GA, DeSilva P, Taylor CM, Stanbury SW.** 1975 Vitamin D Metabolism, and parathyroid funciton in man. Clin Sci Mol Med. 48:349–365.

20. **Parfitt AM.** 1998 Osteomalacia and related disorders. In: Avioli LV, Krane SM, eds. Metabolic bone disease and clinically related disorders, 3rd Ed. San Diego: Academic Press; 327–386.
21. **Clements MR, Davies M, Hayes ME, Hickey CD, Lumb GA, Mawer EB, Adams PH** 1992 The role of 1,25-dihydroxyvitamin D in the mechanism of acquired vitamin D deficiency. Clin Endocrinol (Oxf). 37:17–27.
22. **Lumb GA, Stanbury SW.** 1974 Parathyroid function in human vitamin D deficiency and vitamin D deficiency in primary hyperparathyroidism. Am J Med. 56:833–839.
23. **Harinarayan DV, Gupta N, Kochupillai N.** 1995 Vitamin D status in primary hyperparathyroidism in India. Clin Endocrinol (Oxf). 43:351–358.
24. **Patron P, Gardin J-P, Paillard M.** 1987 Renal mass and reserve of vitamin D: determinants in primary hyperparathyroidism. Kidney Int. 31:1174–1180.
25. **Keynes WM, Caird FI** 1970 Hypocalcaemic primary hyperparathyroidism. Br Med J. 1:208–211.
26. **Dent CE, Jones PE, Mullan DP.** 1975 Masked primary (or tertiary) hyperparathyroidism. Lancet. 1:1161–1164.
27. **Silver J, Naveh-Many T.** 1997 Vitamin D and the parathyroid glands. In: Feldman D, Glorieux FH, Pike JW, eds. Vitamin D. San Diego: Academic Press; 353–367.
28. **Cooke NE, Haddad JG.** 1997 Vitamin D binding protein. In: Feldman D, Glorieux FH, Pike JW, eds. San Diego: Academic Press; 87–101.
29. **Parfitt AM, Fyhrie D.** 1997 Gompertzian growth curves in parathyroid tumors: further evidence for the set-point hypothesis. Cell Proliferation. 30:341–349.
30. **Parfitt AM, Wang Q, Palnitkar S.** 1998 Rates of cell proliferation in adenomatous, suppressed and normal parathyroid tissue: implications for pathogenesis. J Clin Endocrinol Metab. 83:863–869.
31. **Hendy GN, Arnold A.** 1996 Molecular basis of PTH overexpression. In: Bilezikian JP, Raisz LG, Rodan GA eds. Principles of bone biology. San Diego: Academic Press; vol 54:757–767.
32. **Pettifor JM, Daniels ED.** 1997 Vitamin D deficiency and nutritional rickets in children. In: Feldman D, Glorieux FH, Pike JW, eds. Vitamin D. San Diego: Academic Press; 663–678.
33. **Thomas MK, Lloyd-Jones DM, Thadhani RI, et al.** 1998 Hypovitaminosis D in medical inpatients. N Engl J Med. 338:777–783.
34. **Parfitt AM.** 1975 The effect of cellulose phosphate in primary hyperparathyroidism. Clin Sci Mol Med. 49:91–98.
35. **Kleerekoper M.** 1994 Clinical course of primary hyperparathyroidism. In: Bilezikian JP, Levine MA, Marcus R, eds. The parathyroids: basic and clinical concepts. New York: Raven Press; 471–483.
36. **Stock JL, Marcus R.** 1994 Medical management of primary hyperparathyroidism. In: Bilezikian JP, Levine MA, Marcus R, eds. The parathyroids: basic, and clinical concepts. New York: Raven Press; 519–529.