CL-126

Oral calcium load test: Diagnostic and physiologic implications in hyperparathyroidism

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An oral calcium load test (CLT) (1 gm Ca/50 kg) was administered to 11 control subjects and 35 patients with overt hyperparathyroidism to assess its efficacy in diagnosis of hyperparathyroidism. All participants were placed on a low-calcium diet 3 days before the CLT. Intact parathormone and ionized calcium (Ca_i) levels were measured 0, 1, 2, and 3 hours after CLT. Initial Ca_i and parathormone (mean ± SE) were 1.22 ± 0.01 mmol/L and 2.94 ± 0.03 pmol/L in the control group compared with 1.43 ± 0.02 mmol/L and 10.6 ± 2.2 pmol/L in the group with hyperparathyroidism. Both groups had a similar percent increase in Ca_i values (control, 5.9% ± 0.8%; hyperparathyroidism, 6.3% ± 0.6%) ($p > 0.1$). A decline in parathormone levels of 47.6% ± 2.8% in patients with hyperparathyroidism was significantly less than the 75.3% ± 5.3% decline observed in control subjects ($p < 0.025$). Three hours after CLT, parathormone was suppressed in control subjects, whereas a rebound occurred in patients with hyperparathyroidism. Postoperative CLT demonstrated a higher mean percent Ca_i increase and percent parathormone decline (Ca_i, 8.9% ± 1.1%; parathormone, 67.9% ± 1.8%) compared with preoperative values (Ca_i, 6.0% ± 1.0%; PTH, 49.6% ± 4.3%) ($p < 0.025$), and 3 hours after calcium intake, parathormone remained suppressed, similar to control subjects. After surgery, three patients had elevated parathormone and low normal Ca_i levels and parathormone response to a CLT confirmed the diagnosis of secondary hyperparathyroidism. In conclusion, a CLT (1) can confirm the diagnosis of hyperparathyroidism and successful parathyroidectomy, (2) distinguished postoperative secondary from persistent primary hyperparathyroidism, (3) demonstrated nonautonomy of abnormal parathyroid glands with a parathormone response to a calcium load characterized by an earlier nadir, decreased suppressibility, and more rapid recovery, and (4) produced dynamic changes that did not distinguish patients with hyperparathyroidism from control subjects or hyperplasia from adenoma. (SURGERY 1990;108:1026-32.)

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CALCIUM TOLERANCE TESTS have been reported previously for use in evaluating patients with renal stone disease and hypercalcuria,[1, 2] for diagnosis of subtle hyperparathyroidism in patients with intermittent hypercalcemia,[3] and for detection of occult parathyroid hyperplasia in patients with multiple endocrine neoplasia syndrome type IIa.[4] Reduction in serum calcium levels and stimulation of parathormone secretion has also been used in an attempt to differentiate hypercalcemia caused by hyperparathyroidism from hypercalcemia as a result of other causes.[5] None of these authors had the advantage of the modern parathormone immunoradiometric assay (IRMA) that, for the first time, can follow rapid changes in parathormone levels. With the advent of the sensitive two-site IRMA for measurement of intact parathormone,[6] we devised an oral calcium load test (CLT) to investigate parathyroid function in a dynamic fashion and attempt to develop a provocative

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Table I. Baseline serum Ca_i and parathormone and urinary cAMP and calcium clearance values before oral calcium administration

Group	No.	Ca_i (mmol/L)	Parathormone (pmol/L)	Urinary cAMP (nmol/L CrCl)	Calcium clearance*
I. Control		1.22 ± .01	2.94 ± .03	30.2 ± 1.8	7.34 ± 1.5
II. Hyperparathyroidism		1.43 ± .02†	10.6 ± 2.2†	46.7 ± 2.4‡	21.6 ± 5.5

Data are mean ± SE.

* $\frac{U_{Ca}}{S_{Ca}} \times \frac{S_{Cr}}{U_{Cr}}$

†Versus controls, $p < 0.025$.

‡Versus controls, $p < 0.05$.

endocrine-suppression test for diagnosis of hyperparathyroidism in patients with intermittent or mild persistent hypercalcemia.

METHODS

All subjects were placed on a low-calcium diet (<300 mg/day) for 3 days and were fasting for at least 8 hours before the CLT. Blood samples for intact parathormone, ionized calcium (Ca_i) and creatinine, and random urine specimens for calcium, creatinine, and cyclic adenosine monophosphate (cAMP) were obtained 0, 1, 2, and 3 hours after administration of 1 gm elemental calcium (calcium; Sandoz) per 50 kg body weight dissolved in 240 ml water. Later in the course of the study, additional blood samples were obtained at 1½ and 2½ hours.

Blood samples were obtained without a tourniquet, with an indwelling canula, separated anaerobically, and stored at 4°C for Ca_i and creatinine and at −40°C for parathormone until ready to be analyzed. Ca_i corrected to a pH of 7.4 was measured with a Radiometer ICA-1 analyzer (Radiometer America Inc., Westlake, Ohio). Intact parathormone (1-84) was measured with a sensitive two-site IRMA (Nichols Institute, San Juan Capistrano, Calif.). In addition, three control subjects underwent midmolecular parathormone measurements (Immunonuclear Corp., Stillwater, Minn.). Serum and urinary creatinine and urine calcium levels were measured by Kodak Ektachem dry-slide technology. Urinary cAMP was measured by radioimmunoassay (New England Nuclear, Boston, Mass.) and expressed as a function of creatinine clearance (nanomoles per liter of creatinine clearance). The urinary calcium clearance ratio was computed according to the formula: $U_{Ca}/S_{Ca_i} \times S_{Cr}/U_{Cr}$. Reference ranges for our laboratory are: Ca_i, 1.17 to 1.33 mmol/L; intact parathormone, 1 to 6.5 pmol/L; and urinary cAMP, 20 to 43 nmol/L creatinine clearance. To date the normal range for urinary calcium clearance ratio in our laboratory has not been established.

The test was performed in 11 normal control subjects (group I) and 35 patients with hyperparathyroidism (group II), 20 with a parathyroid adenoma, 8 with hyperplasia, and 7 medically treated patients. Eleven surgically treated patients underwent both preoperative and postoperative CLTs. In both groups, mean ± SE was determined for initial Ca_i and parathormone, urinary cAMP, and urinary calcium clearance. The absolute and percent changes in serum Ca_i and parathormone and urinary cAMP and calcium clearance were determined for each group after oral calcium administration. The nadir in parathormone decline, the ratio of absolute parathormone decline to rise in Ca_i (Δ parathormone/Δ Ca_i), and the ratio of percent fall in parathormone to percent rise in Ca_i (%Δ parathormone/%Δ Ca_i) were determined for each group. Comparison of results from the control group and the group with hyperparathyroidism was completed with a standard unpaired two-tailed Student t test. A p value <0.05 was considered significant.

All surgically treated patients underwent bilateral neck exploration. Patients with an adenoma underwent resection of the adenoma and biopsy of at least one normal gland, whereas those with hyperplasia were treated with three and one fourth-gland resection and thymectomy. Cure was achieved in all patients, and there was no instance of recurrent laryngeal nerve injury or permanent hypoparathyroidism. Seven patients with hyperparathyroidism were treated without surgery either because of patient refusal or old age in combination with multiple concomitant medical problems or mild recurrent hyperparathyroidism well controlled with oral phosphates.

RESULTS

The control group (group I) consisted of nine women and two men with a mean age of 37 years, ranging from 20 to 73 years. The initial Ca_i level was 1.22 ± 0.1 mmol/L (mean ± SE) and parathormone was 2.94 ± 0.03 pmol/L (Table I). Serum Ca_i and par-

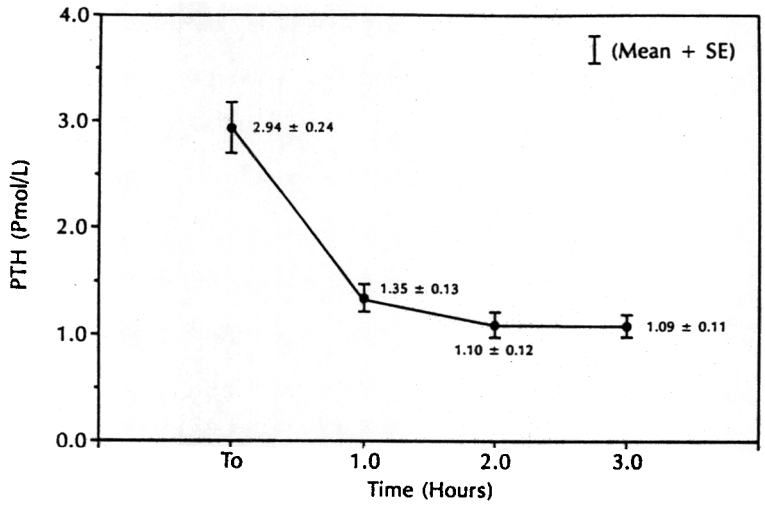

Fig. 1. Parathormone *(PTH)* response after CLT in 11 control patients.

Table II. Change in serum Ca_i and parathormone after oral calcium administration

Group	No.	Ca_i increase (mmol/L)	% Ca_i increase	Parathormone decline (pmol/L)	% Parathormone decline	Δ Parathormone / Δ Ca_i	% Δ Parathormone / % Δ Ca_i
I. Control		0.07 ± 0.01		2.13 ± 0.2	75.3 ± 5.3	39.1 ± 7.4	16.9 ± 3.2
II. Hyperparathyroidism		0.09 ± 0.01		4.15 ± 0.4	47.6 ± 2.8†	55.9 ± 5.8	10.9 ± 1.5

Data are mean ± SE.
*Versus controls, $p < 0.025$.
†$p < 0.025$.

athormone values were within the normal range in all control subjects. After calcium ingestion, serum Ca_i levels rose by 0.07 ± 0.01 mmol/L, a 5.9% ± 0.8% increase from basal levels (Table II). The parathormone level fell by 2.13 ± 0.2 pmol/L or 75.3% ± 5.3% (Table II). The nadir in parathormone occurred 2 or more hours after calcium administration in 8 of 11 controls (82%). Decline of parathormone levels for control subjects after oral calcium administration is displayed graphically in Fig. 1. The change in parathormone levels expressed as a function of the change in Ca_i (Δ parathormone/Δ Ca_i) was 39.1 ± 7.4 and the percent change in PTH expressed as a function of percent change in Ca_i (%Δ parathormone/%Δ Ca_i) was 16.9% ± 3.2% (Table II). By comparison, midmolecule parathormone levels measured in three control subjects remained constant throughout the CLT (data not shown).

Fasting urinary cAMP levels were normal in all control subjects, ranging from 24 to 41 nmol/L creatinine clearance, with a mean ± SE of 30.2 ± 1.8 nmol/L creatinine clearance (Table I). Baseline fasting calcium clearance ratio was 7.34 ± 1.5 (Table I). After CLT, the urinary cAMP level fell 11.9 ± 2.4 nmol/L creatinine clearance, which represented a 36.4% ± 4.9% decline, and there was a 3.4 ± 0.8-fold increase in calcium clearance (Table III).

The group with hyperparathyroidism (group II) consisted of 26 women and 9 men with a mean age of 58 years, ranging from 20 to 80 years. The initial Ca_i level was 1.43 ± 0.2 mmol/L (mean ± SE) and parathormone was 10.6 ± 2.2 pmol/L (Table I). After oral calcium administration, the Ca_i level increased 0.09 ± 0.01 mmol/L or 6.3% ± 0.6% (Table II). Both the absolute and percent increase in Ca_i was higher in patients with hyperparathyroidism than in control subjects, but the differences were not statistically significant ($p > 0.1$). The parathormone level fell 4.15 ± 0.4 pmol/L or 47.6% ± 2.8% (Table II), which was significantly less in patients with hyperparathyroidism compared with control subjects ($p < 0.025$). The difference in percent parathormone decline in patients with an adenoma (40.7% ± 0.83%) versus patients with hyperplasia (56.3% ± 2.88%) was not significant ($p > 0.1$).

Patients with hyperparathyroidism tended to have an earlier nadir in parathormone, occurring before 2 hours in 21 of 35 patients (59%). They also tended to have a

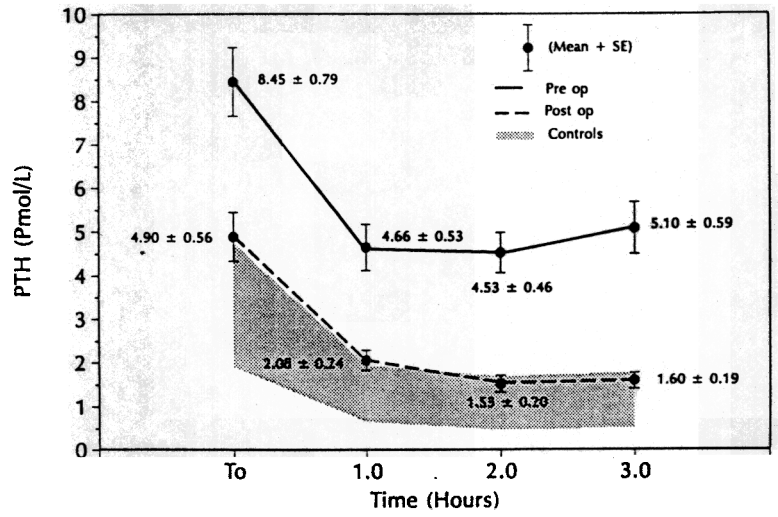

Fig. 2. Parathormone *(PTH)* response after preoperative and postoperative CLT in 11 patients who underwent curative parathyroidectomy.

Table III. Changes in urinary cAMP and calcium clearance after oral calcium administration

Group	*No.*	*Urinary cAMP decline (mmol/L CrCl)*	*% Urinary cAMP decline*	*Increase in calcium clearance**	*% Increase in calcium clearance*
I. Control		11.9 ± 2.4	36.4 ± 4.9	16.9 ± 3.7	340 ± 80
II. Hyperparathyroidism		15.0 ± 1.5	32.2 ± 2.5	50.7 ± 8.9	490 ± 100

Data are mean ± SE.

* $\frac{U_{Ca}}{S_{Ca}} \times \frac{S_{Cr}}{U_{Cr}}$

more rapid rebound in parathormone levels, in contrast to control patients whose parathormone levels remained suppressed 3 hours after CLT. These differences are demonstrated in the graph of parathormone responses to an oral CLT in 11 patients with hyperparathyroidism seen in Fig. 2. The ratio of parathormone decline to rise in Ca_i levels (Δ parathormone/Δ Ca_i) was 55.9 ± 5.8 in patients with hyperparathyroidism, which was greater than in control patients (Table II), but the difference was not statistically significant ($p > 0.1$). The ratio of percent parathormone decline to percent rise in Ca_i (%Δ parathormone/%Δ Ca_i) was 10.9 ± 1.5, which was less than in control subjects (Table II), and the difference just missed statistical significance ($p > 0.05$ and < 0.1).

An initial urinary cAMP level of 46.7 ± 2.4 nmol/L creatinine clearance in patients with hyperparathyroidism was significantly greater than in the control group ($p < 0.05$) (Table I). However, 37% of patients with hyperparathyroidism had a basal urinary cAMP level in the normal range. Although basal calcium clearance levels of 21.6 ± 5.5 nmol/L (Table I) were higher in patients with hyperparathyroidism, there was a 57% overlap between groups and thus differences were not significant ($p > 0.1$) (Table I).

After the CLT, patients with hyperparathyroidism had an absolute reduction in urinary cAMP levels of 15.0 ± 1.5 nmol/L creatinine clearance, which was a 32.2% ± 2.5% decline (Table III). Both the absolute and percent decline in urinary cAMP levels was similar to that of control subjects ($p > 0.1$). There was also a 4.9 ± 1.0-fold increase in urinary calcium clearance ratio, which was not significantly different from that of control subjects ($p > 0.1$) (Table III).

The results of preoperative and postoperative CLTs in 11 surgically treated patients are summarized in Table IV. There was a greater rise in Ca_i levels (8.9% ± 1.1%) ($p < 0.05$), a larger percent parathormone decline (69.9% ± 1.8%) ($p < 0.025$), and a smaller Δ parathormone/Δ Ca_i ratio (35.4 ± 4.9) ($p < 0.05$) after postoperative CLTs. However, the ratios of %Δ parathormone/%Δ Ca_i after preoperative (11.4 ± 2.2) and postoperative CLT (9.0 ± 1.4) were similar ($p > 0.1$).

Table IV. Comparison of preoperative and postoperative CLT results for 11 patients with hyperparathyroidis after curative parathyroidectomy

CLT result	*Initial Ca_i (mmol/L)*	*ΔCa_i*	*% ΔCa_i*	*Initial parathormone (pmol/L)*	*Δ Parathormone*	*%Δ Parathormone*	*$\frac{\Delta \text{ Parathormone}}{\Delta Ca_i}$*	*$\frac{\% \Delta \text{ Parathormone}}{\% \Delta Ca_i}$*
Preoperative	1.42 ± 0.03	0.08 ± 0.01	6.0 ± 1.0	8.4 ± 0.9	4.2 ± 0.6	49.6 ± 4.3	61.4 ± 10.9	11.4 ± 2.2
Postoperative	1.18 ± 0.02*	0.10 ± 0.01	8.9 ± 1.1†	4.9 ± 0.6*	3.3 ± 0.4	67.9 ± 1.8*	35.4 ± 4.9†	9 ± 1.4

*Versus controls, $p < 0.02$!
†Versus controls, $p < 0.05$.

Graphic display of parathormone response to CLT before and after surgery for 11 patients with hyperparathyroidism is seen in Fig. 2. The parathormone response to postoperative CLT was similar to that of the normal control population. The reduced parathormone suppressibility noted in patients with hyperparathyroidism during a preoperative CLT reverted to normal. The nadir in parathormone decline occurred at or later than 2 hours in 10 of 11 patients and parathormone tended to remain suppressed 3 hours after oral calcium administration.

After surgery, three patients had low-normal or normal fasting Ca_i levels with elevated parathormone levels. A postoperative CLT produced a 0.13 to 0.15 mmol/L increase (11% to 13%) in Ca_i and parathormone decline of 60% to 75%. These results indicated the presence of postparathyroidectomy secondary hyperparathyroidism rather than persistent primary hyperparathyroidism. The secondary hyperparathyroidism in these three patients was temporary and resolved after a maximum of 3 months of calcium and vitamin D therapy.

DISCUSSION

Using a sensitive and reproducible two-site IRMA to measure intact parathormone, we observed that parathormone decline after a CLT was significantly less in patients with hyperparathyroidism than in control subjects. This occurred despite higher baseline Ca_i levels and similar increases in Ca_i levels after an oral CLT in patients with hyperparathyroidism. The midmolecular parathormone assay, however, was not sensitive enough to measure rapid changes in parathormone. Other authors have been unable to demonstrate a significant reduction in parathormone after oral calcium administration because of the insensitivity of older parathormone assays that were affected by inactive parathormone fragments.[7]

No difference in parathormone response was observed between patients with parathyroid adenoma and hyperplasia. Our observations varied from those of Reiss and Canterbury,[8] who used a less sensitive parathormone assay and an intravenous calcium challenge and reported parathormone nonsuppressibility in patients with an adenoma and only partial suppressibility in patients with hyperplasia. A mean 41% decline in parathormone values observed in our patients with an adenoma and 56% decline in patients with hyperplasia confirmed that hyperfunctioning parathyroid glands are not autonomous but function around a higher calcium set point.[9, 10] Our in vivo results correlate with previous work by Brown et al.,[11] which demonstrated partial suppressibility of dispersed parathyroid tissue in vitro.

In addition to decreased parathormone suppressibility, other subtle differences in parathormone response were observed in patients with hyperparathyroidism after an oral CLT, including an earlier nadir in parathormone decline and a more rapid rebound in parathormone secretion. Although we observed a different pattern of parathormone response, the differences did not occur uniformly in all patients with hyperparathyroidism.

The results of our investigation also indicated that a single basal fasting Ca_i and intact parathormone level in fasting patients on a low-calcium intake discriminated patients with hyperparathyroidism from normal control subjects in all instances. Ca_i and intact parathormone levels were significantly higher in patients with hyperparathyroidism with almost no overlap with normal control subjects. Basal calcium clearance ratio and urinary cAMP levels were also higher, but they overlapped by 57% and 37%, respectively, with the values from control subjects, making these tests less useful in the diagnosis of hyperparathyroidism.

In response to oral calcium administration, we observed similar increases in serum calcium and urinary calcium clearance ratio, as well as a comparable decline in urinary cAMP values both in patients with hyperparathyroidism and in control subjects. This differed from the results of Broadus et al.,[3] who demonstrated hyperabsorption of calcium in 10 patients with marginal hyperparathyroidism with a mean calciuric response that was twice normal after administration of 1 gm oral calcium. They attributed the difference to intestinal hy-

perabsorption in patients with hyperparathyroidism related to measured increases in serum 1,25 $(OH)_2$ vitamin D_3. 1,25$(OH)_2$ vitamin D_3 levels were not measured in our patients, nor did we have any patients with true marginal hyperparathyroidism as defined by Broadus et al. It may be that patients with marginal hyperparathyroidism are more likely to have elevated 1,25$(OH)_2$ vitamin D_3 levels.

Calcium is known to be absorbed in the duodenum and proximal jejunum. An increase in serum Ca_i levels was seen at the initial 1-hour blood sampling, and peak levels occurred 2 to 3 hours after oral calcium administration. Fall in parathormone paralleled the rise in Ca_i levels; however, it was not unusual for patients with hyperparathyroidism to have a rebound in parathormone secretion while the serum Ca_i level was still rising.

The parathormone response reverted to normal within 3 months of curative parathyroidectomy in 11 patients who underwent preoperative and postoperative CLTs for comparison. The reduced parathormone suppressibility, earlier nadir in parathormone decline, and rapid rebound in parathormone secretion were no longer apparent. After surgery, however, patients were noted to have a significantly greater percent increase in serum Ca_i levels after oral calcium administration. We observed the greatest increases in serum Ca_i levels in patients with low or low-normal postoperative calcium levels. We postulated that this may be the result of higher 1,25 $(OH)_2$ vitamin D_3 levels affecting calcium absorption. Three patients were noted to have temporary postoperative secondary hyperparathyroidism characterized by low or low-normal serum Ca_i and elevated parathormone levels, presumably as a result of bone hunger. Their parathormone response to a postoperative CLT was identical to that of the normal control subjects, distinguishing postoperative secondary from persistent primary hyperparathyroidism. All patients responded to oral calcium therapy with eventual resolution of this postoperative phenomenon of secondary hyperparathyroidism.

In conclusion, the CLT can confirm the diagnosis of hyperparathyroidism by demonstrating reduced parathormone suppressibility. CLT also confirms curative parathyroidectomy and distinguishes postoperative secondary from persistent primary hyperparathyroidism. With a two-site IRMA used to measure intact parathormone, the CLT demonstrated that hyperfunctioning parathyroid glands are nonautonomous, with a parathormone response to calcium characterized by an earlier nadir, reduced suppressibility, and more rapid recovery despite higher basal serum Ca_i levels. However, the dynamic changes in serum Ca_i, intact parathormone, urinary cAMP, and urinary calcium clearance did not clearly discriminate between patients with overt hyperparathyroidism and normal control subjects, nor did it distinguish patients with an adenoma from those with hyperplasia. This was consistent with the results of Madvig et al.,[12] who concluded that oral calcium tolerance testing with measurement of serum urinary calcium and nephrogenous cAMP did not possess the requisite sensitivity or specificity to be useful in the diagnosis of hyperparathyroidism. The CLT did not add additional diagnostic information that was not already established by baseline Ca_i and parathormone levels obtained under standard conditions.

REFERENCES

1. Pak CYC, Kaplan R, Bone H, Townsend J, Waters O. A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. N Engl J Med 1975;292:497-500.
2. Peacock M, Knowles, F, Nordin BEC. Effect of calcium administration and deprivation on serum and urine calcium in stone-forming and control subjects. Br Med J 1968;2:729-31.
3. Broadus AE, Horst RL, Littledike ET, Mahaffey JE, Rasmussen H. Primary hyperparathyroidism with intermittent hypercalcemia: serial observations and simple diagnosis by means of an oral calcium tolerance test. Clin Endocrinol 1980;12:225-35.
4. Heath H, Sizemore GW, Carney JA. Preoperative diagnosis of occult parathyroid hyperplasia by calcium infusion in patients with multiple endocrine neoplasia, type 2A. J Clin Endocrinol Metab 1976;43:428-35.
5. Ljunghall S, Benson L, Wide L, Akerstrom G, Rustad J. Improved differential diagnosis of hypercalcemia by hypocalcemic stimulation of parathyroid hormone secretion. World J Surg 1988;12:496-502.
6. Nussbaum SR, Zahradnik RJ, Lavigne JR, et al. Highly sensitive two-site immunoradiometric assay of parathyrine and its clinical utility in evaluating patients with hypercalcemia. Clin Chem 1987;33:1364-7.
7. Broadus AE, Deftos LJ, Bartter FC. Effects of the intravenous administration of calcium in nephrogenic cyclic AMP: use as a parathyroid suppression test. J Clin Endocrinol Metab 1978;46:477-87.
8. Reiss E, Canterbury JM. Primary hyperparathyroidism: application of radioimmunoassay to differentiation of adenoma and hyperplasia and to preoperative localization of hyperfunctioning parathyroid glands. N Engl J Med 1969;280:1381-5.
9. Murray TM, Peacock M, Powell D, Monchik JM, Potts JT. Nonautonomy of hormone secretion in primary hyperparathyroidism. Clin Endocrinol 1972;1:235-46.
10. McHenry CR, Pollard A, Walfish PG, Rosen IB. Intraoperative parathormone level measurement in the management of hyperparathyroidism. SURGERY 1990;108:801-8.
11. Brown EM, Broadus AE, Brennan MF, et al. Direct comparison in vivo and in vitro of suppressibility of parathyroid function by calcium in primary hyperparathyroidism. J Clin Endocrinol Metab 1979;48:604-10.
12. Madvig P, Young G, Marcus R. Assessment of adenosine 3′5′-monophosphate excretion and an oral calcium tolerance test in the diagnosis of mild primary hyperparathyroidism. J Clin Endocrinol Metab 1984;58:480-7.

DISCUSSION

Dr. Edward Paloyan (Hines, Ill.). Some of us tried to achieve the same results a few decades ago, but we used serum phosphate clearances in a similar manner. Did you measure the serum phosphorus level and have you correlated your findings with phosphate clearance?

Dr. McHenry. Dr. Paloyan, early on in our testing we measured urinary phosphate clearance and found no significant difference between the control population and patients with hyperparathyroidism.

Dr. Murray F. Brennan (New York, N.Y.) About 10 years ago we showed in vitro that you could demonstrate suppressibility of both hyperplastic and adenomatous glands. In some of those patients we had the opportunity to then test the in vivo autograft. I noted that there are people in whom suppression cannot be accomplished. There are people who have what we called "adenomas" that did not suppress either in vitro or in vivo, and we had to remove one autonomous autograft.

In some ways this addresses the same problem that Dr. Attie discussed. It depends on how you define "adenoma." If you define multiple adenomas as enlargement of more than one gland but not all four where there was not persistent or recurrent disease when only the large lesions were removed, then you must be correct. The concept of multiple-gland disease that is not of uniform penetrance is easy to accept. The only question I have is whether your use of the term "calcium clearance" was correct. I believe you are measuring calcium to creatinine clearance.

Dr. McHenry. We measured the ratio of urine calcium to serum calcium multiplied by the ratio of serum creatinine to the urine creatinine, which is a calcium to creatinine clearance ratio.

Dr. John M. Monchik (Providence, R.I.). Before the development of the two-site assay for intact parathyroid hormone, my colleagues and I did a project quite similar to yours. We showed that both adenomas and hyperplasia were stimulated when the calcium was brought down by EDTA and suppressed when the calcium was elevated by an intravenous calcium infusion. We even had one patient, a patient of Dr. Wang's, who had a parathyroid carcinoma in whom the parathyroid hormone level was raised significantly with an infusion of EDTA.

I think that one of the important aspects of your study would be the identification of patients with primary hyperparathyroidism who have minimal elevation of the ionized or total calcium or immunoreactive parathyroid hormone and who have complications of hyperparathyroidism.

Dr. McHenry. Our original purpose for the study was to develop a test for diagnosis of hyperparathyroidism in patients with marginal hypercalcemia and parathormone levels in the upper normal range. However, we first chose to examine the response to an oral calcium load in patients with overt hyperparathyroidism and compare this to that of normal control subjects.

Dr. Richard A. Prinz (Maywood, Ill.). In patients with borderline calcium and parathyroid hormone levels, is your calcium-loading test also going to be borderline? In other words, is this test any better than measuring total or ionized calcium and serum parathyroid levels for making a diagnosis of hyperparathyroidism?

Dr. McHenry. It very well could be. The results of our investigation revealed that a baseline ionized calcium level and a parathyroid hormone level with an immunoradiometric assay were actually more accurate at differentiating patients with hyperparathyroidism from control subjects than the dynamic changes observed after oral calcium administration.

So, whether an oral calcium load test will be useful in patients with marginal hyperparathyroidism remains to be seen.

Dr. Stanley R. Friesen (Kansas City, Mo.). I have done the reverse of this experiment in a patient I think is worth mentioning, a patient with hypercalcemia and all the evidence of hyperparathyroidism except that the parathormone level was undetectable. In this patient we brought the calcium level down. The parathormone level went up to normal. It was at an undetectable level, which indicated to us that the parathyroid glands in that patient were normal and normally responsive; it kept us from operating on the neck.

Dr. P. Schachter (Durham, N.C.). Parathyroid adenoma tissue is more susceptible to declining calcium concentrations than to increases in calcium levels. Have you considered lowering calcium levels to differentiate among patients with borderline hyperparathyroidism and control subjects?

Dr. McHenry. Yes we did. Our protocol consisted of placing all patients on a 300 mg calcium diet for 3 days before testing. All patients also fasted for 8 to 12 hours before the test.

Dr. Schacter. Since all patients and control subjects were on a low-calcium diet for 3 days before the calcium load test, was there any significant difference in starting calcium levels between the patients and the control subjects?

Dr. McHenry. The mean baseline ionized calcium levels were 1.22 mmol/L in the control subjects and 1.43 mmol/L in the group with hyperparathyroidism. These values represented an overall fall in calcium levels compared with levels obtained before placing patients on a low-calcium diet.

Dr. Quan Yang Duh (San Francisco, Calif.). We used to use midregion radioimmunoassay and have recently switched to the immunoradiometric assay. One of the implications of your data is that we have to be more careful about the timing of when we measure parathormone in our patients, because the parathormone levels by the immunoradiometric assay have more variation.

Have you found differences in parathormone levels depending on the kind of diet your patient is on? Do you measure immunoradiomeric assay only after a patient has fasted?

Dr. McHenry (closing). Yes. Our protocol has been to measure calcium and parathormone levels after an overnight fast.

Blood samples are obtained without a tourniquet and we have been measuring pH-corrected ionized calcium levels. This has been our standard protocol for measurement of basal calcium and parathormone levels in all our patients.