Posttransplantation hyperparathyroidism: demonstration of retained control of parathyroid function by plasma ionized calcium\textsuperscript{1-3}

David A. McCarron, M.D., William M. Bennett, M.D., Richard S. Muther, M.D., John M. Barry, M.D., and Siegfried Krutzik, Ph.D.

ABSTRACT Persistent hyperparathyroidism is a common complication of successful renal transplantation. This study sought to address several generally held assumptions concerning this endocrine disorder, i.e., it represents an autonomous condition that involutes with time. Eight normal subjects and 13 renal transplant patients with hyperparathyroidism were studied. Ten blood samples for simultaneous measurement of serum ionized calcium (Ca\textsuperscript{2+}) and parathyroid hormone (PTH) were obtained from each subject in the course of a 4-hr Ca\textsuperscript{2+} infusion (15 mg/kg) and 2-hr EDTA infusion (50 mg/kg). The results demonstrate that a significant ($P < 0.001$) inverse logarithmic (sigmoidal) relationship exists between serum Ca\textsuperscript{2+} and peripheral PTH levels. The slopes of the relationship were similar, but at any level of serum Ca\textsuperscript{2+}, the PTH levels were significantly ($P < 0.001$) higher in the hyperparathyroid transplant recipients. We conclude that posttransplant hyperparathyroidism is not an autonomous condition as the parathyroid gland is equally responsive to acute changes in serum Ca\textsuperscript{2+}. The excessive levels of basal PTH secretion most likely reflect increased gland mass and not altered sensitivity of the parathyroid cell or metabolism of PTH. Proper management of this disorder requires maintenance of the serum Ca\textsuperscript{2+} at some optimal concentration to insure suppression of the gland. If the level of hypercalcemia is unacceptable, surgical intervention with reduction of gland mass is indicated. Am. J. Clin. Nutr. 33: 1536–1540, 1980.

Persistent hyperparathyroidism is a well-known complication of successful renal transplantation. The true prevalence of this endocrine disorder is unknown, but has been variously reported to occur in 5 to 85% of long-term survivors of renal transplantation \textsuperscript{(1–3)}. Precise diagnosis usually depends on the simultaneous measurement of serum ionized calcium; parathyroid hormone, inorganic phosphate, magnesium concentrations and urinary cAMP excretion rates. In addition, maneuvers designed to stimulate or inhibit parathyroid gland function are often required to demonstrate occult parathyroid dysfunction. Persistent hyperparathyroidism has been implicated in the pathogenesis of metabolic bone disease, gastrointestinal disorders, neuropsychiatric disturbances, obliterative atherosclerosis, and hypertension which complicate otherwise successful renal transplants \textsuperscript{(4–6)}.

Except for correction of severe hypercalcemia, little attention has been directed at the proper long-term medical management of posttransplant hyperparathyroidism. This reflects the generally held assumptions that the hyperplastic glands will involute over time and are functioning autonomously outside of normal regulation by the plasma ionized calcium \textsuperscript{(7, 8)}. If these assumptions are correct, no concentration of ionized calcium achievable in clinical practice will ensure maximal suppression of the gland. Our studies sought to address these untested notions.

\textsuperscript{1} From the Divisions of Nephrology and Renal Transplantation, University of Oregon Health Sciences Center, Portland, Oregon 97201; and Nichols Institute, San Pedro, California.

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\textsuperscript{3} Address reprint requests to: Dr. David McCarron, Division of Nephrology, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland, Oregon 97201.

Methods

The protocol was approved by the Human Investigation Committee at the University of Oregon Health Sciences Center. Informed consent was obtained from all the subjects. The studies were carried out in the General Clinical Research Center. Eight normal volunteers and 13 renal transplant recipients were studied. The normals were carefully screened for endocrine disorders and were on no medications including mineral or vitamin supplements. There were five females and three males. The renal allograft recipients were 6 months to 6 years status posttransplantation. Their mean serum creatinine was 1.3 mg/dl. All of the transplant subjects had manifested biochemical evidence of persistent parathyroid overactivity. The screening parameters used were serum total calcium, phosphate and parathyroid hormone concentrations. All patients were mild-to-moderately hyperparathyroid, but did not require specific medical or surgical therapy for their endocrine disturbance.

Each subject had ten blood samples drawn for the simultaneous determination of serum parathyroid hormone (PTH) and ionized calcium (Ca++) concentrations. Two samples were drawn in the basal state at 10:00 AM on separate, noninfusion days. Four samples were collected at time 0, 30 min, 2 and 4 hr during a 4-hr infusion of calcium (15 mg/kg as calcium gluconate). At least 48 hr later and after the serum Ca++ had returned to baseline, each subject received disodium EDTA (50 mg/kg, over 2 hr). Blood was withdrawn at time 0, 15 min, 1 and 2 hr.

Ca++ was determined by a direct-tip, calcium-specific electrode (Appl. Med. Tech., Palo Alto, Calif.). PTH was measured by radioimmunoassay in two independent PTH assays. One assay (N/C) used a guinea pig, antihormone antiserum with approximately 50% aminoterminal and 50% COOH-terminal specificity. The second assay (C) used a guinea pig, antihormone serum with predominant (90%) specificity for the COOH-terminal sequence (53 to 84) of PTH. A Hewlett-Packard programmable computer was utilized for curve-fitting. Two-way analysis of variance was used to determine statistical significance between the PTH levels of the two groups.

Results

Figure 1 depicts the correlation ($P < 0.001$) between the normal subjects’ serum Ca++ (mEq/liter) and PTH-N/C (μEq/ml) concentrations. While the relationship is a logarithmic one, it is equally well described as sigmoidal. It is characterized by an inflexion, with small decreases in Ca++ resulting in large increases in peripheral PTH concentrations and by a basal level of PTH secretory that is independent of suppression by the serum Ca++. Figure 2 summarizes the data on the same two parameters measured in the allograft recipients.

For both groups similar logarithmic relationships were evident and equally significant ($P < 0.001$) when the results of the COOH-terminal PTH assay were substituted for PTH-N/C data. Figure 3 portrays the logarithmic curves relating Ca++ to PTH-N/C for both the normal subjects and the transplant patients. The slopes of these curves are not significantly different from one another. Throughout the range of serum Ca++ studied, however, PTH concentrations were higher ($P < 0.001$) in the transplant recipients.

Discussion

Our results demonstrate that an inverse, nonlinear relationship exists between serum Ca++ and peripheral PTH levels in both normal humans and subjects with hyperparathyroidism. A similar sigmoidal relationship has previously been documented in calves (9–11). The present data are the first evidence in humans of such a regulatory relationship. Recent reports substantiate the validity of measuring peripheral PTH levels as an indirect assessment of acute changes in the secretory rate of the parathyroid gland (12). As is apparent from the data, the relationship is characterized by a basal secretion of PTH that is not suppressible by progressive hypercalcemia. This corresponds to the noncalcium
dependent portion of parathyroid cell function previously noted in in vitro and animal studies (13). Additionally, the relationship indicates that the greatest regulatory effect of plasma Ca$^{++}$ is over a narrow range, i.e., very minimal decreases from base-line in the plasma concentration of Ca$^{++}$ results in dramatic rises in peripheral PTH concentrations.

Of greater import is the observation that the parathyroid function of transplant recipients who are persistently hyperparathyroid is equally responsive to acute changes in plasma Ca$^{++}$. In contrast to previously held notions, the hyperplastic parathyroid gland is regulated, in large part, by the plasma Ca$^{++}$ concentration. Thus, true parathyroid autonomy after successful renal transplantation does not exist. This conclusion is consistent with in vitro work done on dispersed parathyroid cells taken from subjects with either adenomas or hyperplasia. Continued responsiveness of the cells to changes in media Ca$^{++}$ have been shown in these studies (14).

An altered sensitivity of hyperplastic glands to plasma Ca$^{++}$ has been postulated in the past (15). Our results do not support such an hypothesis because, for the same relative change in the plasma Ca$^{++}$, the transplant recipients and the normal subjects responded in a similar fashion. This conclusion is implicit in the similarity of the slopes of the curves for each population's Ca$^{++}$-PTH relationship. The simplest explanation for the excessive PTH secretion seen in posttransplant hyperparathyroidism is increased gland mass and not altered sensitivity of the

**FIG. 2.** Relation of serum Ca$^{++}$ and PTH levels determined simultaneously during Ca$^{++}$ and EDTA infusion in hyperparathyroid transplant recipients.
parathyroid cell or abnormal degradation of the hormone. The latter possibility appears to be less likely as a result of the data from the COOH-terminal specific assay. If altered degradation of the hormone by the renal allograft contributed significantly to high PTH levels, then utilizing the COOH-terminal specific assay, one would expect a different \( \text{Ca}^{++} \)-PTH relationship. Such was not the case in our study. Comparable effects on PTH-C were evident with both assays, as serum \( \text{Ca}^{++} \) changed during the course of the infusions in both the normal and transplant subjects.

Our findings have both diagnostic and therapeutic implications for the management of posttransplant hyperparathyroidism. The sigmoid relationships between serum \( \text{Ca}^{++} \) and PTH concentrations indicate that even minimal increases in the serum total calcium and PTH levels are likely to reflect significant residual parathyroid hyperplasia. Precise delineation of the magnitude of the increased gland mass, though, will require provocative maneuvers designed to maximally stimulate and suppress the "calcium-dependent" limb of parathyroid gland function. Simply relying upon random serum \( \text{Ca}^{++} \) or PTH concentrations will not suffice to adequately evaluate the individual patient or provide accurate data on the true prevalence of posttransplant hyperparathyroidism. The provocative tests may also be of substantial value in the presurgical (parathyroidectomy) evaluation of the hyperparathyroid transplant recipient. They would provide some estimate of gland mass and a reference standard by which the long-term effects of either surgical or medical management could be judged.

Since posttransplant hyperparathyroidism is not an autonomous condition, it is important to maintain transplant recipients at some optimal plasma \( \text{Ca}^{++} \) concentration. Attempts at reducing the serum \( \text{Ca}^{++} \), usually by oral phosphate therapy, will only serve to stimulate parathyroid hormone secretion more. If the patient is unable to tolerate the hypercalcemia or the excessive basal secretion of PTH, then the definitive therapy should be reduction of gland mass. This can be accomplished by either partial parathyroidectomy or total parathyroidectomy followed by reimplantation of a portion of one gland.

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