

# Long-term Results of Subcutaneous Parathyroid Grafts in Uremic Patients

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**Hypothesis:** Parathyroid glands are normally surrounded (entirely or partially) by fatty tissue. Subcutaneous parathyroid grafts are thus located in a normal environment. Therefore, we postulated that the late results of subcutaneous implantation of parathyroid tissue in uremic patients should be at least as good as those reported for intramuscular grafting. We also challenged the idea that the recurrence rate of renal hyperparathyroidism after surgery depended solely on the type of hyperplasia (diffuse vs nodular) observed in the implanted tissue.

**Design:** A retrospective study of a series of patients without loss to follow-up.

**Setting:** A university hospital and 9 affiliated dialysis units.

**Patients and Interventions:** Fifty-nine patients (33 women and 26 men) operated on for renal hyperparathyroidism underwent the resection of at least 4 parathyroid glands followed by presternal subcutaneous implantation of parathyroid tissue. They were followed up for 12 to 130 months (median, 38 months).

**Main Outcome Measures:** Failure of treatment, recurrence of disease, and hypoparathyroidism.

**Results:** During the study period, 9 patients had to undergo another operation: 2 (3%) for persistent hyperparathyroidism due to a fifth ectopic gland and 7 (12%) for recurrence of hyperparathyroidism resulting from hy-

pertrophy of the subcutaneous grafts. Four patients received a kidney transplant. The prevalence of hypoparathyroidism (intact parathyroid hormone serum level  $<1.6$  pmol/L with a normal or low serum calcium concentration) was 14% (8 of 59 patients), and the curve representing the distribution of intact parathyroid hormone serum concentrations among operated on patients was shifted to the left when compared with the curve of patients who underwent hemodialysis and who had no indication for parathyroid surgery. In this latter group, the peak of the curve was situated between 1 and 2 times the upper normal limit, while it was in the normal range 12 to 130 months after total parathyroidectomy and subcutaneous parathyroid autotransplantation. No relation was observed between the recurrence rate of the disease and the histological characteristics of the parathyroid grafts. Also, their function was not influenced by the presence or absence of aluminum deposits in bone biopsy specimens that were obtained at the time of cervical exploration.

**Conclusions:** The late results of total parathyroidectomy and presternal subcutaneous grafting compare favorably with the published data on other surgical techniques proposed for the treatment of renal hyperparathyroidism. The ease with which the hypertrophied grafts are removed when the disease recurs warrants further use of this procedure.

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**S**UBCUTANEOUS grafting of parathyroid tissue after total parathyroidectomy in uremic patients has seldom been described.<sup>1-3</sup> Resection of hypertrophied grafts is easy when hyperparathyroidism recurs after this procedure, but the published series<sup>1-3</sup> are small with a rather short follow-up. The present study determines how the late results of this procedure compared with those reported for other surgical techniques used in the treatment of renal hyperparathyroidism. We also investigated if the recur-

rence rate of the disease was related to the type of grafted parathyroid tissue (nodular vs diffuse hyperplasia).

## RESULTS

Fifty-nine patients (33 women and 26 men) operated on for renal hyperparathyroidism were followed up for 12 to 130 months (median, 38 months) after undergoing total parathyroidectomy and subcutaneous implantation of autologous parathyroid tissue. Five parathyroid glands were excised in 2 patients; and in all the

## PATIENTS AND METHODS

### SURGICAL PATIENTS AND THE POPULATION THAT UNDERWENT HEMODIALYSIS

The patients included in the surgical series were selected from a group of patients treated by parathyroidectomy who underwent subcutaneous implantation of parathyroid tissue for renal hyperparathyroidism between November 1, 1986, and August 31, 1996. Patients in whom fewer than 4 parathyroid glands had been resected before the grafting procedure were excluded from the study. No patient was lost to follow-up. The population that underwent hemodialysis comprised patients who presented no indication for surgical treatment. Their blood calcium levels were normal, and they were treated prophylactically with cholecalciferol, calcium supplements, or both. They did not receive aluminum-containing medications. Patients with diseases interfering with calcium and phosphorus metabolism, such as myeloma, Paget disease, bone metastases, and sarcoidosis, were excluded. The sex ratio and age distribution were similar in both groups. None of the patients had diabetes.

### INDICATION FOR OPERATIVE TREATMENT AND SURGICAL PROCEDURES

Surgery was performed in all patients (first procedure and subsequent operations) when prophylactic treatment with calcium and cholecalciferol supplements failed because of spontaneous or induced hypercalcemia and a high blood phosphorus level. The patients underwent the excision of all visible parathyroid glands and the subcutaneous implantation of autologous parathyroid tissue in front of the lower third of the sternum.<sup>2</sup> The exact number of glands removed during the procedure was determined by microscopic examination of all resected specimens. Parathyroid glands showing diffuse hyperplasia were preferentially used for grafting. However, when the amount of diffusely hyperplastic endocrine tissue was insufficient, nodular tissue was also implanted subcutaneously. At the time of cervical exploration, some patients underwent a bone biopsy of the iliac crest performed with an 8-mm trocar.

other patients, 4 glands were resected. During the follow-up period, 9 (15%) of the patients underwent a second operation. A fifth gland was resected at 6 and 13 months after the surgery in 2 (3%) of the patients who had persistent hyperparathyroidism. The supernumerary glands were located in the thyroid gland and in the mediastinum. Excision of hypertrophic subcutaneous parathyroid grafts was required for recurrent hyperparathyroidism in 7 (12%) of the patients 15 to 108 months (median, 39 months) after the first operation.

Four of the 50 patients who did not require a second operation for renal hyperparathyroidism received a kidney transplant 7 to 31 months after total parathyroidectomy and subcutaneous parathyroid implantation. At the last follow-up examination, 32 to 60 months after cervical exploration, their blood calcium and phosphorus concentrations were normal. Two patients had normal PTH blood concentrations, but 2 women whose blood creatinine levels were 124 and 133  $\mu\text{mol/L}$  (1.4 and 1.5

### MEDICAL TREATMENT

Hemodialysis was carried out 3 times a week for 3 to 4 hours with a dialysate made with pure water obtained by reverse osmosis and containing 2.5 or 3.0 mEq/L of calcium depending on blood calcium and phosphorus concentrations. The patients were treated with oral calcium salts and 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> supplements in dosages adapted to their blood calcium and phosphorus levels. Moreover, at the beginning of the study, several patients had previously taken oral aluminum-containing phosphate binders.

### PARATHYROID FUNCTION

Intact parathyroid hormone (PTH) levels were obtained in all patients using an immunoradiometric assay (N-tact PTH IRMA; Incstar Corp, Stillwater, Minn) (normal values,  $\leq 5.8$  pmol/L). *Hypoparathyroidism* was defined as an intact PTH serum level below 1.6 pmol/L with a normal or low blood calcium level (normal, 2.12-2.62 mmol/L [8.5-10.5 mg/dL]).

### HISTOLOGICAL STUDIES

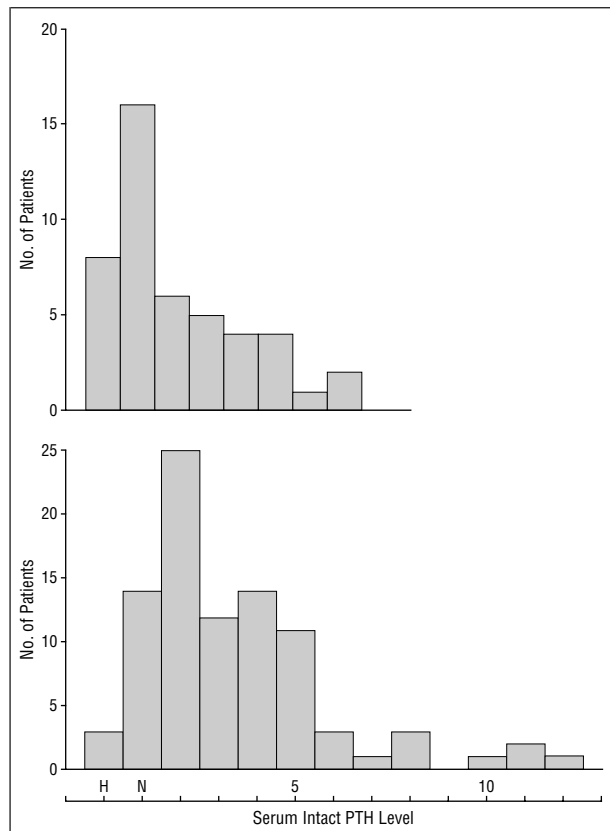
During the study period, the parathyroid glands were examined by 3 senior pathologists. These specimens were recently reviewed by a fourth (I.S.) who has a special interest in endocrine diseases and who was unaware of the clinical evolution of the patients. The histological characteristics of the glands were defined according to the criteria established by Akerström et al.<sup>4</sup> Bone biopsy specimens were stained for aluminum by the aurintricarboxylic acid method and studied by histomorphometry.<sup>5</sup>

### STATISTICAL ANALYSIS

Distribution data were analyzed by the Fisher exact test. The comparison of intact PTH serum levels in different groups of patients was performed with an unpaired *t* test using log-transformed data. Linear regression analysis was used to study the relation between serum intact PTH concentrations and delay after operation.

mg/dL) had intact PTH levels of 6.5 and 11.4 pmol/L, respectively. The remaining 46 patients were treated by long-term intermittent hemodialysis. Serum levels of intact PTH were below 1.6 pmol/L in 8 patients, elevated above 5.8 pmol/L in 22 patients, and between 1.6 and 5.8 pmol/L in 16 patients. All patients received cholecalciferol, oral calcium supplements, or both, and their blood calcium levels were maintained within the normal range.

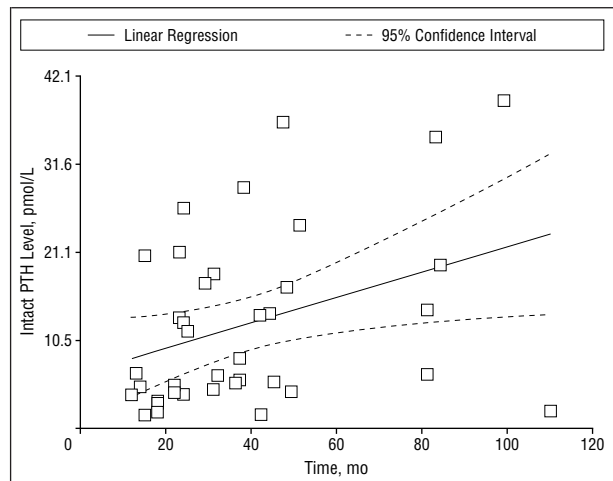
The prevalence of hypoparathyroidism was higher after parathyroidectomy and subcutaneous autografting than in a population of 90 patients who underwent hemodialysis and who had no indication for parathyroid surgery: 8 (14%) of 59 vs 3 (3%) of 90 (odds ratio, 4.55; 95% confidence interval, 1.15-17.93; *P* = .03). Moreover, the distribution of intact PTH blood levels was different in both groups, the peak of the curve being in the normal range in the first while it was situated between 1 and 2 times the upper normal value in the second (**Figure 1**). Among the surgical patients, the frequency



**Figure 1.** Distribution of serum intact parathyroid hormone (PTH) levels in 46 surgical patients (top) and in 90 other patients undergoing hemodialysis (bottom). H indicates hypoparathyroidism (serum intact PTH level < 1.6 pmol/L); N, serum intact PTH concentration in the normal range (1.6-5.8 pmol/L). The figures correspond to multiples of the upper normal limit of serum intact PTH concentration. For example, 5 corresponds to a value greater than 4 times up to 5 times the upper normal limit.

of hypoparathyroidism was 7 (21%) of 33 women and 1 (4%) of 26 men, but this difference did not reach the level of statistical significance (odds ratio, 6.37; 95% confidence interval, 0.77-58.75;  $P = .07$ ). The results of bone biopsies performed at the time of cervical exploration were available for 46 patients. All the samples showed typical features of pure hyperparathyroidism or renal osteodystrophy, and 13 presented with aluminum deposits in 5% to 74% of the total trabecular surface. There was no relation between parathyroid graft function and the presence or absence of aluminum deposits in these bone specimens ( $P = .63$ ).

Precise information concerning the histological characteristics of the grafted tissue was available in 48 of the 55 patients who did not receive a kidney transplant during the follow-up period. Because of the insufficient amount of parathyroid tissue with diffuse hyperplasia, nodular tissue was used in 26 patients. Excision of the parathyroid grafts was not required more often after subcutaneous implantation of nodular tissue when compared with parathyroid tissue showing diffuse hyperplasia (3 of 26 patients vs 3 of 22 patients). In patients who did not undergo another operation for recurrent hyperparathyroidism, the mean ( $\pm$ SEM) intact PTH level was higher in those receiving nodular tissue ( $12.8 \pm 2.5$  pmol/L) than in the group grafted with parathyroid tis-



**Figure 2.** Relation between serum concentrations of intact parathyroid hormone (PTH) and length of follow-up in patients undergoing hemodialysis, who had functioning parathyroid grafts, and who have not undergone another operation for recurrence of the disease.

sue showing diffuse hyperplasia ( $7.4 \pm 1.4$  pmol/L). However, this difference was not significant ( $P = .31$ ). In addition, the mean ( $\pm$ SEM) follow-up was longer, although not significantly different, for patients receiving nodular grafts when compared with patients receiving parathyroid tissue showing diffuse hyperplasia ( $45.3 \pm 5.8$  vs  $30.3 \pm 3.0$  months;  $P = .10$ ).

**Figure 2** shows the relation between intact PTH blood levels and time after total parathyroidectomy and subcutaneous parathyroid grafting in patients treated by hemodialysis who did not have permanent hypoparathyroidism and who did not require excision of the parathyroid grafts during the study period. Although there is a wide variability of individual results, intact PTH blood concentrations tended to increase with time: intact PTH level (measured in picomoles per liter) =  $6.5 + [0.15 \times \text{time (months)}]$  ( $r = 0.36$ ,  $P = .02$ ).

#### COMMENT

The most popular surgical procedures used to treat renal hyperparathyroidism are subtotal parathyroidectomy and total parathyroidectomy with intramuscular implantation of parathyroid tissue. A small amount of abnormal parathyroid tissue is left in the patient with both techniques. As chronic renal failure persists after the operation, this glandular tissue is continually stimulated, and hyperparathyroidism may recur. Some researchers presently advocate total parathyroidectomy without grafting to avoid these recurrences. They state that the absence of PTH has no significant clinical consequence on the bones of patients who undergo hemodialysis and who are treated with calcium and cholecalciferol supplements.<sup>6-9</sup> These conclusions are, however, questioned by other investigators.<sup>10</sup> The ideal blood concentration of intact PTH is not known for uremic subjects. Histomorphometric analysis of iliac crest bone biopsy specimens showed that it should be elevated to maintain a normal bone turnover, but the levels advocated by different researchers<sup>11-13</sup> varied from 1.5 to 4.0 times the upper normal limit. As some secretion of PTH seems necessary, we

ected to continue our program of autotransplantation of endocrine tissue, but instead of putting the parathyroid pieces into a muscle where their later resection can be difficult, we implanted the grafts subcutaneously in front of the lower third of the sternum where they can be easily located and excised under local anesthesia.<sup>2</sup>

Previous excision of the totality of parathyroid tissue is essential to evaluate correctly the function of these grafts. In the present study, all the patients underwent the resection of at least 4 parathyroid glands. In this selected series of 59 patients, parathyroidectomy was, however, incomplete in 2 patients (3%) who had to undergo another operation for persistent hypercalcemia, and a fifth gland was found in both patients. Also, the prevalence of excision of the grafts required by recurrence of the disease was 12% (7 of 59 patients). In the beginning of the 1990s, 2 independent reviews<sup>14,15</sup> of the English, German, French, and Italian literature including many patients reported rates of late hypercalcemia of 5.8% and 6.6% after subtotal parathyroidectomy and 6.6% and 10.7% after total parathyroidectomy and intramuscular autotransplantation. At first sight, these figures seem lower than in our series, but many articles in both reviews reported few cases, most with short follow-up periods. More recent studies<sup>16-20</sup> found late reoperation rates of 6% to 8% after subtotal parathyroidectomy and 5% to 15% after total parathyroidectomy and intramuscular autotransplantation. Higgins et al<sup>6</sup> even observed that after 5 years the parathyroid grafts had been excised in 30% of patients who underwent hemodialysis and who were treated by total parathyroidectomy and intramuscular autotransplantation. All these publications rarely differentiated between persistent and recurrent disease after surgery. Indeed, most of the series included patients in whom fewer than 4 glands had been discovered during cervical exploration. In a prospective, randomized, clinical trial, Rothmund et al<sup>14</sup> compared 20 cases of subtotal parathyroidectomy with 20 cases of total parathyroidectomy and intramuscular autotransplantation followed up for a mean duration of more than 40 months. Hypercalcemia was less frequent (4 vs 1) and no patient underwent another operation after the latter procedure.<sup>14</sup>

In vitro investigations<sup>21,22</sup> comparing the function of cells from parathyroid nodules with cells from areas of parathyroid hyperplasia suggested that grafting nodular tissue should be avoided to prevent recurrences. Our series shows that it was impossible to implement such a policy in more than 50% (26 of 48 patients for whom the information was available) of our patients because of an insufficient amount of tissue showing diffuse hyperplasia in the resected parathyroid glands. Gagné et al<sup>23</sup> reported that patients with parathyroid nodular hyperplasia had higher rates of recurrence (defined as an intact PTH level higher than twice the upper normal limit) than those with diffuse hyperplasia after subtotal parathyroidectomy or total parathyroidectomy plus intramuscular grafting. In a preliminary study, we could not demonstrate a relation between parathyroid function and histological characteristics of the glands described in the pathological reports of operative specimens. Therefore, the slides were recently reviewed by a pathologist (I.S.) who was blinded to the clinical evolution of the pa-

tients. We were again unable to confirm the observation made by Gagné et al. The reoperation rate was the same in both groups, and the intact PTH serum levels were not significantly higher in patients with nodular grafts. The slight increase that was observed could actually be explained by their longer follow-up compared with the patients with grafts of tissue showing diffuse hyperplasia.

**R**ECENT PUBLICATIONS<sup>11,24-26</sup> have shown that a significant proportion of uremic patients treated by maintenance hemodialysis present with hypoparathyroidism that consequently could not be attributed solely to the surgical procedure used in all our patients. Therefore, we compared the surgical patients with a population of patients treated by hemodialysis and who were not candidates for parathyroidectomy. There was a shift to the left of the curve representing the distribution of the intact PTH serum levels after total parathyroidectomy and subcutaneous autotransplantation when compared with this second group. As there is no consensus concerning the adequate intact PTH levels in patients with chronic renal failure, hypoparathyroidism was arbitrarily defined as an intact PTH level lower than 1.6 pmol/L. Admittedly, this definition does not include all the patients with a PTH secretion insufficient to maintain a normal bone turnover, but it allows a comparison with previously published data. In our study, the prevalence of late hypoparathyroidism after operation was 8 (14%) of 59 patients, which was significantly higher than the 3 (3%) observed in the 90 patients who underwent hemodialysis and who were not operated on, but was lower than the 29% and 38% reported by Gagné et al<sup>23</sup> for total parathyroidectomy with intramuscular autotransplantation and subtotal parathyroidectomy, respectively. The discrepancies between both studies should, however, not be attributed only to differences in surgical technique. The evolution of the function of parathyroid grafts depends on multiple other factors, among which the prescribed therapy and the compliance of the patients are of utmost importance.

At the beginning of the present study, some uremic patients had received aluminum-containing phosphate binders as part of their treatment before undergoing parathyroid surgery. This type of medication is no longer administered in our unit to patients undergoing hemodialysis. Therefore, it was necessary to investigate separately the question of aluminum intoxication. Indeed, aluminum accumulates in parathyroid glands and is known to inhibit their hormonal secretion.<sup>27-30</sup> We found no relation between the presence of aluminum deposits in bone biopsy specimens and the function of parathyroid subcutaneous grafts. This is in keeping with the results of Berland et al,<sup>27</sup> who found that the aluminum content of parathyroid glands was similar in patients with or without bone aluminum deposits and was only correlated with serum aluminum levels. Moreover, in vitro studies<sup>29</sup> with dispersed bovine parathyroid cells demonstrated that the suppression of PTH secretion was not an irreversible phenomenon. The PTH production returned to normal when aluminum was removed from the culture medium. Ac-



tually, hypoparathyroidism was also observed in patients who had not been exposed to aluminum and tended to be more frequent in women, which seems to indicate that some other factors, possibly technical, hormonal, or both, could be responsible for the lack of secretion of the grafts.

Finally, the slow progressive increase of blood intact PTH concentrations with time suggests that, in the future, other patients could require excision of the hypertrophied grafts. This is not a matter of concern because the procedure is quick and simple for presternal subcutaneous implants.

In conclusion, the late results of total parathyroidectomy with presternal subcutaneous autotransplantation compare favorably with published data on other forms of surgical treatment of renal hyperparathyroidism. The present results warrant further use of this procedure.

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