

General Weakness as an Indication for Parathyroid Surgery in Patients With Secondary Hyperparathyroidism

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Hypotheses: There are factors that affect patients with general weakness owing to secondary hyperparathyroidism and as reported by results noted after parathyroidectomy and autotransplantation.

Design: Case series and consecutive samples.

Setting: Tertiary care center.

Patients: From July 1996 to June 1998, 56 patients with secondary hyperparathyroidism underwent total parathyroidectomy and autotransplantation. Their ages were 45 ± 13 years (mean \pm SD) and preoperative duration of dialysis was 75 ± 37 months. Prior to surgery the patients were divided into 2 groups: group A comprised 2 men and 19 women who had some general weakness; and group B, 15 men and 20 women who reported no general weakness. The etiologies of renal failure, such as diabetic nephropathy ($n = 3$) or hypertensive nephropathy ($n = 3$), were found only in group A patients.

Interventions: Serum levels of calcium, phosphorus, alkaline phosphatase, and parathyroid hormone (intact) were checked preoperatively and 1 day, 1 week, and 3 months after surgery. Extension force of the quadriceps femoris muscle was measured at 60° of right knee flexion preoperatively and 3 months after surgery. The extension force was expressed as newtons (N) in 2 different quantities: peak force and average force. The degree of general weakness was classified into 4 groups: 0, no weakness; 1, some subjective weakness and/or walking with assistance; 2, the patient was wheelchair bound; and 3, the patient was bedridden.

Main Outcome Measures: The *t* test was used for paired and unpaired data; Wilcoxon signed rank and Fisher exact tests were incorporated for nonparametric data. Any values of $P < .05$ were considered significant.

Results: Prior to surgery, 2 patients in group A reported degree 3 weakness; 5, degree 2 weakness; and 14, degree 1 weakness. Three months after surgery, the peak force was noticed to have increased from 185 ± 56 N to 249 ± 82 N (mean \pm SD) ($n = 11$, $P = .003$), and the average force showed an increase from 136 ± 45 N to 202 ± 69 N ($n = 11$, $P = .003$). Postoperatively, only 5 patients had degree 1 weakness, 1 had degree 2 weakness, and none had degree 3 weakness. The patient with degree 2 weakness after surgery had diabetes mellitus and a femoral neck fracture prior to parathyroidectomy. Improvement in condition of general weakness was found ($P < .001$) between preoperative and postoperative periods. Serum levels of calcium were higher in group A (2.82 ± 0.23 mmol/L [11.3 ± 0.9 mg/dL]) than in group B (2.64 ± 0.27 mmol/L [10.6 ± 1.1 mg/dL]) ($P = .013$), and serum levels of parathyroid hormone (intact) were lower in group A (108.9 ± 39.2 pmol/L) than in group B (139.8 ± 39.6 pmol/L) ($P = .006$). Except for sex, other data such as phosphorus and alkaline phosphatase levels, age, and duration of dialysis were not significantly different between the 2 groups.

Conclusions: General weakness that is commonly observed in patients with secondary hyperparathyroidism is found more frequently in women and only in patients with diabetic nephropathy or hypertensive nephropathy. Patients with general weakness had relatively higher levels of calcium and lower levels of parathyroid hormone (intact). We found that improvement of muscle power and general weakness can be achieved by parathyroidectomy and autotransplantation. In addition to itchy skin, bone pain, and soft tissue calcification, general weakness that may cause disability is also an indication for surgery in secondary hyperparathyroidism.

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TRADITIONALLY, bone pain, itchy skin, and soft tissue calcification are indications for parathyroidectomy in those with secondary hyperparathyroidism.^{1,2} We recently discovered that general weakness that is frequently observed in conditions of secondary hyperparathyroidism could be improved by para-

thyroidectomy and autotransplantation. In this article we report the factors that affect patients with general weakness and the postoperative results.

RESULTS

Group A comprised 2 men and 19 women with an age of 49.7 ± 15.2 years; and group

SUBJECTS, MATERIALS, AND METHODS

From July 1996 to June 1998, 56 patients (17 men; 39 women) with secondary hyperparathyroidism (parathyroid hormone [intact] [I-PTH] more than 10 times the reference levels) who were undergoing total parathyroidectomy and autotransplantation of 60 mg of parathyroid tissue were enrolled in the study. The most frequent causes of renal failure were chronic glomerulonephritis in 24 patients (42.9%), diabetic nephropathy in 3 (5.4%), hypertensive nephropathy in 3 (5.4%), interstitial nephritis in 3 (5.4%), obstructive uropathy in 2 (3.5%), polycystic kidney in 1 (1.8%), systemic lupus erythematosus in 1 (1.8%), and idiopathic in 19 (33.9%).

The indications for surgery were bone pain in 10 patients (17.9%), itchy skin in 7 (12.5%), both bone pain and itchy skin in 27 (48.2%), general weakness that caused disability in 7 (12.5%), chest tightness in 1 (1.8%), growth retardation in 1 (1.8%), heart failure in 1 (1.8%), generalized edema in 1 (1.8%), and disorientation in 1 (1.8%). The degree of patients' weakness was classified into 4 groups: 0, no general weakness; 1, subjective weakness and/or walking with assistance; 2, the patient was wheelchair bound; and 3, the patient was bedridden. The conditions of the patients were recorded preoperatively and 3 months postoperatively. Patients were divided into 2 groups: group A included those who reported general weakness, and group B included patients who experienced no general weakness.

Serum levels of calcium, phosphorus, I-PTH, and alkaline phosphatase of all patients were recorded before surgery and 1 day, 1 week, and 3 months after surgery. Forty-nine patients had undergone hemodialysis, and 7 had

undergone peritoneal dialysis. Patients undergoing hemodialysis had regular dialysis 3 times a week and 1 day before surgery. No patient received a kidney transplant during the follow-up period in this study. One patient undergoing peritoneal dialysis was changed to hemodialysis later in the course of treatment. Before surgery, a baseline level of serum aluminum was checked to rule out any aluminum intoxication.

Surgical exploration of the neck was performed under general anesthesia, with removal of all glands, autotransplantation of 60 mg of parathyroid tissue, and cryopreservation of all the other tissues. A transcervical thymectomy was performed routinely and cautiously to remove any supernumerary parathyroid glands or embryologic rests of parathyroid tissue. Subcutaneous autotransplantation to the forearm without arteriovenous fistula was performed on 49 patients and to the right thigh on 7. The detailed procedure of autotransplantation was reported in our previous research study.³ After surgery, all blood samples were drawn from the antecubital veins of the forearm with implantation or without arteriovenous fistula. Extension force of quadriceps femoris muscle was measured with an isometric dynamometer (Kin-Com 500H; Kinetic Communicator, Chattanooga, Tenn) with the patient in a sitting position and at 60° of right knee flexion. The extension forces thus measured were classified as peak force and average force, expressed in newtons (N). The test was performed before surgery and 3 months after surgery.

Statistical significance of the measurements was assessed by means of the *t* test for paired and unpaired samples, by Wilcoxon signed rank test, and by Fisher exact test for nonparametric data. Statistical data analyses were performed using the Statistical Package for the Social Science (SPSS Inc, Chicago, Ill). Any values of *P* < .05 were considered significant. Data are presented as mean ± SD.

B had 15 men and 20 women with an age of 42.2 ± 10.2 years. There was no significant difference in age (*P* = .06) between the 2 groups. There was no significant difference in the etiology of secondary hyperparathyroidism between the 2 groups. However, women were observed to have more chances of general weakness (*P* = .015), and patients with diabetic nephropathy or hypertensive nephropathy were found only in group A. Four glands were found in 49 patients; 3 glands, in 6; and 5 glands, in 1. The weight of the parathyroid gland in group A was 4.2 ± 3.8 g, and in group B it was 3.7 ± 2.3 g. The difference was not significant between the 2 groups.

The calcium levels of group A were 2.82 ± 0.23 mmol/L (11.3 ± 0.9 mg/dL) (*n* = 21), and those of group B were 2.64 ± 0.27 mmol/L (10.6 ± 1.1 mg/dL) (*n* = 35) (*P* = .013). The I-PTH levels of group A were 108.9 ± 39.2 pmol/L (*n* = 21) and those of group B were 139.8 ± 39.6 pmol/L (*n* = 35) (*P* = .006). The average force of right knee extension at 60° in group A was 138 ± 67 N (*n* = 18) and in group B, 253 ± 106 N (*n* = 31) (*P* < .001). The peak force of right knee extension at 60° in group A was 188 ± 77 N (*n* = 18) and in group B was 323 ± 133 N (*n* = 32) (*P* < .001). Other data, such as levels of phosphorus and alkaline phosphatase and duration of dialysis, showed no significant differences between the 2 groups (**Table 1**). Serum calcium levels decreased markedly 1 week after surgery and gradually returned to reference levels

Table 1. Preoperative Duration of Dialysis, Blood Chemistry, and 60° Right Knee Extension Force Between the 2 Groups*

Preoperative Condition	Group A† (n = 21)	Group B‡ (n = 35)	P
Duration of dialysis, mo	81 ± 35	65 ± 41	.12
Calcium, mmol/L (mg/dL)	2.82 ± 0.23 (11.3 ± 0.9)	2.64 ± 0.27 (10.6 ± 1.1)	.01
Phosphorus, mmol/L	2.00 ± 0.29	2.03 ± 0.43	.82
Alkaline phosphatase, U/L	227.4 ± 192.6	285.7 ± 215.8	.31
Parathyroid hormone (intact), pmol/L	108.9 ± 39.2	139.9 ± 39.6	.006
60° Extension average force, N§	138 ± 67	253 ± 106¶	<.001
60° Extension peak force, N#	188 ± 77	323 ± 133**	<.001

*Values are given as mean ± SD except where indicated.

†Patients with general weakness.

‡Patients without general weakness.

§Total for groups A and B, 211 ± 108.

||*n* = 18.

¶*n* = 31.

#Total for groups A and B, 274 ± 133.

***n* = 32.

3 months later. No patient had to take more than 1 g/d of calcium carbonate and 0.25 µg/d of calcitriol 3 months after the surgery to keep serum calcium levels in the reference range. Serum levels of phosphorus decreased

Table 2. Serum Levels of Calcium, Phosphorus, Alkaline Phosphatase, and Parathyroid Hormone (Intact) at 1 Day, 1 Week, and 3 Months After Surgery*

Component, Reference Range	1 Day (N = 56)	1 Week (N = 56)	3 Months (n = 46)
Calcium, 2.0-2.5 mmol/L (8-10 mg/dL)	2.22 ± 0.37 (8.9 ± 1.5) (1.47-3.0 [5.9-12.0])	2.05 ± 0.40 (8.2 ± 1.6) (1.32-3.09 [5.3-12.7])	2.17 ± 0.22 (8.7 ± 0.9) (1.62-2.64 [6.5-10.6])
Phosphorus, 0.8-1.5 mmol/L	1.74 ± 0.48 (0.48-3.00)	1.26 ± 0.48 (0.36-3.00)	1.29 ± 0.45 (0.42-2.36)
Alkaline phosphatase, 24-95 U/L	245 ± 190 (53-897)	398 ± 344 (84-1694)	140 ± 104 (33-669)
Parathyroid hormone (intact), 1.1-6.8 pmol/L	5.7 ± 10.9 (0.1-44.9)	5.5 ± 10.9 (0.1-47.4)†	10.9 ± 17.2 (0.1-67.6)‡

*Values are given as mean ± SD (range).

†n = 55.

‡n = 45.

Table 3. Preoperative and Postoperative Degree of Muscle Weakness in 56 Patients*

Weakness	Wilcoxon Signed Rank Test†	
	Preoperative	Postoperative (3 mo)
Without general weakness, 0	35	50
Subjective weakness and/or walking with assistance, 1	14	5
Wheelchair bound, 2	5	1
Bedridden, 3	2	...

*Ellipses indicate not applicable.

†P < .001.

Table 4. Preoperative and Postoperative 60° Right Knee Extension Force in 2 Groups of Patients Using a Paired t Test*

	Group A† (n = 11)	Group B‡ (n = 21)	Total (N = 32)
60° Extension average force, N			
Preoperative	136 ± 45	270 ± 115	224 ± 116
Postoperative, 3 mo	202 ± 69	314 ± 120	275 ± 117
P	.003	.004	<.001
60° Extension peak force, N			
Preoperative	185 ± 56	347 ± 127	291 ± 133
Postoperative, 3 mo	249 ± 82	397 ± 146	346 ± 145
P	.003	.007	<.001

*Values are given as mean ± SD.

†Patients with general weakness.

‡Patients without general weakness.

1 week after surgery and remained constant 3 months later. Serum alkaline phosphatase levels increased 1 week after surgery but gradually returned to reference levels 3 months later. Serum I-PTH levels decreased markedly 1 day to 1 week after surgery but gradually returned to reference levels 3 months later (Table 2). Three months after surgery, 16 (31%) of 51 patients had I-PTH levels below the reference point (1.1 pmol/L), but no patient needed reimplantation of the cryopreserved tissue since normocalcemia was maintained with low-dose daily treatment with calcium carbonate and calcitriol.

In the preoperative conditions, 14 of 21 group A patients had degree 1 weakness; 5, degree 2 weakness; and 2, degree 3 weakness. Three months after surgery, only 5 patients had degree 1 weakness, 1 had degree 2 weak-

ness, and nobody reported degree 3 weakness. The difference between the preoperative and postoperative groups was significant (P < .001) (Table 3). The only woman who was wheelchair bound (degree 2 weakness) after surgery had diabetes mellitus and a femoral neck fracture before the operation. She had received a hip prosthesis before parathyroidectomy and had been bedridden since that earlier surgery. After parathyroidectomy, her condition improved from degree 3 to degree 2 weakness, and she managed to be in a wheelchair but could not walk with assistance. Peak extension force of the right knee at 60° showed improvement in all patients irrespective of group. Similar results were also found for the average extension force of the right knee at 60° (Table 4).

COMMENT

The population of patients receiving maintenance dialysis is growing, and with it, the number who develop various muscular and skeletal complications. While most patients undergoing dialysis can be managed medically, some 3.4% to 15.0% will develop complications of secondary hyperparathyroidism and require surgical intervention.⁴⁻⁶ Bone pain, itchy skin, abnormal bone structure, general weakness, and an increased risk of fracture are well-known manifestations of elevated I-PTH levels in patients with primary or secondary hyperparathyroidism. We have studied the function of the parathyroid tissue after parathyroidectomy and autotransplantation. We found that there was no difference between subcutaneous and intramuscular autotransplantation.³ Six months after surgery, almost all patients had serum I-PTH levels within or above reference limits. In this study we adopted the method of total parathyroidectomy and autotransplantation of 60 mg of parathyroid tissue into the subcutaneous tissue, irrespective of how many glands were found during surgery. Although there were 7 patients who had high levels of I-PTH (>13.7 pmol/L) immediately or 3 months after surgery, only 1 had 3 glands removed during exploration. These patients showed improvement of their preoperative symptoms, such as itchy skin and bone pain, and the levels of I-PTH decreased to one third of the preoperative levels. No further study was carried out on these patients.

Muscle weakness of patients with uremia seems to appear slowly, with the patient unable to climb stairs easily or to rise from a sitting position without help. Such

an afflicted patient may be confined to a wheelchair or bed. Muscle weakness can be caused by secondary hyperparathyroidism, phosphate depletion, abnormal metabolism of vitamin D, aluminum loading, and peripheral neuropathy.^{7,8} Moreover, patients with uremia may sometimes show a definite component of proximal muscle weakness,^{7,9} a finding that is probably often overlooked. Muscle weakness with disability was found in 7 patients (12.5%) in this study and was quite similar to a previous report (12%).¹⁰ Secondary hyperparathyroidism in uremia might be a major cause of this proximal weakness. We found that both average extension force and peak extension force were much less in the group of patients with general weakness than in those without any general weakness. The levels of calcium were higher and the levels of I-PTH were lower in the group with general weakness. However, the age of the patients and the duration of dialysis had no effects on general weakness in this study. Three months after parathyroidectomy, in 17 (30%) of the patients the I-PTH levels were still below reference limits, but the levels of calcium were well within reference limits, indicating that high levels of I-PTH and hypercalcemia were the factors that might cause general weakness. It was reported in several previous studies¹¹⁻¹⁴ that the muscle force—especially muscle force of the knee extension and flexion—increased after parathyroidectomy.^{7,15} We were surprised at the recovery of those patients with general weakness and disability after surgery. Prior to surgery, 7 patients were wheelchair bound or bedridden, while after surgery, only 1 patient was wheelchair bound and none were bedridden. The patient in a wheelchair had diabetes mellitus and a femoral neck fracture prior to parathyroidectomy, and recovery from surgery was not satisfactory. We therefore suggest that patients with secondary hyperparathyroidism and diabetic angiopathy and neuropathy may not be ideal candidates for surgery. We also found that the extension force of the quadriceps femoris muscle increased whether patients had general weakness or not. In other words, clinical improvement of the degree of weakness was more prominent in patients with general weakness. Observing these factors, we conclude that, ex-

cept for itchy skin, bone pain, and soft tissue calcification, general weakness that may cause disability could also be an indication for surgery in patients with secondary hyperparathyroidism.

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Announcement

The *Archives of Surgery* will give priority review and early publication to seminal works. This policy will include basic science advancements in surgery and critically performed clinical research.