



Assessment of operative treatment of patients with tertiary hyperparathyroidism after kidney transplantation

Ocena operacyjnego leczenia chorych z trzeciorzędową nadczynnością przytarczyc po przeszczepieniu nerki

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Abstract

Introduction: The purpose of the study was to assess the results of operative treatment of patients with tertiary hyperparathyroidism (tHPT) after kidney transplantation.

Material and methods: The study included 30 patients in whom kidney transplantation was performed between 2006 and 2013, and in whom parathyroidectomy had to be performed at a later time because of tHPT. There were 17 (56.7%) women and 13 (43.3%) men in the group, aged 18–64, mean 46.1 years. In order to locate the lesion before the operation, all patients had to undergo USG, and 14 had scintigraphy MIBI in addition. Serum levels of PTH, ionised calcium, and creatinine were determined together with glomerular filtration rate (GFR). The results of control tests were compared with those performed one day before parathyroidectomy (PTX) and three days after the operation.

Results: Among 30 patients, 19 (63.3%) underwent total resection of three parathyroid glands and 3/4 of the fourth. Two parathyroid glands were resected in eight (26.7%) patients, and one in the remaining three (10%) patients. Histopathological examination showed one parathyroid adenoma in six (20%) patients, and one parathyroid adenoma and hyperplasia of the remaining glands in one (3.3%) patient. Five (16.7%) patients had hyperplasia of two parathyroid glands whereas no changes were observed in two patients. On the other hand, hyperplasia of all glands was noted in 18 (60%) patients. Serum PTH level was significantly lower compared to the level before operation ($p < 0.001$), being 5.5–58.5 pg/mL, on day 3 postoperatively. Differences in the levels of serum-ionised calcium were also significant ($p < 0.0001$) after eight months.

Conclusions:

1. Surgical resection of parathyroid glands is a management of choice in patients after kidney transplantation accompanied by hypercalcaemia lasting longer than one year.
2. Resection of 3 3/4 parathyroid glands because of hyperplasia in patients with hyperparathyroidism after kidney transplantation enables restoration of normal calcium metabolism.
3. Moreover, resection of 3 3/4 parathyroid glands can allow avoidance of autotransplantation, which is necessary in cases of total resection of parathyroid glands. (*Endokrynol Pol* 2015; 66 (5): 422–427)

Key words: tertiary hyperparathyroidism; parathyroidectomy

Streszczenie

Wstęp: Celem pracy była ocena wyników operacyjnego leczenia chorych z trzeciorzędową nadczynnością przytarczyc (tHPT) po przeszczepieniu nerki.

Materiał i metody: Badaniem objęto 30 chorych po przeszczepieniu nerki dokonanym w latach 2006–2013, u których w późniejszym czasie pojawiła się konieczność usunięcia przytarczyc z powodu tHPT. Było 17 (56,7%) kobiet oraz 13 (43,3%) mężczyzn w wieku 18–64 lat, śr. 46,1 lat. W celu lokalizacji zmienionych przytarczyc u wszystkich chorych wykonano przedoperacyjne badanie USG, a u 14 również scyntyografię MIBI. Oznaczano u nich stężenie PTH w surowicy, wapnia zjonizowanego, kreatyniny oraz wskaźnik przesączania kłębuszkowego (GFR). Wyniki badań kontrolnych porównano z badaniami wykonanymi dobę przed parathyreoidektomią (PTX) oraz trzy dni po wykonaniu operacji.

Wyniki: Spośród 30 chorych u 19 (63,3%) dokonano wycięcia całkowitego trzech przytarczyc oraz 3/4 czwartej. U ośmiu (26,7%) chorych z kolei usunięto dwie zmienione przytarczycy, zaś u pozostałych trzech (10%) jedną. W badaniach histopatologicznych u sześciu (20%) chorych stwierdzono obecność gruczolaka jednej przytarczycy, u jednego (3,3%) zaś rozpoznano gruczolaka jednej przytarczycy, w pozostałych obserwując rozrost. U pięciu (16,7%) chorych rozpoznano rozrost dwóch przytarczyc, zaś dwie pozostawały niezmiennione. Natomiast u 18 (60%) operowanych rozpoznano rozrost wszystkich przytarczyc. W trzeciej dobie po operacji usunięcia przytarczyc pomiar stężenia PTH w surowicy chorych ulegał ustabilizowaniu, obniżając się zmiennie w zakresie 5.5–58.5 pg/ml w porównaniu z okresem sprzed operacji ($p < 0,001$). Również po ośmiu miesiącach różnice te miały charakter zmienny ($p < 0,0001$).

Wnioski:

1. Chirurgiczne wycięcie przytarczyc stanowi postępowanie z wyboru u chorych po przeszczepieniu nerki z hiperkalcemią trwającą ponad rok.
2. Wycięcie 3 i 3/4 przytarczyc z powodu ich rozrostu u chorych z nadczynnością przytarczyc po przeszczepie nerki, pozwala u leczonych na przywrócenie prawidłowej gospodarki wapniowej.
3. Wycięcie 3 i 3/4 gruczolą może pozwolić też na uniknięcie potrzeby dokonywania autotransplantacji jak to ma miejsce w przypadku całkowitego usunięcia przytarczyc. (*Endokrynol Pol* 2015; 66 (5): 422–427)

Słowa kluczowe: trzeciorzędową nadczynnością przytarczyc; parathyreoidektomia



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Introduction

Tertiary hyperparathyroidism (tHPT) is usually defined as excessive persistent secretion of PTH following kidney transplantation in patients with secondary hyperparathyroidism and in dialysis patients [1, 2]. Most patients receive normal function of their kidney after transplantation, but about 1–5.6% will have to undergo and operation for tHPT [3]. Still existing hyperparathyroidism may lead to production of stones within the transplanted kidney followed by disturbances in the transplant function, osteopaenia, pathological fractures, and finally mental disorders [4].

A management of choice in patients with tHPT after kidney transplantation is operative treatment. Although calcimimetic cinacalcet is fairly effective, its therapeutic effect is strictly confined to the period of its usage [5].

Indications for operation because of tHPT seem therefore to include:

- no availability of successful medical treatment for more than 12 months;
- hypercalcaemia > 3 mmol/L;
- increasing osteoporosis and pathological fractures;
- disturbances in the transplanted kidney function and signs of calculosis [6, 7].

The purpose of the study was to evaluate the late results of operative treatment used for patients with tertiary hyperparathyroidism following kidney transplantation.

Material and methods

The study included 30 patients who underwent kidney transplantation between 2006 and 2013 and necessary resection of parathyroid glands at a later time because of tHPT. There were 17 (56.7%) women and 13 (43.3%) men aged 18–64, mean 46.1 years. Kidney failure was caused by glomerulonephritis in 22 (73.3%) patients, pyelonephritis in two (6.7%), congenital polycystic kidney disease in three (10%), and diabetic complications in another three. Duration of haemodialysis until kidney transplantation was 8–132, mean 54.3 months, and mean time from the transplantation to the resection of parathyroid glands was 49.2 months (3–180 months).

In order to locate the lesions before the operation, all patients received USG, and 14 of them scintigraphy MIBI in addition. At the operation time all patients had a kidney transplant and were receiving immunosuppressants.

Follow-up examinations were performed after a minimum of eight months from parathyroidectomy (PTX). Physical examinations were followed by testing

serum level of PTH, levels of ionised calcium and creatinine together with glomerular filtration rate (GFR) in MDRD formula. These examinations were compared with those performed one day before PTX and three days after the operation.

Statistical analysis was performed basing on STATISTICA data analysis software system v. 10 (StatSoft Inc. 2011). Shapiro-Wilk test was used for sample distribution to compare time series among the groups, and ANOVA for repeated measures with post-hoc Bonferroni test. Upon sample distribution, kidney activity was assessed by Student's *t* test for related values. The data were presented as means and standard deviations with reference to absolute numbers and percentages. The values of $p < 0.05$ were considered as significant.

Results

Clinical symptoms in patients with tertiary hyperparathyroidism referred to operative treatment are shown in the table (Table I).

One (3.3%) patient received PTX after three months from kidney transplantation as he was under threat of parathyroid crisis in spite of using calcimimetics. Another nine (30%) patients were operated between 12 and 24 months from the transplantation, and eight (26.7%) between 24 and 36 months. The remaining 12 (40%) patients received PTX between 48 and 180 months from the kidney transplantation.

In the group of 30 patients, three and 3/4 parathyroid glands were resected in 19 (63.3%), two were resected in eight (26.7%), and one in the remaining three (10%). In these last 11 patients biopsy specimens were taken from the remaining parathyroid glands for intra-operative histopathological examinations. No pathology was shown in the results.

Histopathological examinations showed one parathyroid adenoma and normal glands in six (20%) patients, and one parathyroid adenoma and hyperplasia of the remaining glands in one (3.3%). Hyperplasia of two parathyroid glands and two normal were found in five (16.7%) patients. Hyperplasia of all parathyroid glands was found in 18 (60%) patients.

During the follow-up, four (13.3%) patients died, after 14, 15, 17, and 26 months from the operation. One of them had cerebral haemorrhage, and three died from progressive circulatory failure.

In general, the mean level of serum PTH was 679.8 ($n = 15$ –65) pg/mL (135.8–3291 pg/mL) before the operation, while the mean level of ionised calcium was 1.5 ($n = 1.12$ –1.27) mmol/L (0.97–1.73 mmol/L). Three (10%) patients showed serum-ionised calcium of 1.2 mmol/L (0.97, 1.02, 1.16) before PTX in spite of

Table I. Characteristics of 30 patients operated between 2006 and 2013 for tertiary hyperparathyroidism**Tabela I. Charakterystyka 30 pacjentów operowanych w latach 2006–2013 z powodu trzeciorzędowej nadczynności przytarczyc**

Description	No. of patients (%)
Sex	
Women	17 (56.7%)
Men	13 (43.3%)
Age (years)	18–64. mean 46.1
Cause of kidney failure	
Glomerulonephritis	22 (73.3%)
Pyelonephritis	2 (6.7%)
Congenital polycystic kidney disease	3 (10%)
Diabetic complications	3 (10%)
Symptoms before operation	
Bone pains	27 (90%)
Signs of depression	12 (40%)
Excessive sweating	9 (30%)
Significant weakness	8 (26.7%)
Calcifications in the transplanted kidney	8 (26.7%)
Signs of osteopenia	6 (20%)
Persistent itching of the skin	3 (10%)
Extraskeletal calcifications	2 (6.6%)
Myopathy	2 (6.6%)
Duration of dialyses before kidney transplantation (months)	8–132. mean 54.3
Length of time from kidney transplantation to PTX (months)	3–180. mean 49.2
Range of operation	
Resection of 3 3/4 parathyroids	19 (63.3%)
Resection of 2 parathyroid glands and collection of specimens from the rest	8 (26.7%)
Resection of 1 parathyroid gland and collection of specimens from the rest	3 (10%)
Histopathological diagnosis	
Hyperplasia of all glands	18 (60%)
Hyperplasia of 2 glands + 2 normal	5 (16.7%)
Adenoma on 1 gland + 3 normal	6 (20%)
Adenoma on 1 gland + hyperplasia of the rest	1 (3.3%)
Duration of follow-up after PTX (months)	6–87. mean 35
Alive	26 (86.8%)
Dead	4 (13.2%)
Causes of death	
Cerebral haemorrhage	1 (3.3%)
Circulatory failure	3 (10%)

PTX — parathyroidectomy

high values of the parathormone (PTH) i.e. 3291, 1712, and 1309 pg/mL.

On day 3 after the operation, the level of serum PTH decreased remarkably compared with before the operation ($p < 0.001$) and ranged between 5.5 and 58.5 pg/mL (Fig. 1). Only three (10%) patients showed higher PTH level, i.e. 78.5 and 621.8 pg/mL, respectively. Follow-up examinations, performed a minimum of eight months after PTX in 26 patients, showed normal values and ranged between 19.3 and 55 pg/mL. The differences were significant relative to the examinations performed before the operation ($p < 0.001$). However, this level exceeded the upper limit of the range and was 87.5, 96, 68.4, and 114 pg/mL, respectively. Differences in the levels of serum ionised calcium after eight months were also significant as compared with the preoperative period ($p < 0.0001$) (Fig. 2). The level of ionised calcium in all patients, including the four who had an increased PTH level, did not exceed the reference limits and was 1.17, 1.2, 1.24, and 1.29 mmol/L, respectively.

After a minimum of eight months from the operation, the differences in creatinine levels or GFR values were not significant relative to the preoperative period ($p = 0.507$; $p = 0.353$) (Fig. 3 and 4). However, it may be important to note that the value of GFR after PTX exceeded 50% only in nine patients.

Discussion

Chronic kidney failure can lead to retention phosphorus and disturbances in production of 1.25-hydroxyvitamin D. This will cause a decrease in serum calcium leading to strong and extended stimulation of parathyroid glands, resulting in secondary hyperparathyroidism (sHPT). Generally, most patients with sHPT lose their hypocalcaemia gradually during the first year after successful transplantation because of normal PTH stimulation [8]. But patients with tHPT show normal function of the kidney after transplantation and no normal PTH secretion, the latter becoming autonomic and nonspecific relative to the level of serum calcium [9].

The stage of tHPT seems to depend on sHPT severity before the transplantation and on the duration of dialyses [10, 11]. Therapeutic management of tHPT remains a controversial issue. Currently, a well accepted opinion is that patients with persistent hypercalcaemia, if lasting longer than one year after kidney transplantation, should be considered as candidates for PTX [1, 5, 12, 13], whereas operative treatment in the first year after the transplantation should only be taken into account if no response to pharmacological treatment is obtained. This is confirmed by our patients, among whom only one received PTX after three months from the transplanta-

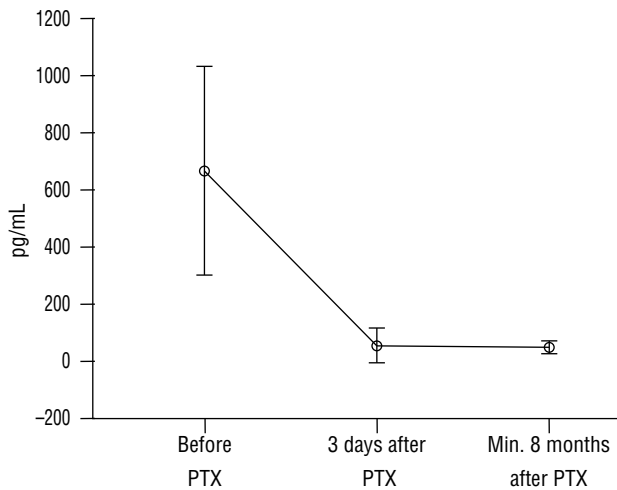


Figure 1. Level of PTH (pg/mL) before PTX; 3 days and minimum 8 months after PTX

Rycina 1. Stężenie PTH (pg/ml) przed PTX, oraz wczesnym i odległym okresie po PTX

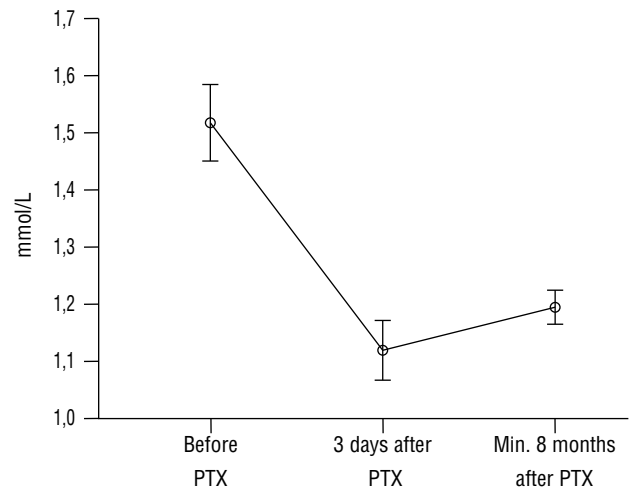


Figure 2. Level of ionized calcium (mmol/L) before and; 3 days and minimum 8 months after PTX

Rycina 2. Stężenie wapnia zjonizowanego (mmol/l) przed i po PTX (mL/min/1.73 m²)

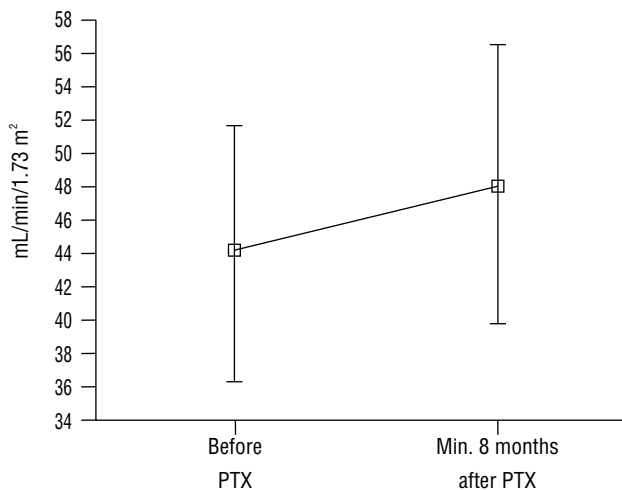


Figure 3. The values of glomerular filtration rate (mL/min/1.73 m²) using MDRD formula in patients before and after PTX

Rycina 3. Wartości wskaźnika przesączania kłębuszkowego (mL/min/1,73 m²) według MDRD u pacjentów przed i po PTX

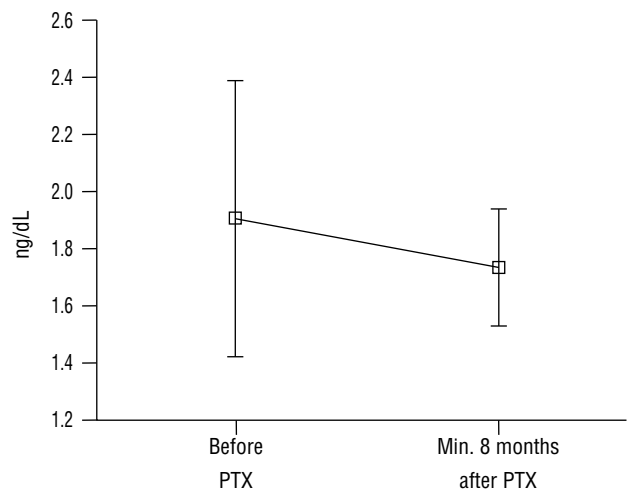


Figure 4. The values of creatinine (mg/dL) in patients before and after PTX

Rycina 4. Stężenie kreatyniny (mg/dl) u pacjentów przed i po PTX

tion because he was in threat of parathyroid crisis and had sharp pains.

Operative treatment for tHPT can consist of total PTX and autotransplantation, or subtotal PTX [1, 7, 8]. The latter is only suggested if one or two glands are enlarged (14,15). A consensus in this matter has not yet been reached. Contrary to earlier authors reporting that PTX has no harmful effect on the transplanted kidney, it is nowadays accepted that PTX may cause a dysfunction of the transplant [16]. In our Department we follow a rule that if an adenoma has been recognised, we only resect one parathyroid gland, taking specimens from the rest for histopathological examinations. If any

doubts arise, another gland is resected, as was done in two of our patients, with good results. Undoubtedly a problem remains in recognising hyperplasia of two glands with no changes in the rest. In such situations we only decide to resect the hyperplastic glands (of course provided the histopathologist has no doubts as to the remaining glands).

On the other hand, if all parathyroid glands are found hyperplastic, we resect 3/4 glands as a rule. We believe that 1/4 of the gland is enough to reach therapeutic effect — proper control of calcium metabolism — and to avoid implanting the gland into the forearm or sterno-mastoid muscle as recommended by some

authors in case of total PTX [2, 11, 14]. Our management of 16 surviving study patients suggested that leaving the gland portion in situ might give satisfactory results. Remote examinations only showed in two (12.5%) patients a very slight increase in PTH level to 68.4 and 87.5 pg/mL. In these patients serum ionised calcium level was 1.29 and 1.17 mmol/L, respectively. However, among seven surviving patients after resection of two parathyroid glands, serum PTH level was found to increase to 96 and 114 pg/mL in two (28.6%) and ionised calcium level to 1.2 and 1.24 mmol/L.

We would like to stress here that in case hyperparathyroidism has been suspected, irrespective of the cause, we are definitely against performing preoperative biopsy of the gland for diagnostic purposes. We believe that biopsy procedure can easily damage the delicate capsule of the organ, no matter how cautious or careful the approach taken. Consequently, an undesired dissemination and insertion of the parathyroid cells into adjacent tissues would take place leading to what is called parathyroidismus. Moreover, some adhesions are likely to develop around the gland, causing problems with its atraumatic preparation. Also, we avoid using mini-invasive techniques because our opinion is that classic parathyroidectomy causes a small problem for the patient allowing the collection of specimens from all glands, if necessary, and making the procedure quicker and easier, especially when intra-operative measurement of PTH concentration is required.

In this group of 37 patients, Schmidt observed an increase in the level of acute implant rejection reaction after PTX for tHPT [2, 17]. Lee reported a negative effect of subtotal PTX on transplanted kidney function in 22 patients [18]. Garcia described persistent damage to kidney function after PTX in patients who showed an increase in serum creatinine level preoperatively [19]. PTH and calcium levels in all our patients who underwent PTX during 54 months on average (23–142) were normal, and no disorders related to PTX were found with reference to the implant function.

Damage to implants is possibly connected with the operation method. Patients who underwent total resection of PTX accompanied by autotransplantation showed significant decrease in serum PTH and calcium levels, but a decrease in GFR was also noted. On the other hand, patients who had subtotal or restricted PTX showed a smaller decrease in PTH and calcium levels, and a slow increase in GFR during three months after PTX, although the differences in GFR values were not significant. Schwarz [20] demonstrated that changes in PTH levels are an important factor that influences kidney function. He observed a direct correlation between a decrease in PTH after the

operation and creatinine clearance. Also, Schlosser demonstrated that surgical technique has a direct influence on postoperative transplant function. This was confirmed in Park's study [2, 21].

Park's examinations are restricted from the point of view of remote results. Results of all examinations indicate that PTX may cause regression of tHPT symptoms as the serum calcium level goes back to normal. However, kidney transplant must be controlled for its efficiency before PTX because resection of parathyroid glands may be connected with a risk of damaging its function. Based on laboratory research it is assumed that subtotal PTH, instead of total PTH with autotransplantation (AT), helps to avoid the risk of damaging the transplant function in tHPT patients. Therefore, restricted PTX is recommended in selected patients where the lesion evidently refers to one or two glands [8, 9, 11]. Our study confirmed beneficial late results of subtotal PTX in patients with multiglandular hyperplasia. Leaving a fragment of one parathyroid gland untouched allows the avoidance of AT procedure, maintaining correct function of the transplant, and providing correct calcium metabolism.

Conclusions

1. Surgical resection of parathyroid glands is a management of choice in patients after kidney transplantation and with persistent, over one-year long hypercalcaemia.
2. Resection of 3 3/4 parathyroid glands for hyperplasia in patients with hyperparathyroidism, after kidney transplantation, allows calcium metabolism to return to normal.
3. Moreover, resection of 3 3/4 parathyroid glands can allow avoidance of autotransplantation, which is necessary in cases of total resection of parathyroid glands.

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