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ORIGINAL SCIENTIFIC REPORT

Cardiovascular and Cerebrovascular Events After Parathyroidectomy in Patients on Renal Replacement Therapy

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Abstract

Background A majority of patients with end-stage renal disease suffer from secondary hyperparathyroidism, which is associated with osteoporosis and cardiovascular disease. Parathyroidectomy (PTX) is often necessary despite medical treatment. However, the effect of PTX on cardio- and cerebrovascular events (CVE) remains unclear. Data on the effect of PTX from population-based studies are scarce. Some studies have shown decreased incidence of CVE after PTX. The aim of this study was to evaluate the effect of PTX on risk of CVE in patients on renal replacement therapy.

Methods We performed a nested case–control study within the Swedish Renal Registry (SRR) by matching PTX patients on dialysis or with functioning renal allograft with up to five non-PTX controls for age, sex and underlying renal disease. To calculate time to CVE, i.e., myocardial infarct, stroke and transient ischemic attack, control patients were assigned the calendar date (*d*) of the PTX of the case patient. Crude and adjusted proportional hazards regressions with random effect (frailty) were used to calculate hazard ratios for CVE.

Results The study cohort included 20,056 patients in the SRR between 1991 and 2009. Among these, 579 patients had undergone PTX, 423 during dialysis and 156 during time with functioning renal allograft. These patients were matched with 1234 dialysis and 736 transplanted non-PTX patients. The adjusted hazard ratio (HR) with 95% confidence interval (CI) of CVE after PTX was 1.24 (1.03–1.49) for dialysis patients compared with non-PTX patients. Corresponding results for patients with renal allograft at *d* were HR (95% CI) 0.53 (0.34–0.84).

Conclusions PTX patients on dialysis at *d* had a higher risk of CVE than patients without PTX. Patients with renal allograft at *d* on the other had a lower risk after PTX than patients without PTX.

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Introduction

Patients with end-stage renal disease (ESRD) often suffer from secondary hyperparathyroidism [1] (sHPT). SHPT is common both in patients on dialysis and in transplanted patients [2] and is associated with interstitial and vascular calcifications [3], cardiovascular disease, high-turnover bone disease [4] and mortality [5]. It can also contribute to calcification of allografts and thereby lead to deterioration of the transplant function [6]. In recent years, new medical treatments of sHPT have been introduced, with promising results [7, 8].

The rate of parathyroidectomies (PTX) has varied over time [9], but PTX is still necessary in patients with severe and/or therapy-resistant sHPT [10]. Reduction in cardiovascular calcification [11] and improvement in blood pressure [12], anemia and serum lipids [13] have been described after PTX. Further, PTX has been associated with an increase in bone density [14], and PTX also seems to improve survival in patients on dialysis [15–21]. Knowledge of the effect of PTX on risk of CVE is scant. Most [22–25] but not all [26] the previous studies reported lower risk of CVE after PTX. The previous studies have been performed on patients on dialysis, and the effect of PTX on risk of CVE among transplanted is still unknown. The aim of this study was to investigate the effect of PTX on the risk of CVE in patients on chronic renal replacement therapy, including both patients on dialysis and patients with renal allograft, in a nationwide population-based cohort.

Methods

Study patients

A matched case–control study was conducted on all patients in the Swedish Renal Registry (SRR) [27] between January 1, 1991, and December 31, 2009. Registration in the SRR is mandatory for all patients starting renal replacement therapy (RRT).

This study was performed and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [28].

Definitions

By linking SRR to the National Patient Register (NPR) with records of all procedure and diagnoses codes from hospital admissions [29], and using the operation code of total or subtotal parathyroidectomy at hospital discharge, we were able to define the occurrence and date of PTX. We also compared the dates for PTX in the NPR with information from the Scandinavian Quality Registry for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA).

We defined CVE as myocardial infarction, stroke and transient ischemic attack (TIA), through discharge diagnoses registered in the NPR, Supplement Table 1. We also used discharge diagnoses to construct comorbidity index according to Charlson [30], by the algorithm described by Quan et al. [31]. The Charlson comorbidity index predicts the 1-year mortality for patients with one or more comorbid conditions, and the algorithm by Quan et al. translates these conditions into ICD codes. All incident PTX patients were identified in SQRTPA and/or in the NPR. The date of hospital admission in the NPR was used as date of PTX for all patients.

Matching

We divided the patients who had undergone PTX in two groups: those who were on maintenance dialysis treatment and those with a functioning renal allograft at the time of PTX. The definition of a patient with a functioning renal allograft is a transplanted patient who does not receive dialysis. The patients in each group were then randomly matched with one to five patients who did not undergo PTX during the study period. The matching criteria were birth year in 10-year categories (decades), sex and cause of ESRD in categories (autosomal dominant polycystic kidney disease, diabetes mellitus, glomerulonephritis, nephrosclerosis, pyelonephritis and other/unknown). Time to CVE was calculated by assigning both case and control patients the calendar date of PTX for the case patient, hereafter referred to as *d*. Patients not alive on *d* were excluded from matching.

Statistical analysis

For continuous variables, means and standard deviations (SD) were calculated, while numbers and column percentages are presented for categorical variables. Patients were censored at death or at end of follow-up, which was December 31, 2009. Proportional hazards regression models with adjustment for random effect (frailty) [32] were used to compare hazard ratios (HR) between PTX and non-PTX patients in the matched sets. The frailty model handled the effect of multiple events. The timescale time from *d* to censoring was used. Both crude and adjusted regressions were calculated.

Separate cox's regressions for PTX versus non-PTX patients, among those on dialysis or with functioning renal transplants, were performed. We adjusted for the following covariates: sex, time with functioning allograft (years), number of renal transplantations, cause of end-stage renal

disease (autosomal dominant polycystic kidney disease, diabetes mellitus, glomerulonephritis, nephrosclerosis, pyelonephritis and other/unknown), Charlson comorbidity index score, time on RRT before *d*, time on dialysis before *d* and CVE before *d*.

To test for non-proportional hazards or competing risks, a sensitivity analysis of the data with the pseudo value method [33] was made.

We considered results with $P < 0.05$ statistically significant. Statistical analyses were made using STATA software version 12 (StataCorp LP, College Station, USA).

Results

Patients and data

There were 20,056 patients in the SRR between 1991 and 2009. Of these, we excluded 45 patients because of errors in reporting of patient information ($n = 18$) and censoring on the same day as initiation of RRT ($n = 27$). From the remaining 20,011 patients, 130 patients were excluded from matching because of PTX occurring before registration in the SRR.

In all, 590 patients had undergone PTX after registration in the SRR. Of these, 11 PTX patients could not be matched according to matching criteria and were excluded. Among the remaining 579 patients, 423 were on dialysis and 156 had a functioning renal allograft at the time of PTX. The patients in the two groups were matched with at least one and as many as possible up to five controls according to the criteria defined above. In total, the two groups of patients were matched with 1234 and 736 patients, respectively.

Table 1 Patient characteristics, whole cohort including the 2549 study patients

Factor	All patients ($N = 20,011$)
Age (in years) at	
Start of RRT	*62.8 (16.5)*
Death[a]	*71.3 (11.7)*
Sex	
Female	7131 (35.6)
Male	12,880 (64.4)
Cause of ESRD	
ADPKD	1572 (7.9)
Diabetes mellitus	4843 (24.2)
Glomerulonephritis	3182 (15.9)
Nephrosclerosis	3651 (18.2)
Pyelonephritis	1009 (5.0)
Other and unknown	5754 (28.8)
Number of transplants	
0	14,951 (74.7)
1	4686 (23.5)
2	347 (1.7)
3	23 (0.1)
4	4 (< 0.1)
Alive at end of follow-up[b]	7045 (35.2)
Follow-up time, months	*48.7 (51.5)*

Italicized numbers indicate mean (SD), numbers (percent)

RRT renal replacement therapy, *ESRD* end-stage renal disease and *ADPKD* autosomal dominant polycystic kidney disease

[a]In 12,966 patients, death occurred before end of follow-up 31/12/2009

[b]31/12/2009

Demographics and patient characteristics

Demographics and patient characteristics of the cohort, PTX patients and matched non-PTX patients on dialysis and with functioning renal allograft are summarized in Tables 1, 2 and 3. Mean age of patients in the cohort population was higher than in the matched sets, both at initiation of RRT and at death. Cohort patients were more often male, more likely to have diabetes mellitus as cause of ESRD and had undergone fewer renal transplantations than the matched patients.

Risk of cardio-/cerebrovascular events

Among patients on dialysis at *d*, we found no significant difference in risk of CVE after PTX compared to control patients in the crude Cox regression, HR (95% CI) 1.00 (0.84–1.19). After adjusting for sex, time with functioning allograft, number of renal transplantations, cause of end-stage renal disease, Charlson comorbidity index score, time on RRT before *d*, time on dialysis before *d* and CVE before *d*, there was a higher risk of CVE after PTX, HR (95% CI) 1.24 (1.03–1.49).

Shorter time with RRT before *d* and polycystic kidney disease as underlying renal disease compared to other causes of renal disease were both associated with lower risk of CVD in patients on dialysis at *d,* (see Table 4).

In patients with renal allograft, there was a lower risk of CVE after PTX both in the crude model, HR (95% CI) 0.62 (0.41–0.94) and in the adjusted model, HR (95% CI) 0.53 (0.34–0.84) than for patients non-PTX patients. Short time specifically with renal transplant before/after *d*, a higher Charlson comorbidity score at *d* and CVE before *d* were associated with an increased risk of CVE (see Table 5).

In the test for non-proportional hazards or competing risks with pseudo values, the treatment effects were similar. As for the proportional hazards assumption, there was

Table 2 Patient characteristics of the individually matched PTX and non-PTX patients, patients on dialysis at *d*

	Parathyroidectomy (PTX) patients (*N* = 423)	Matched reference patients (no PTX) (*N* = 1 234)
Age (in years) at		
Start of RRT	*51.6 (14.7)*	*53.8 (14.4)*
PTX (*d*)[a]	*55.2 (13.9)*	*56.0 (14.2)*
Death[b]	*64.6 (12.3)*	*64.8 (11.9)*
Sex		
Female	219 (51.8)	616 (49.9)
Male	204 (48.2)	618 (50.1)
Time on RRT at PTX (*d*) (years)	*3.6 (3.2)*	*2.2 (2.4)*
Cause of ESRD		
ADPKD	60 (14.2)	173 (14.0)
Diabetes mellitus	64 (15.1)	192 (15.6)
Glomerulonephritis	122 (28.8)	363 (29.4)
Nephrosclerosis	46 (10.9)	132 (10.7)
Pyelonephritis	37 (8.8)	88 (7.1)
Other and unknown	94 (22.2)	286 (23.2)
Number of transplants		
0	214 (50.6)	752 (61.0)
1	167 (39.5)	422 (34.2)
2	36 (8.5)	57 (4.6)
3	5 (1.2)	3 (0.2)
4	1 (0.2)	
Charlson comorbidity score at PTX (*d*)	*1.4 (1.7)*	*1.6 (1.8)*
Alive at end of follow-up[c]	233 (55.1)	604 (48.9)
Follow-up time, months from *d*	*61.3 (45.7)*	*54.6 (43.7)*

Italicized numbers indicate mean (SD), numbers (percent)

RRT renal replacement therapy, *ESRD* end-stage renal disease and *ADPKD* autosomal dominant polycystic kidney disease

[a]*d*, date of PTX or corresponding time for non-PTX patients

[b]In 221/769 patients, death occurred before end of follow-up 31/12/2009

[c]31/12/2009

no statistically significant indication of this assumption not being fulfilled. Analyzing the data with a competing risk model also yields the same results.

Discussion

In this nationwide population-based study including 579 parathyroidectomized patients, we found a higher risk of CVE after PTX in patients on dialysis at the time of PTX, compared to patients without PTX. In contrast, the risk of CVE after PTX was lower in patients with a functioning renal allograft at the time of PTX compared to non-PTX patients.

There are five previous register studies investigating the risk of CVE after PTX compared to non-PTX patients, including only dialysis patients [22–26]. Four of them [22–25] report a lower risk of CVE after PTX compared to non-PTX. In a population-based retrospective cohort study from Taiwan by Ma et al., the risk of acute coronary syndrome (ACS) after PTX was investigated. A total of 1047 PTX patients on dialysis with no previous renal transplantation or acute coronary syndrome, ACS, were matched with 4188 non-PTX patients. PTX patients had a significantly lower risk for ACS than non-PTX patients, with an adjusted HR (95% CI) 0.74 (0.57–0.96) [22]. Further, in a cohort study by Lin et al., 53 non-diabetic patients on maintenance dialysis with severe SHPT (intact PTH > 800 pg/ml) were followed for 72 months. One group of 23 patients had only medical treatment for SHPT due to unwillingness to receive the operation, while 30 patients also had PTX with autotransplantation. PTX was associated with both lower risk of major events (death, cerebrovascular events and myocardial infarcts) and better

Table 3 Patient characteristics of the individually matched PTX and non-PTX patients, patients with functioning renal allograft at *d*

	Parathyroidectomy (PTX) patients (*N* = 156)	Matched reference patients (no PTX) (*N* = 736)
Age (in years) at		
Start of RRT	*46.0 (12.1)*	*44.8 (12.3)*
PTX (*d*)[a]	*51.1 (12.3)*	*50.5 (12.1)*
Death[b]	*62.3 (14.3)*	*59.7 (10.4)*
Sex		
Female	78 (50.0)	359 (48.8)
Male	78 (50.0)	377 (51.2)
Time on RRT at PTX (*d*) (years)	*5.1 (0.3)*	*5.7 (3.7)*
Cause of ESRD		
ADPKD	24 (15.4)	120 (16.3)
Diabetes mellitus	25 (16.0)	125 (17.0)
Glomerulonephritis	57 (36.5)	279 (37.9)
Nephrosclerosis	11 (7.1)	43 (5.8)
Pyelonephritis	11 (7.1)	30 (4.1)
Other and unknown	28 (17.9)	139 (18.9)
Number of transplants		
1	131 (84.0)	674 (91.6)
2	22 (14.1)	57 (7.8)
3	3 (1.9)	4 (0.5)
4		1 (0.1
Charlson comorbidity score at PTX (*d*)	*0.9 (1.3)*	*1.1 (1.6)*
Alive at end of follow-up[c]	125 (80.1)	597 (81.1)
Follow-up time, months from *d*	*76.9 (51.1)*	*73.5 (49.9)*

Italicized numbers indicate mean (SD), numbers (percent)

RRT renal replacement therapy, *ESRD* end-stage renal disease and *ADPKD* autosomal dominant polycystic kidney disease

[a]*d,* date of PTX or corresponding time for non-PTX patients

[b]In 221/769 patients, death occurred before end of follow-up 31/12/2009

[c]31/12/2009

laboratory status and blood pressure [23]. Costa-Hong et al. [24] came to the same conclusion in a study on 118 patients on maintenance hemodialysis unresponsive to medical treatment of SHPT on the waiting list for PTX. PTX was associated with both lower overall risk of death and occurrence of major cardiovascular events. Hsu et al. [25] finally found a lower risk of stroke in 1083 dialysis patients who underwent PTX compared with 1083 patients who did not, in their population-based cohort study, adjusted HR (95% CI) 0.57 (0.41–0.79). Conzo et al. [26] on the other hand found no reduction in risk of cardiovascular morbidity, and the survival rate was unaffected by surgical treatment in their study of 30 PTX patients on dialysis compared with 20 non-PTX patients refusing the operation. Thus, our results for the dialysis group showing increased risk of CVE compared to non-operated patients are in contrast with most former studies. We also found a concluded lower risk of death for PTX patients on dialysis compared to the matched non-operated patients at *d* [15].

In the present study, the risk of CVE after PTX was different in patients on dialysis compared to patients with a renal transplant at *d*. We observed an increased risk of CVE after PTX in patients on dialysis, which is in contrast to the studies reported above. In the comparing studies, there are some differences in study design and populations. Our study comprises all dialysis patients, not only those on hemodialysis as in the studies by Lin et al. [23], Costa-Hong et al. [24] and Conzo et al. [26].

There could be differences in overall health and social factors between patients on institutional dialysis and patients on peritoneal dialysis or home hemodialysis as in the prevalence of the different dialysis modalities in different populations. The lack of data on PTH levels in the study population makes the results difficult to compare to the results by Lin et al. [23] who included only patients with intact PTH > 800 pg/ml. Moreover, our study period was longer than in any of the earlier studies, namely from 1991 to 2009, which comprises a period both before and

Table 4 Relative risk of cardio-/cerebrovascular events for PTX patients compared with controls, on dialysis at d^a (n = 423/1234) [Cox proportional hazards regression and HR (95% CI)]

Factor	Unadjusted	Adjusted
PTX	1.00 (0.84–1.19)	1.24 (1.03–1.49)
Sex men versus women	1.13 (0.84–1.53)	1.21 (0.92–1.58)
Time with functioning graft (year)	0.30 (0.24–0.39)	0.53 (0.39–0.62)
Number of transplantations	0.38 (0.31–0.45)	0.50 (0.40–0.62)
Cause of ESRD, ADPKD reference category		
Diabetes mellitus	2.76 (1.61–4.72)	2.08 (1.28–3.39)
Glomerulonephritis	1.28 (0.78–2.07)	1.18 (0.75–1.84)
Nephrosclerosis	3.38 (1.91–6.00)	2.05 (1.22–3.45)
Pyelonephritis	2.14 (1.15–3.98)	2.46 (1.40–4.34)
Other and unknown	1.59 (0.96–2.64)	1.39 (0.87–2.21)
Charlson score	1.01 (0.95–1.08)	1.00 (0.93–1.07))
Time on RRT before d	1.01 (0.98–1.05)	1.17 (1.08–1.26)
Time on dialysis before d	1.01 (0.96–1.05)	0.81 (0.74–0.88)
Cardio-/cerebrovascular events before d	2.80 (2.33–3.35)	2.28 (1.90–2.75)

The adjusted hazard ratios were adjusted for all the variables in the table

RRT renal replacement therapy, *ESRD* end-stage renal disease and *ADPKD* autosomal dominant polycystic kidney disease

[a]The date of PTX or corresponding date for non-PTX patients

Table 5 Relative risk of cardio-/cerebrovascular events for PTX patients compared with controls, with a functioning graft at d^a (n = 156/736) [Cox proportional hazards regression and HR (95% CI)]

Factor	Unadjusted	Adjusted
PTX	0.62 (0.41–0.94)	0.53 (0.34–0.84)
Sex men versus women	1.42 (0.92–2.52)	1.42 (0.89–2.26)
Time with functioning graft (year)	0.24 (0.17–0.34)	0.23 (0.16–0.33)
Number of transplantations	0.88 (0.60–1.31)	0.88 (0.57–1.36)
Cause of ESRD, ADPKD reference category		
Diabetes mellitus	1.80 (0.75–4.32)	1.62 (0.74–3.52)
Glomerulonephritis	1.12 (0.51–2.44)	0.95 (0.47–1.92)
Nephrosclerosis	1.81 (0.59–5.62)	1.46 (0.51–4.17)
Pyelonephritis	0.76 (0.22–2.63)	0.82 (0.26–2.61)
Other and unknown	1.15 (0.48–2.78)	1.00 (0.45–2.23)
Charlson score	1.61 (1.05–1.28)	1.14 (1.02–1.27)
Time on RRT before d	0.98 (0.93–1.04)	0.96 (0.90–1.02)
Time on dialysis before d	0.96 (0.87–1.08)	0.99 (0.86–1.13)
Cardio-/cerebrovascular events before d	3.49 (2.52–4.83)	3.25 (2.32–4.56)

The adjusted hazard ratios were adjusted for all the variables in the table

RRT renal replacement therapy, *ESRD* end-stage renal disease and *ADPKD* autosomal dominant polycystic kidney disease

[a]The date of PTX or corresponding date for non-PTX patients

after the introduction of calcimimetics. By matching patients for calendar date of PTX, we ensured that both case and control patients in each matched set had the same medical option of treatment with cinacalcet. Thus, the option of cinacalcet treatment depended only on whether the calendar date was before or after the introduction of cinacalcet in Sweden.

The contrasting results from our former study of survival after PTX which showed HR (95% CI) 0.80 (0.65–0.99) for dialysis patients who underwent PTX

compared to non-PTX dialysis patients [15], and the present study with increased risk of CVE might be explained by the fact that early and multiple events after PTX not necessarily lead to mortality. Patients without PTX could have been exposed to more severe events and therefore had a higher mortality than the patients in the PTX-group. Another contributing factor could be that the prolonged survival time among PTX patients, presented in our former study, might increase the risk of having CVE at some point after PTX.

In recent years, more attention has been given to the fact that not only high levels of PTH but also very low levels of PTH are associated with increased mortality [34] and CVE [35, 36]. One of the common complications of PTX is low levels of PTH after the procedure, so this could partly explain the higher risk of CVE for PTX patients. One could also speculate that patients without a functioning renal allograft might have higher levels of PTH than transplanted patients and therefore are more likely to be assigned total PTX than subtotal PTX. Total PTX is associated with lower levels of PTH postoperatively compared to subtotal PTX.

Our study design comprises all patients on RRT, not only those on dialysis but also transplanted patients, none of the other studies included that patient group. In our former study mentioned above, we investigated the survival after PTX compared to non-PTX patients for patients with renal transplants at *d*. We found no difference in survival between the two groups [15]. On the other hand, the risk of CVE was lower among PTX patients in the present study, as for the dialysis patients in the four studies above. Since there is a known risk of impaired transplant function after PTX [37], the operation is reserved for patients with severe sHPT [38], which might influence the risk of CVE after *d*.

There is evidence of negative effects of sHPT on the cardiovascular system. Mineral metabolism disturbances in calcium, phosphate and vitamin D following sHPT are associated with soft tissue calcification particularly in arteries, cardiac valves and myocardium [39]. Other mechanisms related to sHPT are suggested to lead to cardiovascular calcifications such as decreased calcium-sensing receptor expression on cardiovascular structures and a direct role of PTH in vascular calcifications through activation of type-1 PTH/PTHrP receptors [3].

Our study was limited by the lack of certain information. Although we performed matching and adjustment for a number of confounding factors, residual confounding cannot be ruled out. Access to laboratory data of PTH, plasma calcium, phosphate and creatinine in the study patients would have been valuable but were not recorded in the Swedish Renal Registry before 2005 and even after this date reporting was sporadic. Certain demographic and social data would probably also contribute to the analysis model, as would information on renal function, BK and cytomegalovirus, development of new-onset diabetes and relapse of underlying kidney disease among patients with functioning renal allograft.

There are certain strengths in the present study. The national registries that supplied our data contain information on almost all patients on RRT in Sweden between 1991 and 2009. Thus, this is the first truly population-based European study performed on cardio- and cerebrovascular outcome after PTX, and our findings ought to have high external validity and low bias depending on regional differences. Also, the long-term follow-up time includes different eras of PTX incidence and medical treatments.

In conclusion, in the present study, PTX was associated with higher risk of cardio-/cerebrovascular events after PTX for patients on maintenance dialysis. This was in contrast to some former studies. However, the risk was lower for patients with a functioning renal allograft at the time of PTX. The results of the present study need to be confirmed in other, large, prospective trials, preferably including data both on laboratory values and medication use, before any firm recommendations on PTX in relation to cardiovascular risk can be made.

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