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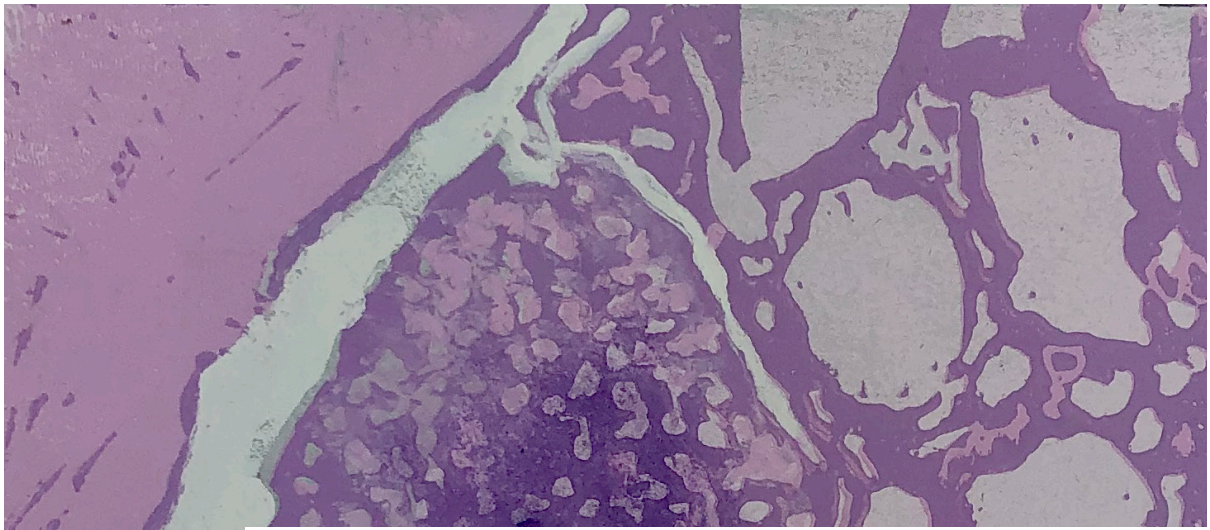

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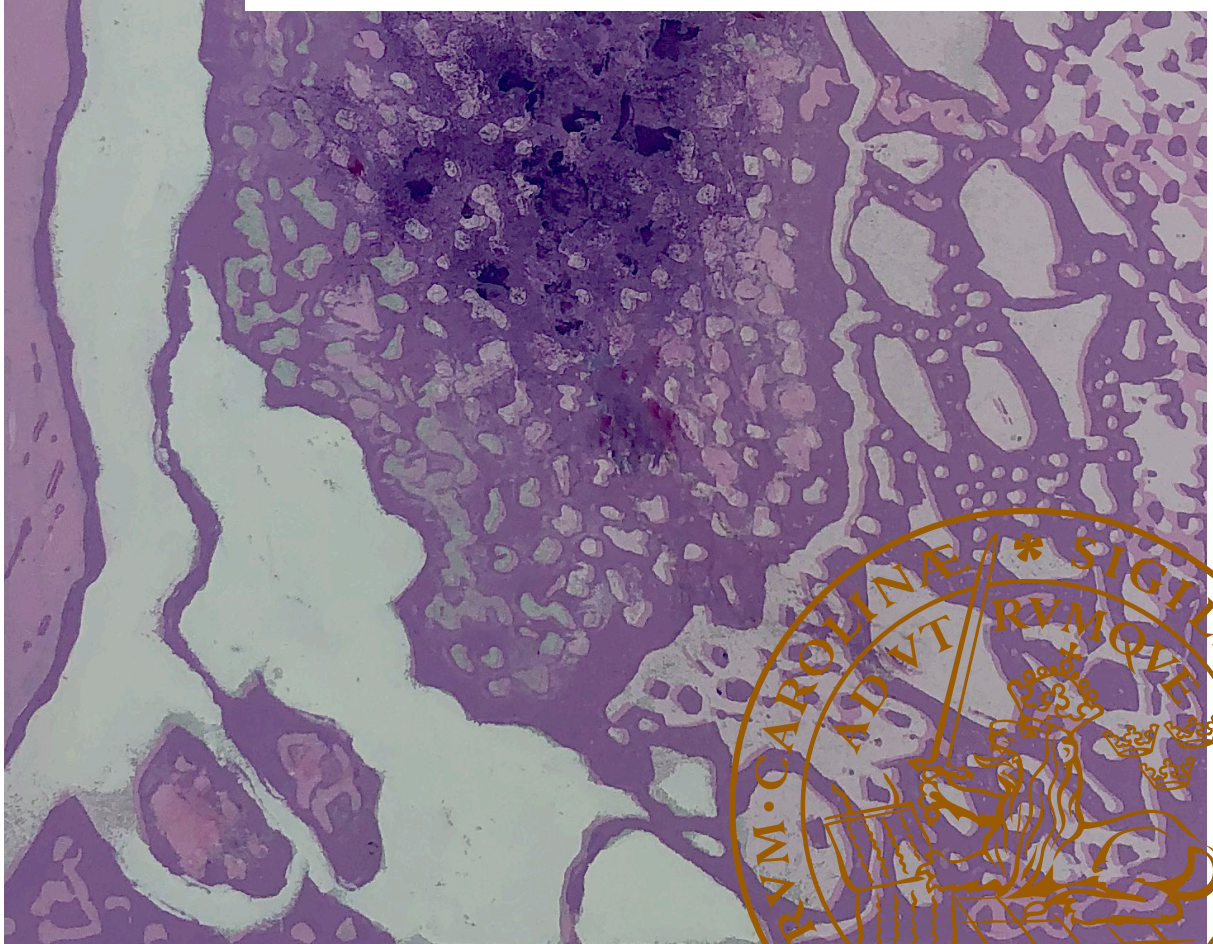
KERSTIN IVARSSON
CLINICAL SCIENCES, LUND | LUND UNIVERSITY



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LUND
UNIVERSITY

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Abstract

Background. Secondary hyperparathyroidism (sHPT) is characterized by over function of the parathyroid glands and disturbances in mineral metabolism as a result of renal failure. It is common among patients with end-stage renal disease (ESRD) and it often persists after successful renal transplantation. sHPT is associated with osteoporosis and cardiovascular morbidity and mortality. There are two main ways to treat this condition, either by medical therapy or surgical removal of the parathyroid glands, parathyroidectomy (PTX). Another complication in patients with ESRD is New-Onset Diabetes After Transplantation (NODAT). Immunosuppressive medications and personal risk factors for diabetes mellitus have been associated with the condition. We aimed to study the effect of PTX on the risk of death, cardio-/cerebrovascular events (CVE), and hip fractures. We also studied the incidence of NODAT at our department and whether there is an association between NODAT and sHPT.

Methods. A nested index-referent study was performed within the Swedish Renal Registry (SRR). Patients on maintenance dialysis or with renal transplant at the time of PTX were included. The PTX patients were randomly matched for age, sex and underlying renal disease with up to five referent patients who had not undergone PTX. To calculate survival time and hazard ratios (HR), indexes and referents were assigned the calendar date (*d*) of the PTX of the index patient. The risk of death, CVE, and fractures after PTX were calculated using crude and adjusted Cox proportional hazards regressions. Data were extracted from patient charts to calculate the incidence of NODAT, and logistic regressions were performed to analyze potential risk factors for NODAT including sHPT.

Results. There were 20 056 patients in the SRR between 1991 and 2009. Of these, 579 (423 on dialysis and 156 with a renal transplant at *d*) incident patients with PTX were matched with 1234/736 non-PTX patients. The adjusted relative risk of death was a HR of 0.80 [95% confidence interval (CI) 0.65–0.99] for dialysis patients who had undergone PTX compared with matched patients who had not. Corresponding result for the patients with a renal allograft at *d* was a HR of 1.10 (95% CI 0.71–1.70). The results for CVE:s were a HR of 1.24 (95% CI 1.03–1.49) for dialysis patients with PTX compared to non-PTX dialysis patients and a HR of 0.53 (95% CI 0.34–0.84) for transplanted patients. The HR for hip fractures in PTX patients was 0.40 (95% CI 0.18–0.88) compared to non-PTX patients. We found a first-year post-transplant incidence of NODAT of 15%, and an odds ratio (OR) of 4.25 (95% CI 1.13-15.92) for the association between PTH levels above twice the normal range and NODAT.

Conclusions. PTX was associated with improved survival in patients on maintenance dialysis. However, there was no survival advantage after PTX in patients with a functioning renal allograft. PTX was associated with a higher risk of CVE after PTX for patients on maintenance dialysis. This was in contrast to some previous studies. However, the risk was lower for patients with a functioning renal allograft at the time of PTX. Parathyroidectomy was associated with a reduced risk of hip fractures in women with sHPT. The first-year cumulative incidence of NODAT was 15% at our department between the years 2000 and 2011. We showed an association between elevated levels of PTH and NODAT in transplanted patients.

Key words
secondary hyperparathyroidism, end-stage renal disease, parathyroidectomy, new-onset diabetes after transplantation, maintenance dialysis, renal transplantation, survival, cardiovascular event, hip fracture

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To my loved ones

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II. Cardiovascular and Cerebrovascular Events After Parathyroidectomy in Patients on Renal Replacement Therapy. Ivarsson KM, Akaberi S, Isaksson E, Reihnér E, Czuba T, Prütz K-G, Clyne N, Almquist M. *World J Surg*. 2019;43(8):1981-8.

III. The Effect of Parathyroidectomy on Risk of Hip Fracture in Secondary Hyperparathyroidism. Isaksson E, Ivarsson KM, Akaberi S, Muth A, Sterner G, Prütz K-G, Clyne N, Almquist M. *World J Surg*. 2017;41(9):2304-11.

IV. Hyperparathyroidism and New-Onset Diabetes after Renal Transplantation. Ivarsson KM, Clyne N, Almquist M, Akaberi S. *Transplant Proc*. 2014;46(1):145-50.

Thesis at a glance

Question	Method	Results	Conclusion
I. What impact has PTX on patient survival in a cohort of patients on dialysis or with functioning renal allograft?	Retrospective analysis of data from 579 PTX patients compared with 1970 matched controls.	The adjusted HR for death after PTX (95% CI) was 0.80 [0.65-0.99] for patients on dialysis and 1.10 [0.71-1.70] for patients with a renal allograft, compared to non-PTX controls for both groups.	PTX was associated with improved survival for patients on maintenance dialysis but not in patients with a renal allograft.
II. What impact has PTX on the risk of CVE in a cohort of patients on dialysis or with a functioning renal allograft?	Retrospective analysis of data from 579 PTX patients compared with 1970 matched controls.	The adjusted HR for CVE after PTX (95% CI) was 1.24 [1.03-1.49] for patients on dialysis and 0.53 [0.34-0.84] for patients with a renal allograft, compared to non-PTX controls for both groups.	PTX patients on dialysis ran a higher risk of cardio- and cerebrovascular events than non-PTX patients. Among transplanted patients, the risk was lower.
III. What impact has PTX on the risk of hip fractures in a cohort of patients on dialysis or with a functioning renal allograft?	Retrospective analysis of data from 579 PTX patients compared with 1970 matched controls.	The adjusted HR for hip fractures after PTX (95% CI) was 0.40 [0.18-0.88] for PTX patients compared to non-PTX controls. When stratifying for sex, the effect was only seen in women.	PTX was associated with a lower risk of hip fracture in women.
IV. What is the incidence of NODAT in patients receiving renal transplantation at our department? Is there an association between sHPT and NODAT in these patients?	Retrospective analysis of data from 245 adult non-diabetic patients who underwent renal transplantation.	The first-year cumulative incidence of NODAT was 15% and the first serum PTH value post-transplantation was above the normal range in 74% of the patients. In patients with PTH > two times the normal range the OR for NODAT was (95% CI) 4.25 [1.13-15.92] compared with patients with PTH within the normal range.	NODAT was common among transplanted patients at our department. There was an association between hyperparathyroidism and NODAT in the first year after transplantation.

Abbreviations

$1.25(OH)_2D$	Inactive vitamin D, calcitriol
25(OH)D	Inactive vitamin D, calcidiol
ACS	Acute Coronary Syndrome
AGE	Advanced Glycation End products
ADPKD	Autosomal Dominant Polycystic Kidney Disease
BMD	Bone Mineral Density
CVE	Cardio- and Cerebrovascular Events
cAMP	cyclic Adenosine MonoPhosphate
CaSR	Calcium-Sensing Receptor
CI	Confidence Interval
CKD	Chronic Kidney Disease
CNI	Calcineurin Inhibitor
CYP27B1	Cytochrome P 27B1
ESRD	End-Stage Renal Disease
FGF23	Fibroblast Growth Factor 23
GFR	Glomerular Filtration Rate
HR	Hazard Ratio
IFG	Impaired Fasting Glucose
KDIGO	Kidney Disease: Improving Global Outcome
LDL	Low Density Lipoprotein
MGP	Matrix Gla Protein
NODAT	New-Onset Diabetes After Transplantation
PTH	Parathyroid Hormone
PTX	Parathyroidectomy
RRT	Renal Replacement Therapy
sHPT	Secondary Hyperparathyroidism
SQRTPA	Quality Registry for Thyroid, Parathyroid and Adrenal Surgery
SIR	Swedish Inpatient Registry
SSR	Swedish Renal Registry
tHPT	Tertiary Hyperparathyroidism
VDR	Vitamin D Receptor
VSMC	Vascular Smooth Muscle Cell

Introduction

Chronic kidney disease (CKD) is a serious condition with multiple complications and reduced life expectancy. The definition is abnormalities of kidney structure or function, present for >3 months, with implications for health[1]. CKD has various causes such as diabetes mellitus, glomerulonephritis, hypertension, chronic interstitial nephritis, renovascular disease and inherited conditions like polycystic kidney disease, Alport syndrome or Fabry disease[2, 3]. There are six stages of CKD from normal kidney function to kidney failure (see Table 1). Usually, kidney function deteriorates over time with an ultimate risk of end-stage renal disease (ESRD) requiring renal replacement therapy, dialysis or renal transplantation. Renal transplantation is the preferred modality since it improves the quality of life[4], overall morbidity[5], and mortality[6, 7]. Long-term dialysis treatment affects many organs and is a risk factor for death[8]. The overall annual mortality for dialysis patients was 19.2% compared to 3.0% for transplanted patients in Sweden in 2018[9]. Not all patients are eligible for renal transplantation due to their health status. Moreover, if a patient does not have a living donor, the time on the waiting list for a deceased donor can be quite long due to a shortage of organ donors. Renal transplantation is also associated with cardiovascular disease[10], bone disorders[11], infections[12] and malignancies due to immunosuppressive medication[13].

In patients with ESRD, secondary hyperparathyroidism (sHPT) is common and associated with excess morbidity and mortality. sHPT is characterized by the excessive synthesis of parathyroid hormone (PTH) and by structural changes in the parathyroid glands such as adenoma or hyperplasia[14]. Some degree of sHPT is almost a uniform finding in patients with ESRD, regardless of the modality of renal replacement therapy[15]. sHPT is associated with osteoporosis, extraosseous calcifications such as atherosclerosis[16], and death[17]. Impaired kidney function in the early stages of CKD affects the kidneys' ability to excrete phosphate. Parathyroid hormone (PTH) and the bone-derived hormone fibroblast growth factor 23 (FGF23) maintain mineral homeostasis including a normal level of phosphate by actions directly or indirectly on the kidney, bone, and intestines[14]. In advanced stages of the condition, the constant stimulation of the parathyroid glands to excrete PTH results in hyperplasia of the glands. At first this is diffuse but later it becomes nodular, resulting in decreased sensitivity to the plasma levels of calcium, vitamin D, phosphate and FGF23. The constant stimulation from PTH on bone leads to high

turnover bone disease and later bone marrow fibrosis. High levels of phosphate and calcium contribute to extraosseous calcifications in blood vessels[18].

There are pharmacological treatment options for sHPT, and these have significantly improved in the last fifteen years[19]. The aim is to regulate phosphate and calcium with phosphate binders and vitamin D receptor activators, and to lower PTH synthesis by improving calcium-sensing receptor (CaSR) signalling[14]. In many cases, it is possible to control sHPT by these actions, but in some cases, the imbalance remains. The option is thus to surgically remove the hyperplastic parathyroid glands by performing a parathyroidectomy (PTX)[20]. PTX improves the mineral metabolism status and reduces pruritus, muscle weakness and bone pain[20].

sHPT often persists after renal transplantation despite improvements[21, 22] in kidney function and mineral metabolism. PTX for this group of patients has been under debate due to a reported association between PTX and loss of graft function[23, 24]. High pre-transplant PTH level is a risk factor for persisting sHPT[21, 23], and the management of sHPT before transplantation is important[24].

New-Onset Diabetes After Transplantation (NODAT) is defined as diabetes diagnosed after organ transplantation, not known prior to transplantation. Diabetes is an important risk factor for cardiovascular disease in addition to CKD and hyperparathyroidism[25]. There are studies showing associations between primary hyperparathyroidism and diabetes[26-28]. To the best of our knowledge, no previous studies of associations between sHPT and NODAT have been performed.

The aim of this thesis was to study the effect of PTX on patient survival and the risk of fractures and cardiovascular events. We include both patients on dialysis and with functioning renal allografts and compare the results for patients undergoing PTX with results for patients on medical treatment only. We also study the incidence of NODAT in patients who have received a renal transplant, the prevalence of hyperparathyroidism in these patients and whether there is any association between these two complications.

The rationale for this thesis was the lack of knowledge concerning which patients should be referred to PTX and when and what the effects of the treatment are. It is also important for the management of transplanted patients to know whether there is an association between sHPT and NODAT, two serious complications of CKD and renal transplantation.

Table 1.
Stages of chronic kidney disease

Stage	GFR in ml/min/1.73 m^2	Kidney function
1	≥ 90	Normal
2	60-89	Normal to mildly decreased
3a	45-59	Mildly to moderately decreased
3b	30-44	Moderately to severely decreased
4	15-29	Severely decreased
5	< 15	Kidney failure

GFR=Glomerular Filtration Rate

Mineral metabolism

Phosphate

Inorganic phosphate is crucial for many biological functions in the human body. It is critical in skeletal development by being an important element in bone mineralization. Furthermore, it is a vital component in phospholipids in cell membranes, energy-providing nucleotides, DNA, RNA and phosphorylated intermediates in cellular signalling[29]. Phosphate is regulated within its physiological range by dietary intake and absorption, bone remodeling, renal excretion, and intracellular and extracellular exchange[30]. Both PTH and FGF23 act to correct elevated levels of phosphate in renal failure. They stimulate excretion by limiting phosphate reabsorption in the proximal tubule through downregulation of the sodium phosphate transport proteins NaPi-2a and NaPi-2c[31]. On the other hand, PTH also stimulates resorption of phosphate from bone and indirectly from the intestines[32]. Phosphate uptake in the intestines occurs in two different ways, the passive paracellular route through intercellular tight junctions, and the active transcellular route, mainly by the transport protein NaPi-2b channels. The upregulation of NaPi-2b in response to active vitamin D (calcitriol) production stimulated by PTH leads to an increase in phosphate absorption[33]. To date, no phosphate receptor has been identified on the parathyroid gland, but high levels of phosphate stimulate the secretion of PTH that in turn stimulate FGF23 in a feedback loop[20].

PTH

PTH is an 84-amino acid peptide hormone synthesized by the chief cells of the parathyroid gland[34]. This whole or bio intact molecule (iPTH) is present in plasma as well as the carboxyterminal fragment C-PTH, which is both secreted from the parathyroid glands and generated from the metabolism of iPTH in peripheral organs. PTH has an essential role in regulating serum calcium levels, both directly and indirectly, and also regulates phosphate in actions on bone and kidney[30].

FGF23 and αKlotho

Since the beginning of this century, much attention has been paid to the role of bone-derived hormone FGF23 in calcium/phosphate regulation. FGF23 acts on the kidneys' proximal tubule by decreasing the expression of NaPi-2a and NaPi-2c and thus stimulating phosphaturia[35]. It also downregulates the proximal tubular expression of 1α hydroxylase and thereby the production of calcitriol. Indirectly, gastrointestinal phosphate and calcium absorption are thus reduced by FGF23[36]. FGF23 can exert its action on mineral metabolism after binding to a receptor complex, FGFR1-αKlotho. The cofactor αKlotho derived from the kidney is essential for the receptor activation and stimulates phosphaturia independently of FGF-23[37]. These receptors have also been found on the parathyroid glands and act after binding to FGF23 as an inhibitor of PTH synthesis and cell growth. Diminishing levels of αKlotho in the early stages of renal failure cause FGF23 resistance and lead to increased FGF23 production[18].

Calcium

Most of the total body calcium is stored in the bone as calcium-phosphate complexes. Calcium gives the bone strength and structure and serves as a dynamic store to maintain both intracellular and extracellular calcium levels.[38] Calcium also has a crucial role in several other processes, such as intracellular and extracellular signaling, nerve impulse transmission and muscle contraction. Extracellular calcium is tightly regulated within a narrow range mainly by PTH, calcitriol, and calcitonin[30]. Low extracellular calcium concentration and thus low binding to CaSR on the parathyroid glands, mediates increased PTH secretion. PTH acts on bone by stimulating the resorption of calcium, increases tubular reabsorption of calcium, and stimulates the hydroxylation of calcidiol to calcitriol in the kidneys. Calcitriol affects the absorption of calcium by the intestines as well as reabsorption of calcium in the kidney and increases the resorption of calcium from bone[18]. Calcitonin inhibits osteoclast-mediated bone resorption and serves as a weak counteraction to PTH and calcitriol[39].

Vitamin D

Vitamin D is a steroid hormone that is essential for various functions in the body such as dental and bone formation, the immune system and regulation of phosphate, calcium, and magnesium. A deficit increases the risk of bone disorders, malignancies, inflammatory and autoimmune diseases as well as metabolic disorders[40]. Most tissues and cells have vitamin D receptors (VDR), and vitamin D is an important regulator of calcium/phosphate homeostasis[41]. The first forms of vitamin D, cholecalciferol and ergocalciferol are derived from exposure to sunlight or from the diet and are hydroxylated by 25-hydroxylase into calcidiol, 25(OH)D, in the liver. The active form of the vitamin, calcitriol, $1.25(OH)_2D$, is formed after hydroxylation mediated by 1-α-hydroxylase, (CYP27B1) in the kidney[42]. Calcitriol binds to VDR and stimulates transcriptional regulation of target genes. PTH and a bone-derived hormone, FGF23, as well as the amount of substrate, calcidiol in serum, regulate the level of calcitriol. PTH stimulates hydroxylation to calcitriol in the kidney while FGF23 lowers the production.[30].

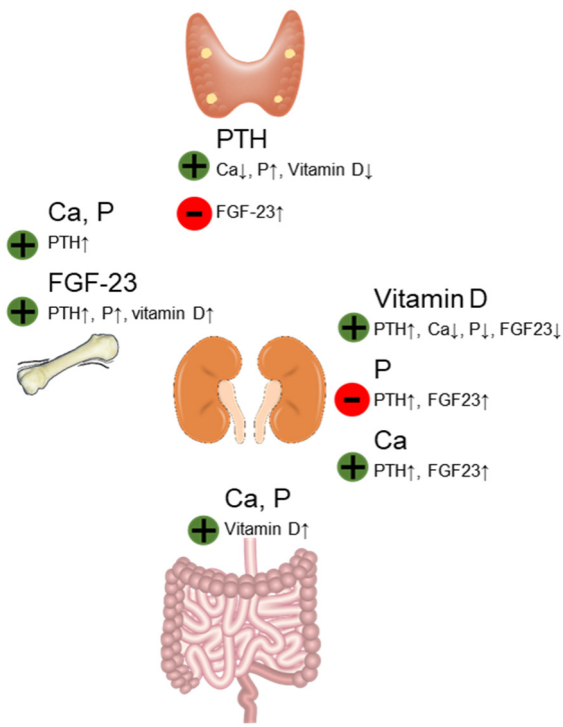


Figure 1. Overview of mineral metabolism homeostasis, stimulating and suppressing factors.

Secondary hyperparathyroidism, sHPT

Development of sHPT

The overview of mineral metabolism above describes homeostasis dependent on normal renal function. In the early stages of CKD, the kidneys' ability to excrete phosphate and hydroxylate calcidiol to calcitriol declines. FGF23 both stimulates phosphaturia and suppresses calcitriol production. With lower levels of calcitriol, the absorption of calcium in the intestine is impaired. PTH is then synthesized and secreted to stimulate activation to calcitriol in line with the feedback loop presented above. PTH indirectly increases the absorption of both calcium and phosphate from the intestine and stimulates renal calcium reabsorption and the resorption of calcium and phosphate from bone[43]. This regulation by FGF23 and PTH often maintains both phosphate and calcium in plasma within the normal range until GFR falls below 30 mL/min/1.73m^2 [30].

The constant stimulation of the parathyroid glands results in a proliferation of secretory cells, and later diffuse hyperplasia. As the glands grow, the number of VDR, CaSR and FGF1-αKlothocomplex receptors on the parathyroid glands decreases. This leads to a reduced sensitivity to serum levels of phosphate, calcium, calcitriol, and FGF23[35]. FGF23 also increases secondarily to a reduction of αKlotho levels that affects the binding affinity of FGF23 to FGFR1. This increase starts in the early stages of CKD [44]. As the parathyroid glands grow in response to the decreasing GFR and the increase in PTH secretion, the diffuse hyperplasia evolves into nodular transformation with adenomas, and with accentuated loss of feedback function from plasma levels of calcitriol, calcium, phosphate, and FGF-23[35]. To summarize, high serum levels of PTH along with hyperplasia of the parathyroid glands define sHPT.

Persistent sHPT in transplanted patients

Since the pathogenesis for sHPT is a declining renal function, successful renal transplantation can ameliorate the condition. After successful renal transplantation and recovery of kidney function, most metabolic and endocrine imbalances improve[45]. However, transient hypercalcemia and hypophosphatemia are often seen post-transplant [46] with PTH levels remaining above the normal range in a majority of patients during the first year after transplantation[21, 47-49]. After the early stages of sHPT with diffuse hyperplasia of the parathyroid glands reflecting increased production and secretion of PTH, a transformation to monoclonal hyperplasia and formation of adenomas take place. VDR, CaSR, and FGFR1 are downregulated, making the parathyroid gland insensitive to feedback from plasma levels of

calcitriol, calcium, and FGF23[50]. The term 'tertiary hyperparathyroidism' (tHPT) is used to describe excessive autonomous secretion of PTH due to long-standing hyperparathyroidism with a lack of suppression of PTH production[51, 52]. There seems to be a consensus regarding the need for careful management of sHPT before renal transplantation since high pre-transplant PTH levels are a risk factor for high post-transplant levels[21, 53, 54].

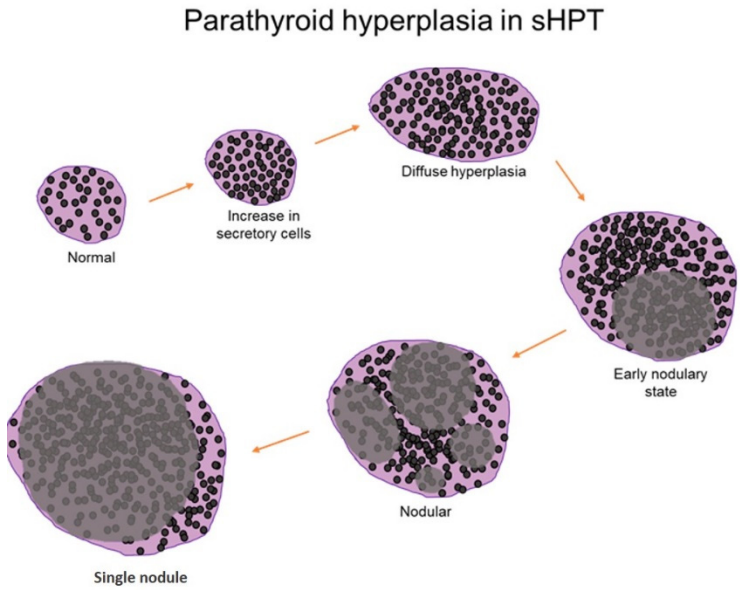


Figure 2. Parathyroid hyperplasia in secondary and tertiary hyperparathyroidism. The normal parathyroid gland responds to an increase in phosphate and FGF23 and lower levels of calcium and calcitriol in the early CKD stages. Prolonged synthesis and secretion of PTH lead to an increase in secretory cells and later downregulation of VDR and CaSR. The diffuse polyclonal hyperplasia transforms into monoclonal nodular gland hyperplasia with low sensitivity to the levels of calcium, calcitriol, phosphate, and FGF23 in later stages of CKD[50]. Inspired by and simplified from a figure by Tominaga Y, Takagi H. Molecular genetics of hyperparathyroid disease. Curr Opin Nephrol Hypertens. 1996; 5: 336–34.

Consequences of SHPT

Laboratory abnormalities

A short summary of the mineral metabolism disturbances in sHPT described above follows here: sHPT disturbs calcium, phosphate and calcitriol homeostasis, and both FGF23 and PTH increase progressively as renal function declines[18]. The FGF23 level rises initially and rapidly[55] and the FGF1R cofactor αKlotho decreases in early CKD[56, 57]. The phosphate levels are often kept within the normal range by the

increase in FGF23 and PTH until the later stages of CKD, stages 4 or 5[58]. The level of calcitriol decreases progressively, despite the effect of PTH[58] (see Figure 3).

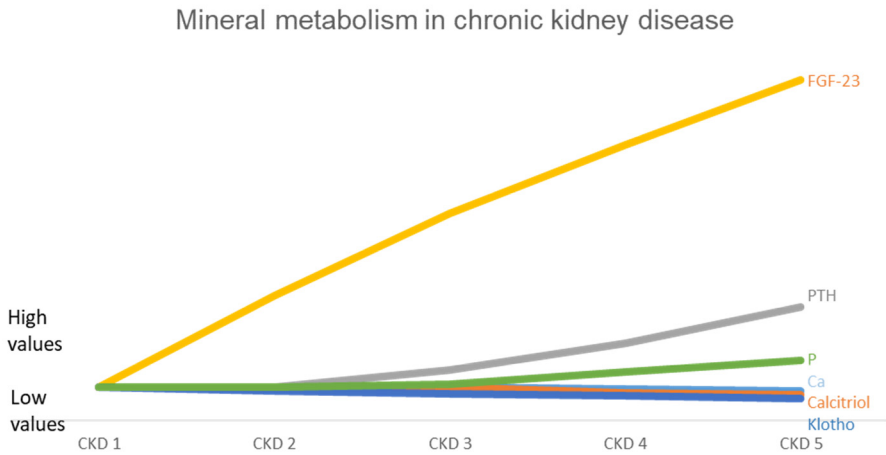


Figure 3. Illustration of fibroblast growth factor 23, parathyroid hormone, phosphate, calcium, calcitriol, and αKlotho in different stages of chronic kidney disease, in theory without medical or surgical interventions.

Renal osteodystrophy

sHPT has a strong impact on the development of bone disease in CKD[18]. The main clinical manifestations are fractures, extra-skeletal calcifications, bone pain, skeletal deformities, and pruritus[59]. The risk of hip fractures among patients on dialysis is four times higher than in the general population[60, 61] and is associated with prolonged hospitalization and death[62]. Skeletal complications seen in the different stages of CKD represent a multifactorial disorder of bone remodeling[59]. Renal osteodystrophy has various histological features, from high to low bone turnover.

Osteitis fibrosa

Osteitis fibrosa, a high turnover bone disease, is most common in patients in ESRD[63]. High serum levels of PTH stimulate the activity of osteoclasts and osteoblasts affecting calcium/phosphate absorption, thus increasing bone remodeling. PTH, together with calcitriol deficiency and locally derived cytokines, activates mesenchymal cells. They differentiate into fibroblast-like cells that secrete fibrous tissue into peritrabecular spaces. Long-standing stimulation causes these fibrous islets to merge and form strands that can spread to the trabecular bone, finally leading to fibrosis in the bone marrow space[59].

Mixed bone disorder

A mixed bone disorder that displays features from both high and low turnover disease is often a combination of osteitis fibrosa and osteomalacia. Osteomalacia is an impairment of mineralization of the bone matrix caused by chondrocytes and osteoblasts, resulting in a soft, fragile bone. Patients with osteomalacia suffer from pathological fractures, bone pain and tenderness, and proximal muscle weakness. Different factors are thought to be important in the pathophysiology. Besides lack of calcitriol, phosphate, and calcium, acidosis and the accumulation of trace elements such as aluminum and fluoride are associated with the condition[64]. This form of renal osteodystrophy is rare[65].

Adynamic bone disorder

PTH is an important proliferative growth factor for bone remodeling, and aggressive suppression of PTH can induce another serious bone disease, adynamic bone disorder[66]. This form of osteodystrophy is characterized by low osteoblast- and osteoclast activity, which in turn results in a reduction of the rapidly diffusible ion pool which reduces the body's ability to buffer extracellular calcium and phosphate ion concentrations[67]. There are reports of an association between adynamic bone disease and vascular calcification[68]. Recent studies suggest that adynamic bone disease is present in the early stages of CKD, partly due to resistance to PTH, calcitriol deficiency, and uremic toxins. The reduced expression of PTH receptors in bone tissue that has been studied in vitro is probably linked to the early resistance to PTH. The diminished expression of PTH receptor genes in osteoblasts is thought to be induced by uremic toxins[69]. In the later stages of CKD, with higher concentrations of PTH, the disease changes to higher bone turnover[65].

Extraosseous calcifications

Patients with sHPT have a higher cardiovascular morbidity and mortality rate than the general population[70], and in patients on dialysis, the relative risk of cardiovascular mortality is more than 10 times higher[71]. Contributing to the risk are elevated levels of extracellular deposits of phosphate and calcium, which are associated with the development of vascular calcification[35].

Atherosclerosis

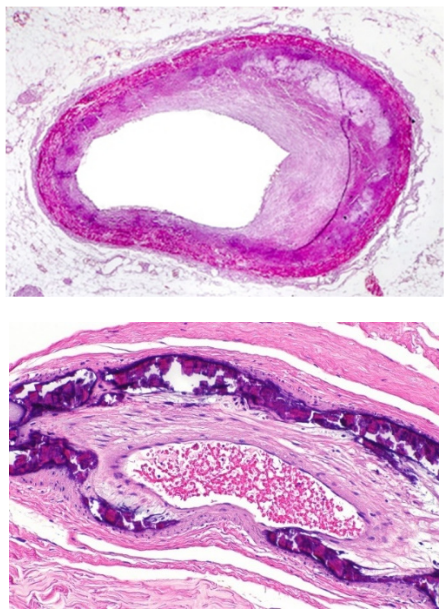
Calcification of the tunica intima is related to the formation of atherosclerotic plaques, and is common in this group of patients. In atherosclerosis, lipid-loaded macrophages accumulate in the subendothelial area of the arterial wall. These macrophages promote inflammation, and multiple pathological consequences such as hemorrhage, rupture, and calcification[72]. This process is linked mainly to traditional risk factors for cardiovascular disease such as smoking, hypertension,

hypercholesterolemia, diabetes, obesity, and stress[73]. Intimal thickening is considered a marker of early atherosclerotic changes[74]

Arteriosclerosis

In sHPT, normal aging and diabetes, calcification of the tunica media is also seen. It is called arteriosclerosis, which occurs at the internal elastic lamina of the medial layer and primarily affects the aorta. It later extends to the peripheral small vessels[75]. Coronary artery calcification is seen more frequently in patients on dialysis than in the general population[76, 77] and seems to progress more rapidly[78]. Calcification of the cardiac valves is another risk factor identified in patients on dialysis[79].

The pathophysiology behind medial vascular calcifications includes transdifferentiation of vascular smooth muscle cells (VSMC) to phenotypic osteoblastic cells that synthesize transcription factors and calcification regulating proteins found in bone tissue[80]. There are both inhibiting and activating minerals and proteins regulating the transdifferentiation of VSMCs. Fetuin, matrix Gla protein (MGP), osteoprotegerin, and osteopontin have been mentioned as important natural inhibitors, while phosphate, vitamin D, oxidized low density lipoprotein (LDL), uremic toxins, proinflammatory cytokines, and advanced glycation end products (AGE) are activators of the process[75]. These calcifications are associated with vessel stiffness and reduced vessel elasticity[81]. The rigidity can lead to an increase in pulse pressure and left ventricular hypertrophy[82, 83]



Figures 4a and 4b. 4a. Coronary atherosclerosis, light micrograph showing cholesterol-containing plaque in heart coronary artery. **4b.** Medial calcific sclerosis.

Calcific uremic arteriolopathy, calciphylaxis, is a rare but often fatal complication to sHPT. It is characterized by cutaneous ischemic infarctions caused by occlusions of blood vessels in subcutaneous fat and skin[84]. The occlusions are a result of progressive narrowing due to calcification of the tunica media and proliferation of endothelial cells and fibrosis underneath the tunica intima. Besides ESRD with disturbances in mineral metabolism, demographic risk factors such as obesity, diabetes and female sex as well as vitamin K deficiency have been identified[85]. The condition causes severe pain and infections and has a mortality rate of 20-80%,[86-88].

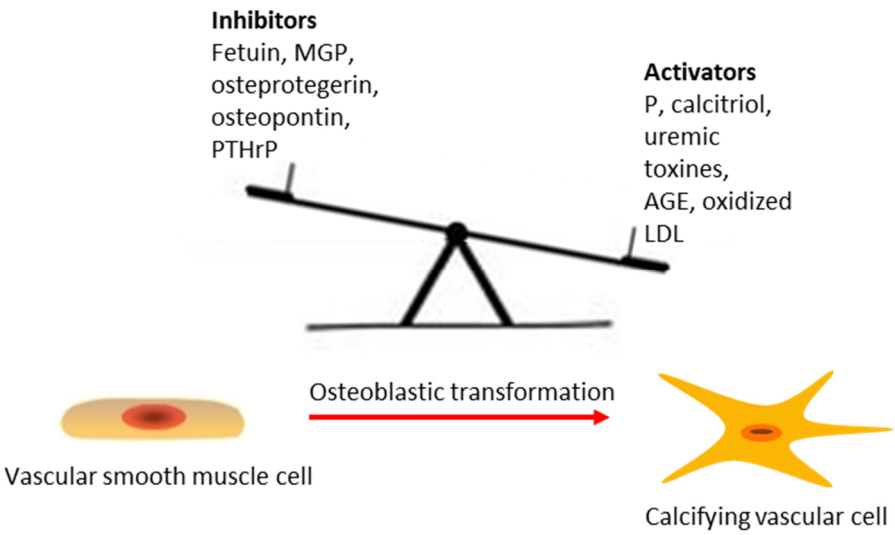


Figure 5. Inhibitors and activators involved in transdifferentiation of VSMCs to calcifying osteoblastic cells in arterials. Inspired by and simplified from a figure by Derici U, El Nahas AM. Vascular calcifications in uremia: old concepts and new insights. *Semin Dial*. 2006;19(1):60-8.

Pharmacological treatment of sHPT

Guidelines regarding the medical treatment of sHPT have been published by the global organization Kidney Disease: Improving Global Outcome (KDIGO). They state that clinical management should be individualized and based on clinical symptoms and regular assessments of plasma calcium, phosphate, and PTH. Besides recommendations regarding medical treatment and PTX, limitations in dietary phosphate intake and calcium concentration in dialysate are discussed in their last update of 2017[89].

Phosphate

Phosphate is an independent predictor of cardiovascular mortality[90-93], and is an important factor in the development of vascular calcification and associated with arterial stiffness[94], valvular rigidity[95] and left ventricular hypertrophy[96]. KDIGO recommends plasma phosphate to be kept within the normal range in CKD 3-5D (GFR <60 mL/min/1.73 m^2)[89]. Besides dietary restrictions and clearance during dialysis, phosphate binders are usually used to obtain normalized levels[14]. The aluminum salts first used were effective but had serious adverse effects, such as central nervous system toxicity, impact on hematopoiesis and osteomalacia[97]. They were replaced by calcium-based phosphate binders (calcium carbonate and calcium acetate), which carry the risk of raising serum calcium and contributing to vascular calcification[82, 98]. The non-calcium-containing phosphate binders mostly used today, sevelamer and lanthanum carbonate, have been proved to lower serum phosphate. However, it is not fully known how they affect the risk for extra-osseous calcifications and cardiovascular mortality [99]. In mice and rats with chronic renal failure, sevelamer has been shown to improve vascular calcification, aortic stiffness, and diastolic function and to prevent left ventricular hypertrophy [100-102]. In comparison with calcium-based phosphate binders, sevelamer has been associated with improvements of coronary and aortic calcification[103-105].

Calcium

Both hypo- and hypercalcemia are seen in sHPT and are associated with increased mortality[106]. Moreover, hypercalcemia is associated with vascular calcification[107]. KDIGO recommends avoiding hypercalcemia by careful use of calcium-containing phosphate binders and regulation of dialysate calcium concentration[89]. Hypocalcemia can be corrected by supplements and indirectly through calcitriol or vitamin D analogs. Calcitriol and the vitamin D analogs raise calcium by stimulating absorption from the intestine. The treatment is individualized and the calcium balance is sometimes difficult to obtain [14]. Currently, it is not clear if there is a lower risk of hypercalcemia with vitamin D analogs than with calcitriol[108, 109].

PTH

The u-shaped curve for morbidity and mortality in different PTH levels has created yet another dilemma in the treatment of disturbances in mineral metabolism[110, 111]. Both hyperparathyroidism and hypoparathyroidism are associated with higher mortality[112, 113]. Evidence to confirm optimal PTH levels is still lacking [89], but reports from two different multicenter Dialysis Outcomes and Practice Patterns Studies (DOPPS) from 2008 and 2015 in patients on dialysis show a lower risk of mortality with PTH levels between 100 pg/ml and 600pg/ml and 150pg/ml and

300pg/ml respectively[112, 113]. VDR and CaSR are typically both downregulated on the parathyroid gland in later stages of CKD, and the inhibition of PTH is therefore diminished. Calcitriol levels are low because of poor kidney function and high serum levels of FGF23. Treatment with calcitriol or a vitamin D analog can, therefore, result in reduced serum PTH[114]. Over the past 15 years, the use of calcimimetics has emerged as an effective treatment of sHPT[19]. The most commonly used calcimimetic today, cinacalcet, binds to CaSR on the parathyroid glands and lowers the threshold for receptor activation by extracellular calcium ions. It also increases the expression of CaSR in parathyroid tissue[115, 116] without risk of calcium augmentation[117]. However, cinacalcet has been associated with gastrointestinal intolerance[118] and hypocalcemia.[119]. In addition, high cost[120] and poor compliance[121] have been observed among dialysis patients. KDIGO suggests PTH-lowering therapy with calcimimetics, calcitriol or vitamin D analogs, or a combination of calcimimetics and calcitriol or vitamin D analogues[89].

Parathyroidectomy, PTX

Parathyroid glands

In 1850, the British anatomist and curator of the Natural History Museum, Sir Robert Owen, identified parathyroid glands when he dissected a rhinoceros that had died at the London Zoo. However, he did not get credit for his discovery due to the lack of histological confirmation[122]. Seventeen years later, human parathyroid glands were discovered by a Swedish medical student, Ivar Sandström. He found four grain-shaped structures that differed from the surrounding thyroid tissue under the microscope. At that time the function of the gland was unknown[123].

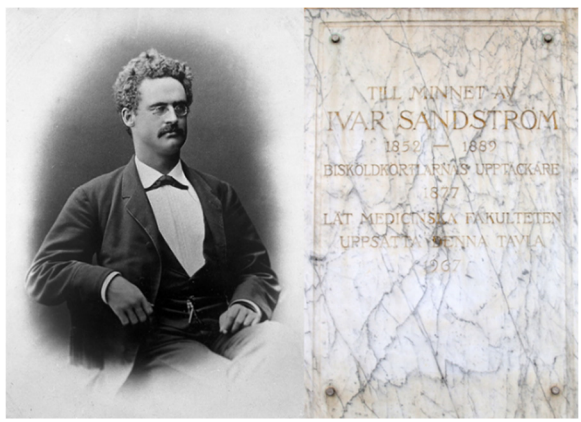


Figure 6. Ivar Sandström, the Swedish physician who discovered parathyroid glands in humans in 1867.

Parathyroid glands are four or more nodular structures, typically located on the dorsum of the thyroid gland at each of its four poles[124]. They consist of PTH-producing chief cells and oxyphil cells of unknown function[125]. The regulation of calcium balance can be disturbed by increased activity of the parathyroid glands, either from an intrinsic abnormal excretion of PTH (pHPT or tHPT) due to adenomas or carcinomas or from an extrinsic change (sHPT) caused by parathyroid receptor stimulation. Renal failure is the most common cause of sHPT[126]

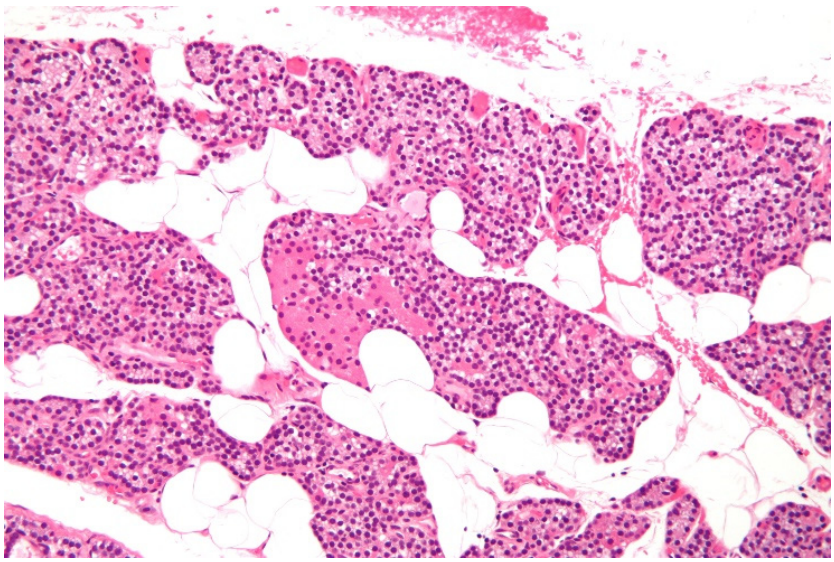


Figure 7. Intermediate magnification micrograph, hematoxylin and eosin stain. The white round structures are fat cells, the small dark structures PTH producing chief cells and the pink structures oxyphil cells.

Indications for PTX

Over time there have been variations in the number of PTX operations performed on patients with sHPT. In a study by Akaberi et al., including all PTX patients on ESRD with sHPT in Sweden between 1991 and 2009, a significant rise in the number of PTX operations performed was seen at the beginning of the year 2000. Between 1991 and 2000, there were on average 8.0 PTX operations /1000 person-years performed every year. During the first four years of the new millennium, that number rose to 12.9 PTX. During the first years after the introduction of cinacalcet in 2004 (2005-2009), there were fewer PTX operations or 6.3/1000 person-years. Furthermore, Akaberi et al. found that female sex, non-diabetic cause of renal disease and age between 40 and 55 were risk factors for PTX[127]. There do not seem to be clear and unambiguous medical indications for PTX. Rather, the number of PTX operations performed seems to be influenced by traditions and trends, since it

is as yet not fully known which patients to refer to surgery and what the long-term effects of the procedure are[128, 129].

Most patients on dialysis with sHPT respond to medical treatment with calcitriol or vitamin D analogues[130, 131], phosphate binders[98] and calcimimetics[132], but in a minority of patients, PTX is necessary to control the condition[133]. KDIGO recommends PTX be performed on patients with GFR<60 mL/min/1.73m^2 who have severe hyperparathyroidism and who fail to respond to pharmacological therapy[89]. Severe hyperparathyroidism is not defined, but in the literature, persistent PTH levels >800-1000 pg/mL (85-106 pmol/L) combined with refractory hypercalcemia, severe hyperphosphatemia and clinical symptoms such as calciphylaxis, severe bone pain or refractory anemia are given as indications for PTX[20, 134]. Studies show improvements in clinical symptoms and plasma calcium-, phosphate and hemoglobin levels after PTX[135-139]. There are very few previous studies of the risk of fractures and cardiovascular events after PTX for patients in ESRD but there are over a dozen observational studies of survival for these patients. Some investigators report associations between PTX and lower risks of fractures, cardiovascular events, and death[140-144], while other studies do not support these associations[145-147].

Surgical procedure

Despite effective medical treatment, PTX is required in about 15% of patients after 10 years on dialysis[148]. PTX is not a curative treatment of sHPT, but rather a method to control the levels of PTH and thus its complications[133]. PTX is performed either as total PTX with the aim of removing all parathyroid tissue, or as subtotal PTX, where tissue corresponding to a normal gland is preserved for autonomous PTH secretion[149]. Sometimes very little parathyroid tissue is preserved in situ, near-total PTX, and sometimes parathyroid tissue is auto transplanted to a heterotopic site[150]. Both total and subtotal PTX can be combined with thymus resection, in order to remove potential ectopic parathyroid tissue. The operation is normally performed in open surgery[54].

There is a debate in the literature regarding which type of operation is most effective and safe, and the method of choice is often based on traditions and personal preferences[151]. Studies have shown a significant decline in PTH levels after both total and subtotal PTX and low rates of short-term fatal complications[149-153]. There are some risks of PTX related to surgery, such as palsy of the recurrent nerve and bleeding[145]. Total PTX is associated with an increased risk of hypoparathyroidism and permanent hypocalcemia[154]. With careful management of hypoparathyroidism after surgery, the risk of serious complications is small[155]. Subtotal PTX carries a higher risk of recurrence of hyperparathyroidism, and sometimes reoperation is required[153].

New-Onset Diabetes after Renal Transplantation (NODAT)

Diabetes mellitus is common in patients on renal replacement therapy. It is one of the leading causes of ESRD[156]. Diabetes mellitus can appear in a transient form in newly transplanted patients and sometimes persists as NODAT[157]. In fact, NODAT is one of the most common complications of renal transplantation[158]. The incidence rates vary from 2% to 50% depending on the diagnosis criteria used[157]. NODAT increases the risk of infection, cardiovascular disease and cardiovascular death in the patient group[159-161]. NODAT has also been reported to be associated with transplant nephropathy and graft failure[162, 163].

Definition

Prior to the year 2003, there was no consensus regarding the definition of NODAT. After a meeting of an international expert panel, consisting of experts from both the transplant and diabetes fields, the International Consensus Guidelines for the Diagnosis and Management of NODAT were written[164]. Currently, NODAT is defined as diabetes mellitus developing in patients without a pre-transplant history of diabetes, with sustained hyperglycemia that meets the diagnostic criteria for diabetes mellitus by the World Health Organization, WHO. These criteria are a fasting plasma glucose concentration ≥ 7.0 mmol/L or a 2-hour plasma glucose level ≥ 11.1 mmol/L during an oral glucose tolerance test [165]. Both impaired insulin secretion and insulin resistance cause NODAT[166].

Risk factors for NODAT

The etiology of NODAT is multifactorial and includes both environmental and genetic factors. Some of these factors are related to the risk of diabetes in the general population. These risk factors can be divided into non-modifiable and modifiable. The non-modifiable risk factors are genetics[167], ethnicity[168], and age[162], while dyslipidaemia[169], metabolic syndrome[168], obesity[170] and infections caused by cytomegalovirus or hepatitis C virus[171, 172] are modifiable and can be affected by treatment.

Among the risk factors related to renal transplantation, immunosuppressant medication is the most important. The diabetogenic effect of corticosteroids is well known. Corticosteroids decrease insulin sensitivity and increase hepatic gluconeogenesis and lipolysis[173]. This effect is dose-dependent[174, 175]. Among the group calcineurin inhibitors (CNI), tacrolimus, a widely used immunosuppressant, also increases the risk of NODAT[176, 177]. Tacrolimus decreases insulin synthesis and

secretion. Thus, tacrolimus in combination with corticosteroids can have a potent diabetogenic effect[168]. Cyclosporine A, a therapeutic alternative to tacrolimus, does not have the same impact on glucose metabolism[176]. Sirolimus, an mTor inhibitor, is another immunosuppressant with a reported risk of contributing to the development of NODAT[178]. Consequently, acute rejections requiring high doses of immunosuppressants pose an added risk for the development of NODAT[179].

Other transplant-specific risk factors for NODAT have been suggested, such as a kidney from a male donor, a cadaveric donor, and human leukocyte antigen mismatch[168].

Screening and treatment

Frequent screening for diabetes after transplantation is important since the incidence of NODAT is high[179] and can occur soon after transplantation with a gradual increase of risk thereafter [166]. In a meta-analysis, performed by Goldmannona et al. in 2016, the estimated incidence rates of NODAT in the United States were 9.1% at three months, 16% at 12 months, and 24% at 36 months post-transplant [180]. Testing for diabetes and prediabetes before transplantation is important because impaired fasting glucose and impaired glucose tolerance are predictive factors for the development of NODAT [181, 182]. There are a number of options for the treatment of NODAT. Lifestyle modifications are often necessary, but not always sufficient. Glucocorticoid tapering, if possible, can be one way to obtain better glucose control and sometimes a change in the CNI regimen is deemed necessary[176]. However, there is a risk of acute rejections when the dosage regimen is changed, which besides the risk of graft loss also increases the risk of NODAT through rejection therapy with high doses of corticosteroids[168]. Peroral antihyperglycaemic agents and insulin are other options for this patient group[166].

Aims

This thesis aims to answer the following questions:

- What is the impact of PTX in patients on dialysis or with a functioning renal allograft
    - on patient survival?
    - on the risk of cardio- and cerebrovascular events?
    - on the risk of hip fractures?
- What is the incidence of NODAT in patients after renal transplantation at our department?
- Is there an association between sHPT and NODAT in patients after renal transplantation?

Methods

All four studies included in this thesis are retrospective observational cohort studies.

Papers I-III

Materials and methods

Patients

We constructed a database consisting of all patients starting on renal replacement therapy (RRT) in Sweden between the 1st of January 1991 and 31st of December 2009. Patients and data were collected from the Swedish Renal Registry (SSR). These data were linked to data from the Swedish Inpatient Registry (SIR) and the Scandinavian Quality Registry for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA). From the database, we retrieved demographic data, underlying renal disease, RRT modalities, diagnosis, codes for surgical interventions, hospital admissions, and date of deaths. The database originally contained 20 056 patients, but 45 were excluded from the study cohort since there was an error in reporting data (n=18) and patients were censored the same day as the initiation of RRT (n=27).

Ascertaining variables

We used the discharge diagnoses and codes for surgical intervention according to the 7th-10th International Classification of Diseases (ICD) in SIR to construct the variables PTX, cardio- and cerebrovascular events (CVE), hip fractures and comorbidity score. ICD7-9 codes were translated into ICD10 by using conversion tables from the Swedish National Board of Health and Welfare.

The inpatient information on PTX, defined as subtotal or total PTX in codes for surgical intervention, was compared with data from SQRTPA. The date of PTX was set to the day after hospital admission for the procedure. We defined CVE as myocardial infarction, stroke and transient ischemic attack through the discharge diagnoses. Discharge diagnosis codes for hip fractures were validated by comparing these with codes for surgical intervention for hip fracture.

Discharge diagnoses were used to construct comorbidity groups according to Charlson et al[183]. The diagnoses included in the comorbidity groups were identified using an algorithm described by Quan et al[184]. CKD was excluded among comorbidities since all patients had this disease. Age over 40 did not add points to the score since age was a matching criterion.

Matching

From the remaining 20 011 patients, 130 were excluded since they had PTX prior to RRT, leaving 19 881 patients included in the matching process. The patients who had undergone PTX after entering the SRR were divided into two groups: patients on maintenance dialysis treatment, and patients with a functioning renal allograft at the time of PTX. The patients in the two groups were then randomly matched with one to five patients without PTX. In all, 423 dialysis patients with PTX were matched and compared with 1 234 dialysis patients without PTX. Corresponding numbers for transplanted patients were 156/736. The matching criteria used were birth year in 10-year categories, sex, and cause of ESRD in categories (autosomal dominant polycystic kidney disease, diabetes mellitus, glomerulonephritis, nephrosclerosis, pyelonephritis and other/ unknown). To calculate survival time, index and referent patients were assigned the calendar date of the PTX of the index patient, referred to as *d*. The matched reference patient was required to be alive on this date and to have the same RRT modality at *d*, i.e. dialysis or a functioning renal transplant.

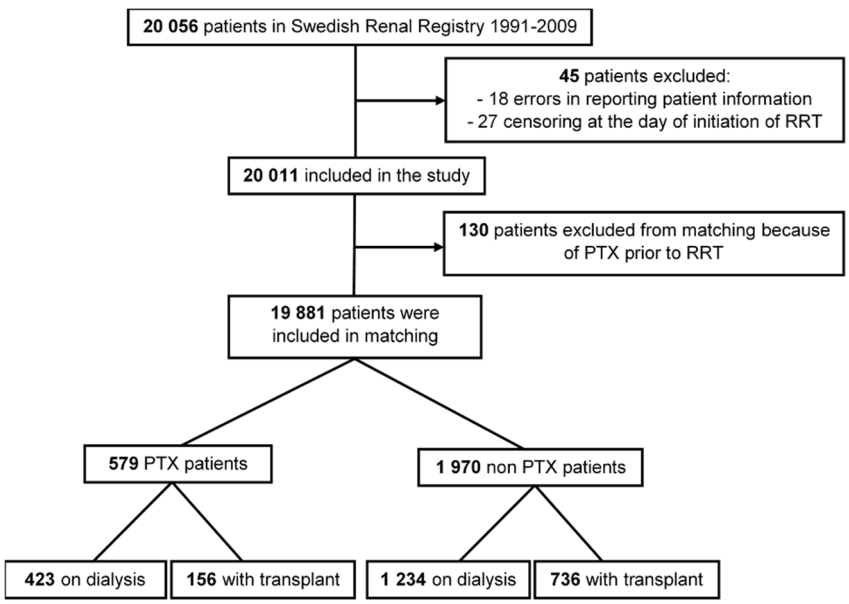


Figure 8. Flow chart, study cohort, papers I-III

Statistical analysis

Crude and adjusted Cox proportional hazards regression models were used to compare the risk of death, CVE and hip fractures between patients with and without PTX. In paper II, the regression models were adjusted for random effect (frailty), a method to handle the effect of multiple events (repeated CVE)[185]. A time scale from *d* to death, CVE and hip fractures, was used to compare the outcomes of the patient groups. Stratification for RRT modality (on dialysis or with functioning renal allograft) and sex was carried out. In paper III, the subgroup with no hip fracture prior to *d* was also studied separately. Time to death and hip fractures in papers I and III were calculated with the Kaplan-Meier method, yielding survival curves. The thirty-day mortality after PTX was calculated in percent in paper I, and the incidence rate of hip fractures per 1 000 person-years was calculated in paper III. Descriptive data results were calculated as means and standard deviations for continuous variables, and number and column percentages for categorical variables.

In all three papers, adjustments for sex, cumulative time in RRT before PTX and Charlson comorbidity index were made in the Cox regression models. In paper I, there were also adjustments for functioning graft at any time, geographical region and dialysis modality (peritoneal dialysis vs hemodialysis). In papers II and III adjustments for time with functioning renal transplant were made. In paper II we adjusted for the number of transplantations, cause of ESRD, time on dialysis and cardio- and cerebrovascular events before *d*. In paper III finally, adjustments for cumulative time with a renal allograft after PTX and hip fractures before *d* were made.

Results with a P-value < 0.05 were considered statistically significant and all statistical analysis was performed using STATA software version 12.

Paper IV

Materials and methods

Patients

All adult kidney allograft recipients with follow-up visits for >1 year between January 2000 and June 2011 at the Department of Nephrology and Transplantation, Skåne University Hospital in Malmö and Lund were included in the study. A total of 335 patients fulfilled the inclusion criteria, and from those, 90 patients were excluded from the study because they had diabetes mellitus at the time of transplantation, age <18 years, or death within the first year after transplantation. The patients were evenly divided between Malmö and Lund (123/122) in terms of

follow-up location. Patient characteristics, treatment details, and PTH values were extracted from patient charts according to a predefined study protocol.

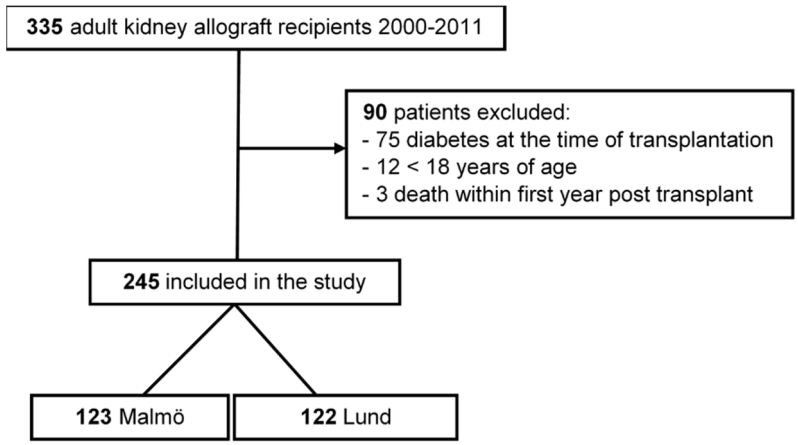


Figure 9. Flow chart, study cohort, paper IV

Definition of NODAT

The diagnosis criteria for NODAT established by the International Consensus Guidelines for the Diagnosis and Management of NODAT was used to define the condition[164]. The physician in charge of the patient established the diagnosis according to the recommendations, and all new cases of diabetes mellitus after the first 14 days after transplantation were defined as NODAT.

Ascertaining variables

The standard immunosuppressive protocol for maintenance therapy for the patients in the study contained steroids, cyclosporine or tacrolimus, and mycophenolate mofetil. Additional immunosuppressive treatment was defined as ABO-incompatible transplantations and/or patients that had undergone rejection therapies and therefore were exposed to higher total cumulative doses of immunosuppressive medication. The PTH values were measured with different immunoassay detection techniques, depending on where the follow-up-visits took place and when. In order to calibrate the values, we used a formula developed by the laboratory units in Malmö and Lund.

We included only patients who had available PTH measurements within six months from transplantation in the statistical analysis, i.e. 222 patients in total. The first recorded PTH value up to six months after transplantation was used in the main analysis and presented in categories based on reference range (normal, above normal but less than twice above normal, and twice above normal range).

Statistical analysis

Logistic regression was used to perform both crude and adjusted analyses of predictors of NODAT. In all, nine factors with up to six different variables were available in the analysis. These factors were; age, sex, body mass index (BMI), preemptive or dialysis treatment before transplantation, number of transplantations, donor type, CNI treatment, additional immunosuppressant treatment, and PTH levels. Those covariates with significant associations in single regressions and age and sex were included in the final regression model. Data were expressed as mean values and standard deviations for normally distributed variables and median values and interquartile ranges for non-normally distributed variables. One-way analysis of variance, ANOVA, was used for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. The chi-2 test or Fisher's exact test was used for categorical variables. Results were considered significant when $P < 0.05$. All statistical analyses were made using SPSS for Windows version 21.0.

Results

Papers I-III

Demographics and patient characteristics

There were differences in demographics and patient characteristics between the whole study cohort and the matched set with PTX and non-PTX patients. The patients in the matched set were younger, had less total time in RRT, were more often women, did not have diabetes mellitus as the cause of ESRD to the same extent, and were more often referred to renal transplantation. The matching yielded patients with or without PTX with small differences in the variables presented above, both in matched and unmatched variables. After stratification for RRT modality, differences were seen between patients on dialysis and those with a renal allograft. The dialysis patients were older at the initiation of RRT, had a higher comorbidity index, a higher hospital readmission rate within 30 days from PTX surgery, and fewer were alive at the end of follow-up compared to transplanted patients (see Tables 2 and 3).

Table 2.
Patient characteristics of the whole patient cohort and individually matched PTX and non-PTX patients.

Factor	Whole study cohort (*N*=20 011)	Matched set, PTX and non-PTX patients (*N*=2 549)
Age (years)		
Start of RRT	62.8 (*16.5*)	50.2 (*14.3*)
Death	71.3 (*11.7*)	64.6 (*12.0*)
Sex		
Female	7131 (35.6)	1272 (49.9)
Male	12 880 (64.4)	1277 (50.1)
Cause of ESRD		
ADPKD	1 572 (7.9)	377 (14.8)
Diabetes mellitus	4 843 (24.2)	406 (15.9)
Glomerolunephritis	3 182 (15.9)	821 (32.2)
Nephrosclerosis	3 651 (18.2)	232 (9.1)
Pyelonephritis	1 009 (5.0)	167 (6.5)
Other and unknown	5 754	547 (21.5)
Number of transplants		
0	14 951 (74.7)	966 (37.9)
1	4 686 (23.5)	1394 (54.7)
2	347 (1.7)	172 (6.7)
3	23 (0.1)	15 (0.6)
4	4 (<0.1)	2 (0.1)
Alive at end of follow-up	7 045 (35.2)	1 559 (61.1)

Italicized numbers indicate mean (SD); number (%) in plain text. ADPKD, autosomal dominant polycystic kidney disease. In 12966 patients, death occurred before the end of follow-up, 31 December 2009.

Table 3.
Patient characteristics of individually matched PTX and non-PTX patients, on dialysis or with functioning renal allograft

Factor	Matched patients on dialysis, PTX, and non-PTX (*N*=1 657)	Matched patients with a renal allograft, PTX, and non-PTX (*N*=892)
Age (years)		
Start of RRT	53.1 *(14.5)*	44.9 *(12.3)*
Death	64.6 *(12.0)*	60.0 *(11.2)*
Sex		
Female	835 (50.4)	437 (49.0)
Male	822 (49.6)	455 (0.51)
Cause of ESRD		
ADPKD	233 (14.1)	144 (16.1)
Diabetes mellitus	256 (15.4)	150 (16.8)
Glomerolunephritis	485 (29.3)	336 (37.7)
Nephrosclerosis	178 (10.7)	54 (6.1)
Pyelonephritis	126 (7.6)	41 (4.6)
Other and unknown	380 (22.9)	167 (18.7)
Number of transplants		
0	966 (58.3)	
1	589 (35.5)	805 (90.2)
2	93 (5.6)	79 (8.9)
3	8 (0.5)	7 (0.8)
4	1 (0.1)	1 (0.1)
Alive at end of follow-up	837 (50.5)	722 (80.9)
Follow-up time (months)	56.3 *(44.3)*	74.1 *(50.1)*
Charlson comorbidity score at *d*	0.8 *(1.3)*	0.6 *(1.2)*
Hospital readmission < 30 days from PTX	127 (30.0)	36 (23.1)

Italicized numbers indicate mean (SD); number (%) in plain text. ADPKD, autosomal dominant polycystic kidney disease. In 12966 patients, death occurred before the end of follow-up, 31 December 2009.

Risk of death

Postoperative 30-day mortality was observed in five out of 590 PTX patients (including 11 unmatched PTX patients), which corresponds to a mortality rate of 0.8%. The patients died from myocardial infarctions, infections, and cerebral hemorrhage. The cumulative five-year survival rate was higher in Kaplan-Meier survival estimates for patients with a renal allograft at *d* compared with the patients on dialysis in the matched set (see Figures 10 and 11.). PTX was associated with improved survival both in crude analysis and after adjustment for total time on RRT before PTX, functioning graft during the study period, region, first modality after entry in RRT and comorbidity score in patients on dialysis at *d*. The risk of death was 20% lower for the patients receiving PTX compared to non-PTX patients after adjustments. Improved survival was also observed among the dialysis patients with a shorter time on RRT before *d*, time with a renal transplant during the study period and lower comorbidity index (see Table 4). When performing the same analysis for patients with a renal allograft at *d*, there was no improvement in survival for PTX patients compared to non-PTX patients, either in the crude or adjusted analysis. The only factor reducing mortality found in the analysis was the lower Charlson comorbidity score (see Table 5).

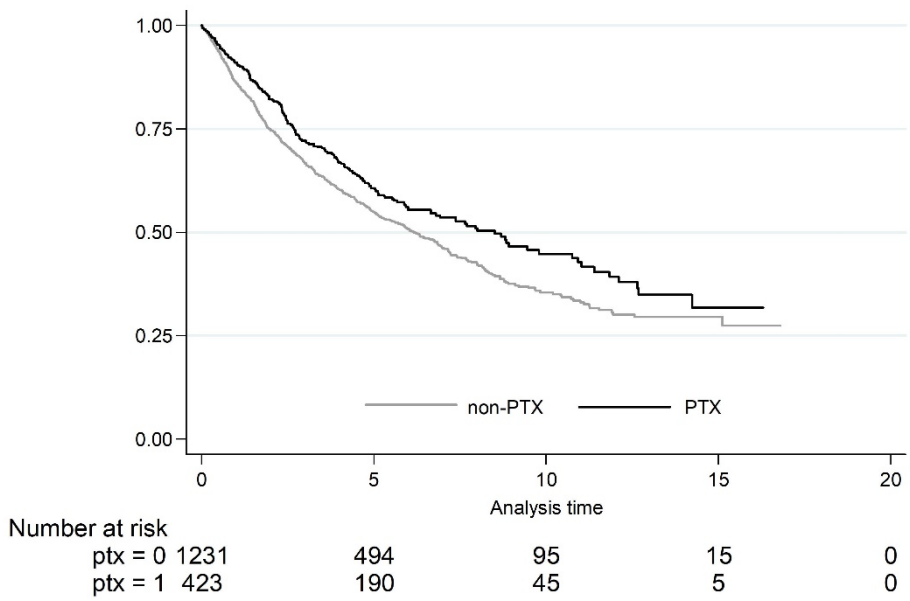


Fig 10. Kaplan-Meier survival estimate for parathyroidectomy (PTX) and non-PTX patients on dialysis at *d*

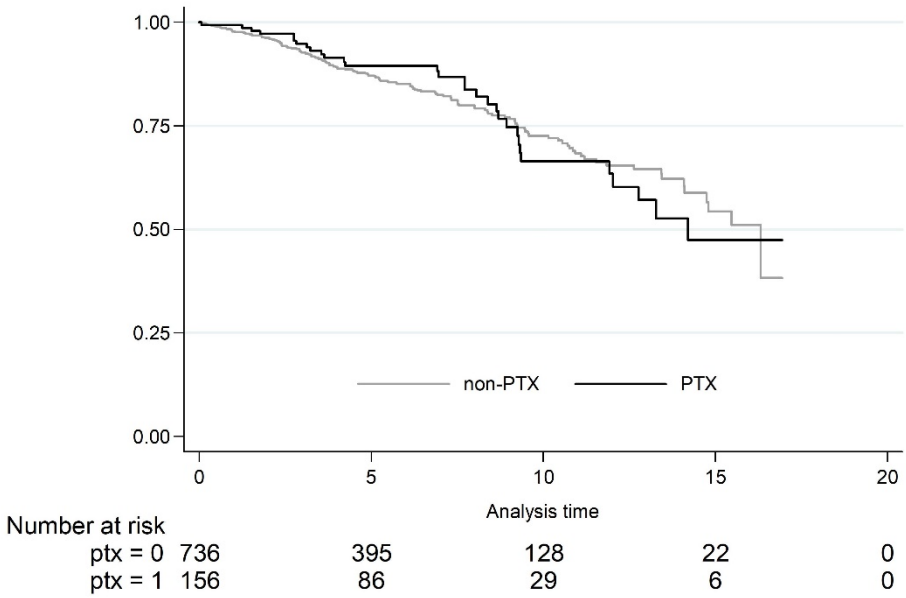


Figure 11. Kaplan-Meier survival estimate for parathyroidectomy (PTX) and non-PTX patients with a functioning renal allograft at *d*.

Table 4.
Relative risk of death for PTX patients compared to references in patients on dialysis at the time of PTX or *d*[a] (n=423/1234). Cox proportional hazards regression, HR (95% CI).

Factor	Unadjusted	Adjusted
PTX	0.74 (0.62-0.90)	0.80 (0.65-0.99)
Time on RRT before PTX	1.06 (1.02-1.10)	1.11 (1.06-1.16)
Functioning graft at any time, yes/no	0.21 (0.16-0.27)	0.20 (0.15-0.27)
Region compared to Stockholm region		
South	0.87 (0.65-1.17)	0.93 (0.67-1.29)
South-east	1.13 (0.82-1.56)	1.18 (0.84-1.68)
West	1.11 (0.82-1.48)	1.19 (0.87-1.65)
Uppsala/Örebro	1.20 (0.90-1.59)	1.39 (1.02-1.90)
North	0.94 (0.66-1.36)	1.01 (0.68-1.50)
Abroad	0.10 (0.01-0.79)	0.10 (0.01-0.79)
RRT modality, compared to hemodialysis		
Peritoneal dialysis	0.91 (0.75-1.11)	1.02 (0.83-1.26)
Renal transplant	0.91 (0.27-3.05)	2.93 (0.83-10.42)
Charlson index score	1.28 (1.20-1.35)	1.21 (1.14-1.29)

The adjusted HRs were adjusted for all the variables in the table. [a]*d*, date of PTX or corresponding date for non-PTX patients. RRT modality, first therapy after entry in SRR.

Table 5.
Relative risk of death for PTX patients compared to references in patients with a functioning renal allograft at the time of PTX or *d*[a] (n=156/736), Cox proportional hazards regression, HR (95% CI)

Factor	Unadjusted	Adjusted
PTX	1.01 (0.66-1.53)	1.10 (0.71-1.70)
Time on RRT before PTX	1.09 (1.00-1.18)	1.07 (0.98-1.169)
Region compared to Stockholm region		
South	0.98 (0.57-1.70)	1.06 (0.60-1.86)
South-east	1.31 (0.69-2.50)	1.47 (0.76-2.86)
West	0.55 (0.28-1.08)	0.63 (0.31-1.28)
Uppsala/Örebro	0.72 (0.42-1.25)	0.75 (0.43-1.31)
North	0.67 (0.32-1.42)	0.66 (0.31-1.41)
Abroad	0.00	0.00
Charlson index score	1.38 (1.18-1.61)	1.21 (1.14-1.29)

The adjusted HRs were adjusted for all the variables in the table. [a]*d*, date of PTX or corresponding date for non-PTX patients.

Risk of CVE

The improved survival seen in PTX patients on dialysis at *d* did not correspond to a lower relative risk of CVE for PTX patients compared to non-PTX patients. In fact, whereas there was no difference in risk between the two groups in crude analysis, in the adjusted analysis the risk of CVE was 24% higher. Also, a shorter time on RRT before *d*, and polycystic kidney disease as underlying renal disease, when compared to other diseases were both associated with a lower risk of CVE for the patient group factors (see Table 6). On the other hand, in patients with a renal allograft at *d*, there was a lower risk of CVE both in crude and adjusted analysis for PTX patients compared to non-PTX patients. For patients with a renal allograft, a short time with the allograft before and after *d*, a higher Charlson comorbidity score at *d* and CVE before *d* were associated with a higher risk of CVE after PTX (see Table 7).

Table 6.
The relative risk of CVE for PTX patients compared with references, patients on dialysis at [a]*d* (n = 423/1234) [Cox proportional hazards regression and HR (95% CI)]. The table shows the total effect of PTX and the direct effects of the adjustment factors.

Factor	Unadjusted	Adjusted
PTX	1.00 (0.84-1.19)	1.24 (1.03-1.49)
Sex, men vs 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)
CVE before *d*	2.80 (2.33-3.35)	2.28 (1.90-2.75)

The adjusted HRs were adjusted for all the variables in the table. ADPKD, autosomal dominant polycystic kidney disease. [a]*d*, the date of PTX or corresponding date for non-PTX patients.

Table 7.

The relative risk of CVE for PTX patients compared with references, patients with a functioning graft at [a]*d* (n = 156/736) [Cox proportional hazards regression and HR (95% CI)]. The table shows the total effect of PTX and the direct effects of the adjustment factors.

Factor	Unadjusted	Adjusted
PTX	0.62 (0.41-0.94)	0.53 (0.34-0.84)
Sex, men vs 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)
CVE before *d*	3.49 (2.52-4.83)	3.25 (2.32-4.56)

The adjusted HRs were adjusted for all the variables in the table. ADPKD, autosomal dominant polycystic kidney disease. *d*, the date of PTX or corresponding date for non-PTX patients.

Risk of hip fractures

In the matched set, there were 87 hip fractures according to the ICD codes and 70 codes for surgical intervention for hip fractures registered after *d*. Before *d*, 79 hip fractures occurred in the patient group. The frequency before *d* was almost equally distributed among PTX and non-PTX patients (4% versus 3%). The unadjusted incidence rate for hip fractures in the total cohort was 11.0/1 000 person-years, and lower for patients in the matched set (4.1 versus 6.1 per 1 000 person-years for PTX patients and non-PTX patients). In the Cox proportion hazard regressions, the relative risk for hip fractures was significantly lower for PTX patients compared to non-PTX patients after adjustment for a number of variables (see Table 8). This positive effect of PTX was no longer seen in male patients after stratification for sex but was strong in female patients with PTX. The strongest association found in the analysis was between hip fractures before and after *d*. We also found a negative association between time with functioning renal allograft after *d* and the risk of hip fractures.

Table 8.
Risk for hip fracture after PTX, PTX-patients compared to references. [Cox proportional hazards regression and HR (95% CI)]

Factor	Unadjusted	Adjusted
PTX, reference category		
non-PTX	0.61 (0.31-1.18)	0.40 (0.18-0.88)
Charlson index score	0.97 (0.80-1.18)	0.94 (0.76-1.16)
No hip fracture before *d*, reference category		
Hip fracture before *d*	4.86 (1.74-13.59)	5.05 (1.57-16.23)
Cum. time in RRT before PTX 0-2 years, reference category		
2-4 years	1.51 (0.69-3.30)	1.32 (0.57-3.06)
>4 years	2.33 (1.05-5.14)	2.40 (0.92-6.21)
Cum. time with graft before PTX, 0-1 years, reference category		
1-3 years	3.31 (0.55-20.12)	5.28 (0.68-40.75)
>3 years	3.05 (0.44-21.13)	2.73 (0.28-26.79)
Cum. time with graft after PTX, 0-1 years, reference category		
1-4 years	0.81 (0.25-2.56)	0.88 (0.26-3.04)
>4 years	0.19 (0.06-0.66)	0.19 (0.05-0.70)

RRT, renal replacement therapy, *d*= date for PTX (or corresponding date for non-PTX patients).

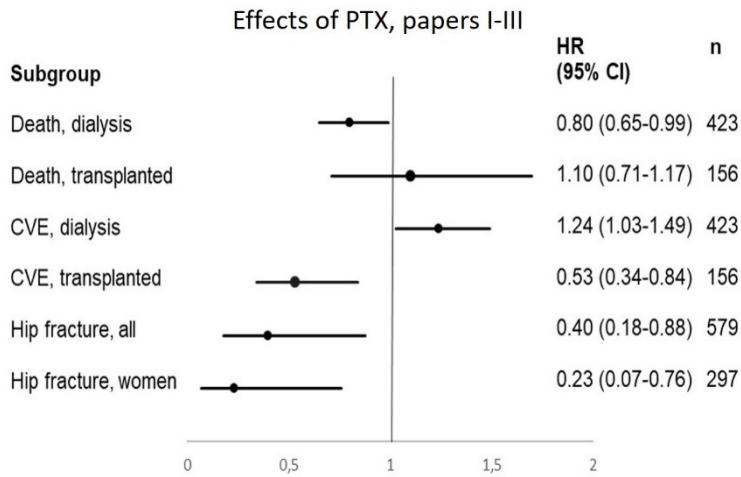


Figure 12. Forest plot of Cox proportional hazards (95% CI) for the main results in papers I-III, after adjustment, see above.

Results of papers I-III, summary

We found positive associations between PTX and survival in patients on dialysis at *d.* Furthermore, an association was also found between PTX and lower risk of CVE in transplanted patients at *d* and hip fractures in female patients. There was a positive association between CVE and PTX in patients on dialysis at *d*. (See Figure 12.)

Paper IV

Demographics and patient characteristics

In the 222 patients with PTH laboratory analysis performed in the first year after transplantation and included in the analysis, the mean age was 50 years, and the majority of the patients were male. Glomerulonephritis was the most common primary renal disease. Most patients had dialysis treatment before transplantation, and a minority of the patients had earlier transplantations. Most patients received a transplant from a deceased donor. Tacrolimus was the CNI prescribed for the majority of the patients, and one-fourth had additional immunosuppressant treatment to the standard protocol. In three out of four patients the first PTH value after transplantation was above the normal range (see Table 9).

Table 9.
Patient characteristics, treatment details and PTH values

Factor	All patients (*n*=222)
Age at transplantation (years)	49.7 ± 13.4
Sex, male/female	145/77
BMI, kg/ m^2	25.6 ± 4.4
Primary renal disease	
ADPKD	43 (19.4)
Glomerulonephritis	91 (41.0)
Nephrosclerosis	14 (6.3)
Pyelonephritis	12 (5.4)
Other and unknown	62 (27.9)
RRT*	
Hemodialysis	126 (56.8)
Peritoneal dialysis	70 (31.5)
Preemptive	26 (11.7)
Time in RRT (months)	27.0 (10.0-53.0)
Number of transplantations, 1/>1	182/40
Type of transplantation, LD/DD	88/134
Immunosuppressive protocol	
Steroids	216 (97.3)
Cyclosporine	37 (16.7)
Tacrolimus	181 (81.5)
Rapamycin	1 (0.5)
Mycophenolate mofetil	217 (97.7)
Additional immunosuppressant treatment	54 (24.3)
PTH after transplantation, pmol/L	
first value	11.0 (6.4-17.0)
log first value	2.4 (1.9-2.8)
median 6 months	9.5 (6.4-14.0)

Mean ± standard deviation, numbers (percent), median (interquartile range). BMI taken ± 3 months from transplantation date (missing in 16 patients, including three of those with NODAT). ADPKD, Autosomal dominant polycystic kidney disease. LD/DD, Living donor/deceased donor. RRT, type of therapy at the time of transplantation. Percentages do not total 100.0% since patients had one or more treatments. Additional immunosuppressant treatment: AB0-incompatibility and/or rejection therapy.

NODAT and PTH

The cumulative incidence of NODAT was 15% during the first year after transplantation. Almost all patients (94%), were diagnosed within the first six months. Most patients were treated with modifications in immunosuppressive therapy only or in combination with insulin, oral diabetic agents or dietary and exercise counseling. The first PTH value after transplantation was above the normal range in 74% of the patients, and the PTH value was significantly higher in NODAT patients compared to non-NODAT patients. After analyzing potential predictors of NODAT in the unadjusted logistic regression model and finding the variables of age

between 45 and 64 compared to <45 years and higher PTH being associated with NODAT, these two variables in addition to sex, were analyzed in multiple logistic regression models. The association remained after adjustment (see Table 10).

Table 10.
Predictors of NODAT, Multiple Logistic Regression

Factor	Odds ratio (95% CI)	*P*	*P*-value for trend
Age, years			
<45	1.00		0.49
45-64	2.80 (1.07-7.36)	0.04	
65-74	1.09 (.24-4.94)	.91	
Sex			
Female	1.00		
Male	1.22 (.53-2.81)	0.63	
PTH after transplantation, pmol/L*			
≤6.90	1.00		0.03
6.91-13.80	2.82 (.76-10.54)	0.12	
>13.80	4.25 (1.13-15.92)	0.03	

*First record up to six months after transplantation. 88% of values measured within three months from diagnosis.

Discussion

In this thesis, we aim to contribute to the knowledge regarding the long-term effects of PTX on survival, CVE and hip fractures in three matched, observational cohort studies. In addition, we shed some light on the possible association between sHPT and another severe condition, NODAT. We found differences in our results between patients on dialysis and those with renal transplants. Among the dialysis patients, PTX improved survival but not the risk of CVE. Among patients with a renal transplant, on the other hand, we found no survival advantage after PTX, but a strong association with a lower risk of CVE. PTX decreased the risk of hip fractures in women. Finally, NODAT was common at our department, the incidence being 15% at the first year post-transplant. We also found an association between NODAT and sHPT.

Earlier studies

There are a number of studies on cardiovascular and all-cause mortality after PTX in the literature. We have found 14 reports with aims and patient characteristics comparable to our study of patient survival after PTX[143, 144, 146, 147, 186-195]. They are all observational and were performed only on dialysis patients. Four of them were published after paper I[187, 189, 190, 192]. The number of patients with PTX studied varies from 26[187] to 4 558[143]. Some of them were performed after[186, 187, 189-191] the introduction of cinacalcet, others before [143, 144, 146, 147, 193] and some in the overlapping time period[188, 192, 194, 195]. Most of these investigations are either unmatched[144] or matched case-control studies[143, 146, 186-188, 192, 194]. Clinical and demographic data have been adjusted for in these studies. The majority of these reports[143, 144, 186-189, 191-195], support our results showing improved survival after PTX after the first postoperative period. In three smaller studies, PTX did not improve patient survival[146, 147, 190] after adjustment for patient characteristics.

There are only a few earlier studies of cardiovascular events after PTX, all on patients on dialysis and from the time prior to the introduction of cinacalcet[142, 146, 195-197]. The definition of cardiovascular events differs between these studies. Hsu et al. studied the risk of stroke after PTX in their population-based 1:1 matched case-

control study from Taiwan. They found a significantly lower risk of stroke for patients who underwent PTX compared to the non-PTX controls: 1 063/1 063 patients (5.63%/9.05%)[197]. In another large population-based study also from Taiwan with 1 047 incident PTX with 4 188 matched controls the risk of acute coronary syndrome (ACS) was the endpoint. The risk of ACS was 26% lower for patients who had undergone PTX than for those who had not[196]. Three smaller studies all had stroke, myocardial infarcts and cardiovascular death as endpoints[142, 146, 195]. Two of them showed lower risk for CVE for patients who had undergone PTX compared to non-PTX patients[142, 195]. One investigator found no association[146] and thus found the same results for patients on dialysis as we did in our study.

Rudser et al. matched 5 918 PTX patients on dialysis with 16 328 non-PTX dialysis patients and studied the risk of fractures. They found 6.0 incident hip fractures per 1 000 person-years among PTX patients, and significantly more, or 9.3 per 1 000 person-years in non-PTX patients[141]. When stratifying for sex, only women had a lower fracture risk after PTX. This result is in line with our results in paper III and associations between PTX and improved bone health in patients with sHPT, measured as improvement in risk of other fractures and an increase in bone mineral density (BMD)[140, 198-200]. No study of hip fractures after PTX in transplanted patients was found in the literature.

The incidence of NODAT among patients with renal transplants varies in the large number of studies[157], depending on definition. In a registry study by Sinagil et al. from 2017 with 420 transplanted patients, the six months post-transplant incidence of NODAT was 16.6%. They compared NODAT patients with non-NODAT patients and found associations between NODAT and higher age, obesity, family history of diabetes, presence of impaired fasting glucose and pre-transplant hypertriglyceridemia. They also found an association between NODAT and hyperparathyroidism in the pre-transplant period[201]. Thus, both the NODAT incidence rate and associations with age and higher PTH were in line with our results in paper IV.

Implications

There seems to be an association between PTX and improved survival among dialysis patients since many studies point in this direction and very few contradict the hypothesis. Several factors may have contributed to these results. Control of PTH production and secretion improves plasma levels of phosphate and calcium, which are associated with vascular calcification and atherosclerosis[202, 203]. Furthermore, the PTH hormone itself acts on cardiomyocytes, VSMC, and endothelial cells and can induce left ventricular hypertrophy[204]. PTH is also

associated with cardiovascular events[205]. sHPT can also contribute to fracture-related death[93].

It was surprising to find that PTX did not reduce the risk of CVE in patients on dialysis; in fact, the risk was higher compared to non-PTX patients. There are some differences in study design and patient characteristics between paper II and comparable studies presented above. For instance, in the population-based study by Ma et al., much more data was available for propensity score matching, such as information on hypertension, hyperlipidemia, chronic obstructive pulmonary disease, alcohol-related diseases and obesity. This, together with the exclusion from the study of patients with time with a renal allograft or ACS prior to PTX or a corresponding date for the controls[196] makes it difficult to compare our study results. Still, in accordance with paper I, an improvement in the risk of CVE could be expected since the same group of patients showed improved survival. One theory could be that the CVE were not fatal due to improved medical treatment in contemporary patient care [206]. Another possible explanation could be that patients had more, but less severe, CVE after PTX. Finally, it cannot be ruled out that the patients referred for PTX had a more severe form of sHPT and therefore continued to have a higher risk of new CVE due to continued vascular calcification and atherosclerosis, as having experienced earlier CVE was the strongest risk factor for CVE after PTX.

Cardiovascular and bone disease are related to sHPT. The osteoblastic and osteoclastic activity stimulated by high levels of PTH is associated with increased bone remodeling and high turnover bone disease[207]. Continuous sHPT causes a net loss of bone mass, bone fragility and increased risk of fractures since the bone resorption exceeds the rate of bone formation[208]. The result is higher plasma levels of calcium and phosphate, in turn leading to stimulation of vascular calcification[43]. PTX reduces PTH production and secretion and thus induces lower serum levels of calcium and phosphate. Calcium levels sometimes drop further as a result of *hungry bone syndrome.* When the osteoclastic stimulation from PTH suddenly decreases after PTX, calcium is absorbed by the bone tissue, resulting in hypocalcemia.[209].

The lower risk of hip fractures only in women after stratification for sex found in both our study and in the study by Rudser et al.[141] may in part be explained by the potential benefit from PTX in women, who generally have worse bone health than men and more hip fractures [210]. This is also true for the dialysis population where women seem to have higher levels of PTH and more fractures[61, 211].

We included all patients on RRT, both those with a renal transplant and those on dialysis treatment, in our cohort in papers I-III. In papers I and II we stratified the patient material and found differences between the results for patients on dialysis and with renal transplant. There was no difference in mortality between PTX and non-PTX patients with transplants. This may in part be attributable to the better

survival of all transplanted patients. At the end of follow-up, 81% of these patients were alive, compared to only 51% of the dialysis patients. They also showed less comorbidity. The risk of new CVE among transplanted patients after PTX was lower than for non-PTX patients. Transplanted patients are younger and healthier than those on dialysis, and can in most cases be assumed to be eligible for PTX if there is an indication, reducing the risk of comparing a selected, healthier group of PTX patients with those who cannot be referred for surgery. In paper III we studied all patients for risk of hip fractures after PTX or *d*. In the Cox proportional hazards regression, a cumulative time with functioning renal allograft after *d* of more than four years reduced the risk of hip fractures by 81% in the adjusted analysis. There is a debate on whether it is safe to perform PTX after transplantation since there are reports of loss of graft function and even graft loss when PTH levels fall after PTX[212]. Still, more than one-fourth of our study patients undergoing PTX had a functioning renal allograft at the time of the procedure. It is surprising that the effect of PTX on this group of patients has received so little attention in the literature.

The association between sHPT and NODAT was expected. In the literature, there are studies of both pHPT and sHPT showing associations with glucose tolerance, insulin secretion, and diabetes[213-217]. In two studies, beneficial effects on glucose control from PTX were seen[218, 219], while in one it was not[220]. The mechanisms behind these associations are not fully understood. Experimental studies have shown that high levels of PTH can cause suppression of insulin signaling in adipocytes via the cyclic adenosine monophosphate (cAMP) pathway and thereby cause insulin resistance[221, 222]. In addition, insulin deficiency can occur because of elevated resting levels of cytosolic calcium in the pancreatic islets, related to high levels of PTH[223, 224]. Levels of phosphate[225, 226] and calcitriol[227] are also suggested to be involved in this association.

Observational studies

All four studies in this thesis are retrospective observational studies. Papers I-III were performed on the same patient cohort, in a database with over 20 000 patients from two quality registries and registries from the Swedish National Board of Health and Welfare. The database contained information on demographics and patient characteristics, diagnosis, and treatments. This patient material enabled case-control studies with three different endpoints: death, cardio- and cerebrovascular events and hip fractures. In Sweden and the other Nordic countries, nationwide registries with high validity and coverage (nearly 100%) are available for medical research. The unique personal identification number enables linkages between different registries[228-231].

Although randomized controlled trials are considered the golden standard for clinical research and they reduce bias and provide an opportunity to examine cause-

effect relationships between an intervention and outcome[232], it is unlikely that experimental studies of effects of PTX will take place[232]. Practical obstacles and ethical issues need to be considered. There are several options for study design in registry studies: cohort, case-cohort, case-control, case-crossover and cross-sectional studies with data collected either prospectively or retrospectively[233]. Matching and matching with propensity score in case-control studies can be useful when a treatment effect is studied. The individual matching of patients is a method to control for confounding, and propensity score estimating is a way to simplify the matching process by combining all confounders into a single value[234]. With Cox proportional hazards regression analysis the relative risk of treatment effects can be calculated, and adjustments for covariates can be made. One has to aware of the different problems and biases that can occur in registry studies such as loss of follow-up, selection biases, data not missing at random, competing risk, confounding by indication and internal and external validity deficiency. The potential for valuable research in our large registries with high validity is great but such research demands deep knowledge of statistical methods and design. Multicenter registry studies between the Nordic countries may offer a future possibility for gaining knowledge of the effects of PTX in patients on RRT[228].

Weaknesses and strengths

There are limitations to the studies reported in this thesis. One of them is the retrospective design. Another is the lack of certain information. We performed matching and adjustment for a number of confounding factors in papers I-III. Residual confounding can still not be ruled out. The studies would benefit from information on laboratory data such as PTH, plasma calcium, phosphate, and creatinine. Also, information on health factors such as hypertension, hyperlipidemia, chronic obstructive pulmonary disease, alcohol-related diseases, and obesity would have been useful. In transplanted patients, knowledge about renal function, BK- and cytomegalovirus and relapse of underlying renal disease would have added validity to the studies. In paper IV, knowledge of the family history of diabetes was missing.

There are several strengths to this thesis. Papers I-III are truly population-based studies, with data from national registries that contain information on virtually all patients in RRT in Sweden. We did not exclude patients with a renal allograft or diabetes mellitus as underlying renal disease. The long follow-up time for almost two decades includes different eras of PTX incidence and medical treatments. In paper IV, the diagnosis was made by the physicians in charge of the patients in accordance with recommendations from the World Health Organization regarding the definition of diabetes mellitus.

Conclusions

The studies presented in this thesis showed that:

- PTX was associated with improved survival in patients on maintenance dialysis. However, there was no survival advantage after PTX in patients with a functioning renal allograft.
- PTX was associated with higher risk of CVE 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.
- PTX was associated with a reduced risk of hip fractures in women with sHPT.
- The first-year cumulative incidence of NODAT was 15% in our department between 2000 and 2011.
- We showed an association between elevated levels of PTH and NODAT in transplanted patients.

Future perspectives

There is still much more to learn about PTX in patients on renal replacement therapy. We do not fully understand who to refer for surgery, or what effects to expect from the treatment, and when. We do not even know how to perform PTX to achieve the best results. But we do know that despite the development of non-invasive treatments of secondary hyperparathyroidism, PTX will be an important factor in improving bone and cardiovascular health as well as survival in the foreseeable future. There seems to be a survival advantage of PTX in patients on dialysis, but patients with renal transplants need more attention. Studies of risk of cardio-/cerebrovascular disease and hip fractures are lacking for all patients on renal replacement therapy. Study design may also develop, supported by better data from national quality registries. Maybe we will see Nordic multicenter registry studies in the future with both high power and validity. The association we found between sHPT and NODAT may be of importance and should be further studied. The two very serious complications of ESRD clearly represent a threat to patients' health and quality of life.

Popularized scientific summary in Swedish

Mineralerna kalk och fosfat är nödvändiga för bland annat skelettet, tänderna, hjärtat och blodkärlen. I en frisk kropp regleras dessa ämnen så att nivåerna i blodet hålls jämna och att tillräckligt mycket av dem finns lagrat i skelettet. Patienter med kronisk njursvikt löper stor risk att utveckla rubbningar i kalk- och fosfatbalansen. Den försämrade njurfunktionen leder till en minskad förmåga att utsöndra fosfat och uppta kalk i njurarna och tarmen. Även bildandet av aktivt vitamin D som sker i njurarna, hämmas vid en försämrad njurfunktion. Vitamin D är viktigt för bland annat immunförsvaret och mineralomsättningen i kroppen.

För att bibehålla normala nivåer av kalk, fosfat och vitamin D i blodet stimuleras bildningen av hormoner i benvävnaden och bisköldkörtlarna som motverkar effekterna av njursvikten. Bisköldkörtlarna är fyra, risgrynstora körtlar som sitter bakom sköldkörteln på halsen utsöndrar ett hormon, *parathormon*. Vid längre tids njursvikt och stor utsöndring av parathormon växer dessa körtlar sig större och förlorar sin känslighet för mineralnivåerna i blodet. Den ökade mängden parathormon leder till skörare skelett och förkalkningar i blodkärlen. Dödligheten ökar också.

Under de senaste decennierna har läkemedlen mot rubbningar i kalk- och fosfatbalansen förbättrats. Patienterna behandlas med vitamin D, fosfatbindare och läkemedel som gör bisköldkörtlarna känsligare för de faktiska nivåerna av kalk, fosfat och vitamin D i blodet. Många får kontroll på mineralnivåerna genom dessa läkemedel, medan en del patienter behöver kirurgisk behandling mot tillståndet. Det mesta av bisköldkörtelvävnaden opereras då bort för att hejda utsvämningen av parathormon.

Patienter som transplanterats löper en ökad risk att utveckla diabetes. Detta fenomen är välkänt och kan till stor del härledas till den immunhämmande behandling som patienterna får i syfte att förhindra en avstötning av det nya organet. Alla njurtransplanterade behandlas efter ungefär samma protokoll, vissa patienter får diabetes och andra inte. Varför är det så? Det finns tidigare studier som visat ett samband mellan förhöjt blodsocker eller diabetes och en ökad utsöndring av parathormon hos dem som får tumörer i bisköldkörtlarna.

I detta avhandlingsarbete har vi studerat vilken effekt operation har som behandling för överfunktion i bisköldkörtlarna hos patienter i dialys eller med njurtransplantat när det gäller överlevnad, hjärtinfarkter, stroke och höftfrakturer. Vi har använt oss av registerdata från sjukvården och socialstyrelsen och identifierat ca 600 patienter i Sverige som genomgått bisköldkörteloperation mellan åren 1991 och 2009. Jämförelser av hur det gått för dem som opererats och patienter som enbart läkemedelsbehandlats gjordes. Vi tog bland annat hänsyn till kön, ålder, om patienterna haft dialysbehandling eller varit njurtransplanterade, vilken njursviktsdiagnos de haft, samsjuklighet och om de tidigare haft höftfrakturer, hjärtinfarkter eller stroke.

Till avhandlingen hör också en studie på patienter som njurtransplanterats mellan åren 2000 och 2011 och som följdes på mottagningarna i Malmö och Lund. Med hjälp av registerdata har vi tittat på hur många som utvecklade diabetes det första året efter transplantation. Vi tittade också på om det fanns något samband mellan risken för diabetes och förhöjda nivåer av parathormon.

När det gäller överlevnaden såg vi att patienter i dialysbehandling hade en bättre överlevnad jämfört med kontrollgruppen, detta samband kunde vi inte se hos de njurtransplanterade. Hjärtinfarkter och stroke var fler hos de opererade med dialysbehandling, medan risken var lägre för de njurtransplanterade. Vi såg en lägre risk för höftfrakturer för patienterna som opererats. När vi gjorde en uppdelning efter kön såg vi att det bara var gruppen kvinnor som hade en riskminskning för höftfraktur efter operation. Andelen patienter som insjuknade i diabetes inom ett år efter njurtransplantation var hög, 15%. Vi fann också ett samband mellan nydebuterad diabetes och förhöjda nivåer av parathormon.

En del av resultaten i avhandlingen var väntade. Att överlevnaden förbättrades av operation har visats i tidigare studier av patienter i dialysbehandling, liksom färre höftfrakturer hos kvinnor. Det förvånade oss dock att inte risken för hjärtinfarkter och stroke minskade hos gruppen patienter i dialysbehandling. Man kan spekulera om huruvida de som blir opererade har en värre sjukdomsbild med mer kärlförkalkning än de som inte blir opererade, vilket ger en ökad risk för nya hjärt-/kärlhändelser. Dessa kanske inte leder till döden i lika stor utsträckning som bland dem som inte blivit opererade i bisköldkörtlarna. Resultaten för transplanterade finns inte att jämföra med i några tidigare studier.

Forskningsläget är fortfarande osäkert vad gäller vem som ska opereras i bisköldkörtlarna, när och vilken nytta operationen har, även om det verkar som om överlevnaden förbättras efter operation för patienter i dialysbehandling. Effekterna bör studeras vidare, och framförallt måste gruppen njurtransplanterade med överfunktion av bisköldkörtlarna efter transplantationen undersökas närmare. Diabetes efter njurtransplantation är vanligt förekommande och en allvarlig risk för hälsan, till risken kan adderas den som överfunktion i bisköldkörtlarna ger.

Erratum

In Paper I, in Abstract under Results and Table 3, the total number of matched reference patients with a renal allograft at *d* is N=736 instead of N=892.

Acknowledgments in Swedish

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Hyperparathyroidism and parathyroidectomy in patients on renal replacement therapy

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