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Renal hyperparathyroidism, parathyroidectomy and transplantation

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Renal hyperparathyroidism, parathyroidectomy and transplantation

Renal hyperparathyroidism, parathyroidectomy and transplantation

Elin Isaksson



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DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
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<p>Abstract</p> <p>Renal hyperparathyroidism is a complication of renal failure which is characterised by overfunction of the parathyroid glands, high levels of parathyroid hormone (PTH), disturbed mineral balance, bone disease and vascular calcifications. It is one of the factors contributing to the high risk of mortality, cardiovascular disease and fractures seen in patients with chronic renal failure. There are two major clinical situations that cause a rapid change in renal hyperparathyroidism with a sudden drop in PTH one is renal transplantation and the other is parathyroidectomy (PTX). It is today unknown which factors determine the degree of persistent renal hyperparathyroidism after renal transplantation and which pre-transplant levels of PTH are most beneficial for post-transplant morbidity outcomes. It is unclear which patients to select for PTX or whether PTX has any effect on fractures. It is also not known whether the surgical technique, total or subtotal PTX, affects morbidity outcomes.</p> <p>This thesis provides evidence that the major determining factor for the post-transplant degree of renal hyperparathyroidism is the pre-transplant level of PTH and the type of treatment of renal hyperparathyroidism. After renal transplantation, PTH falls but stabilises at six months. One year after transplantation, 67% of patients still have raised PTH in relation to graft function. Low pre-transplant levels of PTH are associated with a higher risk of cardiovascular disease in the post-transplant period compared to moderate and high levels of pre-transplant PTH. The suggested mechanism is that some patients develop a shift from high to low bone turnover after renal transplantation, inducing an increased risk of vascular calcifications.</p> <p>Furthermore, we provide evidence that female patients undergoing parathyroidectomy have a reduced risk of hip-fracture; the same effect was not seen in male patients. This could be explained by the higher rate of osteoporosis in female patients due to hormonal changes and by female patients being more susceptible to abnormal parathyroid activity. Finally, we provide novel data regarding differences in outcomes between the surgical techniques used in parathyroidectomy for renal hyperparathyroidism. Total PTX, resulting in lower levels of PTH is associated with a higher risk of cardiovascular disease compared with subtotal PTX. Patients with prevalent cardiovascular disease were at highest risk. Subtotal PTX on the other hand is associated with a higher risk of recurrent renal hyperparathyroidism. The suggested explanation for the higher risk of cardiovascular disease seen after total PTX is low bone turnover disease as described above.</p> <p>In summary, this thesis shows that for patients on the renal transplant waiting list, the management of renal hyperparathyroidism is important, and both high and low PTH levels should be avoided. Low levels of PTH before renal transplantation can lead to cardiovascular morbidity in the post-transplant period. When aiming to reduce the risk of hip fractures in patients with renal hyperparathyroidism, PTX is only beneficial for female patients. Total parathyroidectomy can lead to insufficient levels of PTH and an increased risk of cardiovascular disease, especially if the patient has prevalent cardiovascular disease. This thesis underlines the need for clinically available methods of determining bone health to use before deciding on procedures that rapidly change mineral metabolism in patients with chronic kidney disease.</p>				
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Renal hyperparathyroidism, parathyroidectomy and transplantation

Elin Isaksson



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To my extraordinary family

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Original papers

I. Early Development of Secondary Hyperparathyroidism following Renal Transplantation Isaksson E, Sterner G. Nephron Clin Pract 2012;121:c68–c72.

II. Is low pre-transplant parathyroid hormone a risk marker for cardiovascular disease in long-term follow-up of renal transplant recipients? Isaksson E, Seeberger A, Almquist M, Sterner G. Manuscript.

III. The Effect of Parathyroidectomy on Risk of Hip Fracture in Secondary Hyperparathyroidism. Isaksson E, Ivarsson K, Akaberi S, Muth A, Sterner G, Prütz K-G, Clyne N, Almquist M. World J Surg. 2017;41:3204-2311

IV. Parathyroidectomy in secondary hyperparathyroidism. Does surgical technique affect short and long term survival, cardiovascular disease and recurrent disease in patients with chronic kidney disease? Isaksson E, Ivarsson K, Akaberi S, Muth A, Sterner G, Prütz K-G, Clyne N, Almquist M. Manuscript.

Thesis at a glance

	Question	Method	Results	Conclusion
I	Which pre-transplant factors determine the degree of secondary hyperparathyroidism one year after renal transplantation?	Retrospective analysis of 132 renal transplant recipients followed to one year after transplantation.	Pre-transplant levels of PTH, and medical treatment affected one-year levels of PTH.	Pre transplant management of sHPT determines the degree of post-transplant sHPT.
II	Is the level of pre-transplant parathyroid hormone associated with increased risk of cardiovascular outcomes after renal transplantation?	Retrospective comparative analysis of 258 renal transplant recipients divided by pre-transplant quartiles of PTH followed six years.	Low pre-transplant levels of PTH were associated with a higher risk of cardiovascular disease after transplantation.	Over-suppressed levels of PTH before transplantation can lead to higher risk of post-transplant CVD
III	Does parathyroidectomy affect the risk of hip fractures in patients on dialysis or with a renal transplant?	Retrospective analysis of 579 patients undergoing parathyroidectomy and 1970 matched controls.	Parathyroidectomy was associated with lower risk of hip-fracture in female patients.	Female patients have beneficial effects on risk of hip fracture when undergoing PTX for sHPT.
IV	Does the surgical technique used in parathyroidectomy for secondary hyperparathyroidism affect outcomes in patients on dialysis or with a renal transplant?	Retrospective analysis of 388 patients undergoing total PTX and 436 patients undergoing subtotal PTX.	Total PTX was associated with a higher risk of cardiovascular disease. Subtotal PTX was associated with higher risk of recurrent disease.	Total PTX is effective for sHPT treatment but with the cost of increasing the risk of cardiovascular disease.

Abbreviations

ALP	Alkaline Phosphatase
AT	Autotransplantation
BMD	Bone Mineral Density
CaSR	Calcium Sensing Receptor
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease – Mineral and Bone Disorder
CVD	Cardiovascular Disease
CYP24	Cytochrome P 24
CYP27B1	Cytochrome P 27B1
Dkk1	Dickkopf 1
eGFR	estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
FGF23	Fibroblast Growth Factor 23
GFR	Glomerular Filtration Rate
HDL	High Density Lipoprotein
KDIGO	Kidney Disease: Improving Global Outcome
K/DOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low Density Lipoprotein
OPG	Osteoprotegerin
PTH	Parathyroid Hormone
PTX	Parathyroidectomy
RANK-L	Receptor Activator of Nuclear factor Kappa b – Ligand
RT	Renal Transplantation
sHPT	Secondary Hyperparathyroidism
SRR	Swedish Renal Registry
SQRPTA	Scandinavian Quality Registry for Thyroid Parathyroid and Adrenal surgery
TMV	Turnover Mineralization Volume
VDR	Vitamin D Receptor
VSMC	Vascular Smooth Muscle Cells
Wnt1	Portmanteau of Wingless and Integrated 1
1,25(OH) ₂ D	Active Vitamin D
25(OH)D	Inactive Vitamin D

Introduction

When treating a patient with chronic kidney disease (CKD) the clinician is handling one of the most challenging tasks in clinical practice. Few failing organs have such a widespread impact on the organism as the kidney. Patients with end stage renal disease (ESRD) have a mortality risk 10-20 times higher than patients with normal renal function, and the major cause of death is cardiovascular disease¹. Patients with ESRD also develop bone disease and have a higher risk of fractures compared to the general population². The complex relation between the kidney, the bones and vascular calcifications led to the definition in 2005 of Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD) by Kidney Disease International Improving Global Outcome (KDIGO)³. Secondary hyperparathyroidism (sHPT), with increased volume of the parathyroid glands and increasing levels of parathyroid hormone (PTH), is a major element of CKD-MBD and it develops over time in the vast majority of patients with CKD⁴. Vascular and bone-related outcomes as well as increased mortality are a direct effect of sHPT^{4, 5}.

Treatment guidelines regarding CKD-MBD were published in 2009 by KDIGO. The authors also pointed out that numerous questions remained unanswered due to insufficient data and the lack of randomised controlled studies with hard endpoints⁶. However, these guidelines do recommend to medically correct underlying mineral disturbances such as phosphate, calcium and vitamin D before assessing the PTH value. It is also stated that for patients not yet on dialysis the optimal PTH level is not known. In dialysis it is suggested that the optimal PTH value is two to nine times above the upper normal limit for the PTH assay. After correction of underlying mineral disturbances, the guidelines suggest, that anti sHPT medications should be used to control rising levels of PTH. The target range of PTH is wide, which is why it has been proposed that there might be subgroups in this heterogeneous population that would benefit from other target ranges of PTH⁷.

Apart from medical treatment the other option is surgical removal of the parathyroid glands, parathyroidectomy (PTX)⁸. This is recommended if PTH continues to rise despite medical treatment especially in combination with hypercalcaemia⁶. Parathyroidectomy is an effective way to lower levels of PTH⁹ and has been shown to reduce mortality for patients on dialysis^{10, 11}. However, the effect of parathyroidectomy on cardiovascular and bone-related outcomes is unclear. Furthermore, it is not known which level of PTH to aim for after PTX.

Thus the surgical approach of either removing all parathyroid glands (total PTX) or leaving some parathyroid tissue (subtotal PTX) is performed without evidence of its superiority¹².

After renal transplantation, renal function increases and the mineral metabolism dramatically improves. In recent years the knowledge concerning sHPT after renal transplantation has increased. However, treatment recommendations are still vague and no target PTH levels exist today for renal transplant recipients⁶. Furthermore, it is not known whether PTX should be performed before or after renal transplantation, and the question is under debate¹³. There are studies demonstrating a decrease in renal function when PTX is performed after transplantation¹⁴. The advantages in mortality rates after PTX seen in patients on dialysis have not been shown for patients with a renal transplant¹¹.

In this thesis I examine secondary hyperparathyroidism in two situations when mineral metabolism drastically changes. First, I study sHPT in a cohort of Swedish patients before and after renal transplantation and the relation between parathyroid hormone and bone and vascular outcomes in the short as well as long-term. Secondly, I study fracture risk after parathyroidectomy in a cohort of Swedish patients either on dialysis or with a renal graft. In the same cohort I also investigate whether the surgical technique has any influence on mortality, bone- and cardiovascular outcomes.

The parathyroid glands

The parathyroid glands are four small glands usually positioned behind the left and right lobes of the thyroid, and are part of the endocrine system. There can be supernumerary glands, which are most often situated in the thymus tissue but can also be found at a number of other sites. The parathyroid gland consists of two types of cell: chief cells and oxyphil cells. Chief cells synthesise and release parathyroid hormone. Even though oxyphil cells increase in number in CKD and express many of the genes present in chief cells their function is still unknown¹⁵. The main function of the parathyroid gland is to maintain a normal calcium homeostasis. On the surface of chief cells, calcium-sensing receptors (CaSR)¹⁶ activate the synthesis and release of PTH when calcium levels drop below a certain threshold. A high level of calcium inhibits the release of PTH.

Parathyroid hormone acts to mobilise calcium in three ways. The first is by activating osteoblasts, which in turn activate osteoclasts, resulting in net calcium release from the skeleton¹⁷. The second is by increasing calcium reabsorption in the distal tubuli in the kidney¹⁸. The third way PTH increases calcium is by stimulating the activation of vitamin D, which in turn acts to increase calcium absorption in the intestine¹⁹. Increased levels of phosphate also stimulate PTH

release, but the mechanism is unclear²⁰. The parathyroid gland receives negative feedback via Fibroblast Growth Factor 23 (FGF23)²¹, vitamin D²² and high levels of calcium.

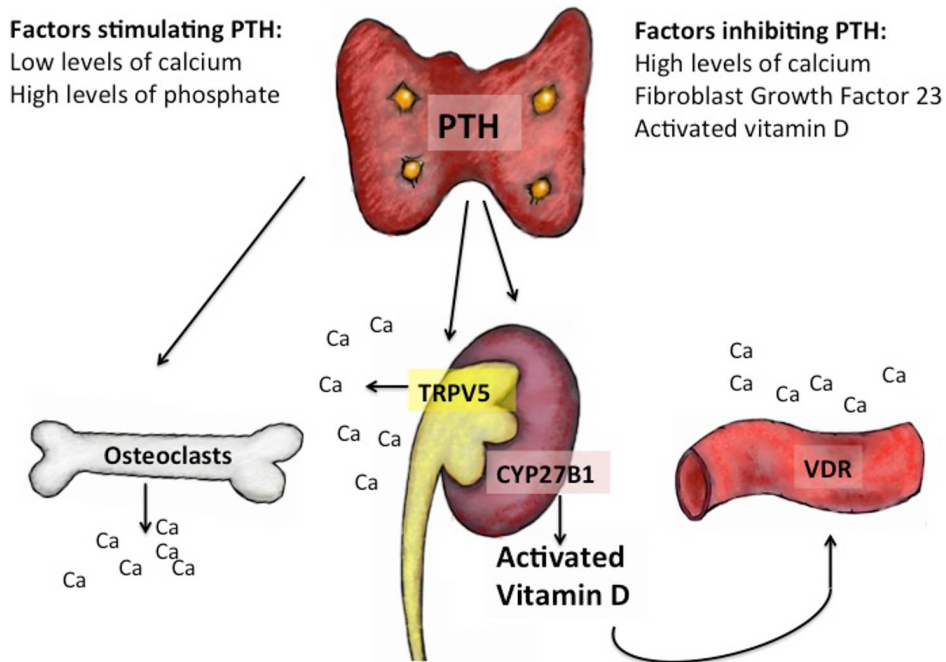


Figure 1. Actions of parathyroid hormone on calcium mobilisation.

PTH = Parathyroid hormone, TRPV5 = Transient Receptor Potential Vanniloid 5 (calcium channel), CYP27B1 = Cytochrome P 27B1 (enzyme catalysing the activation of Vitamin D), VDR = Vitamin D Receptor, Ca = Calcium.

Hypo- and hyperparathyroidism

Reduced function of the parathyroid gland, hypoparathyroidism, is uncommon and is characterized by decreased levels of PTH, hypocalcaemia and hyperphosphataemia. Iatrogenic damage to the parathyroid glands, usually due to neck surgery, is the most common cause of hypoparathyroidism. Other causes are autoimmune diseases and genetic disorders²³.

Increased function of the parathyroid gland with hypercalcaemia and inappropriate increased levels of PTH are more common and usually caused by a single benign adenoma, which is the cause of primary hyperparathyroidism²⁴. Secondary hyperparathyroidism is defined as increased function of the parathyroid gland caused by external factors. A common form is renal hyperparathyroidism

caused by reduced renal function. In sHPT there is a diffuse proliferation of the parathyroid gland cells²⁵. The third and last type of hyperparathyroidism is tertiary hyperparathyroidism when nodular hyperplasia is developed after long-standing sHPT²⁶. Tertiary hyperparathyroidism is sometimes also used to define secondary hyperparathyroidism after renal transplantation²⁷.

The Kidney

Apart from filtering the blood of waste products, maintaining acid-base homeostasis, regulating blood pressure and producing erythropoietin the kidney also plays a major role in mineral metabolism. After the filtration of blood to primary urine in the glomeruli, passive and active re-uptake of essential minerals takes place in the proximal and distal tubuli to balance mineral homeostasis. The active re-uptake of calcium is mediated by a calcium channel (Transient Receptor Potential Vanniloid 5, TRPV5) in the distal convoluted tubuli, driven by a gradient of low intracellular calcium. TRPV5 is also activated further by PTH¹⁸ which is instantly released from the parathyroid gland when calcium levels are low, as described above.

Phosphate re-uptake takes place in the proximal convoluted tubuli mostly by type 2 sodium/phosphate co-transporters²⁸. Dietary intake and tubular handling determine the levels of phosphate. To excrete excess phosphate, sodium/phosphate co-transporters in the proximal convoluted tubuli are down-regulated. A novel theory in phosphate-PTH-calcium regulation is that high phosphate in the distal nephron forms complexes with calcium, thus lowering levels of calcium in the distal tubuli, which stimulates PTH secretion to enhance calcium reuptake²⁹. PTH also acts in a phosphaturic manner by reducing sodium/phosphate co-transporters³⁰. The other major phosphaturic hormone, FGF23, acts similarly by degrading the same co-transporter³¹ resulting in lower phosphate levels in the blood.

The kidney also has endocrine functions related to mineral metabolism. In the proximal convoluted tubuli the enzyme CYP27B1 catalyses the 1 α -carboxylation of inactive vitamin D, (25(OH)D), to the active form 1.25(OH)2D^{32, 33}. Vitamin D has many effects in the body and one of them is stimulating the uptake of calcium and phosphate in the intestine. Parathyroid hormone, hypocalcaemia, hypophosphataemia, growth hormone, and oestrogen are some of the stimulators that induce activation of vitamin D³⁴. Active vitamin D can also be degraded in the kidney by another enzyme, CYP24. This pathway is stimulated by FGF23 and 1.25(OH)2D itself³⁵.

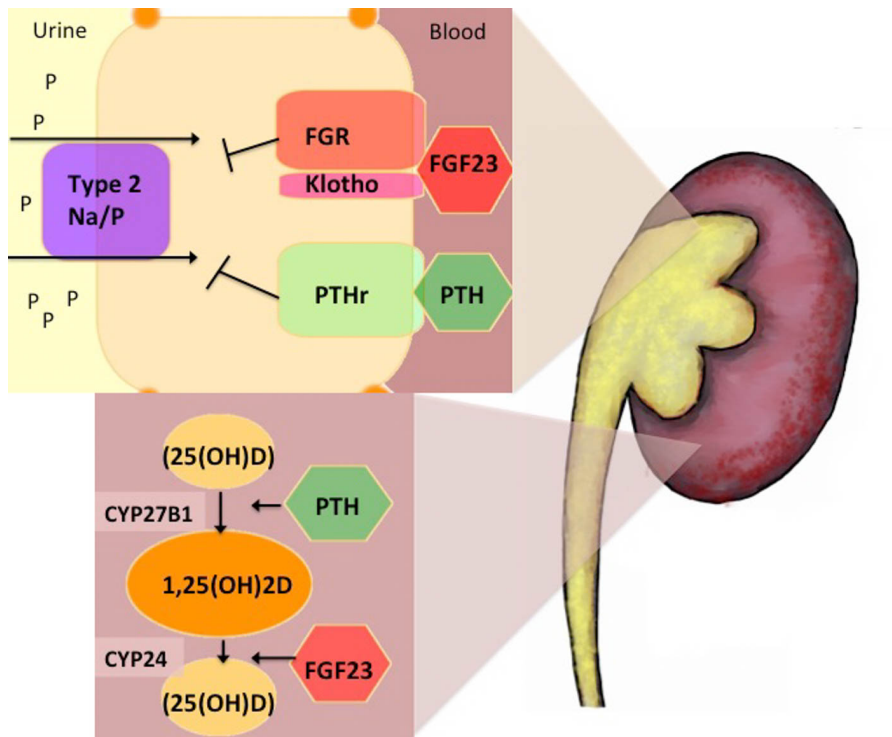


Figure 2. Actions by parathyroid hormone and Fibroblast Growth Factor 23 on phosphate and Vitamin D. Both parathyroid hormone (PTH) and Fibroblast Growth Factor 23 (FGF23) acts by blocking the type 2 Sodium (Na) Phosphate (P) cotransporter in the kidney, thus leading to increased loss of phosphate in the urine. PTH increases the activation of Vitamin D via induction of the enzyme CYP27B1. FGF23 decreases active vitamin D, (1,25(OH)2D), by inducing CYP24 which degrades active Vitamin D to its inactive form, (25(OH)D). FGR = Fibroblast Growth Hormone Receptor, PTHr = Parathyroid hormone receptor, CYP = Cytochrome P enzymes.

The Bone

The bone consists of mineralised connective tissue and four types of cells: osteoblasts, bone lining cells, osteocytes and osteoclasts. It is also the main storage for calcium and phosphate, which in the bone are joined together in the form of hydroxyapatite crystals. The bone is a highly dynamic organ and is constantly resorbed by osteoclasts and reformed by osteoblasts³⁶. The “coupling” between bone resorption and bone formation is fundamental in bone remodelling; thus, a decrease in resorption is always followed by a decrease in formation and vice versa³⁷. Osteoclasts are members of the monocyte/macrophage family, and one of the major cytokines that stimulates activation and genesis of osteoclasts is NF-κB Ligand (RANK-L). Osteoblasts are protein-synthesising cells producing osteoid

into the extracellular matrix. Osteoblasts produce osteoprotegerin (OPG), which inhibits RANK-L to bind to its receptor, thus inhibiting osteoclastic activity. Osteoblasts also produce RANK-L, which is why they are able to stimulate bone resorption³⁸. Another important regulation mechanism of osteoblasts is the canonical Wnt/ β -catenin pathway³⁹, which stimulates osteoblastogenesis and inhibits osteoblastic apoptosis. This pathway is inhibited by dickkopf1 (Dkk1) and sclerostin.

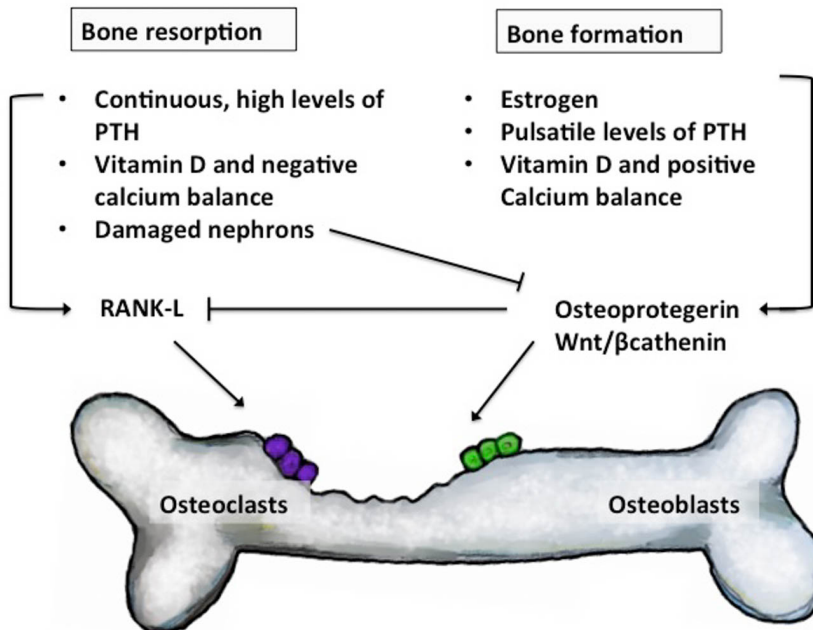


Figure 3. Some of the factors affecting bone resorption and formation in chronic kidney disease.

Bone resorption is mainly activated by RANK-L (NF- κ B Ligand) which is one major activator of osteoclastic activity. Osteoprotegerin is a factor promoting bone formation and is produced by osteoblasts. Osteoprotegerin inhibits RANK-L from binding to its receptor. The Wnt/ β -catenin pathway also stimulates osteoblasts thus increasing bone formation but factors from damaged nephrons can block this pathway thus inhibiting osteoblastic activity.

Bone resorption and formation is a process that is strictly regulated by hormones, including oestrogen, PTH and active vitamin D³⁸. Oestrogen leads to a suppression of RANK-L and also an increase in OPG, thus decreasing bone resorption³⁷. Parathyroid hormone stimulates osteoblastic activity and can either stimulate bone formation or bone resorption, depending on dose and time. Continuous elevations in PTH stimulate the osteoblasts to produce RANK-L, thus activating resorption by osteoclasts. Intermittent low doses of PTH stimulate OPG production, reducing resorption, thus PTH also have anabolic effects⁴⁰. Active vitamin D is of major

importance for bone formation by calcium uptake from the intestine. There are vitamin D receptors (VDR) in osteoblasts and osteocytes, and active vitamin D seems to increase bone formation when the calcium balance is positive and increases resorption when the calcium balance is negative⁴¹. In renal disease, nephron repair factors such as Wnt1 (portmanteau of Wingless and integrated) are released together with its inhibitors Dkk1 and sclerostin. Dkk1 and sclerostin act by inhibiting bone formation via the canonical Wnt/ β -catenin pathway³⁹.

Bone disease in CKD

Bone disease has been known to be related to CKD and hyperparathyroidism since the early 20th century^{42, 43} but the definitions and histological diagnostics have been inconsistent⁴⁴. To better define bone disease in CKD, KDIGO stated that the term “renal osteodystrophy” should be used for all bone disease in CKD³. Also the Turnover, Mineralisation, Volume - TMV classification for histological examination of bone was minted to better describe bone abnormalities in CKD⁴⁵. When discovered, bone disease in CKD was dominated by high bone turnover and defects in mineralisation. After the introduction of aluminium containing phosphate binders and later the introduction of treatment with active vitamin D for patients in CKD, low bone turnover became more and more frequent^{44, 46}.

Today the dominant pattern of bone disease in CKD is low bone turnover⁴⁷. High turnover is usually seen together with high levels of PTH (as described above), and low levels of PTH often accompany low turnover. Current guidelines recommend using levels of PTH to distinguish between low and high bone turnover^{6, 48}. However, there are many exceptions where PTH does not correlate with the type of bone disease⁴⁹. Low bone turnover is characterised by decreased number and size of osteoblasts and osteoclasts, and is associated with vascular calcifications⁵⁰. The link between bone and vascular calcifications in CKD has been extensively studied in recent years and some of the possible mediators between bone and vessels are: FGF23, PTH, vitamin D, OPG, Dkk1, Wnt1, RANK-L, vascular endothelial growth factor, klotho and uremic toxins⁴⁷. When bone turnover is low it has been shown that medications such as calcium containing phosphate binders and active vitamin D increase vascular calcifications^{51, 52}. It is suggested that the adynamic/inactive bone fails to buffer episodes of hypercalcaemia (from medications) thus the calcium, along with phosphate is incorporated in vascular smooth muscle cells^{50, 53}.

Although traditional osteoporosis is common in CKD, traditional bone mineral density (BMD) measures have not been successful in kidney disease⁵⁴ since BMD does not predict fracture rates and correlates poorly with the type of bone disease in CKD⁶. Bone biopsies have been the only way to determine accurately the type

of bone disease in CKD, but due to their invasive nature they have not been used in clinical practice⁵⁵. Instead, the research has been focused on finding bone markers more specific than PTH to detect and define which type of bone disease dominates in the patient and thereby guide further treatment⁵⁶.

Development of secondary hyperparathyroidism

The initial development of secondary hyperparathyroidism in renal failure is still not known. The major components in sHPT development as we know it today are: FGF23, α -Klotho, phosphate, PTH, vitamin D and calcium. Below, all of these factors are explained in order of appearance in sHPT development.

FGF23 and α -Klotho

Fibroblast Growth Factor 23 is a hormone produced by osteocytes and osteoblasts. Its main function is to regulate levels of phosphate and it is released when levels of phosphate increase⁵⁷. As described above, FGF23 inhibits phosphate re-uptake in the distal tubuli thus increasing the levels of phosphate in urine and lowering levels of phosphate in blood. FGF23 also inhibits PTH synthesis and secretion in the parathyroid glands²¹ and inhibits activation of vitamin D by inhibiting the CYP72B1 and inducing the CYP24 pathways³⁵. FGF23 receptors cannot be activated solely by FGF23 but need a co-receptor called α -Klotho⁵⁸. α -Klotho is highly expressed in renal and parathyroid tissue⁵⁹. When renal function deteriorates the first detectable change in sHPT markers is reduced expression of α -Klotho. How this change occurs is unknown⁶⁰. Decreased expression of α -klotho leads to FGF23 resistance, thus levels of FGF23 rise to compensate⁶¹. The resistance to the FGF23 receptor reduces the lowering effects on phosphate and PTH, which is why PTH levels rise.

Phosphate and Vitamin D

Phosphate levels in blood rise late in renal failure due to the compensatory mechanisms of FGF23 and PTH. However, it has recently been discovered that locally in the nephron high phosphate levels form complexes with calcium, thus levels of calcium in the distal tubuli decreases which stimulates to PTH secretion to enhance calcium re-uptake²⁹. This, together with the FGF23 resistance, leads to elevated PTH levels.

Levels of active vitamin D fall in CKD due to inactivation by FGF23 and loss of nephrons. However, deficient native vitamin D (25(OH)D) is also common in patients with early CKD due to albuminuria, low exposure to sunlight, and poor dietary intake⁶². This too reduces levels of active vitamin D. Active vitamin D binds to the VDR, which is expressed in the parathyroid cells, and activation of VDR leads to a decreased synthesis and release of PTH. VDR activation also inhibits the proliferation and hyperplasia of parathyroid cells²². Thus, with decreasing levels of vitamin D, PTH levels increase and parathyroid cells proliferate. Vitamin D is the major activator of calcium uptake from the intestine, and vitamin D deficiency is accompanied by hypocalcaemia, which occurs later in CKD. This is of course a direct stimulator of PTH release.

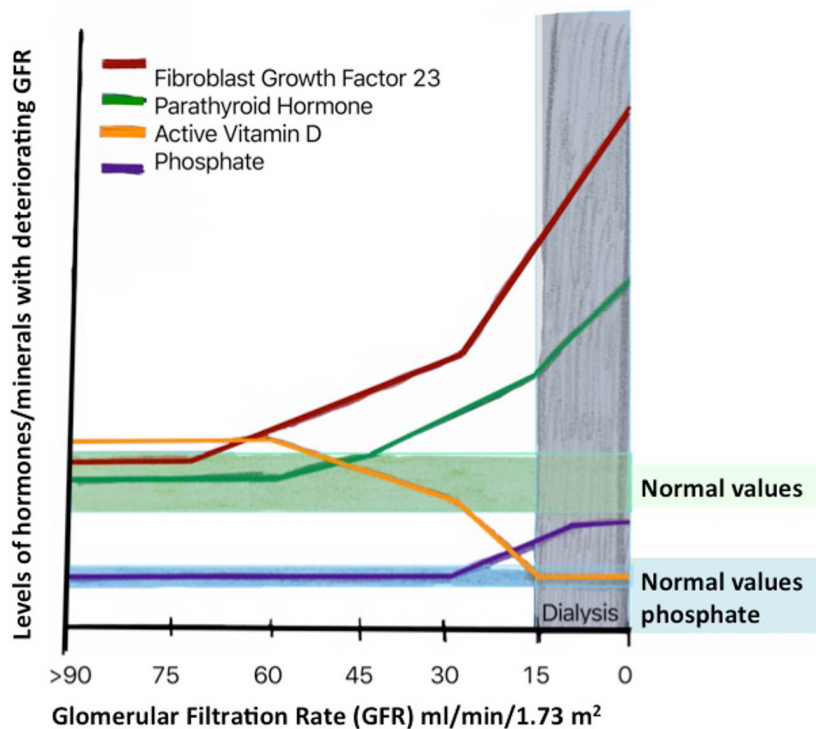


Figure 4. Levels of mineral markers in relation to renal function in the development of secondary hyperparathyroidism. Reproduced from Wolf, M. J Am Soc Nephrol 2010;21:1427-1435.

Parathyroid cell proliferation and hyperplasia

With more advanced CKD, levels of phosphate rise and phosphate reuptake in the tubuli is maximally inhibited by FGF23 and PTH. The reduction in α -Klotho is attenuated and PTH release from the parathyroid gland increases. Also, hyperphosphataemia stimulates PTH secretion from the parathyroid gland but the direct function is unknown. With the constant stimulation by hyperphosphataemia, hypocalcaemia, α -Klotho and vitamin D deficiency parathyroid cells proliferate and grow²⁵. With the proliferation, VDR expression is reduced, thus feedback mechanisms to inhibit PTH release are impaired. It has also been shown that lack of activation of VDR stimulates cell proliferation of parathyroid cells⁶³. The CaSR is also less expressed in hyperplastic parathyroid glands and tolerates higher calcium levels without reducing PTH secretion²⁵. Thus, with increasing parathyroid volume and grade of sHPT the possibility to modify PTH secretion with medications is reduced.

Vascular Calcifications

Cardiovascular-related mortality is several times higher in CKD patients compared to the general population and it exceeds the risk of cardiovascular disease (CVD) in diabetes⁶⁴. The risk of CVD in patients with renal failure is in part due to the development of sHPT and CKD-MBD³. The specific risk factors for CVD in renal failure are phosphate, FGF23 and vascular calcifications⁶⁵⁻⁶⁷. These factors are also associated with CVD risk in the general population. The vascular calcifications in renal disease are usually seen either in the intimal layer of the arterial wall, or more traditionally in the medial layer of the arterial wall.

It has been shown that vascular smooth muscle cells (VSMC) undergo an osteoblastic transformation in CKD⁶⁸. Hyperphosphataemia has been shown to increase vascular calcifications in CKD⁶⁹. Loss of klotho and elevations in FGF23 also seem to be involved in the osteoblastic transformation of VSMC's⁷⁰. Also, the Wnt/ β -catenin pathway is probably involved in this process since elevated levels of Dkk1 and sclerostin (Wnt inhibitors) have been found in CKD patients⁵⁶ and reductions in Dkk1 have been shown to reduce vascular calcifications in CKD⁷¹. However, the role of sclerostin is still unclear⁷².

Vascular calcifications have been associated with low bone turnover disease and low levels of PTH^{50, 73}, but also with markedly high levels of PTH⁷⁴. Episodic hypercalcaemia together with hyperphosphataemia seems to be involved in this process.

Parathyroid hormone

Parathyroid hormone is a peptide hormone circulating in different molecular forms: intact PTH (PTH1-84) and various truncated forms (i.e. PTH7-84). First generation immunoassays for determination of PTH were not specific to active PTH and were therefore replaced by the second generation PTH assay which identifies the N-terminal region 1-34 and is more specific to intact PTH⁷⁵. However, even though second generations assays are most often used in clinical practice they still detect some of the inactive forms of PTH which accumulate in CKD⁷⁶. Also, in the various second generation immunoassays used today, PTH levels differ up to two to three times depending on brand⁷⁷, which leads to difficulties in determining target PTH levels in sHPT guidelines⁷⁵.

Relation between PTH and outcomes

Levels of PTH have been used in recent decades to determine sHPT treatment, mostly with the purpose of lowering PTH. These recommendations have been based solely on observational data. Many studies have found an increased risk of mortality with higher PTH values^{78, 79}. But higher mortality rates have also been found in the extremes of both high and low PTH⁸⁰. The lack of reliable studies led to a meta-analysis by Palmer et al. in 2011 who showed that levels of PTH had no association with overall mortality or cardiovascular mortality in CKD⁸¹. Probably PTH should not be used as the only marker for sHPT but in combination with calcium and phosphate^{82, 83}. Later studies have shown many examples of over-suppressed PTH combined with increased risk of vascular disease^{84, 85} which can be associated with the increasing rate of low bone turnover in CKD⁴⁷.

The relation between PTH and risk of fractures has also been shown to have a U-shaped curve; however the association is weak⁸⁶. Also, low levels of PTH together with low levels of calcium have been associated with fractures among a large cohort of patients on dialysis⁸⁷.

PTH in current guidelines

Even if PTH is unreliable in CKD and the association with major outcome has been questioned it is still used in clinical practice since new markers of CKD-MBD have not yet become clinically available. Due to the above described difficulties with PTH determinations, the lack of reliable studies and the late awareness of over-suppression of sHPT, KDIGO stated that for CKD patients not

on dialysis the optimal level of PTH is not known. However, it is suggested that patients with PTH levels above upper normal range for the assay should first be evaluated for hyperphosphataemia, hypocalcaemia and vitamin D deficiency. In patients on dialysis the suggested recommended target range for PTH was set to approximately two to nine times the upper normal limit for the assay⁶. Since 2009 the CKD-MBD guidelines by KDIGO have been updated⁵⁵ but in spite of new studies pointing towards a lower mortality risk when reducing PTH levels the authors still recommend the wide target range of PTH. Prior guidelines from the Kidney Disease Outcomes Quality Initiative (K/DOQI) have target ranges for PTH according to grade of CKD, thus with decreasing glomerular filtration rate (GFR) a higher PTH is tolerated. Similar to KDIGO it is suggested that the same range of PTH as for patients in CKD for renal transplant recipients should be used⁴⁸.

Medical treatment

For patients in CKD the first sHPT treatment is to reduce dietary intake of phosphate. Phosphate-rich nutrients include egg yolk, meat, dairy products and industrially processed foods with phosphate additives⁸⁸. The medical treatment for sHPT consists of the following options: calcium supplements, oral phosphate binders, vitamin D derivatives and calcimimetics^{89, 90}. For patients on dialysis the weekly dose of renal replacement therapy with control of hyperphosphataemia, calcium concentration in the dialysate, and removal of uremic toxins is also an important factor²⁵.

Phosphate binders

The basics of sHPT treatment are to correct hyperphosphataemia and to avoid hypo- or hypercalcaemia. Phosphate binders are the basic treatment for hyperphosphataemia and have been shown to reduce mortality in CKD⁹¹. There are different types of phosphate binding agents. Calcium containing phosphate binders has a well-documented phosphate lowering effect⁹⁰ but a large meta-analysis found increased mortality for patients treated with calcium containing phosphate binders compared to non-calcium-containing calcium binders⁹². The increased mortality seems to be driven by the progression of vascular calcifications due to the combination of hyperphosphataemia together with episodically hypercalcaemia^{51, 93}. Non-calcium-containing phosphate binders are often expensive but have been shown to slow the progression of vascular calcifications for patients on dialysis and to reduce levels of LDL and increase levels of HDL⁵¹. Today, phosphate binders are recommended for use in CKD but

for patients with documented vascular calcifications or hypercalcaemia, it is recommended to restrict the use of calcium-containing phosphate binders⁶.

Vitamin D

Treatment with active vitamin D is an effective way of lowering PTH but at the cost of increased risk for hypercalcaemia and/or hyperphosphataemia⁹⁴. Treatment with active vitamin D varies between clinics and is sometimes overused when comparing PTH levels with KDIGO recommendations⁷⁸. Native vitamin D supplements may have a role in early sHPT treatment since many CKD patients suffer from native vitamin D deficiency⁹⁵. Native vitamin D supplements may lead to control of sHPT⁹⁶⁻⁹⁸ but as renal function declines, the more potent effect of active vitamin D is preferred²⁵. There are numerous studies showing reduced mortality rates in patients treated with vitamin D compounds; however, a recent Cochrane analysis could not demonstrate any differences in hard endpoints for any of the vitamin D compounds used in ESRD⁹⁴.

Calcimimetics

A new type of PTH lowering agent was developed in the millennium shift namely calcimimetics⁹⁹. Calcimimetics modify the CaSR and make it more sensitive to calcium. They have also been shown to prevent parathyroid hyperplasia¹⁰⁰, improve high turnover renal osteodystrophy¹⁰¹ and halt the progression of vascular calcifications¹⁰² in CKD. Treatment with calcimimetics has been shown to reduce the need for parathyroidectomy (PTX)¹⁰³. The effect on mortality, cardiovascular disease and fractures has been studied in the randomised controlled trial EVOLVE, but was only significant in subgroup and post-hoc analyses^{104, 105}. Even though the PTH lowering effects are well demonstrated a recent Cochrane meta-analysis could not demonstrate any favourable outcomes in mortality or cardiovascular events for calcimimetics¹⁰⁶.

Consistent control of calcium, phosphorus and PTH has been found to be a strong predictor of survival in haemodialysis patients¹⁰⁷, but in spite of advances in the medical treatment of CKD-MBD, few patients reach the target levels of calcium, phosphate and PTH⁷⁸.

Parathyroidectomy

The surgical treatment for sHPT is called parathyroidectomy (PTX), meaning surgical removal of the parathyroid glands. In primary hyperparathyroidism there is usually a single adenoma causing the disease, which is why if that particular gland is removed the patient is cured. Parathyroidectomy in sHPT is not as predictable since the sHPT patient usually suffers from advanced hypocalcaemia postoperatively and is often in need of intensive follow-up after PTX¹⁰⁸.

There are two principal but different techniques used when performing PTX in CKD: total and subtotal parathyroidectomy. In total PTX, all identifiable parathyroid glands are removed¹⁰⁹. In subtotal PTX parathyroid tissue equivalent to "normal" parathyroid volume is left in site. Total PTX can be combined with autotransplantation (AT) meaning that some parathyroid tissue is transplanted back to the patient. Traditionally the site for autotransplantation has been the forearm to make a reoperation in the event of recurrent disease more accessible¹¹⁰. Parathyroidectomy can also be combined with thymectomy to remove the most common site for supernumerary glands¹⁰⁹.

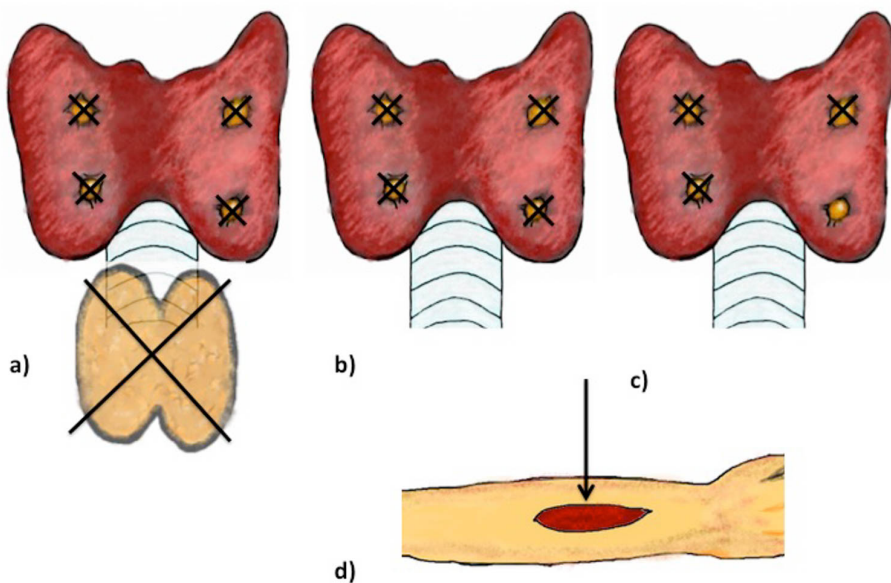


Figure 5. Schematic image over surgical approaches in parathyroidectomy (PTX) for renal hyperparathyroidism.

a) Total PTX, where all visible parathyroid glands are removed. Here combined with thymectomy to remove any supernumerary glands. b) Total parathyroidectomy without thymectomy. c) Subtotal PTX, where an amount of parathyroid tissue equivalent to "normal" parathyroid gland size is left in site. d) Autotransplantation (AT) of parathyroid tissue can be performed, usually the site of AT is the forearm.

Since the target PTH after PTX is not defined there is today no recommendation as to which type of technique should be used. In short-term outcomes, total and subtotal PTX have not shown any differences but there has been a trend towards an increase in recurrent disease for patients treated with subtotal PTX¹¹¹. With today's knowledge it is suggested that total PTX with AT be performed for patients on dialysis and subtotal PTX for patients in pre-dialysis or patients awaiting renal transplantation in the near future¹⁰⁹.

Changes in mineral markers after PTX

Parathyroidectomy leads to a marked decrease in levels of PTH, which lasts over time^{9, 112}. Levels of calcium and phosphorus drop immediately after surgery¹¹³⁻¹¹⁵. This represents increased bone formation with a shift of calcium and phosphate into the bone¹¹⁶. Hungry bone syndrome is a description of the drastic and often prolonged hypocalcaemia after parathyroidectomy seen in many patients after PTX¹¹⁷. Factors associated with risk of hungry bone syndrome are younger age, rapid onset of hypocalcaemia and concomitant hypophosphataemia^{114, 117}. Studies of changes in other sHPT related markers after PTX have emerged, for example one study have shown decreased FGF23 and increased levels of α -Klotho after parathyroidectomy¹¹⁸. The fall in FGF23 could be explained by hypophosphataemia but the rise in α -Klotho is still unexplained.

Parathyroidectomy - effects on outcome

Since PTX is performed in advanced sHPT when medical treatment fails to control PTH there is a lack of randomised controlled studies on the effects of outcomes comparing PTX to medical treatment¹⁰⁹. Thus, all our knowledge in this field is based on observational studies.

There are many studies showing reduced long-term mortality for patients on dialysis undergoing PTX compared with controls^{11, 119}. However short-term mortality seems to increase after PTX^{119, 120}. Meta-analyses are scarce but one recent study by Chen et al. showed decreased long-term overall- and cardiovascular-related mortality rates in dialysis patients undergoing PTX compared to controls¹⁰. Also PTX has been shown to lower the risk of cardiovascular disease^{121, 122} but in subgroup analyses this was only true for patients with prior vascular comorbidity. Other studies have failed to show any significant effect on risk of cardiovascular outcomes¹²³.

There are few studies on the effect of PTX on the risk of fractures. Rudser et al. studied nearly 6000 patients on dialysis undergoing PTX and matched them to over 16000 controls, and found a reduced risk of hip- and any fracture after

PTX¹²⁴. However Ishani et al. studied over 4000 patients in dialysis undergoing PTX and found no differences in fracture rates before, compared to one year after PTX. The fracture rate during the studied year after PTX, however, was overall low in their cohort¹²⁰.

Thus, there are little data on hard outcomes after PTX. This, together with the risk of selection bias in the matched control studies, where the patients undergoing PTX might be in overall better health compared to controls, makes it hard to draw any firm conclusions about the effects of PTX on morbidity and mortality outcomes.

Secondary hyperparathyroidism after renal transplantation

With a renal transplant, renal function increases, thus the abnormalities of mineral metabolism driven by renal insufficiency are improved. Before renal transplantation phosphate, FGF23 and PTH are elevated and levels of calcium and active vitamin D are low¹²⁵. The transplanted kidney excretes phosphate and the increased levels of FGF23 and PTH cause a marked hypophosphataemia seen early in the vast majority of renal transplant recipients¹²⁶. Levels of FGF23 decrease after renal transplantation, and stabilise after three months¹²⁶, α -klotho increases after renal transplantation¹²⁷. Hypophosphataemia usually normalises after the first month and levels of phosphate stabilise after two to six months¹²⁵. The elevated excretion of phosphate in the tubuli combined with increasing calcium levels can cause allograft calcifications, which has been suggested to reduce allograft function¹²⁸. However, recently a large study found better graft and cardiovascular survival for patients with hypophosphataemia after renal transplantation. The results were adjusted for allograft function¹²⁹.

Levels of calcium drop immediately after transplantation but increase again within the first two weeks. In the first one to six months, hypercalcaemia is common¹²⁵ and associated with high levels of post-transplant PTH¹³⁰. Levels of native and active vitamin D are low immediately after transplantation but rise towards normal levels within the first three to six months after transplantation^{131, 132}. Levels of PTH drop immediately after transplantation since the improved renal function leads to decreased accumulation of PTH. After six months, PTH stabilises if the renal function is preserved but many patients show PTH levels above the normal reference range after transplantation¹²⁵. After the first six months the mineral homeostasis is stable and the remaining degree of sHPT can be determined after this stage¹³.

Persistent sHPT after renal transplantation is common, and risk factors for post-transplant sHPT are pre-transplant levels of PTH and calcium, time spent on dialysis before transplantation and nodular hyperplasia of the parathyroid glands¹³.

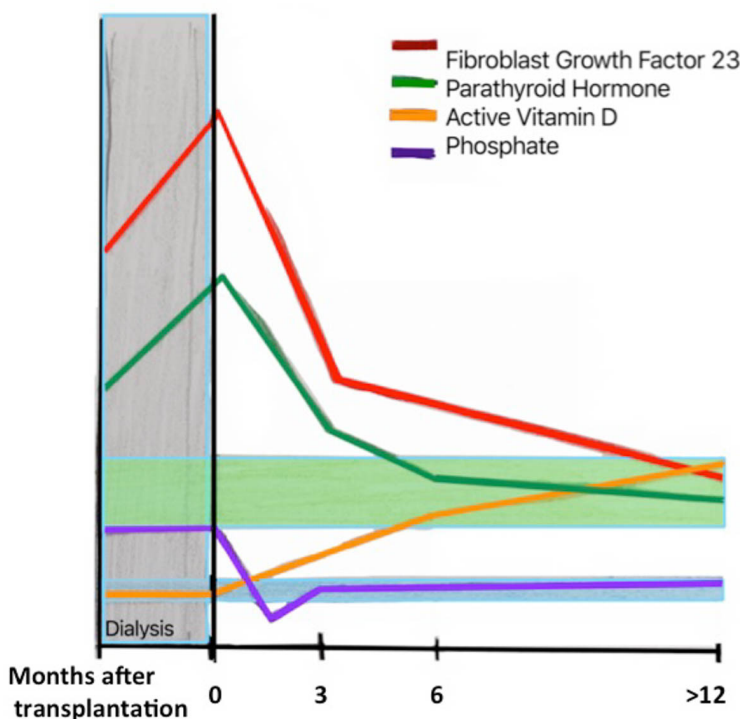


Figure 6. Levels of mineral markers the first year after renal transplantation. Reproduced from Wolf, M. J Am Soc Nephrol 2010;21:1427-1435.

Bone disease after renal transplantation

Bone disease is common after renal transplantation. The most common pattern is increased bone resorption with a loss of bone volume as a result. Apart from sHPT there are also factors specific to the transplantation procedure which affect the bone, such as corticosteroids¹³³ and other immunosuppressive agents¹³⁴. Bone biopsies after renal transplantation show a variety of histological patterns. In one study the most common finding was impaired bone formation, impaired osteoblastogenesis and early osteoblastic apoptosis. In this study there was a positive correlation between osteoblast number and size and higher levels of PTH whereas a negative correlation was noted with corticosteroid use¹³⁵. In a recent study the most common finding in bone biopsies one year after transplantation was

impaired bone resorption and an increase in low turnover bone disease compared with biopsies taken directly after transplantation¹³⁶. In that study no correlations between levels of PTH and histological outcomes could be found but dose of corticosteroids was associated with higher loss of bone volume. The differences in patterns of bone disease after renal transplantation has resulted in a lack of robust treatment guidelines, thus larger studies in this field are needed, in particular studies identifying factors associated with fracture outcomes¹³⁴.

Cardiovascular disease after renal transplantation

Cardiovascular disease is the leading cause of death in renal transplant recipients¹³⁷. Traditional risk factors for CVD are the same in renal transplant recipients but there are also other additional risk factors for CVD specific to patients with a renal transplant¹³⁸. In the first year after renal transplantation, age, sex, diabetes, prevalent CVD, donor type, Body Mass Index and time on dialysis prior to transplantation are factors independently associated with post-transplant CVD¹³⁹. After the first year donor type is no longer associated with CVD risk but instead delayed graft function increases risk of post-transplant CVD. Vascular calcifications increase the risk for CVD in renal transplant recipients and are associated with disturbed mineral balance. Low levels of active vitamin D as well as phosphate have been associated with progression of vascular calcifications¹⁴⁰. The results of studies investigating the relation between PTH and vascular outcomes in renal transplant recipients are conflicting but a correlation between mortality and high levels of PTH has been found¹⁴¹. Also high as well as low levels of PTH have been associated with the combined endpoint of mortality, graft failure and cardiovascular disease¹⁴².

sHPT treatment after renal transplantation

Because renal transplant recipients often have hypercalcaemia and hypophosphataemia, traditional sHPT treatments such as phosphate binders and calcium supplements are not indicated. Current guidelines state that there is insufficient data to give recommendations on sHPT treatment after transplantation⁶. It is suggested to treat sHPT after transplantation in the same manner as for CKD patients not on dialysis. It is also suggested to measure levels of vitamin D and to supplement deficiencies⁶. In daily practice, administration of active vitamin D (if levels of calcium are appropriate), calcimimetics or parathyroidectomy are the treatments of choice in sHPT after transplantation. Treatment with both native and active vitamin D seems to have positive effects on

bone and vascular morbidity after renal transplantation but there are insufficient data to confirm this yet¹⁴³.

Patients treated with calcimimetics before transplantation should not discontinue the drug after transplantation since this can lead to hypercalcaemia and aggravated sHPT¹⁴⁴. There is also an increased risk of parathyroidectomy after transplantation in patients discontinuing calcimimetics at the time of transplantation¹⁴⁵. Treatment with calcimimetics has been safely used in renal transplant recipients¹³. However, pre-transplant calcimimetics signals that the patient has severe sHPT and thus might be in need of parathyroidectomy in the future. The use of parathyroidectomy for renal transplant recipients is currently under debate. It has been shown that PTX decreases graft function in renal transplant recipients but not when performed before transplantation¹⁴. Thus studies point towards the necessity of identifying patients in need of PTX before transplantation. Total PTX might have a higher risk of hypoparathyroidism after renal transplantation compared with subtotal PTX¹⁴⁶. Thus, subtotal PTX is the recommended method if the patient either has a renal transplant or is likely to receive a renal transplant in the near future¹⁰⁹. Note that these findings are all based on small observational studies, which reflects the lack of guidelines described above.

Aims

This thesis focuses on the following aims:

- Which factors before renal transplantation increase the risk of secondary hyperparathyroidism after renal transplantation?
- Is the level of pre-transplant parathyroid hormone associated with increased risk of cardiovascular outcomes after renal transplantation?
- Does parathyroidectomy affect the risk of hip fractures in patients on dialysis or with a renal transplant?
- Does the surgical technique used in parathyroidectomy for secondary hyperparathyroidism affect outcomes in patients on dialysis or with a renal transplant?

Methods

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

Papers I & II

Patients

In paper I we included all patients undergoing renal transplantation at Skåne University Hospital, Malmö between 2007 and 2009, who were above 18 years of age. In paper II, all patients undergoing renal transplantation at Skåne University Hospital, Malmö and Karolinska University Hospital, Huddinge between 2003 and 2005 were included.

Parathyroid Hormone

Measurements of parathyroid hormone were retrospectively collected and second generation iPTH assays were used at all laboratories. The PTH analyses used at the time were Cobas e411/Elecsys, Roche or Immulite 2000, Siemens. Since the different PTH assays were not entirely comparable we used an adjusting formula ($\text{Cobas} = 0.7439 * \text{Immulite} + 0.7351$) defined at the Department of Clinical Chemistry at Skåne University Hospital. All PTH levels were converted to pmol/L. In paper I, patients were divided into three groups based on PTH levels before transplantation. We used target PTH levels for patients in CKD (no guidelines exist for renal transplant recipients) defined by K/DOQI guidelines⁴⁸ and patients were classified as above, below or within the target range.

In paper II we analysed patients undergoing PTX or not before renal transplantation separately. Patients without PTX before transplantation were divided into four groups based on quartiles of pre-transplant PTH. Patients with a post-transplant PTX were divided into two groups, above and below the median of PTH before transplantation.

Outcomes

Measurements of plasma levels of PTH, calcium, phosphate and alkaline phosphatases (ALP) were obtained regularly after transplantation. Patient journals were thoroughly examined, and data on mortality, cardiovascular events (myocardial infarction, coronary revascularization procedure, cerebral infarction, transient ischemic attack, peripheral vessel revascularisation, amputation or death from cardiovascular disease) were obtained. Only the first event after renal transplantation was noted. In paper I, fractures (hip, spine, rib or wrist) after transplantation were also noted.

Statistical analyses

In paper I, pre-transplant factors predicted to correlate with secondary hyperparathyroidism were tested with simple linear regression to one-year levels of PTH. Factors with significant correlation were then tested in a multivariate regression model with one-year PTH as the dependent variable. In this thesis we show results from a multivariate regression model using the logarithm (log) transformation of one year PTH not shown previously. Differences in continuous outcomes (laboratory measurements) were examined between groups of pre-transplant PTH with Mann Whitney or Kruskal Wallis tests where appropriate, since the data were of non-normal distribution. Differences between outcomes in categorical parameters (events) were studied using a Chi2 test.

In paper II, Kaplan-Meier curves over cardiovascular event-free survival were estimated in the different PTH subgroups of both PTX- and non PTX-patients. Crude and adjusted Cox proportional models adjusting for known risk factors for post-transplant cardiovascular disease were built. Differences in baseline characteristics, medical use and laboratory measurements during follow-up were performed with a Kruskal Wallis test, a Mann Whitney test or a Chi2 test where appropriate.

All continuous variables were expressed in mean \pm standard deviation or median (interquartile range), and categorical variables were expressed as number (percent). All statistical analyses were performed using SPSS 18.0 and 22.0 respectively.

Papers III & IV

Patients

From a cohort consisting of all patients in the Swedish Renal Registry (SRR) from 1991 to 2009 we identified all patients undergoing parathyroidectomy after either starting dialysis or receiving a renal transplant. Data were linked with the Scandinavian Quality Registry for Thyroid Parathyroid and Adrenal surgery (SQRPTA) as well as with the Swedish Inpatient Registry and Swedish Cause of Death Registry. In paper III, patients undergoing parathyroidectomy were matched with controls from the database. Matching criteria were age, gender, original renal disease and whether the patient had a renal transplant or not at the calendar date for parathyroidectomy (or corresponding date for controls).

In Paper IV the SRR cohort was supplemented with patients up until 2013. Also, data on laboratory measurements such as PTH, calcium and phosphate available from the SRR were used. Furthermore, data from the Swedish Medical Records were obtained to collect information on sHPT treatment (vitamin D compounds, calcium supplements and calcimimetics). All patients undergoing parathyroidectomy while registered in the SRR were studied in paper IV and no controls were used.

Definition of parathyroidectomy

Through the inpatient registry we identified surgical procedure codes specific to parathyroidectomy. Patients undergoing parathyroidectomy before inclusion in the SRR were excluded from the analyses. Dates on parathyroid surgery were compared with dates of surgery in SQRPTA. All patients undergoing parathyroidectomy while registered in the SRR were defined as cases. In paper IV, patients were further classified as either total or subtotal PTX based on the surgical procedure codes from the inpatient registry. This classification was also compared with data from SQRPTA. Codes for autotransplantation and thymectomy were noted in paper IV but not to distinguish between total and subtotal PTX, only for descriptive purposes.

Definition of outcomes

In paper III, all hip fractures after PTX (or the corresponding calendar date for controls) were noted from the inpatient registry. We also noted procedure codes

for hip fracture surgery to validate the event of a hip fracture. Only the first hip fracture after PTX was noted.

In paper IV the date of death was noted from the Swedish Cause of Death Registry. The first cardiovascular event (myocardial infarction, ischemic stroke, haemorrhagic stroke, ruptured aortic aneurysm and acute emboli/thrombosis in a peripheral artery) as well as the first hip fracture was noted from the inpatient registry. Any new PTX occurring after the first PTX was also noted. Short-term outcomes such as reoperation, wound infection, bleeding, recurrent nerve palsy, 90-day mortality and re-admittance were also noted from the inpatient registry.

Statistical analyses

In paper III, differences in risk of hip fractures between the matched control set of non-PTX and PTX patients were estimated by Kaplan-Meier survival curves. Crude and adjusted Cox proportional hazard models over risk of hip fractures were made adjusting for available risk factors. Cox regressions were also made for subgroups of patients.

In paper IV, patients undergoing total PTX were compared with patients undergoing subtotal PTX. Kaplan-Meier event-free survival curves were estimated on all outcomes (mortality, cardiovascular disease, hip fractures and re-PTX). Crude and adjusted Cox proportional hazard regressions over outcomes between total and subtotal PTX were calculated, adjusting for possible and known confounders. Cox regression models were also made for outcomes in tertiles of PTH after PTX in all patients and in subgroup analyses. Differences in short-term outcomes and baseline descriptives were calculated using a Chi 2 test for categorical variables and two sample t-tests or a Wilcoxon signed rank test for numerical variables, depending on whether data were normally distributed or not.

Continuous variables were expressed in mean \pm standard deviation or median (interquartile range) and categorical variables were expressed as number (percent). All statistical analyses were made using STATA versions 12 and 13.

Results

Paper I

The first paper examined the short-term evolution of sHPT in the first year after renal transplantation (RT) and the factors which could predict one-year levels of PTH. We studied 132 patients and found that prior to transplantation approximately a third of patients had levels of PTH within the K/DOQI target range for CKD patients. The rest of the patients were almost equally distributed into above or below the target range of PTH. Levels of PTH decreased immediately after RT but stabilised after six months. The reduction of PTH was most pronounced in patients with PTH above the K/DOQI target range before RT (Figure 7).

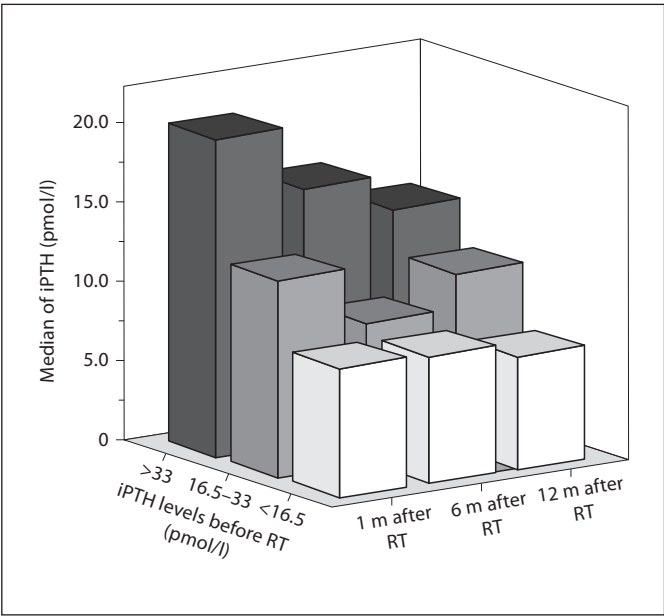


Figure 7. Median values of PTH at 1, 6 and 12 months in the 3 groups based on PTH levels at 3 months (m) before RT.

One year after RT, the majority of patients (67.5%) had PTH levels above K/DOQI recommendations (as well as above the upper limit of the normal reference range).

We found that levels of phosphate decreased rapidly, and low levels of phosphate were more common in patients with high pre-transplant PTH. Levels of calcium rose after transplantation and hypercalcaemia was common up to six months after RT. Levels of ALP were lowest for patients with low pre-transplant PTH levels. We showed a strong correlation between pre-transplant PTH and one-year levels of PTH. In table 1 the results of the multiple linear regression model are summarised. Apart from levels of PTH before transplantation the type of graft (living donor or deceased donor) and treatment with calcimimetics before transplantation were correlated with log transformed one year PTH. Table 1 is supplementary material and was not printed in the original paper I.

This paper shows the short-term evolution of sHPT after renal transplantation and that the rapid decrease in PTH was mostly found in patients with high pre-transplant levels of PTH. A majority of patients had increased levels of PTH one year after transplantation and the pre-transplant PTH predicted the degree of sHPT one year after transplantation.

Table 1.

Multiple linear regression model, dependent variable: logarithm of PTH levels one-year after transplantation. R^2 full model = 0.24, $p < 0.001$. PTH = Parathyroid hormone, RT = renal transplantation, eGFR = estimated Glomerular Filtration Rate, Log = Logarithm.

FACTOR	β COEFFICIENT	P-VALUE
Log PTH before RT	0.36	<0.001
Type of graft	0.18	0.028
Treatment with Calcimimetics before RT	0.21	0.010

Paper II

In this paper we studied the long-term evolution of secondary hyperparathyroidism after renal transplantation and the association between pre-transplant PTH and cardiovascular outcomes in patients with and without pre-transplant parathyroidectomy. We studied 258 patients, of whom 36 had undergone PTX before RT.

Mineral changes were similar as to those described in paper I and no major changes in PTH occurred after year two. Patients with high pre-transplant levels of PTH had higher levels of calcium and lower levels of phosphate through follow-up compared with patients with lower pre-transplant PTH.

We compared outcomes between quartiles of pre-transplant PTH in patients who had not undergone PTX and found no differences in mortality or graft failure between groups. However when studying cardiovascular disease in the adjusted Cox regression model we found a higher risk of cardiovascular disease in the lowest quartile of pre-transplant PTH compared to the other quartiles. The same model was used for patients with a pre-transplant PTX divided by median level of pre-transplant PTH (due to few observations). Similarly, in this adjusted model we found a higher risk of cardiovascular disease in patients below the median of pre-transplant PTH compared with those above median of PTH (Table 2). For both PTX and non-PTX patients the levels of PTH found in the high-risk groups were less than 6.9 pmol/L, which is markedly low.

This paper shows that markedly low levels of PTH after transplantation are associated with post-transplant risk of cardiovascular disease in patients with or without a pre-transplant parathyroidectomy.

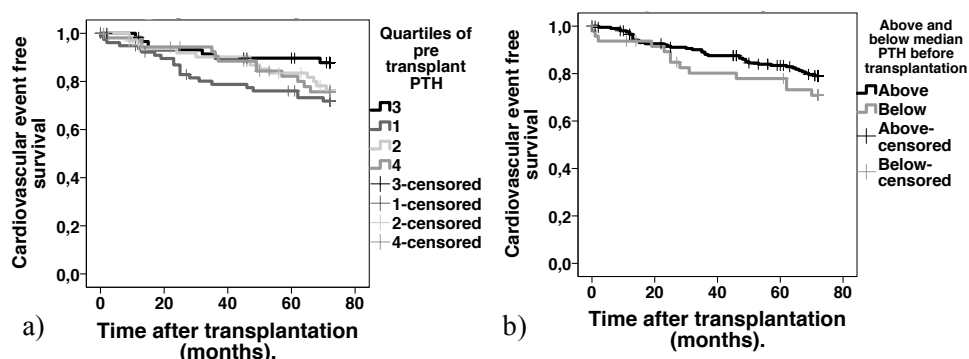


Figure 8. Kaplan-Meier cardiovascular event free survival curves after renal transplantation in a) Patients with no pre-transplant parathyroidectomy, patients divided by quartiles of pre-transplant PTH with quartile 1 being the lowest. b) Patients with pre-transplant parathyroidectomy divided by median level of pre-transplant PTH.

Table 2.

Hazard ratio (HR) (95% CI) of vascular events in renal transplant recipients with or without pre-transplant parathyroidectomy (PTX). Adjusted for age, gender, years in dialysis before transplantation, history of cardiovascular disease, diabetes and body mass index at time of transplantation.

NO PTX	MEDIAN (IQR) OF PRE-TRANSPLANT PTH (pMOL/L)	ADJUSTED HR (95% CI)
Quartile 1	6.5 (4.7-8.5)	2.63 (1.04-6.67)
Quartile 2	12.4 (6.8-13.0)	2.02 (0.80-5.12)
Quartile 3	21.0 (18.6-24.1)	1.00
Quartile 4	44.0 (31.2-68.1)	2.12 (0.81-5.57)
PTX		
Above median	14.0 (9.4-18.0)	1.00
Below median	1.5 (0.7-3.8)	18.2 (1.62-203.8)

Paper III

In this paper, we studied the effect of parathyroidectomy on risk of hip fractures in patients on dialysis or with a renal transplant. We identified 579 patients who had undergone PTX. Cases were matched with 1970 controls. After matching for age, gender, original renal disease and whether the patient had a renal transplant or not at time of PTX (or the corresponding date for controls, t) we calculated the Kaplan-Meier hip fracture event-free survival curves between cases and controls. We found a lower risk of hip fractures for PTX patients compared with controls. In the adjusted Cox proportional hazards model we showed a lower risk of hip fractures in PTX patients compared with controls. In subgroup analyses with the same Cox regression model we found that the lower risk of hip fractures was only seen in female patients (Figure 9).

This paper shows that female patients with renal hyperparathyroidism undergoing parathyroidectomy have a reduced risk of hip fractures.

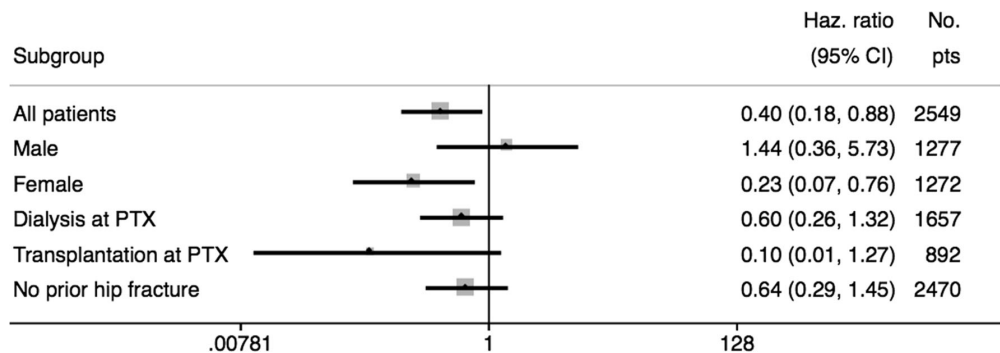


Figure 9. Forest plot of Cox proportional hazards (95% CI) over risk of hip fracture after PTX. In the model adjustments were made for: time in renal replacement therapy before PTX/t, time with a renal transplant before and after PTX/t, Charlson comorbidity score, hip fractures before PTX/t. PTX = Parathyroidectomy.

Paper IV

In paper IV we investigated whether there were any differences in morbidity, mortality and new PTX between total and subtotal parathyroidectomy for renal hyperparathyroidism. We identified 388 patients who had undergone total PTX and 436 patients who had undergone subtotal PTX. We found a higher risk of cardiovascular events in patients undergoing total PTX but no differences in hip fractures or mortality between total and subtotal PTX. There was a higher risk of new PTX for patients who had undergone subtotal PTX. The risk of cardiovascular events was highest in patients with prevalent CVD and in patients on dialysis.

We also tested outcomes between tertiles of PTH in a subgroup of patients (n=266) where PTH measures were available. The risk of cardiovascular disease was found to be higher in patients in the lowest tertile of post-PTX PTH compared to the other tertiles. The risk of re-PTX was higher in patients in the highest tertile of PTH compared to the other tertiles. There were no differences in risk of mortality or hip fractures (Table 3).

This paper shows that there is a difference in sHPT related outcomes depending on which surgical approach is used when performing parathyroidectomy in renal hyperparathyroidism. We showed that the risk of cardiovascular disease is higher for patients undergoing total PTX compared to subtotal PTX. This could be explained by insufficient levels of PTH after total PTX surgery.

Table 3.

Adjusted hazard ratio (95% CI) of outcomes between total and subtotal PTX in renal hyperparathyroidism (n= 824) and between tertiles of post PTX PTH (n=266). Adjusted for age, gender, Charlson comorbidity score, renal transplant at time of PTX, time with a renal transplant before PTX, year of surgery.

COMPARING FACTOR	MORTALITY	CARDIOVASCULAR DISEASE	HIP FRACTURE	NEW PTX
Total PTX	1.00	1.00	1.00	1.00
Subtotal PTX	1.05 (0.75-1.48)	0.56 (0.37-0.86)	1.93 (0.57-6.49)	2.68 (1.25-5.32)
TERTILES OF POST PTX PTH				
Tertile 1	1.00	1.00	1.00	1.00
Tertile 2	0.91 (0.52-1.57)	0.47 (0.23-0.95)	2.10 (0.18-24.9)	3.00 (0.30-30.3)
Tertile 3	1.18 (0.65-2.18)	0.89 (0.45-1.73)	3.54 (0.25-50.8)	22.9 (2.69-195)

Discussion

In this thesis renal hyperparathyroidism has been studied in two different clinical situations where the mineral balance drastically alters. The first was after renal transplantation when levels of PTH drop as the renal function recovers; the other was parathyroidectomy where levels of PTH drop but the renal function is unchanged. By studying these two situations the hope was to gain deeper knowledge of sHPT management and to be able to help the clinical decision-making process in two situations. The first concerns how to manage sHPT prior to transplantation for patients on the waiting list. The other concerns selecting patients for parathyroidectomy and choosing which surgical procedure to use. Here follows a discussion of our findings and how they could be used in clinical practice.

Impact of transplantation on renal hyperparathyroidism – an effect of the uremic history.

According to current guidelines from both K/DOQI and KDIGO over 65% of patients in our study had PTH levels above recommendation one year after renal transplantation indicating persisting sHPT. This is in line with findings from other populations¹⁴⁷⁻¹⁴⁹. The levels of PTH one year after transplantation correlated with PTH levels before transplantation. This is uncontroversial and has been shown previously^{149, 150}. We found that levels of PTH continue to fall for approximately six months after transplantation, thus the involution of hyperplastic parathyroid glands is slow and the uremic past will affect the renal transplant future. Another reason for the large number of patients with persistent sHPT is the renal function. After a successful renal transplantation the renal function improves, but rarely normalises. Thus the mineral balance might still be disturbed and might contribute to further sHPT.

Apart from pre-transplant levels of PTH, pre-transplant treatment with calcimimetics was also related to levels of PTH after transplantation. Patients treated with calcimimetics will probably suffer from advanced sHPT, thus the relation to one-year PTH is not surprising. This relation has also recently been described in other studies^{149, 150}. We also found a relation between type of graft and levels of PTH after transplantation. Patients who received a living donor graft

had lower levels of PTH at one year compared with patients who received a deceased donor graft. This is probably explained by the shorter uremic period before RT as well as better graft survival and renal function outcome in living donor recipients¹⁵¹.

By studying other mineral markers after renal transplantation it is clear that the sPTH before transplantation will affect the post-transplant period. The hypophosphataemia we found immediately after successful renal transplantation is a direct effect of persistent elevations of PTH and FGF23¹²⁶. Hypercalcaemia was common after transplantation in our study, which has been explained by release of calcium from the skeleton driven by PTH¹³⁰. This is also supported by our findings of high levels of ALP in patients with high PTH after transplantation.

Our findings show that mineral metabolism changes dramatically immediately after transplantation but stabilises between six to twelve months thereafter. The major determining factor of persistent sHPT one year after transplantation is the degree of sHPT before transplantation. The sHPT evolution in the first year after transplantation is predictable, which underlines the importance of a well-managed sHPT in patients on the waiting list for a renal transplant.

Renal hyperparathyroidism and cardiovascular risk after renal transplantation - the role of PTH.

Cardiovascular disease is the major cause of mortality in renal transplant recipients¹³⁷ and prior studies have identified several risk factors for post-transplant CVD. Whether PTH alters the risk of CVD after transplantation is not clear and existing studies all use various methods, which is why they are difficult to compare. Prior studies have examined the relation between post-transplant levels of PTH and the risk of CVD and have found both negative¹⁴¹ and positive¹⁴² associations. In the study that found a positive relation, the endpoint was composite, consisting of mortality, graft failure and CVD.

We found an increased risk of CVD after renal transplantation in patients with pre-transplant PTH below 9.5 pmol/L (no PTX pre-transplantation) and 6.6 pmol/L (PTX pre-transplantation). Furthermore, patients having undergone PTX before transplantation with low pre-transplant levels of PTH had a markedly increased risk of CVD. These patients had very low levels of PTH (median 1.5 pmol/L). Thus, contrary to previous studies, low levels of PTH were associated with increased risk. However, in our study, we used pre-transplant levels of PTH, whereas previous studies used post-transplant levels of PTH. Thus studies might not be entirely comparable. However, there is evidence of increased risk of cardiovascular disease and mortality in patients on dialysis with PTH levels below 6.9 pmol/L (upper normal reference for PTH)^{84, 152} and for levels below 5.3 pmol/L⁸⁵ consistent with our findings. Low PTH in dialysis patients has been linked with

both cardiovascular risk but also with progression of vascular calcification, explained by low bone turnover⁸⁴. In line with this, bone biopsies from renal transplant patients in the 21st century show low bone turnover as the most common finding¹³⁶.

We found no association between high pre-transplant PTH levels and adverse outcomes. This could be due to the fact that no patients in our study had very high levels of PTH. Previous studies of patients on dialysis found an increased risk of CVD when levels of PTH were above 60 pmol/L – almost no patient in our study had levels of PTH that high. High PTH in the post-transplant period has been associated with mortality and graft loss but not exclusively with CVD^{141, 142}.

Based on the results of our study, treatment in patients on the waiting list for a renal transplant should not aim for PTH levels below the upper limit of the normal reference range, since this might increase the risk of post-transplant CVD. This is especially important in parathyroidectomy, since this is a non-reversible treatment.

Parathyroidectomy in renal hyperparathyroidism – does it affect the risk of fractures?

We found a reduction in fracture risk after PTX in female patients. This is consistent with the study by Rudser et al. who also found a decrease in fracture risk for female, but not for male patients¹²⁴. Another study comparing fracture rates before and after PTX found no reduction in fracture rate after PTX. In that study, patients were only followed for the first year after PTX and the overall fracture rates were low¹²⁰.

It is known that female patients on dialysis show higher levels of PTH compared to male patients¹⁵³. Women have a more aggressive histological pattern of sHPT¹⁵⁴ and are at higher risk of receiving a PTX compared to men^{8, 155}. These gender differences have not yet been explained but hormonal status and the higher rate of osteoporosis in female patients are likely to affect bone disease in sHPT. Lower bone mineral density scores in women compared with men before PTX support this thesis¹⁵⁶. Also, primary hyperparathyroidism affects twice as many women as men¹⁵⁷, thus female patients might be more susceptible to parathyroid gland hyperactivity than male patients.

We show that if female patients undergo PTX this has a beneficial effect on the risk of hip fractures, and this is also supported by previous studies. Thus, when selecting sHPT-patients for PTX it is reasonable to take gender into consideration when aiming for fracture reduction.

Surgical technique in parathyroidectomy for renal hyperparathyroidism – more or less?

When the decision is made that a patient is in need of a parathyroidectomy another question must be answered: which surgical procedure should be chosen? Most previous studies have focused on the risk of recurrent sHPT as a major outcome, thus total PTX, i.e. removing as much parathyroid tissue as possible, has been recommended in many studies^{111, 158, 159}. Knowledge about differences in other outcomes (mortality, fractures, cardiovascular events) for various surgical procedures in PTX for sHPT is lacking. In a consensus report from the European Society of Endocrine Surgeons the authors underline the scarcity of data in surgical sHPT treatment and give no firm recommendations as to which procedure to be used¹⁰⁹.

We found a higher risk of cardiovascular disease for patients undergoing total PTX compared with subtotal PTX. When comparing subgroups this was only true for patients on dialysis and patients with prevalent CVD. Levels of PTH were only available in a subgroup of patients. When comparing tertiles of PTH after surgery regardless of surgical procedure, we found that patients with low post-PTX PTH had the highest risk of CVD. Patients undergoing total PTX had lower PTH after surgery compared with patients undergoing subtotal PTX. Patients undergoing total PTX had higher preoperative PTH, thus, the difference in pre and postoperative PTH was greater for total PTX compared with subtotal PTX patients.

A rapid shift in PTH, which follows after PTX, can induce low bone turnover and increased vascular calcifications as shown by Hernandez et al¹⁶⁰. This is supported by London et al. who found that patients on dialysis who had undergone PTX had higher coronary calcification scores and a higher rate of low bone turnover disease compared with patients who had not been treated with PTX⁵⁰. Also if a dialysis patient has severe vascular calcifications this is an indication of low bone turnover^{50, 73}.

In line with previous studies we found a higher rate of recurrent disease in patients treated with subtotal PTX compared with total PTX. We found no associations between mortality or hip fractures between surgical techniques.

The findings in paper IV are of importance for surgical management of sHPT but need to be validated in further studies. The key question is likely to be: which level of PTH should we aim for when performing PTX on a patient with renal hyperparathyroidism? Patients on dialysis with prevalent CVD at the time of PTX seems to be vulnerable to low PTH levels, thus total PTX might not be beneficial for these patients.

Conclusions

The studies presented in this thesis show that:

- Persistent secondary hyperparathyroidism is common after renal transplantation. The major determining factors for the severity of sHPT one-year after transplantation are the degree and treatment of pre-transplant sHPT. Low pre-transplant levels of parathyroid hormone are associated with increased risk of post-transplant vascular disease in patients with and without pre-transplant parathyroidectomy.
- Parathyroidectomy reduces the risk of fractures for female patients. Total parathyroidectomy and low levels of PTH after parathyroidectomy are associated with a higher risk of cardiovascular disease in patients on dialysis or with prevalent cardiovascular disease compared with subtotal PTX. Subtotal PTX for renal hyperparathyroidism is associated with a higher risk of recurrent sHPT compared with total PTX.

Future perspectives

This thesis indicates several potential risks associated with low or insufficient levels of PTH in clinical situations. Whether low PTH is harmful or beneficial for the patient is most likely determined by the bone turnover status. The key to help revealing the proper sHPT treatment in the individual patient is having a diagnostic tool to determine bone turnover. Before starting treatments that rapidly change PTH, i.e. parathyroidectomy or renal transplantation, it is crucial to know whether the patient is in a high or low bone turnover state. Today, bone biopsy is the only way to get this information, but it is not widely available and is invasive to the patient. Specific biomarkers for bone remodelling would revolutionise sHPT treatment.

Further large cohort studies are needed to evaluate the differences in vascular and mortality outcomes between different surgical techniques in parathyroidectomy for renal hyperparathyroidism. In these studies, subgroup analyses of different baseline characteristics would help find which patients should be selected for which technique. Much information would be gained from studies comparing outcomes in patients with low and high bone turnover undergoing renal transplantation or parathyroidectomy.

More parameters than the PTH level will be necessary for characterising the patient and planning proper treatment for renal hyperparathyroidism.

Populärvetenskaplig sammanfattning

Det har länge varit känt att njursjuka patienter har en kraftig överdödlighet som i huvudsak förklaras av hjärt/kärlsjukdom. Man har också noterat en speciell form av skelettsjukdom hos njursjuka men det är först på senare år som man kunnat visa att det finns en nära koppling mellan skelett, blodkärl och njursjukdom. Denna kallas för renal hyperparathyroidism. Vid njursvikt sätts många viktiga system ur spel i kroppen och ett av dem är mineralbalansen. Mineralerna fosfat och kalk är livsviktiga och alltför höga eller låga värden leder till att kroppens organ tar skada. Kroppen har ett avancerat hormonsystem som håller balansen i schack. En nyckelspelare i detta system är parathormon som bildas av bisköldkörtlarna.

Bisköldkörtlarna sitter på halsen, är fyra till antalet och är mycket små om de är friska. När mineralbalansen störs växer bisköldkörtlarna och bildar mer och mer parathormon. Parathormon frigör kalk och fosfat från skelettet och ökar inflödet av dessa till blodbanan där de kan deponeras i kärlväggen som åderförkalkning. Resultatet blir ett svagt skelett med ökad risk för benbrott och ett förkalkat kärlträd med ökad risk för hjärt/kärlsjukdom såsom hjärtinfarkt och stroke. Det är sedan tidigare känt att mycket höga nivåer av parathormon kan vara ogynnsamt för patienter i dialys och efter njurtransplantation.

Idag fokuserar man mycket på att försöka återställa balansen av fosfat och kalk genom avancerade läkemedel och kostomläggning. I de fall där bisköldkörtlarna har blivit alltför förändrade kan det krävas en operation där man avlägsnar sjuk körtelvävnad och minskar nivåerna av parathormon. Problemet är att vi idag har för liten kunskap om vilka patienter som har bäst nytta av operationen. Vi vet inte heller om man på lång sikt får mindre hjärtinfarkter och benbrott efter en sådan operation eller vilken operationsmetod som är mest gynnsam. En annan situation där vi saknar tillräcklig kunskap om hur parathormonet förändras är vid njurtransplantation. Mineralbalansen normaliseras till viss del men många patienter har kvarstående höga värden av parathormon långt efter transplantationen. Vi vet inte hur vi ska förutspå vilka patienter som drabbas av komplikationer och vi vet inte heller om höga värden av parathormonet är skadligt i samband med njurtransplantation.

Patienter med njursvikt är en utsatt grupp som kräver stora sjukvårdsinsatser. Den ökade förekomsten av diabetes och högt blodtryck gör att vi ser fler och fler patienter i samhället drabbas av nedsatt njurfunktion. Detta gör att all forskning som kan hjälpa oss att ta hand om dessa patienter på ett bättre sätt har goda

möjligheter att göra stor klinisk nytta. Målet med avhandlingen var att studera vilka faktorer som påverkar varför man kan ha kvarstående förhöjda värden av parathormon efter njurtransplantation samt vilka värden av parathormon som är skadliga efter njurtransplantation. Avsikten var också att studera om operation av bisköldkörtlarna påverkar risken för höftfraktur (brott på lårbenshalsen) och vilken operationsmetod som ger bäst effekt på kärlsjukdom och frakturer.

Resultaten visar att mer än hälften av alla patienter som njurtransplanteras har kvarstående förhöjda nivåer av parathormon. Graden av överfunktion av bisköldkörtlarna redan innan transplantationen avgör hur det kommer se ut ett år efter transplantationen. De patienter som har lägst, och inte de som har högst, nivåer av parathormon före transplantationen tycks få fler kärlkomplikationer efter transplantationen. Vi noterade att operation av bisköldkörtlarna minskade risken för höftfraktur men enbart hos kvinnor. De som behandlats med en operationsmetod där man tog bort alla bisköldkörtlar fick fler hjärtinfarkter än de där man låtit en del av bisköldkörtlarna sitta kvar. Det fanns en koppling mellan låga nivåer av parathormon efter bisköldkörteloperationen och risken för hjärt/kärlsjukdomar.

Både efter en njurtransplantation och efter en operation av bisköldkörtlarna minskas nivåerna av parathormon kraftigt. Vår teori är att de som får mycket låga parathormonnivåer i blodet hamnar i en riskgrupp för komplikationer. Möjligen beror detta på att skelettet behöver en viss nivå av parathormon för att fungera och kunna buffra kalk/fosfatbalansen. Detta stämmer med tidigare studier där man funnit att patienter med njursjukdom och ett inaktivt skelett utvecklar svårare hjärt/kärlsjukdom. Det betyder att inte bara mycket höga utan även mycket låga nivåer av parathormon är skadligt för kroppen vid njursvikt.

Att kvinnor får minskad risk för höftfraktur efter operation av bisköldkörtlarna tror vi hänger ihop med att kvinnor generellt har en ökad risk för benbrott på grund av benskörhet och hormonförändringar. Denna risk förstärks av njursjukdom som ger upphov till skelettpåverkan.

Våra resultat kan praktiskt betyda följande: för patienter som väntar på njurtransplantation skall man inte acceptera mycket låga nivåer av parathormon alltför eftersom riskerna tycks öka för hjärtinfarkt efter njurtransplantation. När man väljer ut vilka njursviktpatienter som skall genomgå operation av bisköldkörteln vet vi nu att kvinnor har bäst effekt för att minska risken för höftfraktur. Vid operation av bisköldkörtlarna bör man sträva efter att lämna kvar en del av vävnaden för att inte riskera att få för låga värden av parathormon vilket kan ge ökad risk för hjärt/kärlkomplikationer.

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