Notes and Comments
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SURGICAL OR MEDICAL THERAPY FOR SEVERE HYPERPARATHYROIDISM OF CHRONIC KIDNEY DISEASE? AN APPRAISAL OF CURRENT PRACTICE GUIDELINES

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Abstract

Long lasting hypocalcemia, hyperphosphatemia, low calcitriol and high fibroblast growth factor 23 could result in progressive parathyroid gland hyperplasia with high, uncontrolled, parathormone production, e.g. severe secondary hyperparathyroidism (sHPT), in 10% of dialysis patients.

Parathyroidectomy (PTX) could be a solution, but has inherent (low) surgical risks and although dramatically decreases parathormone levels, could induce hypoparathyroidism (50-66%) and low turnover bone disease. Moreover, the rate of recurrences is 15-20% at 10 years. Total and subtotal PTX with autografting are equally safe and effective with similar recurrences rates.

Calcimimetics are efficient drugs, but with limited effectiveness in sHPT, as only 25% of patients responded to cinacalcet. In the USA, they are more cost-effective than PTX only in patients with >2 years expected dialysis duration.

As there are not randomized studies to compare surgical to medical therapy, the strength of evidence allows only for suggestions in guidelines. In countries like Romania, where dialysis vintage is high because of the low transplantation rate and calcimimetics are costly, PTX seems a better solution when parathyroid glands are large (diameter >1cm or total mass >500mg), parathormone levels >800pg/mL, in patients who are not candidates for renal transplantation or are anticipated to stay >2 years on dialysis.

Key words: parathyroidectomy, severe secondary hyperparathyroidism, calcimimetics, cinacalcet, dialysis.

INTRODUCTION

Hyperparathyroidism is an overproduction of parathormone (PTH) by the parathyroid gland. In the primary hyperparathyroidism, a rare condition, the source

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of uncontrolled PTH secretion is a parathyroid tumor, either adenoma or neoplasia (sometimes part of multiple endocrine neoplasia). In the secondary hyperparathyroidism (sHPT), the PTH overproduction is driven by alterations in calcium homeostasis (malabsorption or vitamin D deficiency of various causes).

The most frequent form of sHPT is a consequence of Chronic Kidney Disease (CKD), in which low vitamin D, hyperphosphatemia and peripheral resistance to PTH calcemic action concuringly act to increase PTH production and to induce parathyroid gland (PTG) hypertrophy, hyperplasia and even its adenomatous transformation. Somehow misleading, sHPT is called "tertiary" or "autonomous" when PTH production cannot be suppressed by increasing serum calcium (some authors reserve "tertiary" sHPT for patients with renal transplantation). While PTH begins to increase early in the course of CKD, clinically overt secondary hyperparathyroidism occurs in advanced CKD stages, usually in patients treated for long time by maintenance hemodialysis (HD).

Secondary hyperparathyroidism of CKD is part of a systemic disorder. PTH was considered an uremic toxin (1), because many elements of the uremic syndrome (anemia, polyneuropathy, vascular and valvular calcifications, abnormalities in carbohydrate and lipid metabolism) and even mortality, not only bone disease, were related to its levels. As renal bone disease was clinically the most evident, the initial practice guidelines (KDOQI, 2003 (2)) defined management strategies based on target ranges for PTH derived from the ability of PTH levels to predict high and respectively low turnover bone disease diagnosed using X-ray, biochemical markers or bone biopsy. Although the strength of evidence behind these target ranges is debatable, they were largely used in clinical practice and, more important, allowed for international standardization in reporting and comparing data Table 1, (KDOQI, 2003 (2)).

Table 1. Target range of intact plasma PTH by stage of CKD (KDOQI, 2003 (2))

CKD stage	GFR range (mL/min/1,73m^2)	Target "intact"PTH (pg/mL)	Grading
3	30-59	35-70	Opinion
4	15-29	70-110	Opinion
5	<15 or dialysis	150-300	Evidence

CKD - Chronic kidney disease; GFR - Glomerular filtration rate

Recently, a group of KDIGO experts defined Chronic kidney disease – Mineral and Bone Disorder (CKD–MBD) as (3): "A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

– Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism.

– Abnormalities in bone turnover, mineralization, volume, linear growth, or strength.

– Vascular or other soft-tissue calcification.

Thus, PTH abnormalities in CKD are currently regarded as a part of a systemic disorder, not a disease by itself.

When biochemical parameters are severely altered in spite of an adequate therapy (PTH>500-800pg/mL, at least one parathyroid gland with a diameter >1cm, persistent hypercalcemia and/or hyperphosphatemia), skeletal (osteitis fibrosa, brown tumor) or extraskeletal (micro- or macrovascular, ectopic calcifications) lesions are clinically prominent, the hyperparathyroidism is said "severe" or "unresponsive" (as the response to vitamin D therapy is lost). Usually, but not always, "severe" hyperparathyroidism is "tertiary". In this situation, which is frequently described as medical therapy failure, only surgery (2) and, possibly, cinacalcet hydrochloride could provide effective reduction in PTH levels.

To note, in most of the studies, severe sHPT is defined based on PTH level. Still undocumented cut-offs of 800pg/mL (KDOQI (2)), "nine times than the upper normal limit for the assay" (KDIGO (3)) or >500pg/mL (Japan Society of Dialysis (4)) were proposed and used in different studies. Usually, the dimensions of the gland are not considered for diagnosis, which is enforced by the severity of the clinical presentation.

Parathyroidectomy is a surgical procedure performed in patients with a high burden of co-morbidities, and is not without risk. Its long term results seem to be good (5) in terms of patients survival, but are debatable in terms of achieving K/DOQI targets (6).

Determinants of secondary hyperparathyroidism in CKD

Hypocalcemia, hyperphosphatemia, low 1,25 (OH)2 vitamin D3 (calcitriol) and, possibly, high fibroblast growth factor 23 (FGF23) levels are the main drivers of sHPT in CKD. Their combined action results in abnormalities of parathyroid gland itself, which further contribute to the automomous PTH overproduction (Fig. 1) (7-9).

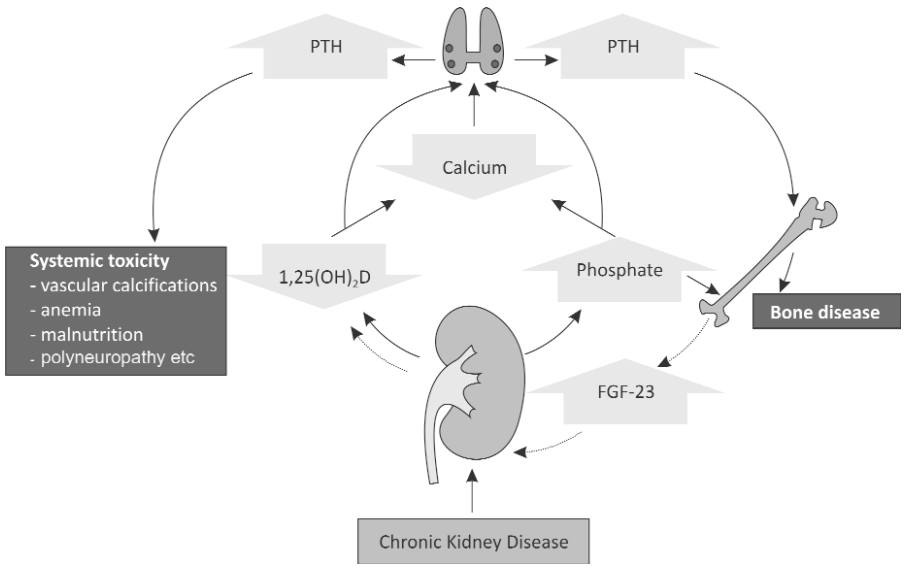

Figure 1. Determinants of secondary hyperparathyroidism of Chronic Kidney Disease. PTH=Parathormone, FGF=Fibroblast Growth Factor, Possible FGF 23 actions are figured by a dotted line. Modified from 7-9. with permission.

Hypocalcemia

Calcemia is the main regulator of PTH secretion. It acts *via* calcium-sensing receptor (CaR), a serpentine membrane protein located on the parathyroid cells membrane (10). Stimulation of the receptor by high serum ionic calcium levels decreases the PTH secretion.

Hypocalcemia has time-dependent effects on PTG mediated by CaR. The degradation of PTH is reduced and secretion is increased within minutes, PTH gene transcription is thereafter increased in the following hours and parathyroid cells proliferation is accelerated in the subsequent days and weeks (11). Therefore, hypocalcemia - resulting from both reduced intestinal calcium absorption because of low calcitriol levels and hyperphosphatemia - was considered the main driver of sHPT in CKD (12). But, as in case of hyperphosphatemia, increase in PTH levels precedes hypocalcemia in the course of CKD.

Abnormalities of the parathyroid gland, e.g. reduction in calcium-sensing receptor number, which parallels the increase in cells number and was observed even in primary HPT, could partially explain such discrepancies (13). Because of a lower number of CaR, higher levels of calcium would be necessary to suppress the PTH production and the basal PTH secretion will be higher, a condition described earlier as increase in calcium set point and rightward shift of the PTH -calcium curve (14) (Fig. 2).

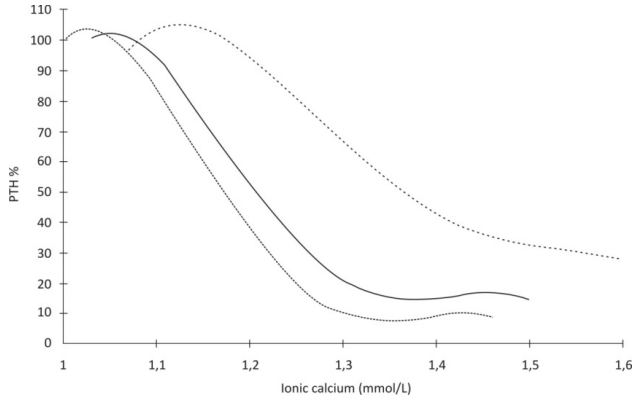

Figure 2. The set point of calcium in patients with normocalcemic (n=16; plain line) and hypercalcemic sHPT (n=19; right dotted line) and in normal subjects (n=14; left dotted line). Maximal PTH secretion is transformed to 100%. The sigmoid curve is shifted to the right in hypercalcemic secondary HPT compared to normocalcemic sHPT and normal subjects (from Malberti F et al. Nephrol Dial Transplant (1999) 14:2398-2406; reproduced with permission of the editor)

Hyperphosphatemia

As renal function declines, the urinary excretion of phosphates decreases followed by hyperphosphatemia. Transient hyperphosphatemia was thought to diminish serum ionic calcium, which in turn increases PTH secretion in order to restore phosphate and calcium levels. Thus, the price paid to maintain calcium –

phosphate homeostasis is the increased PTH level (trade-off hypothesis) (15). However, hyperphosphatemia is a late event in CKD evolution (Stage 4, GFR<30mL/min), while PTH increases from the beginning (Stage 2, GFR<90mL/min) and sHPT was not prevented when hypocalcemia was corrected in CKD patients with persistent hyperphosphatemia (8).

The second mechanism proposed was the hyperphosphatemia induced suppression of calcitriol synthesis, which could induce hypocalcemia (and sHPT) by diminishing calcium absorption (16).

More recently, direct effects of phosphate on parathyroid gland (PTG) were demonstrated. High phosphate concentration seems to increase PTH secretion by a posttranscriptional effect, and more important, to stimulate the growth of the parathyroid gland, a process mediated by transforming growth factor α (TGF-α) and its receptor, epidermal growth factor receptor (EGFr). Recent experimental work by *Dusso et al* suggested that phosphate dependent activation of TGF-α/EGFr pathway could also result in a decrease in vitamin D receptors (VDRs), offering a comprehensive explanation for PTG abnormalities of sHPT (17, 18). Nevertheless, the operating mechanisms are still to be elucidated (8).

Lastly, hyperphosphatemia could stimulate osteocytes to release FGF23 and decrease calcitriol (*vide infra*).

Calcitriol deficiency

Low calcitriol levels could be responsible of both increased PTH secretion (*via* reduced calcium absorption and release of the suppressive action on PTH synthesis mediated by vitamin D receptor) and parathyroid gland hyperplasia (calcitriol prevents parathyroid cell proliferation by inhibiting specific growth factors, like TGF-α and its receptor EGFr, and by stimulating proteins, like p21 and 27, that control the cell cycle) (8, 12, 19, 20).

Calcitriol actions are mediated by VDR, a low molecular cytosolic protein which facilitates 1,25 $(OH)_2$ vitamin D3 association with the nuclear chromatin (21, 22). The expression of VDRs decreases in parathyroid gland with nodular hyperplasia (23). As the main stimulus for VDR formation is calcitriol level, it is not yet clear whether the reduced VDR levels precede or follow development of hyperplasia (8).

Calcitriol, the naturally active vitamin D derivative, is produced by 25 hydroxy vitamin D (calcidiol) hydroxylation in the proximal and distal convoluted tubules nephrocytes, under the control of a cytochrome P435 enzyme, 1α vitamin D hydroxylase. As the renal mass declines, a lower production of calcitriol is expected. Indeed, lower calcitriol levels were detected starting from stage 2 CKD (24). The deficient hydroxylation is further augmented by the phosphate driven increase in FGF23 (25) and, in more advanced stages, by hyperphosphatemia itself which inhibits the 1α vitamin D hydroxylase (12). Also, nutritional vitamin D deficiency could play a role, as nutritional deficiency is highly prevalent and a close correlation between calcitriol and calcidiol levels was demonstrated in CKD, but not in patients with normal renal function (26).

Very recently, abnormalities of a second key cytochrome P435 enzyme

involved in vitamin D derivatives catabolism were demonstrated in both uremic rats and CKD patients (27). This enzyme, 24-hydroxylase, was overexpressed in kidney of uremic rats and in biopsies from patients with kidney disease as compared to controls. Thus, not only a reduced calcitriol production, but also an increased vitamin D sterols degradation could be at the origin of calcitriol deficiency in CKD.

Fibroblast growth factor 23

Fibroblast growth factor 23 is a small protein secreted mainly by bone cells (osteocytes and osteoblasts) in response to increased calcitriol and phosphate blood levels. FGF23 actions are mediated by FGF receptor and need *Klotho* as co-receptor. FGF receptors were demonstrated in kidney and parathyroid gland. Physiologically, FGF23 increases phosphaturia by downregulation of natrium-phosphate co-transporters in the proximal tubular cells. It also decreases calcitriol synthesis by inhibiting 1α 25(OH) vitamin D hydroxylase. Thus, FGF23 was considered as a counterregulatory factor for vitamin D. Additionally, FGF23 decreases PTH secretion (28, 29).

In CKD, FGF23 steadly increases from early stages up to levels 1000 times higher than normal in ESRD, to maintain serum phosphate both by enhancing phosphaturia (in conjunction with PTH) and reducing intestinal phosphate absorption through decreased calcitriol synthesis. Although a compensatory mechanism aiming to maintain phosphate balance initially, on long term, the FGF23 increase may become maladaptative, by severely decreasing calcitriol levels, which promotes secondary hyperparathyrodism (25). Accordingly, FGF23 could be the initiating factor of secondary HPT of CKD, and the original "trade-off hypothesis" could be updated, by replacing PTH with FGF23 (25, 30). Interestingly, a downregulation of FGF23 receptors was described by some but not all authors (31), similar to CaR and VDR, which could explain why the FG23 mediated suppression of PTH seen in persons with normal kidney function is lost in CKD (32-34).

Skeletal resistance to parathyroid hormone action

The calcemic response to similar amounts of PTH is lower in CKD than in persons with normal renal function. This was called skeletal resistance to PTH (35). It implies that a higher PTH amount is necessary to obtain the same increase in calcium level, which add to already existing HPT. Possible explanations are hyperphosphatemia and acidosis, calcitriol deficiency, and uremia itself, acting *via* poorly defined uremic toxins (8). Other possibilities are the down-regulation of the classical PTH receptor, PTHR1, which was found decreased in target tissues in experimental uremia, or the accumulation of truncated PTH peptides acting through putative C-terminal PTH receptors (36, 37).

Abnormalities of the parathyroid gland

The classic studies of *Stanbury* (38) and *Parfitt* (39) demonstrated an increase in the mass of all parathyroid glands in CKD patients with a bimodal distribution: glands obtained from patients with bone disease were 20 times heavier and weighted over 1g, while in patients without bone disease the weight was less than 1g. The mass of all glands was similar to that of a single parathyroid adenoma

producing osteitis fibrosa in primary hyperparathyroidism (40). More recently, in the largest series published, *Tominaga et al* reported a mass of resected glands from hemodialysis patients with sHPT of 2.5±1.9g and a PTH level of 1152±4838pg/mL (41). Furthermore, the same group demonstrated a very close correlation between the gland mass and the PTH level (42). Thus, a relationship between the secretory mass of the gland and the amount of PTH produced in sHPT is documented.

Examination of glands obtained by parathyroidectomy in sHPT suggested stadial, time-dependent, structural changes which can be associated to parathyroid gland mass and PTH levels. For instance, 85% of glands weighing more than 500mg had nodular hyperplasia and a PTH over 1000pg/mL is seen when the diameter of a gland is over 1 cm (42, 43) (Fig. 3).

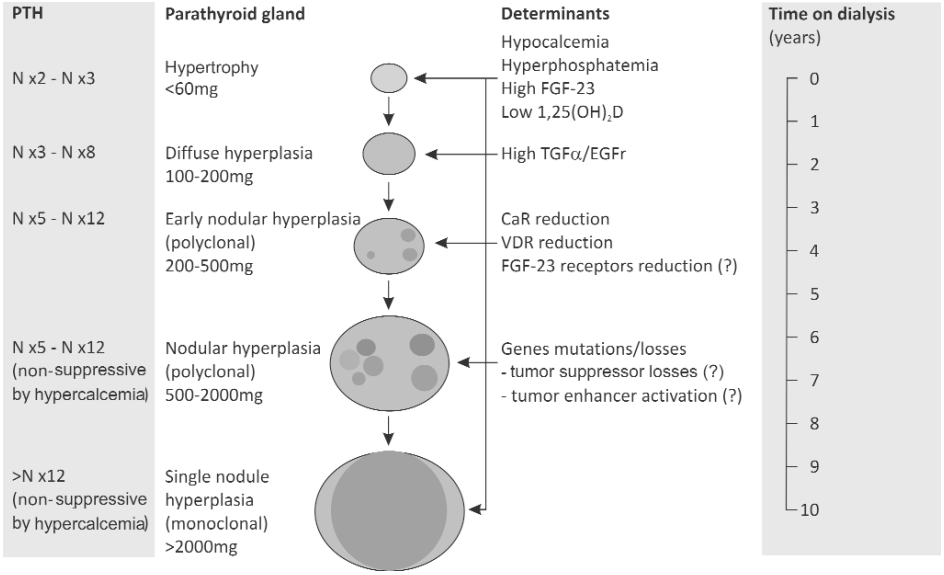

Figure 3. Parathyroid gland abnormalities in secondary hyperparathyroidism of Chronic Kidney Disease (42,43), PTH - parathyroid hormone; CaR - calcium sensing receptor; FGF23 - fibroblast growth factor 23; VDR - vitamin D receptor.

In the first stage, there is an increase in secretory (chief) cells mass, defined as *hypertrophy*. It is followed by *diffuse hyperplasia*, e.g. the total number of cells - chief and oxyphilic – is increased. At this time, CaR and VDR expression by chief cells begins to decline.

Disposition of hyperplastic cells in nodules defines the next stage, *(multi)nodular hyperplasia*. This stage was divided in to *early nodular* (few small nodules) and *nodular* (more than two, well developed nodules). The cells of a nodule are monoclonal (44) and express till 60% fewer CaR (45) and VDR (46) than a normal gland. Consequently, there is a progressive rightward shift of calcium – PTH response curve, the basal PTH secretion is increased and is poorly suppressed by calcium levels. Occasionally, high PTH levels coexist with high

serum calcium, a situation defined as "tertiary" or "autonomous" hyperparathyroidism. Because of the reduced VDR number, there is also a resistance to conventional therapy with vitamin D derivatives, described as "refractory" secondary hyperparathyroidism. For this reason, *Fugakawa* regarded the late nodular hyperplasia as a "point of no return", imposing surgery (47).

Hyperplasia can eventually become *mononodular* and adenoma formation can be seen in one or more nodules. The last stage could be *parathyroid carcinoma*, a very rare condition: only 20 cases in hemodialysis patients out of a total of 700 parathyroid carcinoma were reported till 2005 (48, 49).

As multi- or mononodular hyperplasia was found in over 90% of PTG with a mass of more than 500mg (the largest diameter >10mm), the dimensions of the gland could predict its structural changes (42, 43). However, the dimensions of PTG are not an unquestionable indicator of refractory sHPT as nodular hypertrophy was also found in glands weighing less than 500mg.

Currently, these structural changes of PTG are regarded as a consequence of a persistent functional demand of increased PTH secretion imposed by hypocalcemia resulting from hyperphosphatemia, low calcitriol levels and uremic milieu. This functional pressure allows for the selection of some secretory cells with somatic mutations favouring growth, which explains the monoclonality (50). Although acquired mutations or allelic losses in genes encoding tumor enhancers or tumor suppressors were supposed, none was proved so far. (51).

Time is also an important parameter. For instance, in *Tominaga et al* series, the mean HD vintage was 11.8 years, 1 out of 10 patients were on hemodialysis for 10 years, and 1 out of 4 for more than 25 years when parathyroidectomy (PTX) was performed for severe sHPT (52). Another study reported a PTX rate of 3.3 case per 1000 patient-years for patients receiving renal replacement therapy for less than 5 years, and 30 cases per 1000 patient-years for those receiving renal replacement therapy for more than 10 years (53). Thus, a long lasting, usually more than five years, "functional pressure" seems to be a prerequisite for the development of nodular hyperplasia.

The increase in the parathyroid gland mass in sHPT could result from hypertrophy (increase in cell mass) and hyperplasia (increase in cell number). If hypertrophy can rapidly appear and is reversible, hyperplasia is a slower process, of a higher magnitude and a low reversibility (40).

The normal parathyroid gland is characterized by a low cell turnover, a low rate of mitoses and no separate stem cells (40, 50). The secretory cells have a mean life span of 20 years. They must stop secretion before entering cell cycle to divide when the need of PTH is high. The parathyroid gland is then a low conditionally renewing tissue, where cell loss would theoretically appear by apoptosis or necrosis. Necrosis is a rare phenomenon even in primary HPT and is related to intraglandular hemorrhage (51). The existence of apoptosis was till recently doubtful, direct proofs of apoptosis were not found experimentally and were occasionally reported in glands obtained from patients with sHPT, probably because of low number of cells affected

(1 in 10.000 cells) (54, 55). On the other hand, studies investigating the decrease in PTG size following various therapeutic interventions gave discordant results, possible because of the limits in the evaluation of currently used imagistic methods.

Considering its antiproliferative actions, calcitriol could be an inductor of apoptosis in parathyroid cells. However, the systemic administration of calcitriol or its active derivatives, even in pulse therapy, gave discordant results in terms of PTG morphology (decrease in dimensions) or function (decrease in PTH levels, calcium-PTH curve left shift), probably because of the reduced number of VDR observed in nodular hyperplastic glands. Recently, *Shiizaki et al* reported reduction in PTG dimensions (evaluated by sonography), decrease in PTH levels and reversal of PTG responsiveness to calcium in patients with severe sHPT after direct intraparathyroidian injection of an active vitamin D derivative (maxacalcitol) (56). Moreover, they confirmed their clinical results in a mouse model of severe sHPT where apoptosis was demonstrated by light and electron microscopy, TUNEL method and DNA electrophoresis.

Thus, in sHPT, nodular hyperplasia is a late consequence of hypocalcemia, hyperphosphatemia and low calcitriol combined and persistent action. Nodular hyperplasia is the usual substrate of the parathyroid gland enlargement over 500mg and seems seldom, if ever, morphologically reversible (41). Nevertheless, when 20 hyperplastic parathyroid glands instead of 2 (the normal number of PTG in rat) were transplanted from uremic rats to a normal recipient rat, the initially high PTH secretion declined to normal in 3 days and severe sHPT was reversed in a week after isogenic kidney transplantation (57). Therefore, even hyperplastic glands can be functionally controlled by the removal of the demand for increased PTH level, in spite of persistent anatomical abnormalities.

Clinical epidemiology of severe sHPT

The incidence of parathyroidectomy can be a surrogate of severe sHPT. Reported incidence varies from region to region and within a region by time. For instance, in the USA an incidence rate of 14.2/1000 patient-years was reported between 1995-1999 (58), and of 7.16 between 1990-1999 (59). In Lombardy the incidence was 5.28/1000 patient-years (between 1983-1996) while in Okinawa region, 15.2/1000 patients-years. The prevalence was estimated in Europe and Lombardy at 42.1 and 54.6/1000 (53). Because of similar conditions, it is likely that in Romania the incidence is closer to the Japanese one or higher, e.g. about 120 new parathyroidectomies per year.

The clinical profile of severe hyperparathyroidism can be evaluated using data from observational studies investigating retrospectively the clinical epidemiology of parathyroidectomy in HD patients (Table 2) (53, 58, 60, 61). However, when interpreting such data, the selection bias must be considered, as patients with severe co-morbidities are excluded because of surgical high-risk. Regional differences must also be taken into account, as HD population and the therapy of mineral metabolism abnormalities could differ not only from country to country, but also from centre to centre.

In all studies, patients over 64 years are less likely to undergo PTX than their

younger counterparts. This maybe due to the selection for surgery of younger patients, but also to a lower prevalence of sHPT in older persons. In fact, lower PTH levels were reported in the elderly HD patients (62). Moreover, the lower average time on dialysis in older patients could be not long enough to allow the development of sHPT.

Table 2. Clinical epidemiology of severe secondary hyperparathyroidism requiring parathyroidectomy

Parameter	Malberti *et al* [53]	Young *et al* [60]	Slinin *et al* [58]	Jorna *et al* [61]
N PTX/Control population	184/10591	165/17236	NA/10588	33/202
PTX incidence(cases per patient-years)	5.28	7	14.2	NA
Age	>64 years [<64years]# 0.23 (0.12-0.45)	[Per year]* 0.99	45 - 64 yrs [<45 yrs]† 0.65 (0.53-0.80)	NA
Gender	F [M]2.28 (1.68-3.03)	Male [female]* 0.85	Female [male]† 1.20 (0.99-1.45)	Female [male]‡ 2.50 (1.28-5.26)
Diabetes mellitus	DM [non-DM]# 0.09 (0.12-0.64)	DM* 0.65	[Glomerulonephritis]† 0.67 (0.44-1.02)	NA
Calcium	NA	[Per 1mg/dL]§ 1.58 (1.35-1.85)	>10.3mg/dL [<8.7mg/dL]† 5.09 (3.64-7.10)	>2.46mmol/L [<2.46mmol/L]‡ 3.23 (1.19-8.33)
Phosphate	NA	[Per 1mg/dL]§ 1.17 (1.09-1.25)	6,4 to 7.5mg/dL [<4.4mg/dL]† 2.17 (1.52-3.11)	>1,85mmol/L [1,85mmol/L]‡ 2,63 (1.22-5.26)
Parathormone	NA	[Per 00pg/mL]§ 1.07 (1.05-1.09)	>480pg/mL [<37pg/mL]† 2.28 (1.68-3.08)	>20pmol/L [<20pmol/mL]‡ 3.23 (1.79-7.69)
Hemoglobin	NA	-	10.5-11.2g/dL [<8.8g/dL]† 0.68 (0.51-0.90)	NA
Renal replacement therapy	PD [HD]# 1.62 (1.17-2.25)		NA	NA
HD vintage	NA	[Per year]* 1.04	5-9.9 years [<1 year]† 1.57 (1.02-2.41)	NA
Vitamin D therapy	NA	Yes [No]* 1.31	NA	NA

DM - diabetes mellitus; HD - hemodialysis; NA - not assessed/not available; PD - peritoneal dialysis; PTX - parathyroidectomy.
Data in [brackets] represent referent
relative risk and (95% confidence interval) for parathyroidectomy;
* adjusted odds ratio (95% confidence interval) for parathormone >300pg/mL;
§ adjusted relative risk (95% confidence interval) for parathyroidectomy;
† adjusted hazard ratio (95% confidence interval) for parathyroidectomy;
‡ relative risk (95% confidence interval) for parathyroidectomy (univariate analysis)

Women have a two times higher risk for severe sHPT imposing parathyroidectomy than men, a similar situation to primary hyperparathyroidism, which suggest an endocrine-related causality (63). Patients with diabetes mellitus and sHPT have a 30% lower risk of parathyroidectomy. A higher prevalence of low turn-over bone disease was reported in diabetics (64, 65) and was related to lower calcitriol/calcidiol levels and to the accumulation of advanced glycosylation end-products with pro-apoptotic action on osteoblasts observed in this population (66). On the other hand, the high surgical risk could impose a negative selection in diabetic patients known to have a lot of comorbidities.

As expected, a combination of high calcium, phosphate and PTH was invariably reported in patients with severe sHPT selected for PTX, although indications for surgery are highly variable across the world. For instance, a calcium over 10.3 mg/dL increases the PTX risk five times as compared to a calcium under 8.7 mg/dL, the risk is 17% higher for each 1mg/dL increase in phosphate and with 7% for each 100pg/mL increase in PTH (60).

Medical therapy of mineral disturbances of CKD, e.g. phosphate binders, vitamin D and calcium concentration in dialysis fluid, influences also the progression to sHPT. In DOPPS data, previous therapy with vitamin D made PTX less likely, while the risk of PTX inversely correlated with calcium concentration in the dialysis fluid (60).

Similarly, the renal replacement therapy method is important. Two large studies found that the risk of sHPT is higher in peritoneal dialysis than in hemodialysis patients and is the lowest in transplanted patients (53, 59). A higher risk of PTX in peritoneal dialysis than in hemodialysis patients is surprising, as the peritoneum depurates better phosphate than the dialyzer and adynamic bone disease, characterized by low PTH levels, is more common in peritoneal dialysis (59).

Lastly, HD therapy duration is directly correlated with the risk of PTX: a 4% increase per year was observed in DOPPS (60), which is consistent with *Tominaga et al* (52) and *Malberti et al* (53), where PTX was indicated for 1 out of 10 patients with a HD vintage over 10 years. The usual patient needing PTX had been treated by dialysis for at least 5 years.

The cardiovascular comorbidities are a distinct problem as the cardiovascular morbidity and mortality are more than 10 times higher in CKD patients and hyperparathyroidism is thought to be a major contributor. Therefore, a very high cardiovascular burden is to be expected in patients with severe sHPT. On the other hand, cardiovascular disease increases the surgical risk which could influence the referral for PTX. In a study by *Slinin et al* (58) in the American hemodialysis population (n=10588), 38% had coronary artery disease, 26% peripheral vascular disease, 17% stroke or transient ischemic attack and congestive heart failure was diagnosed in 42%. None of these cardiovascular comorbidities had any influence on the probability of a previous parathyroidectomy, which signifies that parathyroidectomized patients had the same cardiovascular profile as the whole hemodialysis population and the presence of cardiovascular disease had a minor

Table 3. Parathyroidectomy for severe secondary hyperparathyroidism of chronic kidney disease - "CI Parhon" Institute and "Dr Carol Davila" Hospital of Nephrology experience

Parathyroidectomies* (nov 1999 - nov 2009)		N=196 (100%)	
Follow-up (median)		3.9 [3.6 to 4.4] years	
Patients characteristics			
Sex (M)		84 (43%)	
Age (median)		52.0 [51.0 to 55] years	
Primary renal disease			
Primary glomerulonephritis		93 (47%)	
Interstitial nephropathy		21 (11%)	
Ereditary nephropathies		20 (11%)	
Hypertension and vascular nephropathy		8 (4%)	
Diabetic nephropathy		2 (1%)	
Other		7 (4%)	
Unknown/unavailable		46 (23%)	
Renal replacement method			
Hemodialysis		167 (85%)	
Peritoneal dialysis		7 (4%)	
Renal graft		4(2%)	
Not available		17 (9%)	
Renal replacement therapy duration (median)			
Biochemical parameters	Pre surgery	Post surgery	p
PTH			
Median	1595 [1433 to 1751] pg/dL	40 [24 to 61] pg/dL	<0.0001
>800pg/dL	92%	5%	<0.0001
800-600pg/mL	8%	5%	
300-600pg/mL	-	4%	
100-300pg/mL)	-	15%	
<100pg/mL	-	69%	
Calcium			
Median	10.0 [9.8 to 10.2] pg/dL	8.3 [8.1 to 8.5] mg/dL	<0.0001
>10.5mg/dL	28%	4%	0.01
>8.5 mg/dL	92%	46%	0.03
<8.5mg/dL	8%	54%	0.01
Phosphate			
Median	6.1 [5.8 to 6.5] mg/dL	5.2 [4.9 to 5.7] mg/dL	<0.0001
<5.5mg/dL	34%	54%	0.03
Calcium phosphate product			
Median	60 [56 to 66] mg2/dL2	43 [39 to 47] mg2/dL2	<0.0001
<55 mg^2/dL^2	40%	78%	0.05
Alkaline phosphatase (median)	337 [300 to 459] UI	91 [79 to 114] UI	<0.0001

Data are presented as median and [95% confidence interval of the median]
* Total parathyroidectomy with autotransplantation
†All caused by ectopic (mediastinal) glands
‡ Hematomas

Table 3 - continued. Parathyroidectomy for severe secondary hyperparathyroidism of chronic kidney disease - "CI Parhon" Institute and "Dr Carol Davila" Hospital of Nephrology

Outcome	Nb (%)
Lost to follow up	20 (10%)
Alive	144 (74%)
Death	32 (16%)
First 30 days	3 (1.5%)
First year	6 (3%)
After more than 1 year	23 (12%)
Reintervention†	2 (1%)
Post surgical complication‡	2 (1%)

Data are presented as median and [95% confidence interval of the median]
* Total parathyroidectomy with autotransplantation
†All caused by ectopic (mediastinal) glands
‡ Hematomas

contribution when selecting patients for surgery.

In our experience, patients were younger than reported in other series (median age 52 years), females were more prevalent (57%), diabetes mellitus was also uncommon, most of the patients were treated by hemodialysis (85%) and had a long dialysis vintage (median 6.9 years). Severe cardiovascular comorbidities were not highly prevalent (Table 3).

Thus, severe sHPT is most frequently seen in middle aged non-diabetic female patients with a duration of dialysis therapy higher than 5 years, previously treated with vitamin D, but with uncontrolled calcium, phosphate and PTH, and a high cardiovascular comorbidity burden.

Surgical therapy for severe hyperparathyroidism of CKD

Surgical methods

Open surgery, introduced by *Mandl* (1925) for primary hyperparathyroidism (67), and by *Standbry* (subtotal PTX; 1960) and *Ogg* (total PTX; 1967) in secondary hyperparathyroidism, is still the most favoured intervention. Currently, total parathyroidectomy (4/4 glands) with autografting a 5/6 fragment of the smallest gland - in the muscle (pectoral, radiobrachial muscle) or in the subcutaneous fat (presternal, forearm, abdominal) - and subtotal parathyroidectomy (3.5/4 glands) are the most popular procedures.

The benefits of the total parathyroidectomy with autografting would be the removal of the whole PTG tissue, which prevents HPT recurrence at the original site and, consequently, a risky reintervention, and an easy access in case of relapse at graft site. The advocates of subtotal parathyroidectomy claim similar efficiency with total PTX but with a lower risk of hypoparathyroidism.

In practice, the long-term (10-20 years) rate of HPT recurrence was similar (15-20%) with both methods if recurrence from ectopic glands were excluded, and grafts proved to be sometimes more difficult to remove than a neck reintervention (67-70) (Table 4). To avoid HPT recurrence from the graft, examination with a stereoamplifier or by extemporaneous histopathology was proposed for selection of

fragments with diffuse but not nodular hypertrophy, although the reported results are conflicting (54, 71, 72). Thus, there are no valid arguments in favour of one or another of the open surgical techniques.

In both techniques, a careful inspection, including the carotidian sheath, for ectopic supranumerary glands (which could be the source of recurrence) is mandatory. In fact a recent metaanalysis showed that reintervention was due to inadequate cervical explorations in 42% of patients who had undergone a subtotal PTX and in 34% of patients who had undergone a total PTX (73). Some recommend the custom resection of thymic tissue, another frequent location for ectopic gland, at the same time.

The most extensive experience with total parathyroidectomy with autografting comes from Japanese authors (41,74). In Japan, the renal transplantation rate is very low. Consequently, the number of hemodialysis patients is high and the proportion of long time survivors on HD is important (25% over 10 years). Although these characteristics differ from those seen in the European or North American practice, they are very similar to Romanian conditions and favour a high rate of severe secondary hyperparathyroidism. That is why we adopted the same surgical technique.

Endoscopic surgery was more recently introduced initially for big parathyroid adenoma of primary HPT and thereafter for subtotal or total PTX of secondary hyperparathyroidism, but the experience with these techniques is still limited.

Percutaneous ethanol injection therapy (PEIT)

In this method, introduced by *Solbiati* (1985) and refined by *Fugakawa* (1996), the biggest glands (those with diameter >5mm, ideally with a volume >500mm$^{3)}$ are localized and injected with ethanol under ultrasound control, using a special needle. The resultant reduction in gland secretory mass restores the response to medical therapy and allows to maintain PTH in target range (150-300pg/mL) in up to 80% of patients (75, 76).

Although efficient, PEIT needs skilled operators, its usefulness being limited to patients in which PTG can precisely be echographically localized. Furthermore, laryngeal recurrent nerve lesions are not infrequent and if surgery is requested after PEIT, the remaining parathyroid tissue is very difficult to be recognized (41).

How risky is parathyroidectomy in dialysis patients?

An increased post-operative risk is to be expected in dialysis patients. The overall post-operative mortality is 4% and morbidity about 50% in this at risk population, irrespective of the type of surgical intervention (77). A high burden of cardiovascular comorbidity, fragile fluid and electrolyte balance, bleeding disorders, the propensity to infections, altered drugs kinetics and drugs interactions are possible explanations.

In case of patients with severe hyperparathyroidism, vascular (and valvular) calcifications are the rule and calcific arteriolopathy is frequently encountered. For instance, in one study (78), 40% of patients submitted to PTX suffered previous cardiovascular events (angina pectoris, myocardial infarction or arrhythmias). In *Slinin et al* (58) data from the American hemodialysis population, 38% had coronary artery disease, 26% peripheral vascular disease, 17% stroke or transient

ischemic attack and congestive heart failure was diagnosed in 42%. None of these cardiovascular comorbidities was significantly different from cohort of PTX patients. Thus, the cardiovascular comorbidities are frequent in patients who underwent surgery. Moreover, calciphylaxis, a severe condition with a mortality over 75%, was reported in 25% of patients in *Strake et al* (79) series and in 4.28% in a group of 140 hemodialyzed patients in one Center from Romania (80).

Particular conditions to sHPT, like rapid postoperative shifts in serum calcium and phosphate levels could occur and the need of anticoagulation for hemodialysis therapy also compound the already increased risk.

In spite of these, a 0.17% to 5% unadjusted risk of mortality in the first 30 days after parathyroidectomy was reported in most of the published series, which is similar to other surgical procedures in dialysis patients, but higher than in PTX for primary hyperparathyroidism (Table 3). However, in experienced specialized centers the risk could be significantly lower (0.17% - *Tominaga et al* (41); 0.7% - *Jofré et al* (81)). In our series, the unadjusted risk of death was 1.5% in the first 30 days, 6% in the first year (Table 4).

A study using a large data base defined some features of the population at risk (*Kestenbaum et al* (5)). In this study, 4.458 dialysis patients who underwent PTX were compared to a similar number of dialysis patients matched for age, gender, ethnicity, ESRD cause, dialysis modality and duration. The risk of death in the first 30 days after surgery was 3.1%. As expected, the adjusted relative risk of death in the first 90 days after surgery was almost twice higher in PTX patients than in controls (risk ratio 1.84; 95%CI 1.52-2.22). The risk was higher in African-Americans and in diabetic patients, as well as in patients with short duration (<1 year) of dialysis therapy, but it was not significantly influenced by gender, age or the dialysis modality. Unfortunately, the influence of pre-surgical comorbid conditions on death risk was not measured in this study.

However, selection bias should also be considered, since referral for PTX could be limited to patients in a relatively good condition. For instance, in a study by *Trombetti et al* (78), only 22% of PTX patients had a high Charlson comorbidity index, as compared to 58% in the control group of dialysis patients, but in *Young et al* (60) study, no difference was found among PTX patients and the rest of hemodialysis American patients.

In hospital stay is 5-9 days in case of open surgery (67,82). The main surgery-related complications reported were: hoarseness caused by laryngeal recurrent nerve lesions, usually transient (1-15%), hemorrhage (0.5-1%) and reintervention because of hematoma (1%) (67,68 ,79,81). In our experience, hoarseness was uncommon and hemorrhage imposed surgical correction in 1% (Table 3). Therefore, in experienced hands, if the selection of patients is appropriate, the surgical risk in severe hyperparathyroidism of CKD is acceptable.

Results of surgical therapy

In accordance with the recent KDIGO recommendations, the PTX results should be evaluated in terms of biochemical parameters, bone disease and vascular calcification (3).

Table 4.Outcome of parathyroidectomized patients with severe nephrogenic secondary hyperparathyroidism

Author	Patients	Intervention	hPTR	Outcome	
				Mortality (30 days)	sHPT recurrence
Punch JD *et al (67)* (Michigan); 1995	91 (80 HD; 11 TX)	Subtotal PTX	2%	3.8%	4.1%; 11.7% at 1 and 20 years
Neonakis E *et al (69)* (Cardiff); 1995	67 (35 HD; 32 TX)	Total PTX + autotransplantation (n=52) Subtotal PTX (n=15)	25% 0%	1.5%	10.5% 7% at 4.34 years
Stracke S *et al (79)* (Munich); 1999	20 (HD)	Total PTX	30%	5%	33% at 20 months
Gasparri G *et al (83)* (Torino); 2001	446	Subtotal PTX Total PTX Total PTX + autotransplantation	5% 17% 2%	NA	5.1% follow-up NA
Jofre R *et al (81)* (Madrid, Buenos Aires); 2003	148 HD 309 HD (controls)	Total PTX + autotransplantation (n=129) Subtotal PTX (n=19)	16%	0.7%	16% at 3.1±2.1 years
Kestenbaum B *et al (5)* (USA); 2004	4.458 (3.769 HD; 789 PD)	NR	NA	3.1%	NA
Shih ML *et al (82)* (Rep of China); 2008	94 HD	Total PTX (n=44) Total PTX + autotransplantation/subtotal PTX + PTG tissue in situ conservation (n=54)	NA	NA	4.5% 18% at 5 years
Mazzaferro S *et al (6)* (Rome); 2008	77 HD	Subtotal (n=8) Total PTX (n=36) Total PTX + auto-transplantation (n=33)	NA	NA	NA PTH in KDOQI target: 6.5%; 9.1%; 9.1%; 7.8% at 1 mo, 1, 3.5 years
Tominaga Y (Japan) *(41,68)*: 2008; 1997	2.000 HD	Total PTX + autotransplantation	50% (at 7 years)	0.15%	20% at 10 years

HD - Hemodialysis; NA - not assessed/not available; PD - Peritoneal dialysis; PTX - Parathyroidectomy; TX - Renal transplantation.

a) Control of biochemical abnormalities

The objective of surgery should be to reduce the parathyroidian secretory mass in order to restore the normal PTH level, or at least to allow for the control of PTH secretion by medical therapy. Thus, postoperatory PTH levels above and bellow target should be regarded as therapy failure. Unfortunatelly, the PTH target is still to be defined: KDOQI (2003) recommended a 150-300 pg/mL range (2), while KDIGO (2009) a "two to nine times the upper normal limit for the assay" (3). Both recommendations are based on the necessity of a higher PTH level in dialysis patients to overcome the peripheral resistance to PTH actions, are graded as opinion with a weak strength and a low quality of evidence (2, 3). Furthermore, at the time when PTX was introduced, the aim was the control of higher PTH levels, as the risks associated with low PTH levels became evident only a decade later. Thus, the PTX results are difficult to evaluate and data from different series can barely be compared.

In all studies, PTH declined more than 10 times immediately after surgery to values 10-150pg/mL (67, 69, 79, 82, 83). This decline can be used as an indicator of the completeness of PTG removal. The PTH increases in the following years, eventually to >300 pg/mL or higher, a situation defined as recurrence. As various criteria to define recurrence were used in different series, comparisons are difficult, but the rate of recurrence is time-dependent, is not related to the surgical method and seems to be about 5-10% at 5 years and around 15-20% at 10 years (Table 4).

Hypoparathyroidism was reported either as persistent low calcium levels (usuallly under 8.5 mg/dL) in older series or as PTH under 150-60 pg/mL in the more recent ones, with a variable frequency from 5% to 50% at 5 years. It seems to be higher in case of total parathyroidectomy.

Not surprinsingly, in the series which evaluated the PTX results using KDOQI criteria (150-300 pg/mL), only 8% of patients were in target at 5 years and most of them were in the hypoparathyroidism range (6).

Calcium, phosphorus and alkaline phosphatase levels follow the same pattern: a decline immediately after efficient surgery with a rate proportional to the presurgery levels of PTH and alkaline phosphatase, and a progressive increase years thereafter. Only 14% of patients were estimated to be in KDOQI target for calcium at 5 years, and 70% for phosphate in a study by *Mazzaferro et al* (6).

In our patients, five years after PTX, hypoparathyroidism (PTH <100 pg/mL) was present in 69% of patients, while levels suggestive for HPT recurrence (PTH >800pg/mL) were found in 5%. Higher proportions of patients had hypocalcemia (54 *vs*. 8%), phosphate under 5.5mg/dL (54 *vs.* 34%) and a better control of calcium – phosphate product (under $55mg^2/dL^2$: 78 *vs.* 48%). An impressive reduction in alkaline phosphatase levels from 337 (95% CI 300 to 459UI) to 91 (95% CI 79 to 114UI) was obtained (Table 3).

Thus, although PTX efficiently reduces the PTH levels on short time, on long time (5 to 10 years), the frequency of recurrence is high and the proportion of patients with in target values for PTH, calcium and phosphate is small. Moreover, the proportion of patients with hypoparathyroidism is a matter of concern.

b) Control of bone disease

Although symptomatic relief (bone and joint pain) was reported immediately after PTX in 70-80% of patients, few data are available about changes in bone histomorphometry, fractures frequency and bone mineral content (BMD).

While low turn-over bone disease was described 10 months to 5 years after PTX in older studies, with a frequency up to 30% (84, 85), *Yajima et al* found a dramatic decrease in osteoclasts number and activity accompanied by an increase in osteoblasts number and in lamellar osteoid seams, indicating continuing bone formation and mineralization in spite of low PTH levels, 7 days after PTX (86, 87). More recently, the same authors reported the increased osteocytic death and mineralization around the lacunocanalicular system in association with a rapid decline in PTH occurring after PTX.

Changes in bone mineral density six months after PTX were investigated by *Chou et al* in 45 patients (88). They found a significant increase in BMD at lumbar level 6 months after surgery and concluded that PTX had a beneficial effect. Similar results were obtained by a Japanese group in a higher number of PTX patients (89). These authors also reported a post-PTX decrease in serum makers of bone resorption (collagen metabolic products and alkaline phosphatase), which, although uncorrelated with bone mineral content, was suggestive for a conversion from bone resorption to bone formation. To note, similar changes in BMD were observed following PTX for primary hyperparathyroidism (90).

In *Tominaga et al* experience, the bone mineral content increased primary in trabecular bone and only secondary in cortical bone. The cortical bone mineral content could not be normalized after PTX (68).

Recently, in an observational retrospective study, the risk of fractures was comparatively investigated in 5918 PTX dialysis patients and 16328 matched controls. A 32% and 31% reduction in risk of hip and combined fractures was observed, which confirms the beneficial effects of PTX on bone mentioned above (91).

Therefore, in small groups of patients, PTX seems to reverse bone resorption and to enhance bone formation, increasing the bone mineral content on long term (>6 months, probably years), and to reduce the risk of fractures. These observation would be translated in general rules if confirmed by randomized controlled studies.

c) Control of vascular and soft tissue calcifications

Vascular calcifications are highly prevalent in dialysis patients. Aortic, coronary artery and valvular calcifications were reported in about 66%, 75% and in >50%, respectively, as recently reviewed elsewhere (2). Once established, calcifications follow a progressive course (2). Both initiation and progression of vascular calcifications are directly dependent not only on increasing age, diabetes mellitus and male gender, but also on PTH, calcium and phosphate levels (2). Surprisingly, there are no studies addressing the association between severe sHPT and vascular calcifications. In the few longitudinal, generally retrospective studies published, PTX stopped or had no influence on the vascular and valvular calcifications progression (68, 92, 93). Although, a decrease in coronary and carotid calcification score was

reported in a small number of ESRD patients after PTX by *Bleyer et al* (94).

Calcific uremic arteriolopathy (calciphylaxis) is a rare but life-threatening form of skin small vessels calcification. It could be associated with high PTH, calcium and phosphate levels (80). PTX proved to ameliorate prognosis as compared to accepted medical therapy, at least according to one recent metaanalysis (95, 96).

Other cardiovascular effects of PTX should be mentioned. As in primary hyperparathyroidism, a reduction in blood pressure or a better control of hypertension were reported, which were correlated with the left ventricular hypertrophy and dilated cardiomyopathy regression, and the improvement in endothelial dysfunction (97-101).

Tumoral calcinosis is a rare form of metastatic tissue calcification. The most common sites of uremic tumoral calcinosis are shoulders, elbows, and hands. The pathogenesis of this condition is not completely understood, although hyperphosphatemia and increased calcium-phosphate product were the most consistently reported laboratory abnormalities. Calcium phosphate apposition was shown to decrease after PTX (102, 103).

To sum up, the effect of parathyroidectomy on vascular calcifications seems not impressive, with the notable exception of calciphylaxis, possibly because of the late nature of the intervention in a barely reversible process.

d) Reintervention

The rate of sHPT needing reintervention is time-dependent and varies from 5 to 18% at five years and could by as high as 20% at 10 years (68,83) (Table 4). Recurrences originate most often in glands overlooked at the initial operation, ectopic gland or from fragments of the initially resected gland. There are not notable differences in reintervention rates in total *versus* subtotal parathyroidectomy.

In case of total parathyroidectomy with autotransplantation, recurrences from autograft were reported in 20% of cases at five years in *Tominaga* series (68). In our data, only 2% of patients had reintervention caused by HPT recurrence at five years. All originated in ectopic (mediastinal) glands (Table 3).

In an analysis of 500 cases reported in literature from 1983 till 2006, *Richards et al* (73) found that only 17% of reoperative interventions were imposed by persistent sHPT. At reoperation, autograft hyperplasia (49%), supernumerary glands (20%), remnant parathyroid tissue hyperplasia (17%), a missed gland (7%) or a negative exploration (5%) were found. With the exception of autograft hyperplasia, the proportion were similar in total and subtotal PTX.

e) Influence on survival

Using USRDS and Medicare data base, *Kestenbaum et al* (5) conducted an observational study aimed to evaluate survival of dialysis patients after parathyroidectomy. They compared the outcome in PTX patients (n=4558) and in a cohort of dialysis patients matched for age, gender, ethnicity, primary renal disease, dialysis method and duration. The relative risk of death was about twice and one and half higher in the first 30 and 90 days after parathyroidectomy in PTX patients, but decreased thereafter and it was about 15% lower from 3 years through the

remainder of follow-up (to 7 years). The relative risk of death was lower in patients younger than 40 years and with a dialysis duration higher than 3 years. Although the large number of patients and the national sample allowed for overcome local therapeutic policies, the study did not take into account comorbidities and previous medication. Thus, the effect of selection of patients in a better clinical condition for surgery could have been important for survival, but it was not possible to appraise (5).

In another observational study, *Trombetti et al* (78) comparatively evaluated the risk of death in PTX patients (n=40) and in a control cohort of ESRD patients (n=664). The mortality was lower in PTX than in controls, but the advantage in survival was no longer significant when adjusted for comorbidities. Otherwise said, the survival was better in PTX patients as they were selected for surgery because had a better clinical condition. The authors concluded that "ESRD patients who undergo PTX may represent a subset of healthier subjects" (78). More recently, *Slinin et al* (58) also found a survival benefit for PTX patients in an observational study on Dialysis Morbidity and Mortality Study and Medicare data bases (N=10588). In their data, PTX was associated with higher mortality risk ratios in the first year, and progressively lower risk ratios subsequently.

Thus, PTX seems to offer a survival benefit for dialysis patients, at least 1 year after surgery. If confirmed in randomized controlled trials, this observation would condense the previously discussed, not so evident, advantages of parathyroidectomy in the control of CKD-MBD.

When parathyroidectomy is indicated in dialysis patients?

Current guidelines regard parathyroidectomy as a last resort measure in case of CKD-MBD medical therapy failure (12). Both KDIGO and KDOQI guidelines recommend PTX: "in patients with CKD stages 3-5D with severe hyperparathyroidism who fail to respond to medical/ pharmacological therapy, we suggest parathyroidectomy (KDIGO)" (3) and "in patients with severe hyperparathyroidism (persistent serum levels of intact PTH >800 pg/mL (88,0 pmol/L)), associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy. (OPINION) (KDOQI)" (2).

However, these guidelines were largely based on American and Western-European practice data. In other parts of the world, for instance in Japan, conditions may difffer: because renal transplantation is scarce, patients are treated mostly by dialysis and, as the mortality rate is low, over 25% of patients are longtime (>10 years) survivors. Moreover, there was a limited availability of new drugs (4). A similar situation is seen in Romania (104,105). The Japanese guidelines recommend an early PTX: "parathyroid intervention therapy should be recommended in patients with severe hyperparathyroidism (persistent high serum levels of iPTH levels >500 pg/mL), associated with hyperphosphatemia (serum P >6.0 mg/ dL) and/or hypercalcemia (serum Ca >10.0 mg/dL) that are refractory to medical therapy. Moreover, if patients suffer from the clinical symptoms (bone/joint pain, muscle weakness, irritability, itching, bone loss, anemia resistant to erythropoietin, dilated cardiomyopathy, calciphylaxis), parathyroid intervention therapy is absolutely

indicated" (4). On the other hand, because of the demonstrated relationship between PTG dimensions, nodular hyperplasia and PTH levels, parathyroidectomy is indicated when one gland has a diameter >1cm, a weight over 500mg (volume >500mm$^{3)}$ or the total glandular weight is higher than 2000mg (Table 5).

Table 5. Indications for parathyroidectomy [107]

1. High level of PTH (intact PTH >500 pg/mL)
2. Detection of enlarged parathyroid glands by imaging diagnosis (volume of the largest gland >500 mm3)
3. Findings of osteitis fibrosa cystica or high bone turnover by bone metabolic markers
1 + 2 + 3 and at least one of factors refractory to medical treatment
Factors refractory to medical treatment
Hypercalcemia (>10.2 mg/dL)
Hyperphosphatemia (>6.0 mg/dL)
Progressive ectopic calcification
Severe symptoms
Skeletal deformity due to osteitis fibrosa
Progressive bone loss (Bone mineral density)
Calciphylaxis
Anemia resistant to erythropoietin

The Romanian Society of Nephrology guidelines recommend parathyroidectomy in case of "hypercalcemia and/or hyperphosphatemia resistant to therapy, when PTH is severely increased (>800 pg/mL), at least one gland with a diameter over 1 cm can be echographically seen, or mechanical complications (fractures, tendon ruptures) and calciphylaxis develop" (106).

Thus, all guidelines are in agreement that parathyroidectomy should be indicated: (1) as part of an integrated plan of care in CKD-MBD; (2) in certain conditions, generally, when medical therapy fails. Divergences appear in the definition of the intervention moment. The Japanese guidelines (4) tend to place the intervention earlier (PTH >500pg/mL) and rely on parathyroid gland dimensions (one gland with a diameter over 1cm), aiming to prevent the poorly reversible target organs damage, in a dialysis population with low chances of transplantation.

None of the guidelines explicitly discuss the selection of patients. As presented above, there are indices that PTX is recommended in younger patients without a high burden of comorbidities, e.g. diabetes mellitus. As not only the peak PTH value, but also the duration of exposure to high PTH values seems to be important for target organ (bone, vessels) damage, a postponed intervention will exclude from surgery patients who had accumulated comorbidities just as a result of the delayed decision to recommend operation.

Thus, if severe secondary hyperparathyroidism is not prevented by adequate medical therapy and the perspective of long duration dialysis therapy exists, parathyroidectomy shoud be considered as soon as a parathyroid gland has a diameter >1 cm and PTH is persistently over 500 pg/mL, in order to avoid irreversible bone and vessel damage.

Medical therapy for severe hyperparathyroidism of CKD

By definition, severe secondary hyperparathyroidism is poorly responsive to conventional medical treatment, e.g. phosphate binders, calcium, vitamin D analogs in pulse therapy. The discovery and cloning of calcium receptor (Brown, 1993 (10)) opened the way for a new class of drugs, the calcimimetics. It was hoped that cinacalcet hydrochloride, the only calcimimetic clinically available, will prove its efficacy even in severe secondary hyperparathyroidism.

Calcimimetics – mechanism of action

Calcium receptor (CaR) is the main regulator of parathyroid response to serum calcium (10,108). It plays a central role in the pathogenesis of secondary hyperparathyroidism in CKD patients (11) and, consequently, is an attractive therapeutic target.

The term calcimimetics has been coined for those compounds that can modulate the activity of calcium receptors (109). Type II calcimimetics are organic compounds that bind to regions within the membrane-spanning domain of the CaR and have the potential to increase the sensitivity of the CaR to calcium, lowering the threshold of receptor activation by calcium. Thus, they are allosteric modulators of the receptors.

In experimental models, calcimimetics were also shown to up-regulate CaR and VDR expression and to inhibit parathyroid cell proliferation and hyperplasia (110). These actions could allow calcimimetics: (i) to maintain effectiveness during long-term therapy; (ii) to maintain enhanced efficacy in patients with severe disease despite decreased CaR and VDR expression and to avoid the development of severe sHPT if initiated early, in patients with mild or moderate sHPT.

Cinacalcet hydrochloride is a potent and selective type II calcimimetic agent, clinically used in primary HPT (111), secondary HPT (112-121) and even in a case of pregnancy with hereditary hypophosphatemic vitamin D resistant rickets (122).

Cinacalcet in severe secondary hyperparathyroidism

a) Control of biochemical abnormalities

A large number of randomized controlled trials investigated the effects of calcimimetics on the control of sHPT in patients with ESRD (112-121). Several studies compared cinacalcet plus existing therapies - including continued, but restricted, vitamin D analog use - with standard-of-care, consisting of unrestricted use of phosphate binders and vitamin D analogs. Some of these addressed also to patients with severe sHPT (PTH >800 pg/mL) (Table 6).

A meta-analysis by *Strippoli et al* (123) examined some of these studies and concluded that the addition of cinacalcet to standard-of-care significantly improved the control of serum PTH, calcium, phosphate and calcium–phosphate product levels as compared to the standard-of-care alone.

However, whether cinacalcet could control parathyroid hyperfunction in patients with marked parathyroid hyperplasia is controversial. For instance, in the studies which demonstrated the beneficial effects of cinacalcet in sHPT, only few patients with severe hyperparathyroidism were included.

Data from three placebo-controled phase 3 studies investigating the efficacy

Table 6. Cinacalcet hydrochloride trials

Study	Patients (number)		Reduction rate (%)				Patients with in target PTH (%)*
	Total	with PTH >800pg/mL	Ca	P	Ca x P	PTH	
Block et al (2004) [112]	371	72	6,8	8,4	43	63	20
Lindberg et al (2005) [113]	294	102	6,5	7,2	40,5	60	10
Chertow et al (2006) [114]	72	NA	9,7	11,1	48	NA	NA
Arenas et al (2007) [115]	28	NA	13,1	10,4	70	NA	NA
Sterrett al (2007) [116]	99	NA	6,5	3,6	47,8	NA	NA
Lazar et al (2007) [117]	35	NA	8,1	10,1	29,6	NA	NA
Fishbane et al (2008) [118]	87	NA	7,1	1,2	47,3	NA	NA
Messa et al (2008) [119]	368	NA	7	5	46	NA	NA
Fukagawa et al (2008) [120]	72	19	8,1	10,2	54,3	60	25
Ureña et al (2009) [121]	1856	NS	8	9	45	65	21

* in patients with PTH >800pg/mL
NA - not assessed/not available

and safety of a once-daily cinacalcet dose in sHPT were appended and used in a *post-hoc* analysis in order to compare the response to therapy in patients with mild (PTH 300-500pg/mL), moderate (PTH 500-800 pg/mL) and severe sHPT (PTH >800pg/mL) (124). Patients received standard therapy in combination with cinacalcet (n = 546) or placebo (n = 408). Cinacalcet was effective in reducing serum iPTH and Ca x P, even in patients with severe sHPT, but these patients were less likely to achieve the KDOQI targets than those with moderate sHPT. After 6 months of therapy with cinacalcet, 76% of patients with mild sHPT achieved a serum iPTH level of <300 pg/mL as compared to 55% of patients with moderate sHPT. Similarly, 54% of patients with mild sHPT achieved two targets (an iPTH of <300 pg/mL and a calcium-phosphate product <55mg^2/dL^2) as compared with 36% and 9% of patients in the moderate or severe groups, respectively. Thus, the initiation of therapy with cinacalcet at an earlier stage would provide a better control of serum PTH, calcium, phosphorus and Ca x P.

Similar results were reported by *Lindberg et al* (113) and *Fukagawa et al* (120) in 102 and 19 patients with severe sHPT (PTH >800 pg/mL), where the target of PTH was reached in 10% and 25% of patients, respectively.

In a Pan-European observational study (ECHO study) (121), 1865 dialysis

patients with secondary hyperparathyroidism of varying severity were stratified according to baseline iPTH in three groups: mild (300–<500 pg/mL), moderate (500–800pg/mL) and severe (iPTH >800pg/mL) sHPT. The achievement of KDOQI targets for PTH at the 12th month was higher in patients with mild disease (41%) than in those with moderate (29%) and severe disease (21%). In patients with severe disease, the target for phosphorus, calcium and calcium-phosphorus product was obtained in 50%, 50% and 70%. Notably, cinacalcet therapy reduced the number of parathyroidectomies. Before initiation of cinacalcet therapy, 8% of patients underwent a parathyroidectomy; from baseline to month 6 and from months 6 to 12, 0.8% and 2% of patients, respectively, were parathyroidectomized. Again, these data sustain an earlier use of cinacalcet, in less-severe forms of sHPT, aiming to avoid the occurrence of therapy-resistant sHPT.

Experimental studies suggested that calcimimetics could induce parathyroid hyperplasia regression. This possibility was explored in a clinical setting in two studies, where a significant reduction in parathyroid gland volume and vascularization was found. However, these were more evident in smaller glands (<500 mm^3) (125, 126). Therefore, even from an anatomical point of view, the use of cinacalcet in earlier sHPT stages is more beneficial. Additionally, the drug could be used at a lower dosage in earlier stages.

In conclusion, calcimimetics are a solution in about 20% of cases when prescribed to patients with severe secondary hyperparathyroidism (PTH>800 pg/mL), but may reduce up to 4 times the need of parathyroidectomy when prescribed in a lower dosage to patients with moderate or mild sHPT (PTH<500 pg/mL).

b) Control of bone disease

In a study on HD patients (PTH>300 pg/mL) using histomorphometry on bone biopsy, *Malluche et al* (127) failed to prove a significant effect of cinacalcet administered for 52 weeks on bone remodelling as compared to conventional therapy. However, in the cinacalcet-treated patients, circulating N-telopeptide, an indicator of bone reabsorption significantly decreased, while in the control group no significant change was noted. It could be argued that the low number of participants and the inhomogeneity of bone lesions interfered the results.

More important, a 64% decrease in the risk of fractures was reported in an *ad-hoc* analysis of pooled data from all clinical studies comparing a 30-180 mg dose of cinacalcet to standard therapy with a follow-up of at least 6 months (128). However, this was a *post-hoc* analysis and the results are not confirmatory in nature.

c) Control of vascular calcifications

Although a decrease in vascular calcifications after cinaclacet was described in experimental conditions (129), this was not investigated in clinical trials. Although, in the previously mentioned *ad-hoc* analysis (128), cardiovascular, but not all-cause hospitalization was lower in cinacalcet (RR 0.63 95% CI 0.48-0.86). This was confirmed recently in an observational study on a large data base, where both cardiovascular and all-cause mortality were remarkably reduced by 24% and 26% in hemodialysis patients treated (n=5976) with cinacalcet as compared to those who

received conventional therapy (n=19174) (130). If such an impressive effect really exists it should be confirmed in the upcoming EVOLVE trial, designed to test this hypothesis (131).

d) Cost effectiveness

As additional costs incurred by cinacalcet amounted ~1000$ per patient treated/month, a cost utility analysis was conducted in USA by *Narayan et al* (132) comparing parathyroidectomy with cinacalcet therapy in dialysis patients with severe secondary HPT. Cinacalcet was more advantageous for patients "who could expect a brief stay (<16 months) on dialysis therapy". In USA conditions, these patients were either candidates for renal transplantation or patients in a poor condition, with a short life expectancy, at high-risk for surgery.

Another cost–utility analysis was performed in Great Britain. As cinacalcet therapy was found to have an incremental cost-effectiveness ratio of 89000 EUR per quality-adjusted life-year (QALY) and the willingness to pay of the National Health Service was evaluated at 43200 EUR, the authors concluded that "cinacalcet is unlikely to be considered cost-effective" (133).

In Romania, additional costs related to cinacalcet therapy would be 376 EUR per patient treated per month (366 EUR for the drug and 10 EUR supplementary laboratory tests). Because transplantation rate is low and the life expectancy on dialysis is long, the proportion of patients candidates for therapy is probably about 1%. In these conditions, the increase in cost would be 0.3 EUR/HD session. When using PTH criterion: >300 pg/mL (recommended by manufacturer), >500 pg/mL (recommended by Japanese guideline) or >800 pg/mL (recommended by KDOQI), the proportion of patients to be treated would be 42%, 30% and 14%, and the corresponding additional cost per HD session would be: 12.5 EUR, 8.9 EUR and 4.2 EUR, respectively. This is to compare with the cost of a parathyroidectomy which is reimbursed at a rate of about 600 EUR, and in the condition of a 25% rate of failure at 10 years, would represent an additional cost for the system of 11 EUR per PTX patient/year or 0.1 EUR/HD session. Clearly, cost effectiveness favours parathyroidectomy in Romanian patients, suggesting a restrictioned use of cinacalcet to those with severe sHPT and an estimated HD duration less than 16 months, e.g. young patients with high chances of transplantation or patients with severe comorbidities and high surgical risk.

Outline of medical and surgical therapy of severe secondary hyperparathyroidism

There are no controlled studies to directly compare outcome of medically and surgically treated patients with severe secondary hyperparathyroidism. Moreover, neither the efficacy of surgery nor of the medical therapy were adequately tested in this setting. Additionally, cinacalcet is a new drug and clinical experience is still accumulating. For now, we can compare outcome using only data from studies of inequal quality, previously reviewed, evaluating individually each therapeutic method (Table 7).

Biochemical abnormalities (mostly calcium and PTH) of CKD-MBD seem better controlled by cinacalcet, but this should be interpreted with caution, as

Table 7. Outline of medical and surgical therapy in severe secondary hyperparathyroidism

	Parathyroidectomy	Grade of evidence	Cinacalcet HCl	Grade of evidence
Biochemical abnormalities				
Calcium*	14%	B	50%	B
Phosphate*	70%	B	50%	B
Calcium phosphate product*	NA	-	70%	B
PTH*	9%	B	20%	B
Bone abnormalities				
Improvement in bone histology	++	C	±	C
Fractures (risk reduction)	-32%	C	-64%	C
Bone mineral density	++	C	?	-
Tumoral calcinosis	+	C	NA	-
Calciphylaxis	++	C	NA	-
Cardiovascular abnormalities				
Vascular calcifications	?	C	NA	-
Dilated cardiomyopathy	+	C	NA	-
Survival	+15%	B	+26%	B
Therapy related	Reintervention 20% at 5 yrs	B	Continuous therapy	-
Cost effectiveness	+++	A	+	A

The grade of evidence was evaluated as A - strong (randomized controlled trials); B - moderate (observational studies on large cohort); C - low (observational studies on small series of patients); D - very low (occasional reports).
* KDOQI recommendation were used in defining in target proportions of patients. NA - not available

KDOQI recommendations which were used in analysis define a target interval for PTH of 150-300pg/mL, and a large part of PTX patients had values under 100 pg/mL (6, 68). Moreover, reference PTH values are still to be defined for this population (3). Only 14% of PTX patients are in target for calcium, mostly because of lower values, although symptomatic hypocalcemia is unsual, which supports the trend toward hypoparathyroidism after PTX. On the other hand, calcium is better controlled, but only one patient in five responds to medical therapy as judged by PTH. Thus, both therapies have a similar moderate efficiency in controlling biochemical abnormalities. Disadvantages are the risk of hypoparathyroidism for PTX and the low rate of responders for medical therapy.

Improvement in bone histology was documented in PTX patients, but it is still uncertain in cinacalcet treated patients (86, 87, 127). However, the risk of low-turnover bone disease exists in a third of PTX patients (84). In spite of these, the risk of fractures is decreased after parathyroidectomy (91) and bone mineral density ameliorated (88). In cinacalcet patients, the risk of fractures is also decreased (128). Nevertheless, data are from observational studies and in case of cinacalcet the study

population included a significant proportion of patients without severe sHPT. There are some reports describing regression of ectopic (tumoral) calcifications and a favourable evolution of calciphylaxis after PTX (102). Again, both therapies seem to have similar efficiency on bone disease, but the strength of evidence is not impressive.

The effect on cardiovascular abnormalities was not systematically assessed, probably because CKD-MBD was only recently introduced.

Data on survival are from observational not confirmatory studies, and suggest an increase of 15% and 26% in chances of survival for PTX and medical therapy, respectively. If confirmed, it would be unequaled by any therapeutic method tested till now in hemodialysis patients. Parathyroidectomy has the disadvantage of a non-negligible rate of reinterventions, while cinacalcet is a continuous therapy.

Finally, cost effectiveness favours parathyroidectomy in the majority of patients.

The strength of evidence supporting both methods efficacy in severe secondary hyperparathyroidism is at most moderate. Hypoparathyroidism can follow after parathyroidectomy and reinterventions are not infrequent, while in medical therapy duration of treatment is indefinite and the rate of response is low. The methods should be regarded as complementary and cost effectiveness analysis favours parathyroidectomy in patients with anticipated long duration of dialysis and good chances of survival. For those expecting a transplantation in the following months or with a very high comorbidity index, medical therapy is a better option.

In conclusion, both methods, surgical parathyroidectomy and medical therapy address a late stage of chronic kidney disease-MBD, when bone and cardiovascular abnormalities are poorly reversible, a better approach would be to act in earlier stages. An early ”pharmacological parathyroidectomy”, using cinacalcet in combination with conventional therapy, could be a more efficient strategy in CKD-MBD, but this remains to be tested and proved.

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