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UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

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Secondary Hyperparathyroidism: Update on pathogenesis, diagnosis and treatment

GRADUATION THESIS

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This graduation paper was made at Department of Nephrology of Klinicki Bolnicki Centar Sestre Milosdrnice, University of Zagreb School of Medicine under supervision of Doc. dr. sc. Draško Pavlović and it was submitted for evaluation in the academic year 2014-2015.

Mentor: Doc. dr. sc. Draško Pavlović

List of Abbreviations

PTH-Parathyroid Hormone
CKD-MBD-Chronic Kidney Disease-Mineral Bone Disorder
CKD-Chronic Kidney Disease
CaSR-Calcium Sensitizing Receptor
VC-Vascular Calcification
CAC-Coronary Artery Calcium

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Summary

Title: Secondary Hyperparathyroidism: Update on pathogenesis, diagnosis and treatment

Author: Stipe Ivancic

Secondary hyperparathyroidism is a frequently encountered problem in the management of patients with chronic kidney disease (CKD). Its pathophysiology is mainly due to hyperphosphatemia, vitamin D deficiency and resistance. Resistance in the form of downregulation in parathyroid vitamin D and calcium-sensing receptors represent critical steps in pathogenesis. Eventually abnormalities in mineral phosphate, calcium, and vitamin D begin to appear. Lack of control of serum PTH and associated minerals result in bone pathologies and vascular calcification. This condition has a high impact on the mortality and morbidity of dialysis patients. Early diagnosis of secondary hyperparathyroidism is crucial in the management of patients with CKD. Achieving current targets for the key mineral parameters in the management of SHPT set by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines can be challenging. This review summarizes the current understanding and evidence supporting strategies for SHPT treatment in CKD patients. Treatment should include a combination of dietary phosphorus restriction, phosphate binders, vitamin D sterols, and calcimimetics. Parathyroidectomy is effective in suitable candidates' refractory to medical therapy and the standard against which new approaches should be measured.

Key Words: Chronic Kidney Disease-Mineral Bone Disorder, Vascular Calcification, FGF 23, PTH, Bone Biopsy, Calcimimetics, Phosphate Binders, Calcitriol, Paricalcitol

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Introduction

Secondary hyperparathyroidism is a maladaptive response that occurs as a result of declining kidney function. Though this response is adaptive in the early stages, prolonged stimulus leads to several pathologies involving extra skeletal calcification, several possible bone disorders and finally derangements in PTH, phosphate, calcium and vitamin D serum levels. These disorders are labeled under the term CKD-MBD, to replace the previous term of renal osteodystrophy, which focused primarily on CKD related bone pathologies. Skeletal changes that take place in CKD increase the prevalence of hip fracture compared to general population in stages of CKD including dialysis. Dialysis patients in their 40s have a relative risk of hip fractures 80-fold that of age- and sex-matched controls (Alem et al. 2000). Cardiovascular disease accounts for 70% of all deaths in patients with CKD, with an overall mortality of 20% per year in patients with dialysis (USRDS et al. 2003). In individuals with kidney failure on dialysis, cardiovascular mortality rates are 10-500-times higher than in the general population, even after adjustment for gender, race and the presence of diabetes (Foley et al. 1998). One mechanism by which abnormal mineral metabolism may increase cardiovascular risk is by inducing or accelerating arterial calcification. A substantial body of observational data has now established components of disordered mineral metabolism as independent risk factors for adverse outcomes in CKD patients. These include serum levels of phosphate, PTH and FGF-23. With all of these derangements there seems to be an increase in morbidity and mortality in patients with CKD.

Pathogenesis of Secondary Hyperparathyroidism

Physiology of Calcium and Phosphorus Homeostasis

Parathyroid Hormone

PTH acts mainly on two organs: the bone and the kidney. The immediate effect of PTH on bone is to mobilize calcium from skeletal stores that are readily available and in

equilibrium with the extracellular fluid (Talmage & Mobley 2008). Later effects on bone include, PTH activation of bone resorption to further increase calcium (Talmage & Mobley 2008). Renal effects include: calcium reabsorption in the ascending loop of Henle and distal convoluted tubule (Van Abel et al. 2005). Phosphate reabsorption under PTH occurs in the proximal tubule (Pfister et al.1997). This effect is primarily mediated by decreased activity, internalization, and degradation of the sodium-phosphate cotransporter in the luminal membrane of the proximal tubules (Pfister et al.1997). Finally, PTH stimulates the synthesis of 1-alpha hydroxylase in the proximal tubules and thus converts calcidiol to calcitriol (Broadus et al. 1980). Calcium has a negative feedback effect on the parathyroid glands through the calcium sensitizing receptor. Phosphate has shown to have a direct stimulatory effect on parathyroid gland hormone secretion (Brown & Hebert 1997).

Vitamin D

The active form of Vitamin D (1, 25 dihydroxyvitamin D) is synthesized in the kidney by the enzyme 1-alpha hydroxylase. Vitamin D stimulates reabsorption intestinal calcium and phosphate. Along with PTH, vitamin D is a required factor for in the bone reabsorption. It also increases the reabsorption of urinary calcium and phosphorus in the renal tubules. Through the vitamin D receptors it has a direct effect on the parathyroid glands to supress PTH secretion (Ben-Dov et al. 2007).

Fibroblast Growth Factor- 23

FGF-23 is a circulating peptide that plays a key role in the control of serum phosphate concentrations (Llach 1995). FGF-23 is secreted by bone osteocytes and osteoblasts in response to calcitriol, increased dietary phosphate load, PTH, and calcium (Llach 1995). FGF-23's primary function is to maintain normal serum phosphate concentration by reducing renal phosphate reabsorption and by reducing intestinal phosphate absorption through decreased calcitriol production (Llach 1995). FGF-23 also suppresses PTH secretion by the parathyroid gland (Llach 1995).

Calcium and Phosphorus Metabolism in Renal Failure

Hyperphosphatemia

The subclinical hyperphosphatemia that occurs at estimated GFR's of >30 mL/min, is said to be the principal factor leading to the development of secondary hyperparathyroidism (Llach 1995). As GFR decreases so does the filtered phosphate load. The initial increases in phosphate promote the following:

1. The induction of hypocalcaemia by serum phosphate and serum ionized calcium binding (leading to increase PTH synthesis)
2. Decreased formation/activity of calcitriol by direct effects of phosphate at the enzyme level (leads to a decrease in phosphate and calcium absorption in the intestines)
3. Increased PTH gene expression (leading to increase PTH secretion)
4. Increased secretion of FGF-23 (Llach 1995)

From the viewpoint of phosphate homeostasis, the initial elevation in PTH secretion as result of high phosphate is appropriate since the ensuing increase in phosphate excretion lowers the plasma phosphate concentration toward normal. Among patients with severely reduced GFR, PTH inhibits proximal tubule phosphate reabsorption from the normal 80 to 95 percent to as low as 15 percent of the filtered phosphate (Gutierrez et al. 2005). Hyperparathyroidism also tends to correct both the hypocalcemia (by increasing bone resorption) and the calcitriol deficiency (by stimulating the 1-hydroxylation of calcidiol (25-hydroxyvitamin D) (Gutierrez et al. 2005). However, as GFR further decreases, filtered phosphate cannot be excreted and more phosphate is mobilized from bone (Gutierrez et al. 2005). PTH and FGF-23 help maintain normo-phosphatemia until the GFR reaches 20 ml/min (Gutierrez et al. 2005).

To make the situation even more complicated hyperphosphatemia also stimulates the secretion of FGF-23, which acts to suppress PTH secretion and vitamin D synthesis (Gutierrez et al. 2005). FGF-23 molecule synthesis increases at an early stage even

without hyperphosphatemia contributing to the possibility of the revised trade off hypothesis (Rodriguez et al. 2005) (Figure 1). Early target in treatment of secondary hyperparathyroidism revolves on the reduction of phosphate load and reduces mechanisms of the revised trade off hypothesis.

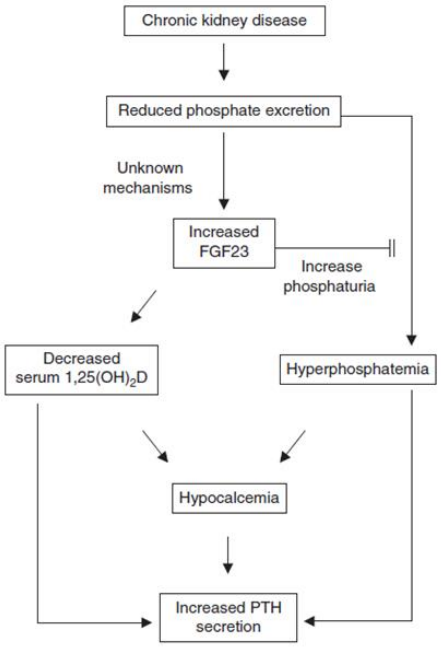


Figure 1. Role of FGF23 in the revised trade-off theory on pathogenesis of secondary hyperparathyroidism, according to: Fukagawa (2013), p 866, from Expert Opinion Pharmacotherapy. The reverse trade off hypothesis is the following: dietary phosphorus load supresses activation of vitamin D within the kidney. FGF-23 is synthesized to reduce serum phosphorus and inhibit vitamin D synthesis. These two mechanisms stimulate PTH secretion.

Calcitriol Involvement

The initial decline in calcitriol synthesis is most likely affected by the increased secretion of FGF-23 by the osteoblasts (the revised trade-off hypothesis) (Fukagawa et al. 2013). This is especially prominent at early stages of chronic renal failure. Other mechanisms such as hyperphosphatemia reduce calcitriol synthesis during later stages of renal failure. The FGF-23 has a direct inhibitory effect on the renal 1-alpha hydroxylase. Low

calcitriol concentrations increases PTH secretion by indirect and direct mechanisms. Indirect effects on PTH are achieved through decreased intestinal absorption of calcium and calcium release from bone, both of which promote the development of hypocalcaemia, which stimulates PTH secretion. Direct mechanisms result from the loss of inhibitory affects at the level of VDR receptors on parathyroid glands (Gogusev et al. 1997). Low calcitriol concentrations appear to play an important role in the decline in VDRs since the defect can be largely corrected by calcitriol supplementation (Gogusev et al. 1997). Calcitriol is given to increase the number of VDR's to sensitize the parathyroid gland for further release of parathyroid hormone (Gogusev et al. 1997).

Hypocalcaemia and Calcium Sensitizing Receptors (CaSR)

The release of PTH from parathyroid glands in response to low concentration of calcium is regulated by the CaSR (Naveh-Many et al. 1995). In CKD, the number of CaSRs may be reduced in hypertrophied parathyroid glands, particularly in areas of nodular hypertrophy (Naveh-Many et al. 1995). Decreased expression of the CaSR appears to be related to the proliferation of parathyroid tissue, and both may be related to increased phosphorus (Naveh-Many et al. 1995). The change in receptor number can lead to inadequate suppression of PTH secretion by calcium, resulting in inappropriately high PTH concentrations in the setting of normal or high calcium concentrations (Naveh-Many et al. 1995). Total serum calcium concentration are low during CKD as a result of all of the aforementioned mechanisms. This low serum calcium can be considered to be a stimulus to increase in PTH secretion (Naveh-Many et al. 1995). The role of the CaSR in regulating parathyroid gland function has direct therapeutic implications. The administration of a calcimimetic agent increases the sensitivity of the receptor to extracellular calcium and can lower PTH secretion from the parathyroid gland (KDIGO et al. 2009).

Skeletal resistance to PTH

Skeletal resistance to the calcemic action of PTH appears to contribute to the genesis of secondary hyperparathyroidism in CKD. Resistance to PTH is primarily due to down regulation of PTH receptors induced by the high circulating PTH concentrations, although both calcitriol deficiency and hyperphosphatemia may play a contributory role (Isakova et al. 2011).

Parathyroid Hyperplasia

Prolonged stimulation of PTH secretion leads initially to diffuse polyclonal hyperplasia followed by monoclonal nodular hyperplasia (Tominaga & Takagi 1996) (Figure 2). These two process ultimately lead to tertiary hyperparathyroidism where PTH is autonomously secreted, that is unresponsive to serum calcium levels (Tominaga & Takagi 1996). Furthermore therapies such as calcimimetic and vitamin d analogs do not reduce the levels of PTH (Drueke et al. 2007). Potential pathogenic factors include down regulation of VDR and CaSR receptors (Tominaga & Takagi 1996). As monoclonal nodular hyperplasia develops, it continues overgrow into an adenoma, further increasing PTH secretion (Tominaga & Takagi 1996). Often these patients require parathyroidectomy's to control calcium-phosphate homeostasis (Tominaga and Takagi 1996).

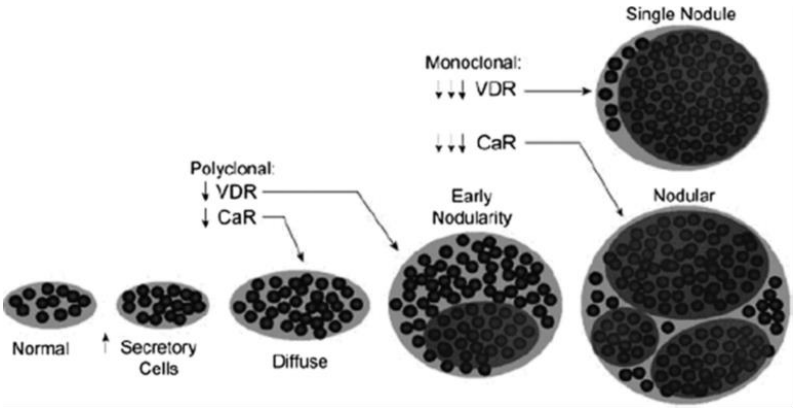


Figure 2. Development of parathyroid hyperplasia, according to: Tominaga (1996), p 339, from Current Opinion Nephrology Hypertension.

Vascular Calcification

The initial step in the development of vascular calcification is the de-differentiation of vascular smooth muscle cells to osteo/chondrogenic-like cells by transcription factors such as Runx2 and Msx2 (Figure 3) (Moe & Chen 2008). These cells can then form matrix vesicles or apoptotic bodies that mineralize on an extracellular matrix, presumably in a manner similar to bone (Moe & Chen 2008). Cells form collagen and non-collagenous proteins in the intima or media and incorporate calcium and phosphorous into matrix vesicles to initiate mineralization and further grow the mineral into hydroxyapatite (Moe & Chen 2008). The existence of abnormal bone remodelling in CKD may accelerate the process by providing excess calcium and phosphate for matrix vesicles (Moe & Chen 2008). The overall pathogenesis is regulated by a balance of pro-calcifying factors and inhibitors (Moe & Chen 2008). Unfortunately in CKD, the procacifying factors including hyperphosphatemia and hyperparathyroidism are common, and inhibitors such as fetuin-A and matrix gla protein are reduced (Moe & Chen 2008).

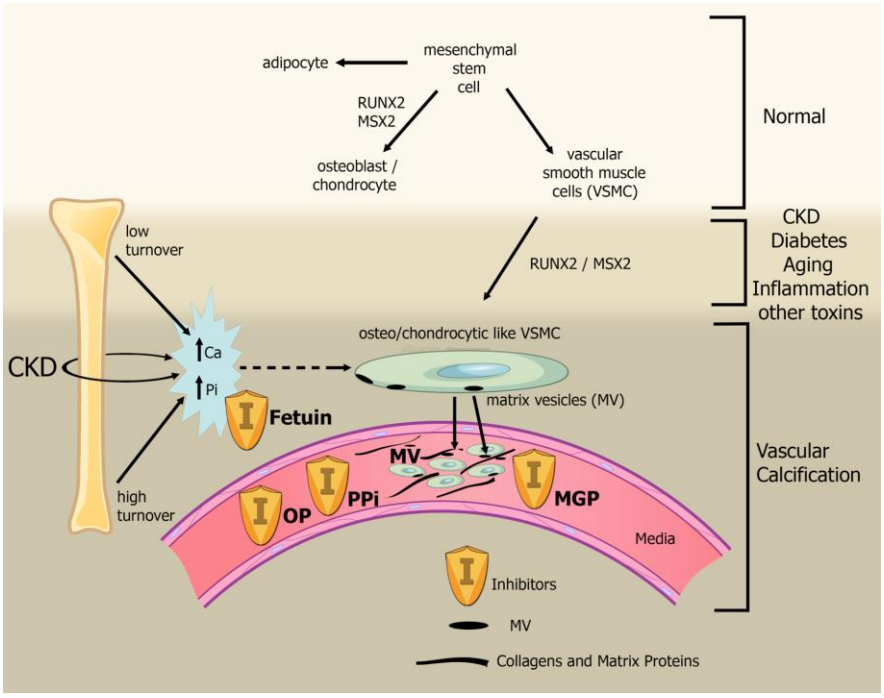


Figure 3. Pathogenesis of vascular calcification according to: Moe (2008), p 215, from Journal of the American Society of Nephrology.

Diagnosis of Secondary Hyperparathyroidism

Diagnosing Bone Pathologies

Overview

Several bone pathologies can occur in patients with CKD (Figure 4). These include the following:

1. Predominant hyperparathyroid-mediated high-turnover bone disease
2. Low-turnover osteomalacia
3. Mixed uremic osteodystrophy
4. Osteomalacia
5. Adynamic bone disease
6. Aluminum deposition bone pathologies (Torres et al. 2014)

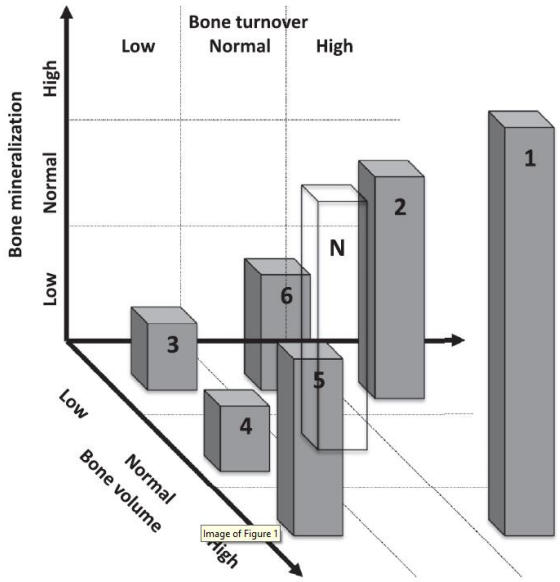


Figure 4. Different bone pathologies according to: Torres (2014), p 615, from Seminars in Nephrology. Column 1 shows typical severe secondary hyperparathyroidism with high bone turnover, volume, and mineralization. Column 2 denotes the case of secondary hyperparathyroidism with low bone volume, normal mineralization, and high bone turnover. Column 3 shows the case of adynamic bone disease with all 3 TMV parameters reduced. Column 4 describes the usual osteomalacia with low bone turnover, low mineralization, but normal bone volume. Columns 5 and 6 show2 situations of mixed osteodystrophy; In column 5 bone volume is high, turnover is low, and mineralization is normal; in column 6 bone volume is low, turnover is normal, and mineralization is reduced.

Bones are evaluated by three parameters: turnover, mineralization, and volume (TMV classification). Each form of bone disease has its own characteristic histologic findings. Regardless of the type of bone disease, fracture risk in CKD patients is 14 to 17 greater than normal controls (Coco & Rush 2000).

Role of PTH

PTH is used as marker for severity of hyperparathyroidism. It cannot predict the underlying bone disease particularly PTH levels in the moderate range (KDIGO et al. 2009). PTH ranges for prediction of underlying bone disease include the following: Intact serum PTH values <100 pg/mL are associated with a decreased likelihood of osteitis fibrosa (OF) and an increased incidence of adynamic bone disease, An intact serum PTH level >450 pg/mL is typically associated with hyperparathyroid bone disease and/or mixed uremic osteodystrophy (MUO) and Intermediate PTH levels between 100 and 450 pg/mL do not correlate well in predicting certain bone disease (KDIGO et al. 2009).

Values mentioned previously have used intact assays for PTH measurement. There have been second and third generational assays in clinical use. Unfortunately present clinical data is based on intact assays (KDIGO et al. 2009). KDIGO guidelines suggest use of caution when using second or third generational assays (KDIGO et al. 2009). Intact PTH assay use a capture antibody against the C-terminal part of the PTH molecule (epitopes 39-84) and a radioiodinated detection antibody directed towards the N-terminal portion of PTH (epitopes 13-34), and therefore detects the intact as well as large C-terminal fragments that lack portions of the N-terminus (that is the first 12 amino) and are termed non-PTH(1-84) (Figure 5) (John et al. 1999). Non-PTH(1-84) fragments are a subset of large C-terminal fragments that lack only a small portion of the N-terminus, and are therefore measured by the intact PTH assay (John et al. 1999). They differ from other C-terminal fragments that lack a large portion of the N-terminus and are not detected by the intact PTH assay (John et al. 1999). In individuals with

normal renal function, non-PTH(1-84) fragments account for 10 percent of all C-terminal PTH fragments and for 20 percent of the PTH detected by the intact PTH assay (Lepage et al 1998). In patients with chronic kidney disease, such as in patients on hemodialysis, non-PTH(1-84) may account for as much as 45 percent of the immunoreactivity measured by the intact PTH assay (Block et al. 2004).
Bioactive assays use antibodies directed at epitopes located at N terminal ends as well as C terminal ends bypassing non-PTH fragments detected by first generational assays. bioactive PTH assay reacted with PTH(1-84) and with another N-terminal PTH fragment, which is not recognized by the intact PTH assays (Figure 5) (D'Amour et al. 2003). In individuals with normal renal function, N-PTH accounts for 4 to 8 percent of PTH detected with a bioactive PTH assay, whereas it accounts for up to 15 percent in patients with renal failure (D'Amour et al. 2003). To further add, there is excellent correlation between intact and bioactive assays. Mean PTH levels in intact assays are larger due to detection of large c-fragments (non-PTH 1-84) mentioned above (D'Amour et al. 2003).

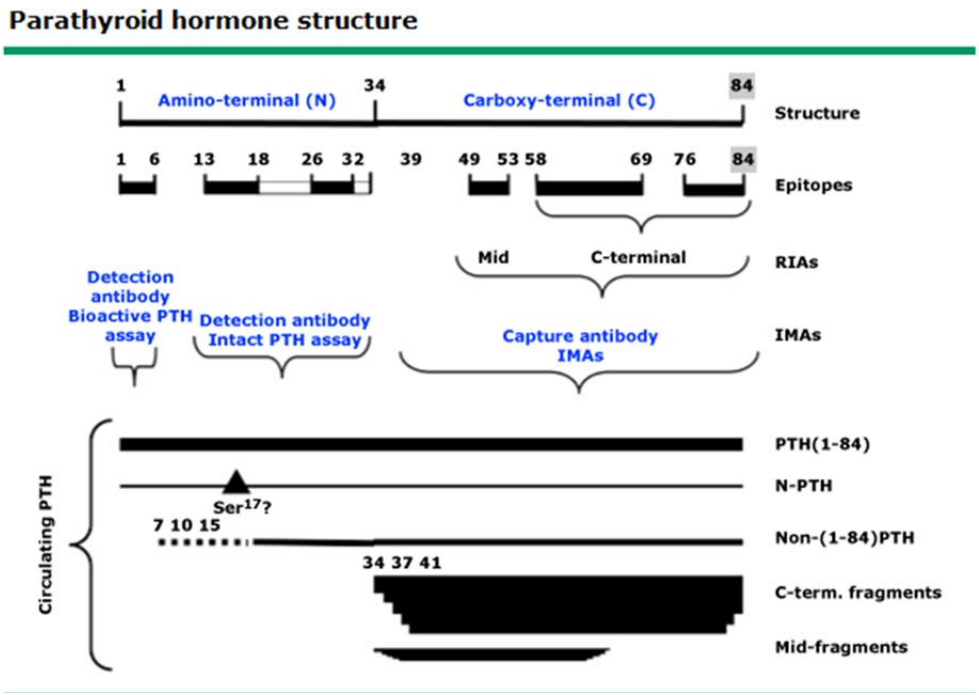


Figure 5. Schematic presentation of PTH(1-84) and the approximate location of the peptide regions recognized by the antibodies used in displacement-type radioimmunoassays and in "two-site" immunometric assays according to Heinrich (2006), p 54 from Clinical Chemistry.

Oxidized PTH occurs in patients with chronic kidney disease due to extensive oxidative stress (Hocher et al. 2012). Oxidized PTH forms the majority of PTH within these patients (Hocher et al. 2012). It's an inactive product and has no effect on the PTH receptor (Hocher et al. 2012). Assays used in these patients particular the intact and bioactive assays detect both oxidized and non-oxidized forms of PTH (Hocher et al. 2012). Intact and bioactive PTH assays detect both oxidized and non-oxidized PTH, resulting in higher PTH levels than when measured with a non-oxidized PTH assay (Hocher et al. 2012). At this point the non-oxidized assay may be useful in those patients requiring dialysis.

Role of Alkaline Phosphatase

Markers of osteoblast–mediated bone formation, such as bone-specific or total alkaline phosphatase, may provide useful information if used in conjunction with PTH serum levels. The combination of a low serum bone-specific alkaline phosphatase concentration (≤7 ng/mL) and a low serum PTH is suggestive of a low remodeling disorder (Ureña & De Vernejoul 1999). An elevated serum bone-specific alkaline phosphatase (≥20 ng/mL), alone or in combination with increased serum PTH (>200 pg/mL), appears to be highly sensitive and specific for high turnover bone disease (Ureña et al. 1996). In Croatia the usage of alkaline phosphatase and PTH levels is sufficient in assessing metabolic bone disease. It is worth mentioning that use of bone metabolic markers in conjunction with PTH or individually to asses' high or low turnover states still lacks sensitivity and specificity (Ureña et al. 1996).

Imaging Techniques

Radiographic examination includes possible detection of subperiosteal absorption on plain radiographs (KDIGO et al. 2012). These changes are associated with progressive hyperparathyroidism (KDIGO et al. 2012). These techniques are less sensitive than PTH and alkaline phosphatase (KDIGO et al. 2012). As a result routine x-rays are only done when there is symptomatic bone disease (KDIGO et al. 2012). Bone mineral

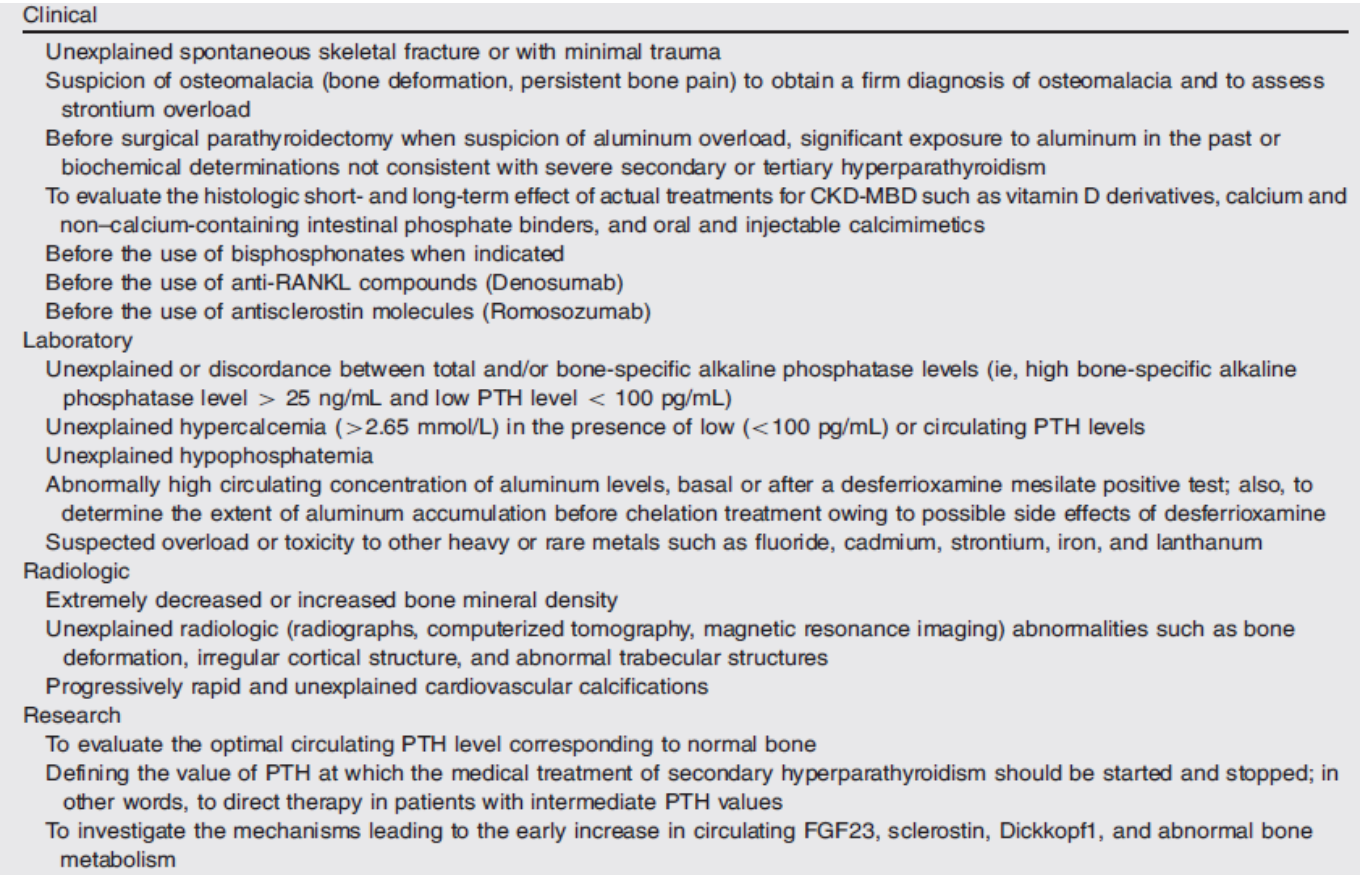
density has limited use in CKD patients in assessing bone disease. 2012 KDIGO guidelines, suggest not performing BMD measurements among patients with an estimated glomerular filtration rate (eGFR) <45 mL/min per 1.73 m2 since information may be misleading or unhelpful (KDIGO et al. 2012).

Bone Biopsy

Bone biopsy remains the gold standard for diagnosis of symptomatic bone disease. As mentioned previously, even though there is good correlation between PTH and bone formation rate, it cannot consistently replace bone histology because normal or even low bone turnover often are seen in a wide range of PTH values (2-9 fold upper normal limit for the assay) (Barreto et al. 2008). However in clinical practice the procedure has significant limitations. Some of the issues are as follows: individual variation in uremic patient's leads to false results; length of time for preparation of the procedure; the invasive nature of the procedure and finally financial cost. To conclude, bone biopsies are not routinely done in Croatia. In hospitals where it's possible to perform the procedure, KDIGO has published guidelines for usage of bone biopsies. Guidelines state:

1. Unexplained fractures, unexplained hypercalcemia, and/or unexplained hypophosphatemia
2. Persistent bone pain
3. Possible aluminum toxicity
4. Before therapy with bisphosphonates (KDIGO et al. 2009)

Indications for bone biopsy can be further divided into Clinical, Laboratory, Radiologic and Research categories (Figure 6).



Clinical
Unexplained spontaneous skeletal fracture or with minimal trauma
Suspicion of osteomalacia (bone deformation, persistent bone pain) to obtain a firm diagnosis of osteomalacia and to assess strontium overload
Before surgical parathyroidectomy when suspicion of aluminum overload, significant exposure to aluminum in the past or biochemical determinations not consistent with severe secondary or tertiary hyperparathyroidism
To evaluate the histologic short- and long-term effect of actual treatments for CKD-MBD such as vitamin D derivatives, calcium and non–calcium-containing intestinal phosphate binders, and oral and injectable calcimimetics
Before the use of bisphosphonates when indicated
Before the use of anti-RANKL compounds (Denosumab)
Before the use of antisclerostin molecules (Romosozumab)
Laboratory
Unexplained or discordance between total and/or bone-specific alkaline phosphatase levels (ie, high bone-specific alkaline phosphatase level > 25 ng/mL and low PTH level < 100 pg/mL)
Unexplained hypercalcemia (>2.65 mmol/L) in the presence of low (<100 pg/mL) or circulating PTH levels
Unexplained hypophosphatemia
Abnormally high circulating concentration of aluminum levels, basal or after a desferrioxamine mesilate positive test; also, to determine the extent of aluminum accumulation before chelation treatment owing to possible side effects of desferrioxamine
Suspected overload or toxicity to other heavy or rare metals such as fluoride, cadmium, strontium, iron, and lanthanum
Radiologic
Extremely decreased or increased bone mineral density
Unexplained radiologic (radiographs, computerized tomography, magnetic resonance imaging) abnormalities such as bone deformation, irregular cortical structure, and abnormal trabecular structures
Progressively rapid and unexplained cardiovascular calcifications
Research
To evaluate the optimal circulating PTH level corresponding to normal bone
Defining the value of PTH at which the medical treatment of secondary hyperparathyroidism should be started and stopped; in other words, to direct therapy in patients with intermediate PTH values
To investigate the mechanisms leading to the early increase in circulating FGF23, sclerostin, Dickkopf1, and abnormal bone metabolism

Figure 6. Indications for bone biopsy according to: Torres (2014), p 618, from Seminars in Nephrology.

Vascular Calcification

VC is most often detected incidentally on imaging obtained for other purposes (KDIGO et al. 2009). Screening is not attempted to quantify VC in all CKD patients since no specific therapy is available beyond careful attention to calcium and phosphate balance (KDIGO et al. 2009). This is in agreement with the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (KDIGO et al. 2009). CT scanning can detect and quantify the level of calcium with CAC scoring (KDIGO et al. 2009).

Treatment of Secondary Hyperparathyroidism

Treatment in Predialysis Patients

The treatment of secondary hyperparathyroidism in CKD differs between different stages of chronic kidney disease. Clinicians should first divide patients according to the severity of kidney disease before deciding on treatment decisions (Figure 7). Recent observational data and multiple clinical trials have shown different clinical outcomes regarding therapy in these two groups of patients. Furthermore patients in the predialysis group still have clinically significant working kidneys. As a result similar therapies used in both groups might produce different outcomes. More clinical trials are required to asses' efficacies of treatment in regards to phosphate binders and vitamin D analogs. There is still ongoing debate in the nephrology community as to what the correct approach is to these patients.

Table 1. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73m^2)
I	Kidney damage with normal/ increased GFR	≥90
II	Kidney damage with mild decrease in GFR	60–89
III	Moderate decrease in GFR	30–59
IV	Severe decrease in GFR	15–29
V	Kidney failure	<15

Figure 7. Staging of kidney disease according to: National Kidney Foundation (2003) from the National Kidney Foundation.

Treatment goals in regards to laboratory values of serum phosphate, calcium and PTH should be tailored to the KDIGO guidelines. The KDIGO guidelines recommend using intact PTH levels to evaluate and manage bone abnormalities (KDIGO et al. 2012). KDIGO suggests initiating therapy when the serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay (KDIGO et al. 2012). The clinician is required to be aware of the particular assay and normal values associated with its use (KDIGO et al. 2012). With respect to calcium and phosphate

levels, the KDIGO working group suggests maintaining serum calcium and phosphorus in the normal range (ie serum phosphorus level (<4.5 mg/dL [1.45 mmol/L]) (KDIGO et al. 2012). Clinicians should focus on trends rather than single laboratory values (KDIGO et al. 2012).

Treatment algorithm is the following:

Step 1- Limiting dietary phosphorus regardless of normal serum phosphate levels is essential in the beginning of treatment and throughout the course of the disease. Patients often have subclinical hyperphosphatemia that is compensated by the increased levels of FGF-23. Reducing phosphorous from the diet can decrease the phosphate load and improve treatment outcomes. The recommended dietary phosphorous intake is 900mg/day (KDIGO et al. 2012). Dietary phosphorus should be derived from sources of high biologic value, such as meats and eggs (KDIGO et al. 2012). Phosphorus from food additives should also be estimated and restricted (KDIGO et al. 2012). Food additives (as are found in processed foods) are an important source of dietary phosphate. In addition to having a high phosphate content, highly processed food provides a more easily absorbed form of phosphate, compared with fresh, unprocessed foods (KDIGO et al. 2012).

Step 2- After two to four months of limiting dietary phosphorous, if PTH levels persist the next step is to introduce phosphate binders. Phosphate binders include calcium and non-calcium containing compounds. Calcium-containing phosphate binders should be used in patients who are hypocalcemic and normocalcemic, particularly if they are not also receive active vitamid D analogs. Vitamin D analogs used together with calcium containing phosphate binders can cause both hypercalcemia and hypophosphatemia with vascular calcification as a consequence. Non-calcium-containing phosphate binders are used for hypercalcemic patients. They are also appropriate in normocalcemic CKD patients, particularly if they are also receiving active vitamin D or vitamin D analogs. Non-calcium-containing phosphate binders are also used for patients with adynamic bone disease and vascular calcification. Calcium containing

binders include calcium carbonate (25% elemental calcium: 169 mg of calcium/667-mg capsule) and calcium acetate (40% elemental calcium: 200 mg of elemental calcium/500 mg of calcium carbonate) (Mia et al. 1989). Calcium acetate is considered to be a more efficient phosphate binder than calcium carbonate (Mia et al. 1989). In Croatia, calcium carbonate and magnesium hydroxide are widely used options. No studies have examined calcium-based binders versus placebo or compared the 2 forms of calcium-based binders with extraskeletal calcification or patient-centered outcomes, such as mortality, fractures, and hospitalizations. Clinicians need to be aware of the effects of calcium compounds and active vitamin D compounds used together. Simultaneous use of both can lead to hypercalcemia and hyperphosphatemia. Also a note for clinicians using calcium phosphate binders: Consider the level of calcium intake when prescribing calcium phosphate binders; likely exceeds the 1500 mg/day limit in end-stage renal disease ESRD patients (NFK et al. 2003). Non calcium containing compounds include sevelamer hydrochloride. Sevelamer hydrochloride is the only available non calcium containing phosphate binder available in Croatia. Sevelamer hydrochloride are nonabsorbable cationic polymers that bind phosphate through ion exchange. Conventional dosing is three times daily but recently less frequent dosing has been used. Side effects include GI intolerance and metabolic acidosis. A decrease in LDL cholesterol has been associated with its use.

When comparing both calcium and non-calcium phosphate binders, non-calcium phosphate binders seem to be more effective. The best available data is from a meta-analysis of 11 open-label, randomized trials (4622 patients), which revealed a 22 percent decrease in all-cause mortality among patients randomly assigned to receive noncalcium-based binders (sevelamer, 10 studies including 3268 patients, or lanthanum, one study including 1354 patients), compared with calcium-based binders (relative risk [RR] 0.78, 95% CI 0.61-0.98) (Jamal et al. 2013). Analysis of three nonrandomized trials (2813 patients) revealed an 11 percent reduction in mortality and, in all trials together, a 13 percent reduction in mortality among patients taking non calcium phosphate binders. Analysis of dialysis and nondialysis CKD patients showed similar reductions in mortality (Jamal et al. 2013). Calcium containing phosphate

binders are also associated with hypercalcemia, adynamic bone disease, vascular calcification, and a positive calcium balance, all which could result in increased morbidity (Jamal et al. 2013). Thus it's prudent to take this factors in consideration when deciding on the type of phosphate binder.

Step 3- If PTH levels further increase or remain elevated over a six-month period with optimal therapy from the previous steps, introduction of a Vitamin D derivative is the next essential step in management. Treatment should not be initiated with Vitamin D derivatives if either serum calcium or serum phosphorous is elevated. Under a general rule a Vitamin D derivative can only be introduced if the corrected serum total calcium concentration is <9.5 mg/dL (<2.37 mmol/L). If the serum level of corrected total calcium exceeds 10.2 mg/dL (2.54 mmol/L) all Vitamin D therapy should be discontinued. Vitamin D therapy should also be discontinued if intact PTH levels become persistently low.

There are several divisions of Vitamin D derivatives. There is the naturally occurring Vitamin D derivative calcitriol, and synthetic Vitamin D analogs paricalcitol and doxecalciferol. We shall discuss calcitriol and paricalcitol as these are the only available Vitamin D derivatives available in Croatia. Four placebo-controlled RCTs of various vitamin D analogues all showed efficacy for PTH lowering compared with placebo (Slatopolsky et al. 1992). No RCTs using vitamin D analogues in this group of patients address key patient-level outcomes (such as mortality, fractures, quality of life etc.). As a result any Vitamin D derivative can be used in treatment of these patients
In regards to paricalcitol it has been examined in one randomized trial. In this phase-III trial of 220 patients with stage 3 and 4 CKD, compared with placebo, paricalcitol resulted in a significant percentage of patients with at least two consecutive decreases in PTH levels of ≥30 percent (91 versus 13 percent) (Coyne et al. 2006). Both groups had similar incidences of hypercalcemia, hyperphosphatemia, and elevated calcium-phosphorus products (Coyne et al. 2006).

Step 4- When all previous therapies fail in control of PTH, cinacalcet be used in treatment. It is still controversial because of the lack of evidence. In fact the (KDIGO) working group recommend not giving cinacalcet, given the paucity of data concerning efficacy and safety in predialysis patients with CKD (KDIGO et al. 2009). Patients in this category of treatment can be managed by other therapeutic interventions such as parathroidectomy. There are risks of hypocalcemia and elevations of serum phosphate in its use. If electrolyte disbalance does occur during treatment, other therapies might have to be adjusted such as Vitamin D derivatives, phosphate binders etc.
Two trials have evaluated cincalcet in this category of patients. The first trial, a A phase-II, 18-week study was performed in which 54 patients were randomly assigned to cinacalcet or placebo, with the dose titrated from 30 to 180 mg/day to obtain a ≥30 percent reduction in PTH levels (Charytan et al. 2005). Inclusion criteria included GFRs between 15 to 50 mL/min per 1.73 m2, one intact PTH level >130 pg/mL, and a serum calcium concentration of 9.0 mg/dL (2.25 mmol/L) (Charytan et al. 2005). Compared with placebo, cinacalcet significantly lowered intact PTH levels (32 percent decrease versus 5 percent increase with placebo) and achieved target reduction in PTH levels (56 versus 19 percent attained a 30 percent reduction from baseline) (Charytan et al. 2005). Increments in serum phosphate levels were observed with cinacalcet, which was likely due to the reduction in PTH levels (Charytan et al. 2005). The second trial was a A long-term, randomized, double-blind, placebo-controlled trial of cinacalcet in 404 patients with stages 3 and 4 CKD reported that active therapy reduced the mean PTH level by 43 percent after 32 weeks of treatment, but also led to an 9 percent decrease in serum calcium level, a 21 percent increase in serum phosphorus level, and a 14 percent decrease in urinary phosphorus excretion (Chonchol et al. 2009). In addition, cinacalcet induced a >50 percent increase in calcium excretion from baseline (Chonchol et al. 2009).

Treatment in Dialysis Patients

Goals of therapy in this group of patients are slightly different than in those in the predialysis group mentioned above. There is some debate as to which guideline should

be used to treat these patients. The new KDIGO guidelines recommend that PTH levels should be 2-9 times the upper limit of normal as is defined by the specific assay. Previous guidelines had specific values in which PTH should be controlled. However these guidelines were based on secondary generation assays that is no longer available. Furthermore there are data suggesting significant variability with PTH results among the different available assays, as well as marked differences based on sample collection and storage. The KDIGO guidelines also state that calcium and phosphorous levels should be in the normal range. However what is considered to be the normal range? For example increased phosphorous levels have been associated with increases in all-cause mortality in certain prospective studies. This was best shown in a meta-analysis of 12 studies that included 92,345 patients with CKD, over 97 percent of whom were on dialysis (Palmer et al. 2011). Among 10 studies that were perceived to be adequately adjusted (in which seven studies were of dialysis patients), serum phosphate >5.5 mg/dL (1.78 mmol/L) was associated with increased mortality (Palmer et al. 2011) The KDIGO guidelines are not specific enough for this recommendation. Based on the previously mentioned statements the following should be the standard goals of therapy:

1. PTH levels should be 2-9 times the upper limit of normal as is defined by the specific assay. (KDIGO et al. 2009)
2. Serum levels of phosphorus should be maintained between 3.5 and 5.5 mg/dL. (NFK et al. 2003)
3. Serum levels of corrected total calcium should be maintained between 8.4 and 9.5 mg/dL. (NFK et al. 2003)

The approach to treatment consists of the following: the initial focus is managing secondary hyperparathyroidism is the management of hyperphosphatemia with diet and/or phosphate binders. Specific interventions are based upon serum phosphate and calcium levels. The next step is to decide whether phosphate binder therapy is sufficient or whether a calcimimetic or vitamin D analog should be added. This is based upon calcium, phosphate, and PTH levels that are measured when administering optimal

phosphate binder therapy. The final step is to adjust the doses of phosphate binders, active vitamin D, and cinacalcet to attempt to attain target values. There is a variable interrelationship between phosphate binders (either calcium or non-calcium containing binders), calcitriol or vitamin D analogs and calcimimetics in treatment. In the end the clinician must balance these medications in order successfully treat hyperparathyroidism.

The approach to treating hyperphosphatemia in dialysis patients is relatively the same as compared to the treatment in the predialysis group. Nonetheless there are certain differences which need to be addressed. In regards to phosphate restriction, protein supplementation (which contributes to high phosphate intake) rather than protein restriction is the goal. In this setting, the patient should be encouraged to avoid unnecessary dietary phosphate while increasing the intake of high-biologic-value sources of protein. The reason for this is that dialysis patients frequently suffer from borderline malnutrition. Restricting dietary protein could affect clinical outcomes by further increasing malnutrition. In regards to phosphate binders treatment principles remain the same as those in the predialysis group. Currently there are no randomized clinical trials for phosphate binders in this group of patients. Any excess phosphate can be removed with hemodialysis. Approximately 1000 mg of phosphate can be removed in each session. Patients have the option of extended dialysis or nocturnal dialysis if time permits. Patients receiving nocturnal dialysis removed twice the amount of phosphorous per week compared with those on thrice-weekly intermittent dialysis. A randomized controlled clinical trial of 51 patient's randomly assigned to 6 times weekly nocturnal dialysis versus thrice-weekly intermittent dialysis showed significant and sustained decreases in serum phosphorus levels over a 6 month period (Walsh et al. 2010).

The general approach to the use of vitamin D analogs was outlined in the predialysis section. The same principles in approach apply to this group of patients. Currently there have been no randomized controlled clinical trials to assess vitamin D analog effects on patient-based outcomes such as fractures and mortality. Furthermore there

is lack of evidence on which vitamin D analog to administer. Here we will discuss evidence on two vitamin D analogs, Calcitriol and Paricalcitol which are available in Croatia. It has been assumed since Paricalcitol has specific actions on target receptors (less gut absorption of calcium and phosphate and less increments in serum values of calcium and phosphate) there could be a survival advantage. However, data from the only prospective, comparative study suggest no significant differences between paricalcitol and calcitriol. In this phase-III, double-blind, multicenter, randomized open-labeled trial, paricalcitol was directly compared with calcitriol among 263 hemodialysis patients with plasma PTH levels >300 pg/mL and a serum Ca x P product <75 (Sprague et al. 2003). To asses effect on mortality, paricalcitol was evaluated in a large cohort (the survival of hemodialysis patients administered paricalcitol (29,021 patients) or calcitriol (38,378 patients)) (Teng et al. 2003). The findings showed that at three-year follow-up, mortality was significantly lower in the paricalcitol group (crude mortality of 18 versus 22.3 percent per person-year for paricalcitol and calcitriol) (Teng et al. 2003). There are some issues with the studies design, such as randomization. This study should not be considered when selecting between the two vitamin D analogs. Currently both compounds can be used until further randomized controlled clinical trials have been performed.

As mentioned previously Cinacalcet is a calcimimetic used often in combination with vitamin D and phosphate binders when levels of PTH are excessive. The indications for calcimimetic therapy are the following: indicated in dialysis patients with PTH levels >300 pg/mL who have serum calcium levels >8.4 mg/dL (>2.1 mmol/L). Hyperphosphatemia is not a contraindication for starting cinacalcet, unlike vitamin D analogs. There are numerous efficacy studies evaluating the effects of Cinacalcet. In one large trial (which was the combination of three phase-III studies), 1136 dialysis patients with iPTH levels of >300 pg/mL were randomly assigned to traditional therapy plus cinacalcet HCl or placebo for 26 weeks (Moe et al. 2005). Some of the findings were as follows: sufficient control of PTH levels, calcium and phosphorous levels compared with placebo (Moe et al. 2005). A combined analysis of the three phase-III trials (which are also analyzed in the previously cited study) and one phase-II trial also

found that, compared with placebo, cinacalcet lowered the risk of parathyroidectomy, fracture, and cardiovascular hospitalization (Cunningham et al. 2005). Does cinacalcet improve all-cause mortality and cardiovascular mortality? In the EVOLVE randomized trial, cinacalcet did not decrease the risk of death or major cardiovascular events among hemodialysis patients (Chertow et al. 2012). Cinacalcet reduced the rate of parathyroidectomy by approximately half (Chertow et al. 2012). Furthermore, in a recent published meta-analysis of all 9 clinical trials involving cinacalcet, there was no reduction in all-cause mortality and cardiovascular mortality (Palmer et al. 2013).

Table 1. Prevalence of secondary hyperparathyroidism in dialysis patients at Department of Nephrology of Klinicki Bolnicki Centar Sestre Milosdrnice, Zagreb Croatia. Different therapy regiments, with serum calcium and phosphate levels are also shown.

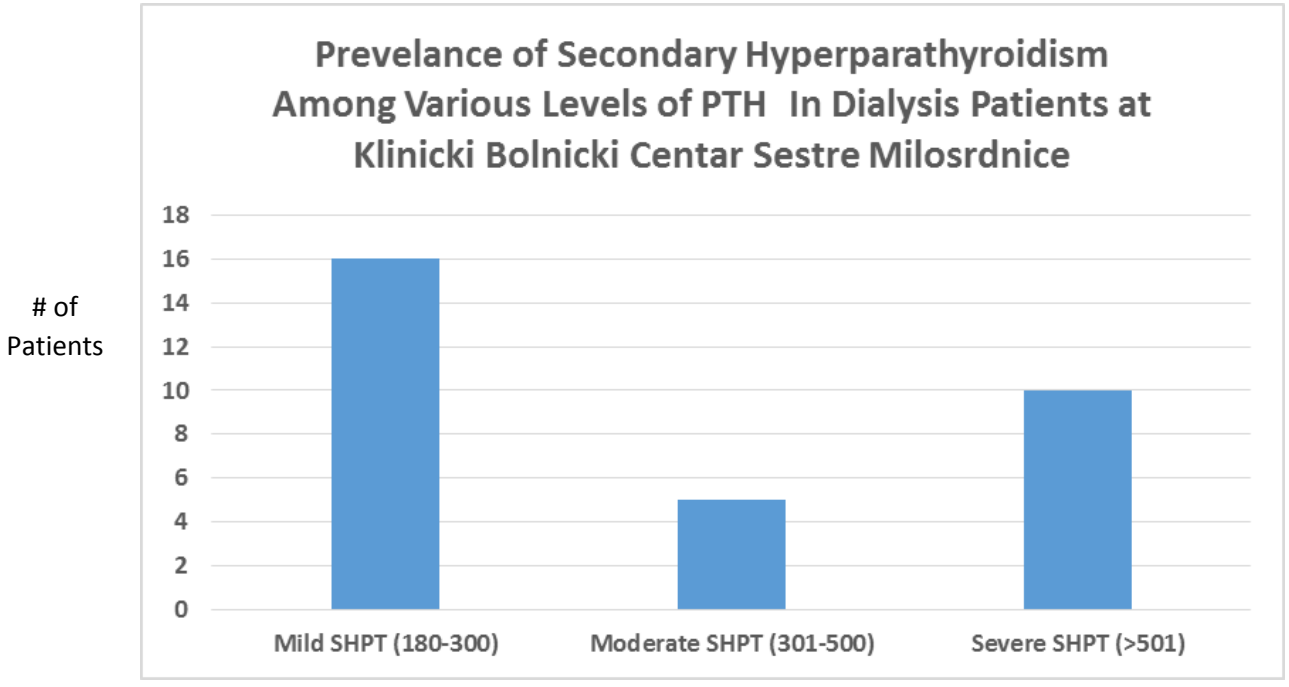
	Sex (F=Female) (M-Male)	**Age**	**PTH (pg/mL)**	**Ca** (Calcium) **(mmol/L)**	**P** (Phosphate) **(mmol/L)**	**Therapy**
1.	F	53	253	2.16	1.15	Zemplar-2mcg 3x/week Osvaren-3x1g (between meals)
2.	F	54	1162	2.63	1.77	Zemplar-4mcg 3x/week Renvela-800mg with meal 3x daily
3.	F	78	629	2.16	1.1	Zemplar-2mcg 3x/week Osvaren-3x1g (between meals)
4.	F	89	232	2.07	1.23	Renvela-800mg with meal 3x daily
5.	F	67	290	2.28	2.85	Rocaltrol-0.25mcg daily Osvaren-3x1g (between meals)
6.	F	57	63	2.43	1.11	Rocaltrol-0.25mcg daily Renvela-800mg with meal 3x daily Calcium Carbonate
7.	M	62	76	2.17	0.63	Rocaltrol-0.25mcg Renvela- 3x1g with meal
8.	F	55	29	2.51	1.63	Osvaren-3x1g (between meals)
9.	M	82	168	2.26	1.52	Zemplar-2mcg 3x/week Osvaren-3x1g (between meals)
10.	M	57	387	2.22	1.01	Rocaltrol-0.25mcg daily Calcium Carbonate
11.	F	60	85	2.08	1.46	Rocaltrol-0.25mcg daily Renvela-800mg with meal 3x daily

12.	M	76	241	2.41	1.39	Rocaltrol-0.25mcg daily Osvaren-3x1g (between meals)
13.	M	62	198	2.34	1.1	Rocaltrol-0.25mcg daily Osvaren-3x1g (between meals)
14.	M	81	32	2.51	0.93	Rocaltrol-0.25mcg daily Osvaren-3x1g (between meals)
15.	M	74	84	2	0.82	Osvaren-3x1g (between meals)
16.	F	65	669	2.28	1.55	Renvela-800mg with meal 3x daily
17.	M	69	780	2.33	1.46	Zemplar-4mcg 3x/week Renvela-800mg with meal 3x daily
18.	M	68	244	2.17	1.00	Osvaren-3x1g (between meals)
19.	M	66	54	2.21	1.29	Currently no therapy
20.	M	59	320	2.43	1.55	Renvela-2g with meal 3x daily Rocaltrol-2.5mcg 3x weekly
21.	F	37	173	2.68	1.31	Renvela-1g with meal 3x daily Rocaltrol-0.25mcg daily
22.	F	74	182	2.17	1.12	Calcium carbonate Rocaltrol-2.5mcg 3x weekly
23.	M	56	79	2.26	1.4	Rocaltrol-0.25mcg daily Osvaren-3x1g (between meals)
24.	F	77	8	2.54	2.55	Renvela-800mg with meal 3x daily Rocaltrol-0.5mcg 3xweekly
25.	M	41	85	2.23	1.68	Rocaltrol-0.25mcg daily
26.	F	86	415	2.47	1.22	Renvela-800mg with meal 3x daily Rocaltrol-0.25mcg daily
27.	F	80	166	2.15	1.45	Renvela-800mg with meal 3x daily Rocaltrol-0.25mcg daily Zemplar-4mcg 3x/week
28.	M	47	249	2.33	1.64	Rocaltrol-0.25mcg daily Renvela-1g with meal 3x daily
29.	F	44	289	2.18	1.98	Renvela-800mg with meal 3x daily Rocaltrol-0.25mcg daily
30.	F	78	62	2.19	1.03	Renvela-800mg with meal 3x daily Rocaltrol-0.25mcg daily
31.	M	60	174	2.33	1.04	Renvela-2g with meal 3x daily Rocaltrol-0.5 mcg daily
32.	F	79	264	2.5	1.75	Rocaltrol-0.25mcg daily Osvaren-3x1g (between meals)
33.	F	77	907	2.27	1.75	Rocaltrol-0.25mcg daily

						Osvaren-3x1g (between meals)
34.	M	62	598	2.31	1.34	Rocaltrol-0.25mcg daily
35.	F	68	9	2.25	1.03	Zemplar-2mcg 3x/week Osvaren-3x1g (between meals)
36.	M	63	433	2.49	2.24	Rocaltrol-0.25mcg daily Renvela-800mg with meal 2x daily
37.	M	72	190	2.25	2.07	Rocaltrol-0.25mcg daily Renvela-800mg with meal 3x daily
38.	F	55	194	2.37	2.06	Zemplar-2mcg 3x/week Renvela-800mg with meal 3x daily
39.	F	45	2027	2.56	1.99	Renvela-1-2g with meal 3x daily Zemplar-2mcg 3x/week
40.	F	32	82	2.41	0.83	Renvela-800mg with meal 3x daily Rocaltrol-0.25mcg daily
41.	M	58	67	2.18	1.5	Renvela-800mg with meal 3x daily Rocaltrol-0.25mcg daily
42.	M	71	503	2.5	1.15	Renvela-800mg with meal 3x daily
43.	F	29	395	2.43	2.86	Renvela-800mg with meal 3x daily Rocaltrol-0.25mcg daily
44.	M	71	508	2.36	1.14	Renvela-800mg with meal 3x daily Zemplar-1mcg 3x/week
45.	M	83	239	2.28	0.8	Zemplar-1mcg 3x/week
46.	M	56	120	2.3	1.6	Rocaltrol-0.25mcg daily Calcium Carbonate
47.	F	67	246	2.3	0.75	Zemplar-2mcg 3x/week Renvela-1-2g with meal 3x daily
48.	M	66	151	2.36	2.52	Rocaltrol-0.25mcg daily Renvela-1-2g with meal 3x daily
49.	M	60	160	2.21	1.55	Renvela-800mg with meal 3x daily Rocaltrol-0.25mcg daily
50.	M	64	67	2.18	1.5	Rocaltrol-0.25mcg daily Renvela-1g with meal 3x daily
51.	F	61	1127	2.03	1.31	Rocaltrol-0.5mcg daily Renvela-800mg with meal 3x daily
52.	M	72	83	2.23	1.88	Rocaltrol-0.25mcg daily Renvela-800mg with meal 3x daily

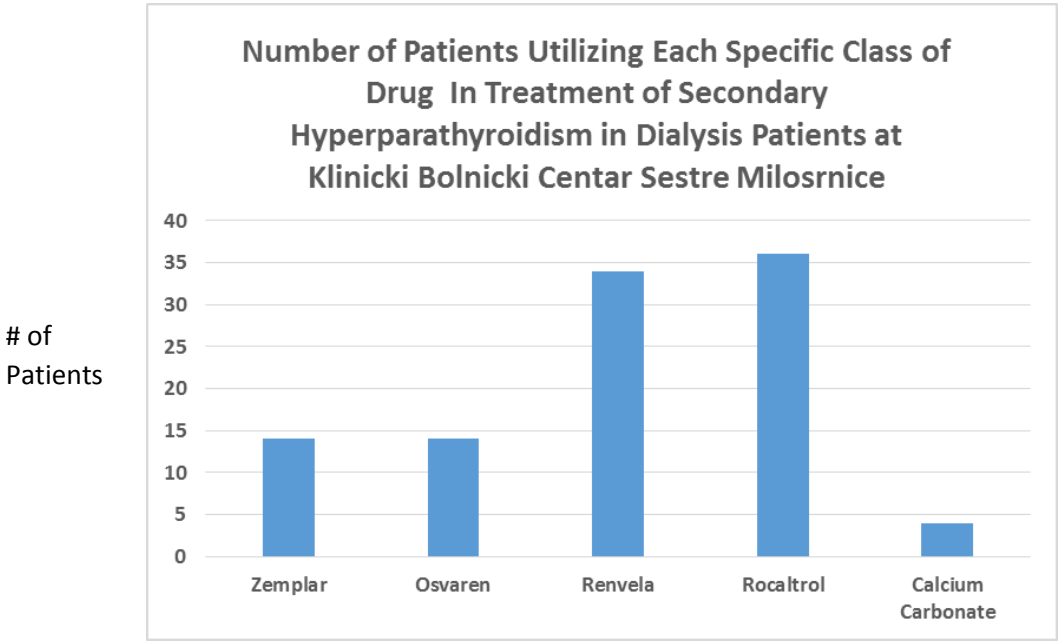
53.	F	77	264	2.12	1.56	Rocaltrol-0.25mcg daily
54.	F	80	136	2.21	1.26	Zemplar-2mcg 3x/week Renvela-800mg with meal 3x daily
55.	M	71	17	2.59	1.24	Rocaltrol-0.25mcg daily Renvela-800mg with meal 3x daily
56.	M	76	192	2.14	1.41	Zemplar-2mcg 3x/week Renvela-1-2g with meal 3x daily

Figure 8.



SHPT=Secondary Hyperparathyroidism
Values are in pg/mL

Figure 9.



Zemplar=Paricalcitol
Renvela=Sevelamer
Osvaren=Calcium Carbonate/Magnesium Hydroxide
Rocaltrol=Calcitriol

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Biography

I was born in Split, Croatia June 6th 1991. Immigrated to Canada when I was very young. Attended Holy Trinity Catholic Secondary School in Oakville, Ontario Canada. Recipient of the dean's award for the 2010-2011 academic year. I have in interest in Internal Medicine, specifically in nephrology and cardiology. I would like to pursue a career in one of those specialities.