New Concepts for Primary and Secondary Hyperparathyroidism

5

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Abstract

Primary hyperparathyroidism and secondary disease from chronic kidney disease are highlighted in this chapter. Up-to-date descriptions of new pathological mechanisms focus on fibroblastic growth factor 23 and its emergent importance in overall pathology. Historical, clinical, and examination findings are highlighted and compliment data on laboratory techniques, diagnostic imaging, and skeletal histology clinical workup of the patients. Treatment options at the dialysis and pharmacological levels are blended with some of the nutritional elements in phosphorus control. The integration of all elements is summarized at the end of the section to emphasize its influence on bone metabolism.

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Pathophysiology and Epidemiology

Parathyroid glands are located in close proximity to the thyroid gland on their posterior surface. In normal health, the parathyroids are small (2–5 mm). Normally the four (sometimes more) glands are derived from the neural crest mesenchyme and the brachial pouch endoderm. The glands are composed of two cell types, of which the "chief cells" are the ones that generate parathyroid hormone (PTH). The larger oxyphilic cells are lighter in staining, fewer in number, and have no known physiologic role. A histological picture of an enlarged, proliferated gland is given in Fig. 5.1.

Excessive secretion of PTH is mostly a consequence of adenomatous proliferation of parathyroid glands in which case it is referred to as *primary (p)* hyperparathyroidism (HPT). The causative circumstance of such benign status is not known. However, in about 1% of pHPT, parathyroid carcinoma is the underlying cause [1]. Some genetic risk loci have been identified among which mutations in HRPT2 and RET [2] are the most important ones. Patients inheriting these genes develop parathyroid carcinoma and phaechromocytoma. In some occasions, pHPT may be associated syndromatically with other endocrinological disorders (multiple endocrinological neoplasia, MEN). In these rare conditions, endocrinological symptoms are often combined
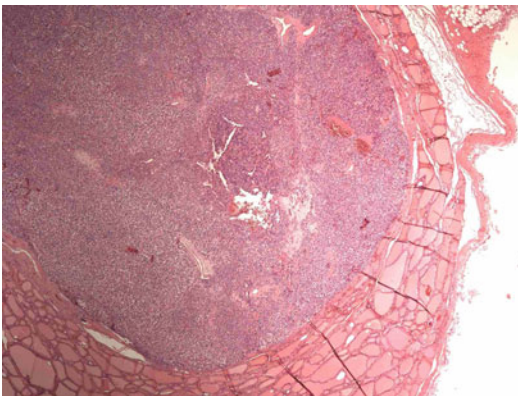

Fig. 5.1 Low magnification of a hyperplastic intrathyreoidal located adenomatous parathyroid gland. Kindly contributed by Andreas Plötner, Pathological Institute, Hospital St. Georg, Leipzig

depending on the type of disease. In MEN type 1, pHPT coincidences with gastrointestinal tumors like insulinoma or gastrinoma. In MEN 2A, pheochromocytoma is the most frequent combination.

In pHPT, PTH oversecretion is frequently followed by impaired renal function due to hypercalcemia, which is a harm to healthy kidneys. Hypercalcemia in pHPT is stimulated by increased dietary calcium absorption and calcium mobilization from the bone hydroxyapatite depot. Therefore, in sustained and nontreated pHPT, renal failure due to hypercalcemia is typical sequelae. This condition causes secondary HPT and, therefore, mixes up with the primary problem of pHPT. Following this situation, a pHPT might not be easy to distinguish from secondary forms, if renal injury is already present. The frequency of newly diagnosed pHPT is higher than one might expect: 1 out of 500 women and 1 out 2,000 men were found to be affected among 60-year-old individuals in a population-based registration in Rochester, MN, in 1989 [3].

Functional hyperplasia and hypertrophy of the parathyroid glands due to chronic kidney disease (CKD) are characterized as "secondary" hyperparathyroidism (sHPT). However, following the subsequent pathophysiological considerations, the phrase "functional" hyperparathyroidism is a more appropriate wording. The morphological and imaging aspects of this disease are characterized in a particular chapter. From a functional point of view, sHPT is sequelae of altered mineral metabolism in CKD.

Healthy kidneys coregulate calcium homeostasis by different mechanisms. The major downstream pathway of kidney metabolism in terms of bone and mineral metabolism has been focused to the parathyroids many years ago. However, in such classical reasoning, the renal–parathyroid axis has been thought to be mediated through downregulation of vitamin D activation only. In fact, it is long known, that hydroxylation and activation of inactive vitamin D into the active form, Di-hydroxyl vitamin D ($1.25\ OH_2D$, calcitriol), take place at the tubular-interstitial compartment of kidneys. Already in early forms of CKD, that activation and subsequently the synthesis of $1.25\ OH_2D$ are abolished. The levels of
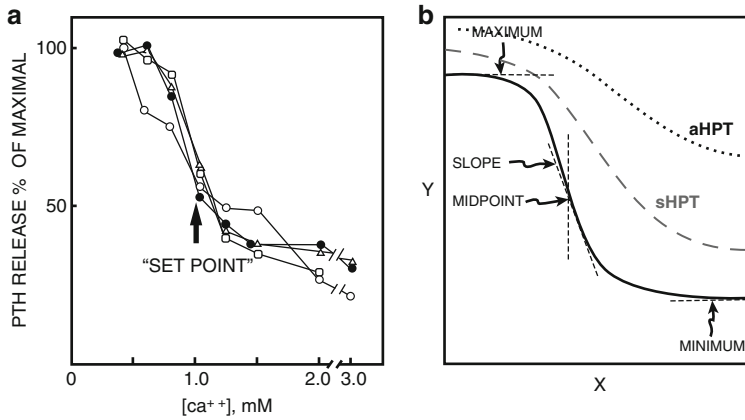
Fig. 5.2 Original (panel **a**, *left*) and schematic (panel **b**, *right*) drawing of the relationship between calcium concentration and PTH response in healthy (**a**) and renal population (**b**) with still functioning response in secondary (s) and autonomous (a) HPT. *Y*-axis PTH concentration, *X*-axis Ca concentration. Response is characterized by slope, midpoint, maximum and minimum which might resemble the functioning status of the Ca–PTH regulation. Adapted from Brown EM, Gardner DG, Brennan MF et al. Calcium-regulated parathyroid hormone release in primary hyperparathyroidism: studies in vitro with dispersed parathyroid cells. Am J Med. 1979;66(6):923–31

1.25 OH_2D in sera of patients with CKD are inversely and linearly correlated with excretory renal function, measured by glomerular filtration rate (GFR) [4].

As this, the classical concept of sHPT reflects the adaptations to decreased 1.25 OH_2D. Since calcium absorption from the bowel wall is mediated by 1.25 OH_2D, a decrease of that hormone results in calcium deficit, particularly present in a reduced level of free serum calcium. In the serum, calcium is partly bound to albumin resulting in a difference between whole and acting/free calcium. Free calcium content of sera is sensed very precisely and tightly by the calcium-sensing receptors (CaR) of the parathyroids [5]. A decrease of free calcium leads to increase of PTH synthesis [6]. PTH increases serum calcium by its action on bowel vitamin D uptake and Ca mobilization from the bone hydroxyapatite depot. By that means, the decrease of 1.25 OH_2D is counter-regulated and the serum-free calcium level, which has much downstream impacts, can be partly maintained through a wide range of renal insufficiency. However, the gross calcium balance including the bone depot is negative and the adaptation maintains serum homeostasis by means of decalcification of bones. During last years, these mechanisms have been discussed

more and more as adaptive ones, i.e., in certain sense as a physiological response. A lot of discussion is ongoing concerning the question, if PTH elevation is a pathological process per se, or if the onset of disease-mediating mechanisms has to be determined at a certain PTH threshold. While this is controversial, from a functional viewpoint, an intact calcium–PTH regulation axis could be seen as one aspect of a truly adaptive process [7, 8]. Such classical experiments establishing a J-shaped Ca–PTH response curve [6] have recently been performed in the end-stage renal failure setting using Ca dialysis bath concentration variation and measuring PTH response [9]. The degree of PTH response, measured as relationship between set point and slope of the curve (Fig. 5.2), can be seen as a measure of appropriate regulation.

By note, serum phosphorus elevation comes into play only in later stages of CKD and acts as further stimulus of PTH elevation. Besides a remarkable degree of excretory renal failure in CKD stage 3 and 4, phosphorus (P) levels usually will be found not elevated in these stages [10]. The reason of that difference in time course (P ↑ late, Ca ↓ and PTH ↑ early) has been clarified at least in part during the last few years. Phosphaturia has been demonstrated to be promoted not only
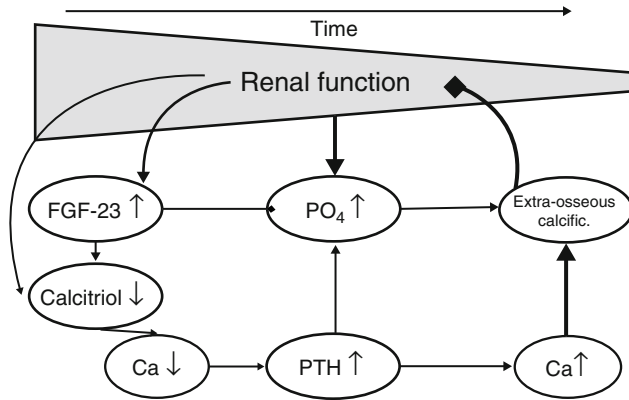
Fig. 5.3 Simplified drawing of time-dependent alterations of mineral metabolism in chronic kidney disease

by PTH but also by fibroblast growth factor 23 (FGF-23), which is secreted mainly from bone-forming osteoblasts [11]. FGF-23 exerts a very strong phosphaturic effect [12–14]. However, it does not only stimulate phosphaturia but also diminish activation of vitamin D by a strong inhibitory effect on 1-α-hydroxylase resulting in 1.25 OH_2D downregulation [14] and does not inhibit HPT [15]. Therefore, FGF-23 is likely to maintain normal phosphate homeostasis in early stages of CKD on the cost of decreased 1.25 OH_2D levels comparable to PTH elevation which is the pay-off to stabilize calcium in early CKD (Fig. 5.3).

In such a concept, looking at PTH and FGF-23, the resulting 1.25 OH_2D deficiency is the key-playing negative regulator in mineral metabolism changes due to CKD. 1.25 OH_2D binds to its receptor (vitamin D receptor, VDR) which is located not only throughout the body, including parathyroids, bowel wall but also in endothelium and immune cells. Like other members of the steroid receptor family, the VDR acts as a ligand-activated transcription factor. Classical down-stream effectors of the 1.25 OH_2D–VDR complex include enhancement of small-bowel calcium absorption and osteoclastogenesis and liberation of calcium from bones. The latter effect is exerted via the regulation of receptor activator of NF-B ligand (RANKL)–receptor activator of NF-B (RANK) interactions and osteoprotegerin interplay through the 1.25 OH_2D–VDR complex. Yet this interaction is complex and altered by PTH. Newer findings suggests

that bone forming in the presence of altered 1.25 OH_2D–VDR complex only transforms to bone resorption when PTH increase is paralleled by active vitamin D deficiency [16]. Inactivation of the 25-hydroxyvitamin D 1-hydroxylase and vitamin D receptor demonstrates independent and interdependent effects of calcium and vitamin D on skeletal and mineral homeostasis. This means that if the Ca/1.25 $OH_2D\rightarrow$PTH response is not functional, bone turnover is abolished resulting in bone loss. This condition is characterized as "dead bone disease" but incorporates not only skeletal but also systemic pathological features.

Pathophysiology of Bone Disorder in CKD-MBD

"Dead bone disease" or low *turnover* renal osteo-dystrophy (ROD) is one of three particular pathologies related to mineral–parathyroid regulation in frame of CKD. While *low-turnover bone disease* is mostly characterized by "arrested" bone metabolism with both inactive osteoblasts and osteoclasts and low PTH, *high-turnover bone disease* is identified by stimulated bone metabolisms and both cell types together with increased PTH.

During recent years, the focus has moved from "bone only" to "bone and vasculature." The hypothesis behind that reasoning is a pathological translocation of calcium salts from bones to vasculature mediated by mechanisms, among which sHPT is one of the best investigated ones. In fact,

the presence of ectopic vascular calcification (VC) and the transition of smooth muscle cells (SMC) to osteoblasts represents a cornerstone of vascular risk and an independent risk factor of mortality [17]. Adjusted for age, the risk of death, is elevated up to 100-fold in patients with CKD 5 compared with healthy controls [18]. However, the molecular mechanisms leading to VC and the possible link between bone disease (somewhat mechanistic seen as "calcification minus") and vessel disease ("calcification plus") have not been established until very recent years. During last years, markers of mineral bone metabolism and parathyroid dysregulation have been clearly associated with patient survival [19]. This is true for the serum concentrations of calcium and phosphorus and, in smaller extent with a more J-shaped mortality association curve, for PTH [19]. The role of FGF-23 in terms of survival has to be investigated in future studies. The pathophysiological impacts, which bone disease might execute on vasculature and cardiovascular risk in renal failure, led to the newly inaugurated entity "chronic kidney disease-mineral bone disease" (CKD-MBD). This scenario comprises risks of osteodystrophy like pathological fractures and sequelae of bone decalcification as calcium salt deposition. That deposition may either occur in an elementary form, e.g., in grafted kidneys resulting in earlier transplant loss [20] or in more complex forms together with phosphorus deposition in "brown tumors" of skin and joints, which are already longer known.

Fig. 5.4 Calcification of intima-media layer of small arteries (→ *arrow*) in calciphylaxis (*von Kossa* staining, ×100 magnification). Kindly contributed by Dr. Jens Plöthner, Pathological Institute, Hospital St. Georg, Leipzig, Germany

Fig. 5.5 Ulcerated skin surface of the lower leg of a patient with calciphylaxis, concomitant with intima-media arterial calcification seen in Fig. 5.3

Calciphylaxis

In particular, changes of the skin comprising painful ulceration and inflammation and occurring along with calcification of middle and small arteries intima-media-layers (Fig. 5.4) have been defined as calciphylaxis (Fig. 5.5), a condition inheriting 50–80% mortality. At current, there are no evidence-based treatment schemes available for such deleterious complication. However, chelation and excretion of calcium salts with sodium thiosulfate [21–28], lowering calcium concentration by intensified dialysis and pharmaceutical regimes and parathyroidectomy (PTX) yielded beneficial results in single cases and small series [29]. Calcification does not occur only in patients who are subjected to

high serum levels of calcium, phosphorus, and PTH. In particular, calciphylaxis and coronary artery calcification have been observed even in patients with normal and low-normal serum calcium. Therefore, the incidence of extraosseous calcification has been thought to be mediated by other factors as calcium, too. Since precipitation of calcium salts and not the presence of dissolved free calcium is the key pathological issue, research on precipitating cofactors has been promoted recently. Among those, fetuin and matrix gla protein have been identified as precipitation inhibitors [30] and a deficiency of these agents has been hypothesized as cofactors of precipitation. In vitro precipitation experiments with fetuin supported that reasoning [30–32]. Since fetuin and matrix gla protein are related to inflammatory activation, a very attractive link has been identified connecting the frequent occurrence of calcification in patients with inflammation. Another important cofactor for precipitation of calcium salts is the inhibition of vitamin K synthesis by warfarin [33], which consequently has to be stopped in calciphylaxis.

Inflammation, particularly subclinical microinflammation, is overrepresented in cohorts with renal disease in general. Without dissecting details, extracorporeal (dialysis) circuits, autoimmune kidney diseases, subclinical transplant rejection, and uremic inflammation are the most important headings pointing to microinflammation in these patients. Taking all recent keys together, to describe a nowadays comprehensive picture of "diseases of parathyroids" in renal patients, hyperplasia and hypertrophy of parathyroid glands with subsequent PTH oversecretion is only one aspect of a more complex disease described as *CKD-MBD* [34]. This complex focuses more on "end-organ-damage" of PTH in terms of calcification of vasculature, specific calcification disease of the skin (calciphylaxis), and renal bone osteodystrophy. That end-organ-damage is mediated by cofactors apart from the calcium–parathyroid axis like precipitation inhibitors and inflammation.

See Chapter 6 for detailed discussion.

Clinical Course, History, and Physical Findings

In primary HPT, which is sometimes a nondiscovered silent disease, hypocalcemia causes the most important symptoms. Central nervous effects of hypocalcemia, if not abrogated by chronic course, are the leading symptoms. Somnolence, cramps, or in lower grade fatigue together with increased serum calcium (in pHPT) must lead to PTH assessment and enable the diagnosis.

An obstacle to withstand a correct and early diagnosis is the later renal effects of hypocalcemia. If pHPT is not diagnosed early, renal calcinosis is a frequent late squeal. In such a situation, as in any CKD, sHPT due to vitamin D deficiency decreases serum calcium and mixes up with the pHPT being the underlying disease in such cases. In general, in more chronic cases of any HPT, clinical symptoms are not very characteristic but must be evaluated by biochemical studies. A summary of symptoms with most observed frequencies is listed in Table 5.1 [35, 36].

Diagnostic Techniques

Imaging

The role of preoperative imaging in HPT is controversial due to varying success rates reported in studies [37]. In the more recent years, ultrasound

Table 5.1 Clinical symptoms of hyperparathyroidism

Symptoms	Frequency (%)
Left ventricular hypertrophy	80
Dullness	70
Arterial hypertension	50
Extraosseous calcification	40
Fatigue	40
Hyperuricemia	30
Joint calcification	20
Obesity	20
Depression	15
Anxiety	10
Cognitive dysfunction	5

Fig. 5.6 (**a**) Ultrasonography of right adenomatous parathyroid gland (+ picture marks of enlarged gland). (**b**) Ultrasonography of left adenomatous parathyroid gland, note central inhomogenous structure (+ picture marks of enlarged gland, ACI=internal carotid artery, VJi=internal jugular vene, Li Lappen=left thyroid lobe)

(US) and technetium 99m-*methoxyisobutyli-sonitrile* (sestamibi) scintigraphy scan has been used most frequently. Mihai et al. [38] found in an evidence-based analysis, that sestamibi is a rec-ommended primary test, but ultrasound in experienced hands turned out to be a valuable alternative (see example in Fig. 5.6). The authors concluded, that if both investigations are concordant,
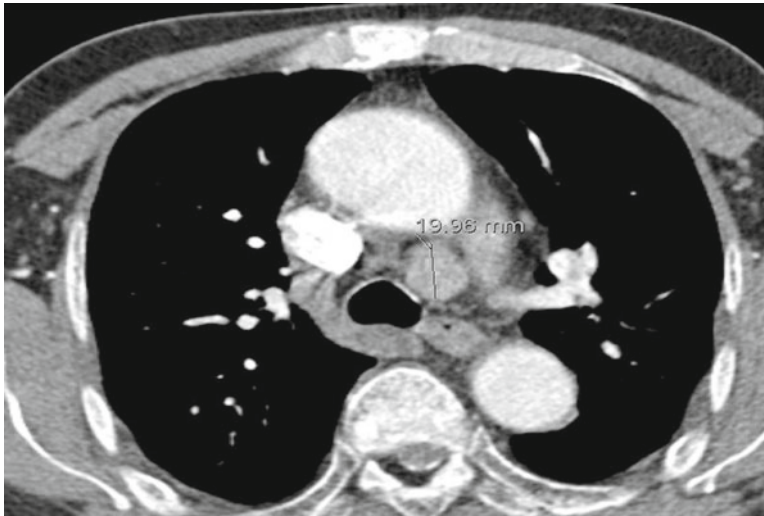
Fig. 5.7 CT scan of atypical localization of parathyroidal glands (between trachea and vena cava)

a minimal invasive surgical approach is indicated, if only one of the two investigations is positive, a unilateral exploration with intraoperative PTH assay should be performed. In case of two negative investigations, a bilateral exploration should be planned [38]. The technological development of US devices (resolution down to 1 mm) currently contributes to use of such methodology. If glands are located atypically, CT scans (Fig. 5.7) might be helpful.

Laboratory Techniques

Most optimal, patients suffering from sHPT and or CKD-MBD should be diagnosed by screening measures during the course of CKD. One of the most discussed issues was establishing thresholds, from which sHPT should be regarded or even treated. Recent guidelines of the Kidney disease global outcome initiative KDIGO [39] discarded further CKD stage-dependent PTH limits and use threshold of up to ninefold "normal" PTH, where normal refers to local reference. This is meaningful, since PTH assays are yet not standardized between different systems and laboratories.

PTH secretion underlies a both short frequent and circadian rhythm. Therefore, for diagnostic studies, standardized assessment time points must be used. Laboratories do use different assay techniques, which target different epitopes of the 84-amino acid protein. The level of PTH compared to baseline can be used to establish surgical success (Table 5.2).

Serum calcium can be measured as free serum calcium or as whole calcium including its albumin-bound proportion. In the latter case, for correct assessment, it must be corrected for plasma albumin concentration

$$\text{Calcium}_{\text{corrected}} = (\text{calcium} / \text{plasma(mmol} / \text{l}))$$
$$+ (40 - \text{albumin} / \text{plasma(g} / \text{l})) \times 0.02.$$

Assessment of Bone Disease

Although no clinical routine method, evaluation of bone status is important to distinguish between conditions of either arrested or stimulated turnover of cellular bone-forming mechanisms. That cellular turnover is denoted by a steady state of activity and number of osteoclasts and osteoblasts at the front of trabecular mineralization. It is meaningful, since therapeutic measures are different in such states. Measuring bone density alone cannot help to distinguish between these entities since it gives only information about

Table 5.2 PTH and calcium thresholds for regarding surgical success, failure, and recurrence

Category	PTH level
Success	Normal or below normal PTH later than 6 months after surgery
Failure	Higher than normal PTH and/or hypercalcemia within 6 months after surgery
Recurrence	Higher than normal PTH and/or hypercalcemia later than 6 months after surgery after initial success criteria fulfilled
Multigland disease	Removal of two or more hyperfunctioning glands during surgery in pHPT evidenced by intraoperative PTH test

**Table 5.3** Histomorphological classification of renal osteodystrophy (ROD)

ROD notation	ROD type	Key pathophysiology
High turnover	1	Elevated cell turnover by PTH stimulation
Mixed uremic osteodystrophy (osteitis fibrosa)	3	Disturbed salt mineralization and PTH stimulation
Low turnover		
Osteomalacia	2	Accumulation of nonmineralized bone matrix
Adynamic renal bone disease	4	Decreased volume of bone matrix along with suppressed cellular turnover

content of mineral salts. The histomorphometric approach is based on standardized parameters, which were described in 1987 [40]. Bone histology must be processed following certain procedures both in harvesting, transfer and preparation of the samples. Prior to biopsy, patients should be given tetracycline 250 mg bid at day minus 20 and minus 5 before biopsy. That substance accumulates at the endosteal mineralization front and allows quantification by spontaneous fluorescence. Bone sample biopsy is usually done using a mechanical-driven drill device. Since such approach includes relevant patients discomfort and pain, we use a 4-mm diameter bone marrow biopsy trochar (Pajunk™), which allows a safe and uncomplicated biopsy with satisfying biopsy samples. As biopsy site, we use the posterior upper iliac spine. Samples must be transferred to acetone solution (using mineral glassware) and can be shipped without cooling to bone histology. For embedding, methyl-*methacrylate* will be used. Pathologists use different staining procedures, with *Masson-Goldner* and *Giemsa* being the most important ones. Quantitative histomorphometry is usually done by manual methods of *Merz and Schenk* [41] or semiautomatically following *Malluche* [42]. A pathological bone status in CKD is considered from a histopathological point of view as ROD (Table 5.3, Figs. 5.8–5.11). However in recent years, with advanced under-
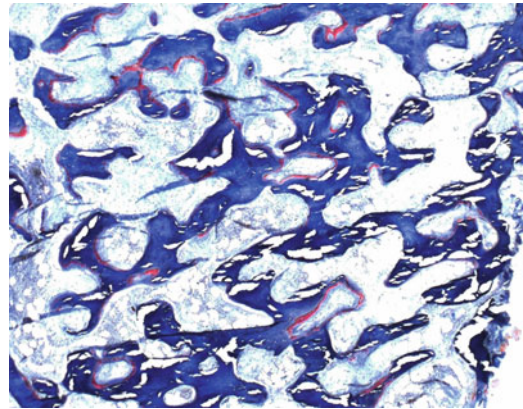
Fig. 5.8 Type 1 ROD. High-turnover variant of osteitis fibrosa with massive osteoclastogenesis (→), high resorptive activity, Masson-Goldner. Kindly contributed by Dr. Gabriele Lehmann, University Hospital Jena, Germany

standing of systemic implications of pathological bone state, the more comprehensive term CKD-MBD has been used for clinical perception.

Biochemical markers of bone status have been studied widely. Although none of these markers have been shown to fit perfectly with the gold standard bone histomorphometry, measuring the bone alkaline phosphatase (ostase) is the most used surrogate. Combination with PTH yielded about 60% fit with histology [43]. Other bone markers include urine cross-links, i.e., fragmentation products of bone collagen. The diagnostic value of these markers is not
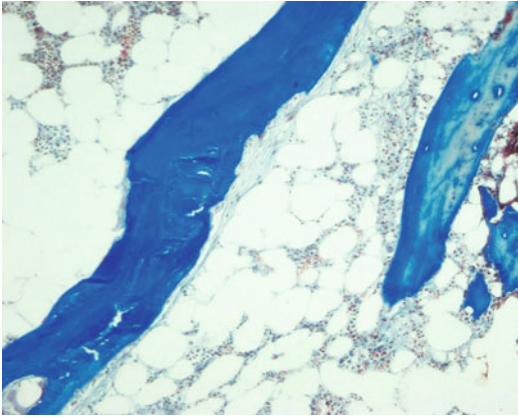
Fig. 5.9 Type 3 ROD mixed osteitis fibrosa, peritrabecular fibrosis (→) and osteoclastic activity (→), Masson-Goldner. Kindly contributed by Dr. Gabriele Lehmann, University Hospital Jena, Germany
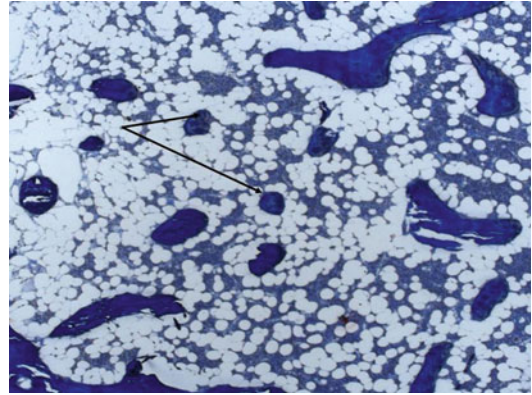
Fig. 5.11 Adynamic bone disease, only small osteoid volume (→) detectable; decreased cellular activity, Masson-Goldner. Kindly contributed by Dr. Gabriele Lehmann, University Hospital Jena, Germany
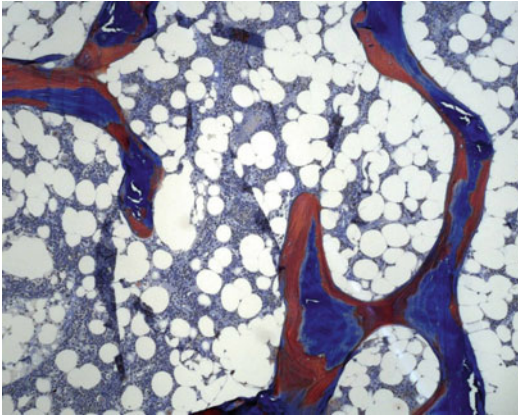
Fig. 5.10 Osteomalacia, intratrabecular disturbed mineralization (→), Masson-Goldner. Kindly contributed by Dr. Gabriele Lehmann, University Hospital Jena, Germany

completely accepted by all. Following trends maybe more helpful than a single-point measurement in time. Therefore, they are promising but must be handled with caution.

Alternative Diagnostic Tools

Biochemical Fine Needle Aspiration

A biochemical fine needle aspiration with PTH measurement allows differentiation of parathyroid tissue from lymph nodes and thyroid tissue with a specificity of 100%. The sample is drawn

through a 25-gauge needle, the aspirate is diluted with 1 ml saline solution; after centrifugation for 10 min, the supernatant is used for the PTH measurement [44]. This technique allows prompt tissue identification without frozen section, thereby limiting the preparation of nonparathyroid tissue. It has been proposed for preoperative procedures although with a weak level of evidence but recommendations at grade B [38].

Differential Internal Jugular Venous Sampling

When the preoperative localization techniques are equivocal, a venous sampling may guide the surgeon to the side harboring the hyperfunctioning gland. It has been proposed to analyze simultaneously samples from both jugular veins and from a peripheral vein. In most cases, indirect regionalization, however, should be reserved for preoperative procedures particularly after an extended previous exploration.

Treatment

Therapeutic intervention in dysbalanced mineral-metabolic pathways should consider multiple pathways as outlined in the pathophysiology chapter. In brief and principle, intervention can be done

at subsequent levels. Vitamin D replacement in "hormonal doses" acknowledges the central role of that hormone in CKD-MBD. Abolishment of the activity of the parathyroid can be performed by either excision of the glands totally or in parts, by pharmacological intervention in PTH secretion by means of calcimimetics or by "pharmacological vitamin D dose intervention" with the active, double hydroxylated form of vitamin D (calcitriol or analogs/derivatives). Not very acknowledged, but helpful, is treating CKD-MBD by modified dialysis conditions, which will be considered first.

Impact of Dialysis Techniques

Both hemo (HD) and peritoneal dialysis (PD) fluids do use external solute conditions which have been based on a positive net calcium balance to suppress PTH secretion of patients in earlier era. In hemodialysis, calcium bath has been set to 1.5 or 1.75 mEq/l, in PD to 1.2 mEq/l. Nowadays, with the focus on avoidance of PTH oversuppression along with low turnover ROD, calcium baths will be fixed at 1.0–1.5 mEq/l in HD or at 0.9–1.2 mEq/l in PD targeting a neutral calcium balance. That goal, however, is influenced by further dialysis conditions and might be difficult to accomplish. Since patients exhibit different bone status, individualization with regard to clinical condition is a necessary tool to consider [45].

Vitamin D Analogues

Prospective studies have shown that pharmacological doses of Calcitriol and other active vitamin D derivatives suppress parathyroid function and lower PTH levels in CKD and reduced even mortality in retrospective data analysis [46]. Osseous effects include a reduction in bone turnover, improvement of osteitis fibrosa, and stimulation of bone mineralization. Side effects comprise hypercalcemia and hyperphosphatemia. Oral and intravenous forms are on the market, which can be adapted to the kind of treatment, to which patients are subjected (Table 5.4).

The correction of vitamin D deficiency (as assessed by low 25 vitamin D 1-25 OH_2D) in CKD patients has not yet been proven to result in better

Table 5.4 Indication for parathyroidectomy in primary HPT

Increase of serum calcium	>0.26 mEq/l above upper reference
Calcium excretion/24 h	>400 mg
eGFR	<60 ml/min
Bone density t-score	<2.5
Age	<50 years

Table 5.5 Indication for parathyroidectomy in secondary HPT

Serum calcium × phosphorus product	>5.5 mEq^2/l^2
Serum calcium	>2.8 mEq/l
Bone pain, pruritus of no other cause	Any
ROD type 1 and 3	Any
Interstitial calcifications, calciphylaxis	Any
Patient awaiting renal transplantation	Need of cinacalcet >30 micg daily

clinical outcomes. However in routine clinical practice, a vitamin D 1-25 OH_2D level of 45 ng/ml is currently considered optimal and can be reached by daily or weekly application of 1,000 or 10,000 international units, respectively. Hypocalcemia, which is on the other hand a frequent side effect of active vitamin D (i.e., calcitriol), is not common with low inactive vitamin D 1-25 OH_2D (i.e., low 25 vitamin D) and the therapy is not costly. Therefore, many nephrologists treat their patients routinely with vitamin D_2 or D_3 during European and American winter seasons with low light conditions.

Parathyroidectomy

In primary HPT due to adenoma, surgery is the primary therapy of choice to avoid secondary end-organ damage with renal calcinosis being the first line (indications in Table 5.5). Indications were defined by a 2002 National Institute's of Health summary statement [47]. A clear indication is given along with high-turnover ROD (types 1 and 3) refractory to active vitamin D and calcimimetics. In non- or oligosymptomatic patients, particularly with psychiatric symptoms, decision-making has to incorporate individual aspects of the patients (Table 5.6).

Table 5.6 Active vitamin D analogs

Generic name	Biochemistry	Dosage intravenous (micg)	Dosage oral
Calcitriol	1,25-Dihydroxyvitamin D$_3$	1–2 micg three times per week	0.25–0.5 micg once daily (up to 2 μg after PTx)
Alfacalcidol	1-Hydroxycholecalciferol	No data	0.25–1 micg once daily (up to 3 μg after PTx)
Doxecalciferol	Synthetic derivative of 1-hydroxycholecalciferol	4 micg three times per week	10 micg three times per week
Paricalcitol	Synthetic derivative of 1,25-dihydroxyvitamin D$_3$	2–6 micg three times per week	1–5 micg three times per week

These "nonspecific" symptoms, however, can be sufficiently treated by PTX. Furthermore, reduction of blood pressure, left ventricular hypertrophy after PTX have been reported [48–53]. In young patients with established but not sufficient effective conservative therapy, indication for surgery should be established more liberally compared to older and multimorbid patients.

Despite the introduction of new therapeutics like calcimimetics or vitamin D derivatives, these classical indications are still valid in the presence of drug resistance [54]. A recent study has shown the increased mortality due to cardiovascular events in chronic renal failure patients [55].

HPT can resolve after kidney transplantation, but persistent disease may occur in 10–50% of the patients [56]. Recently, the consequences of abnormal mineral metabolism after kidney transplantation have been evaluated in a retrospective study. 11–25% of patients showed abnormal serum calcium or an increased Ca × P product within the first year after kidney transplantation. A calcium >10.5 mg/dl at 3 months was identified as an independent risk factor for recipient death (OR 3.0; 95% CI: 1.2–7.4); a Ca >10.5 mg/dl at 12 months was an independent risk factor for death censored graft loss (OR 4.0; 95% CI: 1.2–14) [57]. Other retrospective studies showed reduced graft survival after PTX following kidney transplantation [58], and was augmented by another German [59] but contradicted by Dutch study [49, 60]

Operative Technique

In case of a conventional surgical procedure, a *Kocher's* incision is the standard approach to the thyroid and the parathyroids. The strap muscles


Fig. 5.12 Operative figure of an adenomatous parathyroid gland within the thyrethymic ligament

are divided in the midline, the parathyroids can then be approached on either side. A precise anatomic knowledge is the key for a rapid and safe exploration (Fig. 5.12).

In case of a positive preoperative localization in one or two investigations, a unilateral preparation is justified. After the removal of one enlarged gland, an intraoperative PTH allows to decide whether or not a further neck exploration is required. In contrast to a systematic bilateral exploration, an adequate drop of the PTH in the PTH assay after extirpation of one enlarged gland allows to finish the operation. However the interpretation of the results remains controversial in some details, the success rates of parathyroid surgery using this technique reach 96–98%.

In case of secondary HPT, a bilateral exploration is mandatory in every case. There have been some controversial debates whether to perform a total or a subtotal PTX. Lorenz et al. evaluated the results of total versus subtotal PTX in renal hyperparathyroidism. They showed that measurable PTH following total PTX is the consequence of isolated cell nests that may be responsible for recurrences with time. The authors favored in their conclusions the advantage of total PTX and
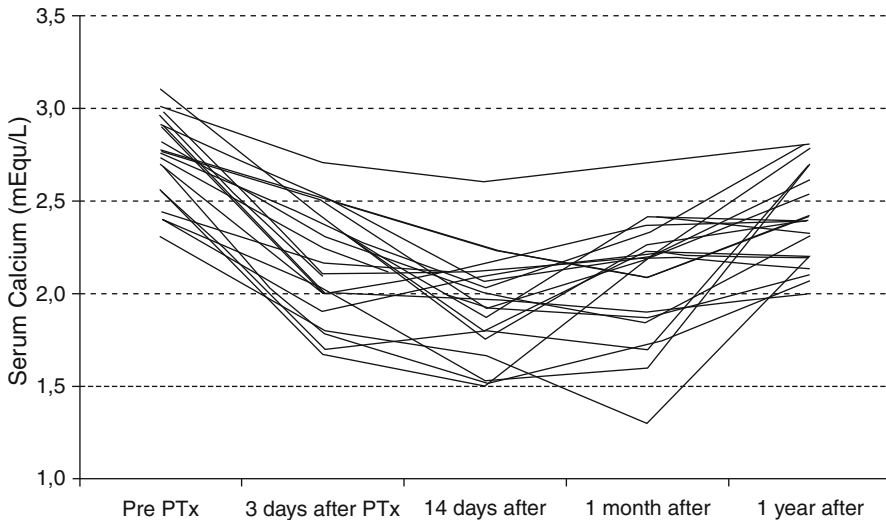
Fig. 5.13 Course of serum calcium after parathyroidectomy in renal transplant patients

cryopreservation with regard to the prevention of recurrence [61].

Follow-up of surgical removal must include close monitoring of serum calcium. Serum calcium level decreases due to recalcification of bones ("hungry bone syndrome") in a typical course within first days and weeks after surgery with the frequent sequela of symptomatic hypocalcemia (Fig. 5.13). Typical symptoms include diathesis and muscular cramps, i.e., the clinical picture of tetanus. Therefore, calcium must be supported orally or even intravenously, necessitating a central venous line. Intravenous calcium infusion raises the danger of cardiac arrhythmia and must not be avoided by using infusion rates less than 5 me/h. Oral calcium frequently causes nausea and vomiting. To overcome these shortcomings, active vitamin D beginning with a (high) daily dose of 2 micg is the therapy of best choice and should be titrated to low-to-normal serum calcium concentration. Since "hungry bone" resolves after weeks to months, that active D therapy has to be adapted following laboratory controls every 1–4 weeks.

Cryopreservation of Parathyroid Tissue
In 1975, S.A. Wells reported his first experiences in autotransplantation of parathyroid tissue [62].

In 29 patients, Wells et al. demonstrated the functional status of the glands 1 year after transplantation. The technique of immediate transplantation of parathyroid tissue during total thyroidectomy of cancer has been proposed in 1977 [63]. The risk of recurrent hyperparathyroidism following transplantation of parathyroid tissue from a parathyroid adenoma has been shown first by Brennan et al. [64]. One case report has shown the occurrence of HPT after transplantation of a normal parathyroid [65].

Questions about the use of cryopreserved tissue and the viability after long-term storage are still matter of debate [66]. Brennan et al. first described viable grafted parathyroids after as long as 18 months of cryopreservation [67].

Independent of the surgical approach, a cryopreservation of parathyroid tissue should be planned in every case of secondary and sporadic or hereditary multiglandular hyperparathyroidism. A frozen section of the parathyroids to be cryopreserved is recommended. The tissue is placed in ice-cold physiologic saline solution, thereafter it is placed into a Petri dish with RPMI 1640 culture medium (RPMI: Roswell Park Memorial Institute). With a sharp scalpel, fragments of 1–2 mm are prepared, 5–8 pieces are stored in one tube, several tubes may be used [68].

Calcimimetics

Calcimimetics interact with the CaR and increase its sensitivity to calcium to lower PTH secretion without increasing calcium serum concentration, which was significantly shown in a controlled, randomized clinical trial [69]. They, moreover, enhance the expression of CaR [70] and VDR [71] and inhibit parathyroid gland proliferation [72]. This differentiates calcimimetics from the vitamin D analogs, which enhance calcium and phosphate resorption from the intestinal tract and increase serum calcium and serum phosphate. The EVOLVE study, a randomized placebo-controlled outcome trial of 3,883 patients to evaluate the influence of cinacalcet on mortality is ongoing and results are expected at the end of 2011 [73]. In a meta-analysis of already conducted studies, the frequency of bone fractures and cardiovascular morbidity (hospital admissions) was reported to be reduced [74]. The KDIGO guidelines [39] give recommendations for using calcimimetics to lower PTH levels.

Calcimimetics after Renal Transplantation

After renal transplantation with a sufficient kidney graft, in the vast majority of cases, sHPT resolves together with reductions of serum calcium and phosphorus. In a few cases that process does not occur appropriately, since parathyroid glands have been proliferated due to long lasting stimulation. That process is comparable to primary HPT with low phosphorus and high calcium both in opposite to sHPT. That condition is called transplant-persistent HPT and should be treated thoroughly since grafts are in danger due to interstitial calcification. Therapy must consider specific pathophysiological features of such state, what usually makes active vitamin D inappropriate due to related hypercalcemia. Cinacalcet has been applied successfully [75–79] but is yet not approved in most European countries and the USA. PTX, in particular, in patients with already injured renal function boosts the risk of graft loss [58] but must be considered anyway in some cases. To overcome the pitfalls, it must be recommended to work-up sHPT in patients awaiting renal transplantation. Patients in need of intensive medical therapy (active vitamin D and cinacalcet >30 mg/day) should be treated with PTX and cryoconservation of glands for later autologous retransplantation.

Phosphorus Control in CKD

Hyperphosphatemia is a key issue in chronic renal disease as outlined in the introductory pathophysiology chapter. Since 50% uptake from the intestine is passive and uncontrolled, renal excretion is of crucial impact for phosphate homeostasis. However, while normophosphatemia is maintained through a wide range of renal failure presumably by the early exert of FGF-23, the association of increased phosphate levels with mortality is out of any doubt. This was shown in dialysis-dependent patients [80], in renal transplantation [57], and even in healthy subjects like the Framingham population [81, 82]. On the other hand, no randomized controlled trial (RCT) has ever been conducted comparing phosphate lowering versus no measure in terms of hard endpoint (mortality). There were, however, numerous efforts to decrease phosphate levels by means of both nonpharmaceutical and pharmaceutical measures.

As for nonpharmaceutical action taking, it is important to recognize that modification of diet with avoidance of phosphate intake is crucial to help patients maintain their phosphate homeostasis. Physicians should convey detailed information to their patients displaying the phosphorus content of daily nutrients. Of note, convenience and preconditioned food is stabilized with phosphate-containing ingredients. Gross amounts of phosphate are carried with Coke (soft drink) of any manufacturer, tinned food and softened cheese, to mention (not comprehensively) the most important ones. Phosphorus can hardly be avoided completely since it comes along with protein-rich food in general. A list of phosphate content of nutrients can be retrieved at a list of the NIH [83]. Patients in stage 5 CKD necessitating dialysis do benefit from formalized nutrition programs which declare phosphorus content and aim to reduce nutritional intake [84]. Phosphate

control is of particular importance in patients undergoing peritoneal dialysis compared to hemodialysis. The overall phosphorus excretion is higher in HD compared to PD [85] and can be increased further by choosing convective procedure modalities like hemodiafiltration and usage of larger dialysis filters. However, the best measure to increase phosphorus elimination is prolongation of dialysis time, e.g., use of nocturnal dialysis three times per week for 8 h [86].

Following the need of protein-rich nutrition in hemodialysis, in a majority of patients, nutritional intake must exceed excretion capability and therefore must be coped by measures to decrease intestinal absorption. Historically (until the mid-1980s), aluminum was the cornerstone of phosphate binding. However, oral administration was complicated by systemic toxicity, which was mainly related to accumulation in brain, bone, and joints. Therefore, aluminum is nowadays mostly excluded from clinical use and clinical research, too. If such neglect is fully justified can only be speculated [87] since the poisonous properties were largely interlinked with covariates like nonsterile dialysis water or bone turnover oversuppression, which have changed significantly in recent times. The first substitute of aluminum, introduced in the late 1980s years, was calcium-based binders [88], namely calcium carbonate and calcium acetate. These drugs have medium phosphate-binding capacity compared to aluminum and were never tested for outcome in RCT. However, they are the most applied binders until recent times. Along with the discussion of extraosseous calcification in frame of CKD-MBD, calcium-containing phosphate binders have been incriminated to promote calcification-related morbidity and mortality [89, 90]. In a small RCT ($n=27$) comparing calcium carbonate and a calcium-free alternative (sevelamer), attenuation of vascular calcification has been reported [91]. Sevelamer was introduced in 1997 and acts through its anion-exchange capabilities within the bowel. Their phosphate-binding capacity is smaller compared to calcium salts and aluminum, and moderate gastrointestinal side effects are common. However, sevelamer showed in RCTs and retrospective studies slowing of calcification and

amelioration of bone disease [92–96]. One RCT exploring mortality could not show a significant effect of sevelamer versus calcium salts [97].

A further calcium and aluminum-free compound is lanthanum carbonate. As aluminum, lanthanum is a triple charged metal and has been therefore discussed widely envisioning cerebral and bone accumulation and toxicity. In fact it deposits in bones, but not at the mineralization front. In animal toxicological experiments, with multiplies of human dosage, it could be detected in rat brains [98, 99] while no human central nervous system toxicity was reported so far [99, 100]. Phosphate-binding capacity is high, so the substance is in principle highly needed nonaluminum, noncalcium choice. RCTs resulted in substantial phosphate lowering capacity and showed no severe side effects [101] but a high incidence of substance discontinuation in verum groups. No RCT was targeted and powered to demonstrate mortality benefit.

Taking these issues together, there is currently no "ideal" phosphate binder available. Our current practice is summarized in Table 5.7 and can be appreciated further in a current comprehensive review from Tonelli et al. [102].

Research on new substances does focus on iron-based binders, niacin, and chitosan chewing gums while no such substances are being currently available on the market. In a phase 1 study, an iron-containing compound (SBR 759) showed phosphate reduction into the KDIGO target using a dose between 3.5 and 15 g [103], which translates into a pill burden of up to 20 tablets per day. Niacin, in opposite to direct intestinal binding of all other substances, inhibits the phosphate uptake into the bowel wall by inhibiting the small bowel phosphate cotransporter [104]. Chewing gums containing chitosan [105, 106] have experimentally shown to absorb phosphate already with salivation in the mouth.

Influencing Bone Metabolism

Serum parameters of mineral metabolism do not depict the whole complexity of CKD-MBD, in particular, the bone features end the vascular

Table 5.7 Phosphate binders, before and together with ordination consider nonpharmaceutical measures

Generic substance	Binding capacity	Indication	Side effects, caveats
Aluminum hydroxide	↑↑↑	Short-term application (2–4 weeks) for critical phosphorus levels without concomitant calcium intake	Accumulation, *brain toxicity*, aluminum osteopathy
Calcium carbonate	↑↑	Cost-effective phosphate decrease in earlier CKD stages in patients with low-to-normal serum calcium	Calcium intake, extraosseous *calcification*
Calcium acetate	↑↑↑	Cost-effective phosphate decrease in earlier CKD stages in patients with low-to-normal serum calcium, with higher binding capacity	Calcium intake, extraosseous *calcification*, plus gastrointestinal (gi) side effects
Sevelamer	↑	Phosphate decrease with no calcium intake, e.g., renal transplant setting	Gi side effects
Lanthanum carbonate	↑↑↑	Phosphate decrease with no calcium intake, e.g., renal transplant setting with higher binding capacity vs. sevelamer	Bone accumulation, CNS toxicity not principally excluded

injury permitted by such disease. To target these aspects, influencing bone turnover has come into scope during recent years again after two decades of neglect along with diminished use of bone biopsy. While having information's about ROD type, influence on bone turnover, i.e., activity of osteoclasts or osteoblasts might be a sufficient choice to treat patients with CKD-MBD.

In low-turnover ROD (type 4), osteo-arresting therapies like bisphosphonates, convey enhancement of bone disease. They are, however, currently widely applied in postmature osteoporosis even in CKD without information on bone status. Bisphosphonates might be helpful in ROD type 1 or 3, which should be established initially by bone histomorphometry. In two studies, alendronat has been proved to influence bone diseases effectively in patients with *primary* HPT [107, 108]. In a clinical analog, pHPT could be translated in sHPT without low-turnover aspects and with high HPT and therefore be treated with bisphosphonates, although no RCT for such reasoning is available

In low-turnover ROD type 4, arrest of osteoblasts must be resolved. In patients with CKD 4 or 5, most frequently, oversuppression of PTH by active vitamin D and/or positive calcium intake by phosphate binders and/or inadequately high calcium dialysis bath concentration (down to 1.0 mEq/l) must be stopped or adopted, respectively. Teriparatide, i.e., synthetic PTH, resembles a pharmaceutical alternative for enhancing

bone turnover. The substance has been used for fracture-prone osteoporosis [109] and could be considered in CKD-MBD associated with abolished PTH secretion as, for instance, after PTX. In a small open-label study in seven patients undergoing chronic hemodialysis with low-turnover ROD, bone mineral density but not coronary calcification scores were improved [110].

Integrative CKD-MBD Therapy

In summary, treatment of secondary hyperparathyroidism must not target PTH levels above certain numerical thresholds alone but has to envision the concept of parathyroid function as a variable of complex regulation of the endocrine–vasculature–bone axis in CKD. A schematic proposal of integrative therapy is given in Fig. 5.14. To conduct such time-dependent and multiple-level approach, continuous monitoring of parameters of CKD-MBD is mandatory. According to recent KDIG guidelines, monthly laboratory monitoring of serum calcium and phosphorus levels in patients dependent from renal replacement therapy is recommended. PTH should be regarded at least every 3 months. Although not directly included in the guidelines, we would recommend additional monitoring of "bone markers" like Ostase every 3 months. Bone biopsy and histomorphometry should be done, when differentiation between high and low-turnover bone
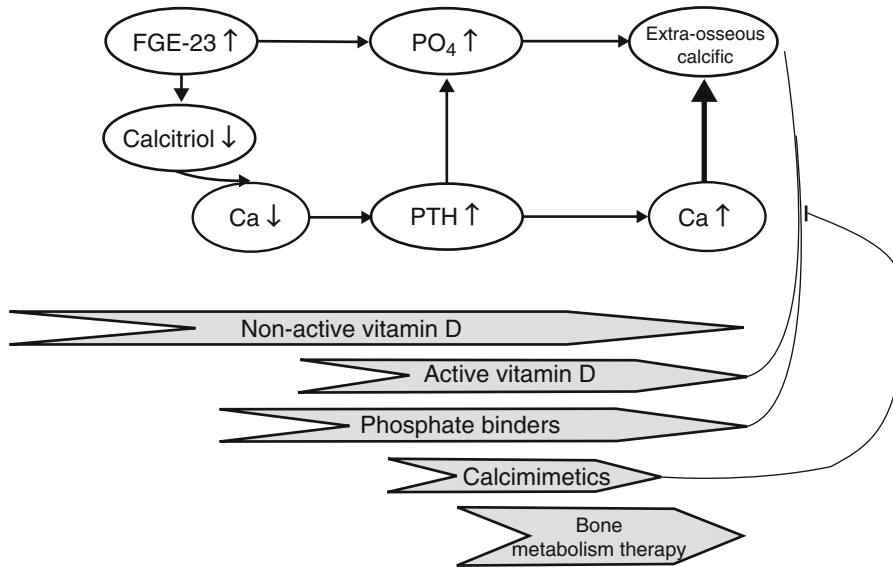
Fig. 5.14 Schematic drawing of integrative therapeutic approach in secondary HPT

disease cannot be done clinically and sufficient therapy choice can be considered. PTX is the therapy of choice in irreversible, autonomous parathyroid hypersecretion along with high-turnover bone disease with a particular regard to patients awaiting renal transplantation.

Overall, the field evolves very rapidly and further implication, e.g., of adipose and muscle tissue can be awaited during the near future. With regard to the excess mortality in CKD, physicians must make any effort, to overcome or at least lighten such disease burden in their patients.

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