Low-turnover (adynamic) bone disease in CKD patients

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Adynamic bone disease; chronic kidney disease; mineral bone disease.

DEFINITION AND CLASSIFICATION
OF CKD-MBD

Chronic kidney disease (CKD) leads to disturbances of bone and mineral metabolism. The former term, renal osteodystrophy (ROD), has been integrated into the term “chronic kidney disease-mineral and bone disorder” (CKD-MBD) thus indicating the close relationship between mineral disorder and bone and renal disease. Renal osteodystrophy consists of several subtypes with important differences in aetiology and fundamental differences in treatment strategies. Long-term dialysis patients exhibit a nearly 100% prevalence of some type of ROD, which illustrates the importance of this sort of comorbidity.

The TMV nomenclature, explained in the recent KDIGO guidelines, discriminates between several variants of MBD. In this system T classifies bone turnover, M bone mineralisation and V bone volume. Bone turnover and bone volume may both be ranked as high, normal or low. Bone mineralisation may be categorised as normal or abnormal. Alternatively to volume, the bone balance may be considered. According to this classification, six types of bone pathology in CKD-MBD can be distinguished (Table I). Despite concerns about the importance of histomorphometric parameters, a CKD-MBD classification is helpful in clinical practice and widely used as the basis for therapeutic approaches.

DEFINITION OF ABD

The term “adynamic” bone disease, introduced in the early 1980s, describes a low-bone turnover with a reduced number and/or activity of osteoblasts and without osteoid accumulation. Low levels of osteoid differentiate ABD from the other low-turnover ROD, i.e. osteomalacia. The “original” ABD is characterised by reduced collagen synthesis, whereas osteomalacia, a defect in bone mineralisation, leads to impaired bone formation. Peritrabecular fibrosis, or marrow fibrosis, is minimal or absent (in contrast to osteitis fibrosa). As a consequence, the bone formation rate is substantially diminished and the number of remodelling sites is low.

Table I

<table>
<thead>
<tr>
<th>NKF-K/DOQI guidelines and renal osteodystrophy classification</th>
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<tr>
<td>– Hyperparathyroid (high-turnover) bone disease.</td>
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<tr>
<td>– Mixed (high-turnover with mineralisation defect) bone disease.</td>
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<tr>
<td>– Osteomalacia.</td>
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<tr>
<td>– Adynamic bone disease (ABD).</td>
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<tr>
<td>– Additionally, two distinct causing agents for ROD are explicitly mentioned: amyloid bone disease and aluminium bone disease.</td>
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**ABD IN BONE HISTOMORPHOMETRY**

The actual KDIGO guidelines recommend bone biopsy in various settings such as unexplained fractures, persistent bone pain, unexplained hypercalcaemia, unexplained hypophosphataemia, possible aluminium toxicity and prior to therapy with bisphosphonates in patients with CKD–MBD. This is in line with the K/DOQI guidelines with one exception. The K/DOQI guidelines also recommend performing a biopsy at intact PTH (iPTH) levels between 100 und 500 pg/ml, if the BAP and phosphate levels are also increased or if there is bone pain (see Table III).

The NKF-K/DOQI guidelines suggest a number of histomorphometric parameters for the classification of ROD (Table II).

Besides static histomorphometric parameters such as bone area and osteoid area, dynamic parameters such as activation frequency (AF), bone formation rate (BFR) and mineral apposition rate (MAR) are of importance. AF is defined as the reciprocal value of the total remodelling time. The latter is the net result of bone resorption, reversal, formation and quiescent periods. Therefore, the activation frequency assesses both osteoclast (resorption) and osteoblast (formation) activity. In contrast, BFR focuses only on osteoblast activity. As the correlation between these two parameters of bone turnover is excellent in ROD, both activation frequency as well as bone formation rate may be used for assessment of bone turnover. KDIGO guidelines recommend measuring the TMV parameters BFR, mineralisation lag time and bone volume (in relation to tissue volume, BV/TV).

**Table II**

<table>
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<tr>
<th>Parameter</th>
<th>Normal</th>
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<tr>
<td>1) bone volume relative to total tissue volume</td>
<td>16 – 23 (%)</td>
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<tr>
<td>2) osteoid thickness</td>
<td>4 – 20 (μm)</td>
</tr>
<tr>
<td>3) osteoid surface relative to total bone surface</td>
<td>1 – 39 (%)</td>
</tr>
<tr>
<td>4) osteoblast surface relative to total bone surface</td>
<td>0.2 – 10 (%)</td>
</tr>
<tr>
<td>5) osteoclast surface relative to total bone surface</td>
<td>0.15 – 1.2 (%)</td>
</tr>
<tr>
<td>6) activation frequency*</td>
<td>0.49 – 0.72 (year)</td>
</tr>
<tr>
<td>7) fibrosis volume relative to total tissue volume</td>
<td>absent (%)</td>
</tr>
<tr>
<td>8) mineralisation lag time</td>
<td>15.0 (days)</td>
</tr>
</tbody>
</table>

→ ABD is diagnosed in the presence of subnormal values in criteria 2 to 6 in the absence of fibrosis

* see text for comment
For a clearer differentiation of hyperparathyroid bone disease, osteomalacia as well as mixed and adynamic bone disease, the parameters bone turnover, fibrosis quantification and bone mineralisation assessment are necessary. Usually three histomorphometric parameters are suitable for this assessment: BFR, osteoid accumulation and presence or absence of fibrosis. However, cut-off levels are inconsistent, which leads to divergent data about the quantification of patients with bone disease.

ABD frequently occurs before end-stage renal disease is reached. Bone biopsies in patients new on dialysis or with advanced CKD (mean age 54±12 years) revealed ABD in 23% of the patients. None of these patients had received calcitriol or aluminium during the course of CKD. An even higher ABD prevalence, 49%, was reported in predialysis CKD stage 5 patients. The prevalence of ABD in advanced CKD or ESRD depends largely upon age, comorbidities, ethnic background, geographical region and also treatment modalities.

### Distinction Between the Subtypes of Renal Osteodystrophy

The gold standard for the diagnosis and classification of CKD-MBD is the histomorphometric analysis of an undecalcified bone sample. A preceding tetracycline labelling, as well as amyloid and aluminium stains, are required for a thorough diagnostic process. To obtain a complete overview of bone metabolism, a combination of dynamic as well as static bone parameters, of cortical and trabecular bone is necessary. A minimum biopsy diameter of 4-5 mm is regarded as being optimal. The sample should be taken 2 cm posterior and 2 cm inferior to the anterior iliac crest.

#### How to Perform Optimal Tetracycline Labelling

To facilitate the assessment of the dynamic bone parameters, bone formation rate, activation frequency and mineral apposition rate, in vivo labelling is necessary using tetracycline. Tetracyclines are fluorescent in ultraviolet light and bind to actively forming bone areas. The administration of calcium-containing phosphate binders should be avoided during tetracycline labelling. For patients with severely impaired renal function, one possible scheme for tetracycline labelling is shown in Table IV. Information is enhanced by using two different tetracyclines with different fluorescent properties. After the second labelling period, 4-6 days should elapse to give the second tetracycline line sufficient time to become incorporated into osteoid. Alternatively, tetracycline hydrochloride and demeclocyclin may be used. A modified, short-term “emergency” labelling scheme is possible.

#### Assessment of Renal Osteodystrophy Without a Bone Biopsy

Due to the discomfort of a bone biopsy for the patient, physicians often use non-invasive parameters for the evaluation of CKD-MBD. However, none of the
known biochemical markers for parathyroid status, bone formation and bone resorption, have reached a sufficient level of diagnostic accuracy (reviews in 1,20) and none so far can replace the diagnostic power of a bone biopsy. Measurements of bone mineral density or planar bone radiographs are not suitable for a diagnosis of CKD-MBD and are discouraged by the new KDIGO guidelines 20,22.

Whereas extreme plasma iPTH levels, i.e. below 50 pg/ml and above 500 pg/ml, are usually associated with ABD and high-turnover bone disease, respectively, in particular levels between about 100 to 500 pg/ml exhibit variable associations with types of bone lesions. This diagnostic uncertainty of intermediate, K/DOQI target-compliant PTH levels has recently been confirmed by bone biopsy studies from Brazil and Portugal 23,24. The situation is complicated further by wide variations in iPTH results when different test assays are employed 25,26 and by potentially variable ratios of agonistic (PTH1-84) and antagonistic (PTH7-84) PTH forms 27. This formed the rationale for a different iPTH target range in the KDIGO guidelines.

Assessment of bone remodelling using serological parameters is difficult, but in cases where a biopsy is not available, serological parameters are the only indicators for bone diseases. The new KDIGO guidelines indicate that iPTH as the single parameter is insufficient. Several studies have evaluated the role of serum markers for the non-invasive diagnosis of ROD 14,28-32.

Bone alkaline phosphatase (BAP) is probably the most useful biochemical parameter for the assessment of bone formation. BAP correlates well with the BFR 17,33. Depending on the patients investigated and the cut-off levels applied, low levels of BAP had PPV of 89, 91 and 100% 13,14,33, corresponding to Youden's Indices between 0.49 – 0.93. Elevated levels of BAP largely exclude an adynamic renal bone disease 20,33; however, elevations of BAP along with total AP may be seen in cases of severe osteomalacia. Combinations of biochemical markers like iPTH plus osteoprotegerin 2 or iPTH plus bone-specific alkaline phosphatase 33 hold promise to distinguish high-turnover versus adynamic forms. Currently, the domain of biochemical markers is the long-term monitoring of ROD evolution. Changes in bone markers, such as bone-specific alkaline phosphatase (or also iPTH), over time may be suitable indicators for the assessment of therapeutic effects.

### ALUMINIUM BONE DISEASE

In the 1980s, aluminium overload was the predominant cause for the development of low-turnover bone disease in dialysis patients. This is regarded as being related to the preparation of the dialysate before the emergence of reverse osmosis 34-35. By reducing both osteoclast resorption and osteoblast surface, aluminium causes mineralisation defects 8. It profoundly decreases PTH synthesis and release 36,37, even in the presence of excessive hyperphosphataemia 38. Clinically, the aluminium-induced ABD forms appear particularly prone to causing bone pain, hypercalcaemia and fractures 8,39.

Aluminium bone disease has also been described in CKD patients ingesting aluminium hydroxide without prior dialysis treatment 40. Aluminium-accumulation may still be of relevance nowadays, as about a quarter of the patients exhibited positive aluminium bone staining in 1995 and in a study from France published in 2004, 57% of the dialysis patients had been treated with aluminium “in the past” 41.

To test for aluminium overload, the performance of a desferrioxamine (DFO) test increases diagnostic accuracy additionally to the basic aluminium serum levels. Depending on the dosage of DFO administered, the aluminium increase in serum regarded as diagnostic varies, from over 50 μg/l 42 to exceeding 200 μg/l 43. Candidates for DFO testing are patients with elevated serum aluminium levels (between 60 to 200 μg/L) and clinical symptoms and/or signs suggestive of aluminium toxicity.

### EVOLUTION OF ABD PREVALENCE OVER THE LAST DECADES

The prevalence of ABD has increased markedly over the last 15 to 20 years, despite the fact that the incidence of aluminium-induced low-turnover bone disease declined 44,45. In a mixed cohort of adult haemodialysis and peritoneal dialysis patients, non-aluminium-induced ABD was the main lesion 45. In particular in diabetic ESRD patients, a prevalence of up to 67% has been observed 45. Accordingly, the former predominance of hyperparathyroid bone disease has diminished 44,46. The growing proportion...
of elderly and diabetic patients and relatively high vitamin D and oral calcium dosages also contribute to the increase in ABD prevalence.

**RISK FACTORS FOR THE DEVELOPMENT OF ABD**

Besides aluminium, low PTH levels are regarded as an important risk factor for ABD (Table V). In a bone biopsy study in dialysis patients, iPTH plasma levels below 120 pg/mL were highly predictive of ABD, while levels > 450 pg/mL virtually excluded it.

<p>| Table V |</p>
<table>
<thead>
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<th>Factors associated with a high prevalence of ABD</th>
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<td>– High calcium load</td>
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<td>– Low PTH levels</td>
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<tr>
<td>– Over-treatment with active Vitamin D (inducing hypercalcaemia)</td>
</tr>
<tr>
<td>– Increasing age of the dialysis patients</td>
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<tr>
<td>– High prevalence of diabetes mellitus</td>
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<tr>
<td>– CAPD compared to haemodialysis</td>
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The regulation of the PTH/PTHrp receptor on osteoblasts may play an important role as well. Down-regulation of this receptor in CKD leads to skeletal resistance to bone-anabolic PTH actions. An abolished PTH pulsatility also contributes to the development of ABD in ESRD.

The pathophysiology of ABD is multifactorial. Uraemic toxins as well as derangements in cytokines and growth factors further influence the development of ABD.

There is no pathognomonic clinical sign of ABD. Symptoms are bone pain, fractures and proximal muscle weakness. Although common in patients with osteomalacia, skeletal pain may occur in all subtypes of ROD. Proximal muscle weakness together with axial skeletal pain and fractures of the ribs, vertebral bodies, pelvis and hips are features of aluminium-induced osteomalacia. These signs and symptoms may also occur in the absence of aluminium overload in patients with osteomalacic bone lesions. However, non-aluminium-induced ABD also carries significant morbidity and mortality (see below) and any type of ABD may cause bone pain.

**ABD AND ECTOPIC CALCIFICATION**

The reduced bone capacity to buffer calcium loads in ABD has now been widely confirmed. As a consequence, the calcium-phosphate product rises even after minor calcium loading which in turn promotes the development of cardiovascular and ectopic calcification. Cardiovascular calcifications is regarded as the main reason for the mortality in patients with ESRD. Several studies have noted a relation between bone metabolism and such calcifications. In 224 prevalent haemodialysis patients, patients with the lowest bone turnover exhibited the most pronounced coronary artery calcification (CAC) scores. A study with 38 dialysis patients identified lower bone volume as a significant risk factor for coronary calcification in the early years (i.e. < 6 years) of dialysis. Increasing calcification scores of the common carotid arteries, the abdominal aorta, iliofemoral axis and legs were associated with decreasing mean iPTH.

Calcific uraemic arteriolopathy (CUA), formerly called calciphylaxis, has also been linked to ABD.

**LOW iPTH AND INCREASED MORTALITY**

In a study by Ganesh et al., a U-curve relationship in a two-year follow-up study in 12,800 dialysis patients showed that both very low (< 32 pg/ml) as well as high iPTH levels (> 496 pg/ml) increased the risk for sudden death. Another investigation in 58,000 ESRD patients revealed that iPTH plasma levels below 150 pg/mL led to a significant, 1.4-fold increase in mortality after extensive multivariate adjustments. However, such a U-shaped relationship between PTH and mortality has not been uniformly confirmed. After multiple adjustments, Block et al. revealed a linear association between the two parameters. Recently, the results of the European ARO-CKD Research Initiative revealed that patients with iPTH, calcium and phosphate levels outside the normal range have an increased risk of mortality compared to those with levels within normal range.

**ABD AND BONE STABILITY**

ABD is associated with a reduced ability to repair microdamage which may result in an increased fracture
risk9,47,70. In a retrospective study in 9,000 haemodialysis patients, a U-curve relationship between fracture risk and plasma iPTH levels was detectable71. Another study demonstrated a 17-fold increased hip fracture incidence in ESRD patients72. One of the significant predictors of fracture risk was an iPTH level below 195 pg/mL. Atsumi et al. retrospectively showed that the lowest tertile of iPTH, in particular in men, was associated with a 22% increase in the risk of vertebral fractures70.

**TREATMENT OF THE PATIENT WITH ABD**

In contrast to high-turnover bone disease, the management of ABD is not well investigated and we are lacking large-scale prospective randomised controlled trials. The goals in ABD treatment are the reduction of calcium and vitamin D load and the restoration of PTH activity (Table VI). Despite the potential success of these strategies, there is a need for large controlled prospective trials in this area.

**Table VI**
 Therapeutic strategies in ABD

- Avoid or diminish calcium-containing phosphate binders, replace with non-mineral-containing phosphate binders.
- Reduce dietary calcium intake to less than 2000 mg/d.
- Reduce or avoid active vitamin D compounds.
- Lower dialysate calcium to 1.25 mmol/L or below.
- In selected cases consider biopsy to confirm diagnosis and to assess bone aluminium content and distribution.
- Stop aluminium exposition; consider aluminium mobilisation and removal (DFO treatment).
- Consider PTH (1-34) in ABD plus severe fracturing bone disease.
- Calcimetics and calcilytics currently of unknown value.
- Avoid bisphosphonates, strontium and fluoride administration.

In the case of exposure to aluminium, the use of desferrioxamin is recommended. DFO mobilises aluminium from bone and decreases the proportion of protein-bound aluminium in plasma, thereby facilitating removal by dialysis. Discontinuation of aluminium and administration of DFO improved signs of aluminium-induced bone lesions in vivo73,74. Human data with serial biopsies after DFO treatment have shown a marked decline in stainable bone-surface aluminium that was associated with an increase in bone formation rate75. Parathyroidectomy should be avoided in patients with aluminium-induced bone disease, since the decrease in bone turnover after surgery may be associated with an accelerated accumulation of aluminium in bone76.

Another treatment option is the reduction of intradialytic calcium. A reduced calcium concentration resulted in improved ABD in haemodialysis and CAPD patients77,78 and a high calcium load in the dialysate resulted in an increased coronary calcium score in patients with elevated serum phosphate > 4.7 mg/dl79. Reducing the dialysate calcium concentration from 1.75 or 1.5 mmol/L to 1.25 mmol/L reduced serum-ionized calcium, diminished episodes of hypercalcaemia, and increased iPTH (four-fold), bone-specific alkaline phosphatase and TRAP-5b levels within 3 to 6 months80.

The current NKF-K/DOQI guidelines recommend limiting daily oral calcium intake (dietary calcium plus phosphate binder) to less than 2000 mg. According to the new KDIGO guidelines, a dialysate calcium concentration of 1.25 to 1.5 mmol/l is recommended.

The use of calcium-containing phosphate binders is regarded as suboptimal by the KDIGO working group. The potential calcium intake may contribute to hypercalcaemia. Recently developed calcium- and aluminium-free phosphate binders now offer alternatives. In two studies investigating the difference between mineral-free phosphate binders compared to calcium-containing binders and their effect on renal bone disease, a benefit for the mineral-free binders was demonstrated24,81. Nevertheless, trials with larger populations are needed to underline the advantage of this therapeutic option.

The indiscriminate administration of active vitamin D compounds reduces bone turnover in CKD patients. For example, alphacalcidol treatment significantly reduced osteoblast surface, number of osteoblasts, eroded surface and bone formation rate82. Biopsy studies indicate that high dosages of active vitamin D (calcitriol) in patients with ESRD may eventually lead to the development of ABD53. Additionally, in these studies, high-dose active vitamin D treatment was associated with higher incidences of hypercalcaemia and higher mean serum calcium levels. Therefore, the KDIGO guidelines recommend to restrict the dosage of calcitriol or vitamin...
D analogues, although uncertainty remains regarding the prevailing need for vitamin D in terms of pleiotropic effects e.g. on the development of cancer and vascular calcification.

Preliminary in vitro data point towards the lower osteoblast activity suppression of novel vitamin D receptor (VDR) agonists (paricalcitol)83. Additionally, paricalcitol increased while calcitriol decreased the PTH(1-84)/PTH C-fragment ratio in haemodialysis patients, indicating a positive effect by paricalcitol on skeletal PTH resistance84. However, no human bone biopsy data are available to verify whether newer VDR agonists indeed affect bone turnover more effectively than calcitriol.

There is an enthralling role for osteoanabolic agents in the treatment of ABD. Currently, the only approved osteoanabolic medications for non-renal osteoporosis are full-length and truncated 1-34PTH. There is a theoretical option in improving bone mass and architecture. The only human trial administering PTH (1-34) in a state of low-bone turnover included patients with “non-renal” hypoparathyroidism. Over a three-year period, teriparatide led to significant elevations of bone turnover markers85. Studies in CKD patients are lacking and may be of interest concerning an improvement of ABD.

The physiological action of PTH on bone seems to depend on its pulsatile secretion50. Calcimimetics may help to re-establish a pulsatile secretion of PTH in patients with ABD. Cinacalcet, to date the only calcimimetic agent, significantly reduces iPTH levels, may help to re-establish a pulsatile secretion of PTH (1-34) in a state of low-bone turnover86. The effect on lowering increased PTH levels has been demonstrated in several animal and human trials of CKD87-90, which indicated that calcimimetics may be a tool to induce pulsatility of PHT levels. The clinical indication is still restricted to secondary hyperparathyroidism and not ABD, although a bone anabolic effect has been shown in in vivo experiments91.

**SUMMARY**

ABD is not an innocent bystander in chronic kidney disease. It is possibly the most prevalent bone lesion in advanced CKD, is associated with impaired calcium-buffering capacity of the bone and linked to cardiovascular disease and mortality in CKD patients. ABD is at least in part often iatrogenic and it is this part in particular which lends itself to prevention or therapeutic intervention. Reducing calcium load is the most widely researched preventive or therapeutic option in non-aluminium-induced ABD.

**Conflict of interest statements:**

TK has received funding from Amgen, Fresenius Medical Care and Shire and honoraria for lectures from Genzyme. VB is a consultant for Abbott and Genzyme, and has received funding from Amgen and Genzyme and honoraria for lectures from the following companies: Abbott, Amgen, Genzyme, Roche, Shire, Novartis. JF is a regular consultant for Amgen and Genzyme and has received honoraria for lectures and panels from the following companies: Abbott, Amgen, Genzyme, and Shire.


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