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NDT Perspectives

Is chronic kidney disease-mineral bone disorder (CKD-MBD) really a syndrome?

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ABSTRACT

The concept of chronic kidney disease–mineral bone disorder (CKD-MBD) does not appear to fulfil the requirements for a syndrome at first glance, but its definition has brought some clear-cut benefits for clinicians and patients, including wider and more complex diagnostic and therapeutic approaches to the management of this challenging set of issues. Admittedly, not all components of CKD-MBD are present in all patients at all times, but these are highly interrelated, involving mineral and bone laboratory abnormalities, clinical and histological bone disease and finally, cardiovascular disease. The presence of typical biological bone ossification processes in an ectopic anatomical location in CKD has helped to define the existence of an unprecedented bone–vascular relationship, extending its interest even to other medical specialities. For now, we believe that CKD-MBD does not reach full criteria to be defined as a syndrome. However, this novel concept has clearly influenced current clinical guidelines. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI™) guidelines in 2003 for instance recommended that calcium-based phosphate binders should be avoided to treat hyperphosphataemia in the presence of cardiovascular calcifications. In 2009, the KDIGO and other guidelines reinforced and extended this recommendation by stating that it is reasonable to choose oral phosphate binder therapy by taking into consideration other components of CKD-MBD. Similarly, it is also considered reasonable to use information on vascular/valvular calcification to guide the management of CKD-MBD. Our current assumption as a working group 'CKD-MBD' is that CKD-MBD has the potential to be defined a true syndrome, such as a constellation of concurrent signs and symptoms that suggest a common underlying mechanism for these components as opposed to the term disease. The term 'syndrome' also implies that in any patient at risk due to the presence of one or a few components of the entire syndrome, the screening for additional components is highly recommended. However, it has not currently been demonstrated that there is an additive predictive value, which can be derived from identifying individual components. Despite all we have learned about this putative syndrome, we

have been left with only a hypothetical framework about how to treat patients. So while we agree that the concept of CKD-MBD has influenced, and continues to influence, our current clinical hypotheses, definitive proof of a benefit of interventions in CKD-MBD is still lacking and a global–multiple therapeutic approach to treat simultaneously several components of CKD-MBD should be tested by well-designed new randomized controlled trials.

Keywords: syndrome, chronic kidney disease, parathyroid hormone, cardiovascular outcome, renal osteodystrophy

INTRODUCTION: WHY IS THE DEFINITION OF CKD-MBD RELEVANT?

The term 'syndrome' comes from the ancient Greek 'συνδρομή' indicating something 'running or occurring together' (from συν or 'syn' = 'along with or together', and δρομή or dromos = 'course or race'). In medicine, it indicates a specific constellation of concurrent signs and symptoms that suggest a common underlying mechanism for these components. Thus, a syndrome may have several items and causes as opposed to the term 'disease', which refers to a cluster of signs and symptoms with a definite single cause.

In recent years, laboratory abnormalities are frequently employed as surrogate markers for risk exposure at the population level, such as cholesterol for cardiovascular risk, glycated haemoglobin for risk of diabetes-associated events, fibrotest for liver disease risk, proteinuria/albuminuria for risk of progression of chronic kidney disease (CKD) or serum creatinine and cystatin C levels to estimate the risk associated with declining kidney function [1–3]. The 'metabolic syndrome' was identified as a complex disorder defined by a cluster of interconnected factors that increase the risk of cardiovascular atherosclerotic diseases. The individual components of the metabolic syndrome include threshold levels for waist circumference (reflecting abdominal obesity), plasma levels of triglycerides and HDL-cholesterol, arterial blood pressure and fasting blood glucose level. Epidemiological studies indicate that people with hallmarks of this syndrome are twice as likely to develop heart disease and five times as likely to develop diabetes as subjects without [4]. However, while the risk prediction is applicable at the population level, it has arguably lower predictive value in the individual patient. As a result, the diagnostic value of the metabolic syndrome has been challenged, and concerns have been raised on its utility in clinical practice [5, 6]. In other words, while it is accepted that cardiovascular risk factors represented within the metabolic syndrome tend to cluster, the concept of whether this syndrome represents more than the sum of its components has been recently disputed [5].

In CKD, abnormalities in circulating parameters of mineral and bone metabolism (e.g. calcium, inorganic phosphorous, vitamin D, PTH and FGF23) are frequently present and associated with adverse clinical outcomes far beyond renal osteodystrophy. In 2006, these mineral and bone disorders (MBD) of CKD patients have been suggested to represent a specific entity, named CKD-MBD [7]. The aim of this paper is to scrutinize if CKD-MBD qualifies as a 'true' syndrome (by examining to what extent it characterizes a distinct clinical condition, apart from CKD *per se*).

DEFINITION OF CKD-MBD

Disorders of mineral metabolism and bone disease are common complications in CKD patients, and they are associated with increased morbidity and mortality and decreased quality of life. There is an increasing body of convincing evidence suggesting that these disorders are causally related to numerous adverse clinical outcomes, in particular cardiovascular disease and increased fracture risk. In December 2004, it was the opinion of the Board of Directors of NKF/K-DOQI™ guidelines (National Kidney Foundation/Kidney-Dialysis Outcome Quality Initiative) that the absence of a precise terminology and uniform classification of these abnormalities hampered communication and comparison of reported research results. The Board of Directors of KDIGO thus chose to address this deficit as a priority action item. As a first step, a Controversies Conference of international experts was convened in September 2005 to develop a consensus on a clear definition and improved classification scheme based on readily available clinical parameters. This would serve to enhance communication and direction of future research and form the basis of evidence-based clinical practice guidelines for the care of CKD patients affected with disordered mineral and bone metabolism. The major goals of this 2005 meeting were to (i) develop the evidentiary basis of the proposed recommendations; and (ii) update the NKF/K-DOQI (National Kidney Foundation/Kidney-Dialysis Outcome Quality Initiative) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease that were published in 2003 and frame them within the new definitions and classifications.

As a result of the conference, a position statement was adopted introducing the new CKD-MBD condition, with the following recommendations: (A) The term 'renal osteodystrophy', until then interchangeably employed to indicate the condition of secondary hyperparathyroidism in uraemia, should be used exclusively to define alterations in bone morphology and bone metabolism associated with CKD. Moreover, the definitive diagnosis of renal osteodystrophy should only be made by bone biopsy followed by standardized bone histomorphometry analysis using a unified classification system that includes parameters of turnover, mineralization and volume (TMV classification). (B) In addition, the new term CKD-MBD should be used to describe broader clinical disorders that develop as a consequence of CKD-related systemic alterations in mineral and bone metabolism (Figure 1). These systemic disturbances may manifest themselves by the presence of any one or a combination of the following three conditions: (i) laboratory abnormalities of calcium, inorganic phosphorus, PTH or vitamin D (Figure 2); (ii) bone abnormalities in turnover, mineralization, volume, linear growth or strength (Figure 3) and (iii) calcification of the vasculature or other soft tissues (Figure 4). Based on the presence or absence of any combination of these three primary components, a potential scoring system, to be validated with future clinical

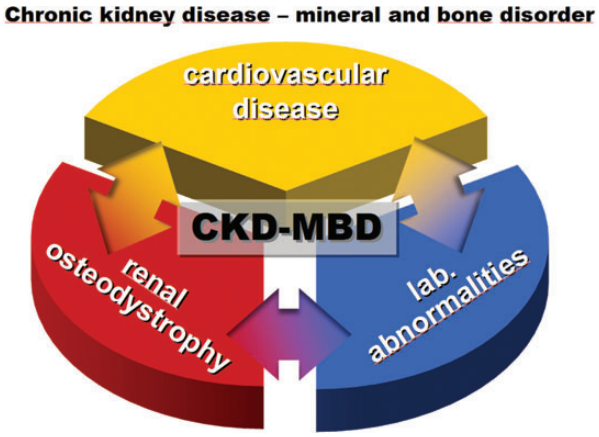

FIGURE 1: CKD-MBD represents a synopsis of three closely related disease conditions: laboratory abnormalities indicative of disturbed bone and mineral metabolism; renal osteodystrophy summarizing the variety of bone lesion subtypes occurring in CKD; cardiovascular disease representing accelerated arteriosclerosis, left ventricular hypertrophy and a variety of additional pathologies in the vasculature and the heart in patients with CKD.

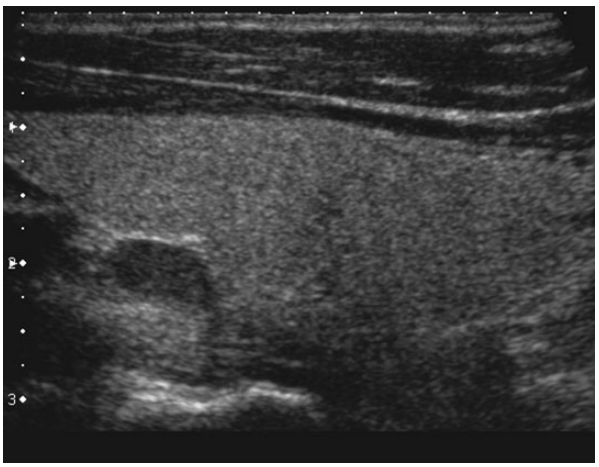

FIGURE 2: Thyroid gland B-mode ultrasonography revealing parathyroid gland hypertrophy of the right upper gland in a dialysis patient with uncontrolled hyperparathyroidism: the parathyroid gland is easily distinguishable as positioned behind the thyroid, oval in shape, with a hypoechoic pattern, when compared with the neighbouring tissue of the thyroid gland.

observations, was also suggested [7]. The association between bone and vascular pathology, dubbed 'bone-vascular axis' has recently been described, and its interest has even extended to other medical specialties [8, 9]. Indeed, the relationship between biomarkers of bone health and vascular calcification is a fascinating but complex phenomenon with many uncertain causal links that still remain to be fully elucidated.

IS CKD-MBD REALLY A TRUE SYNDROME?

Before any attempt to answer the question whether or not CKD-MBD completely qualifies as a syndrome, it is mandatory

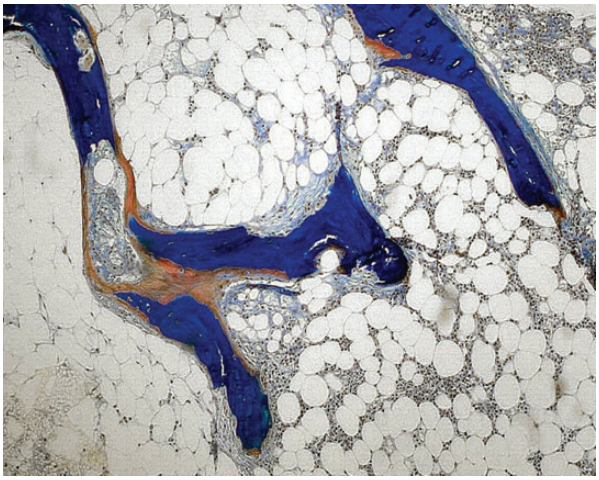

FIGURE 3: Bone histology from iliac crest biopsy: Goldner staining revealing mixed uraemic osteodystrophy characterized by high cellular activity with osteoclastic giant cells in resorption lacunae, osteoid accumulation (red areas) and peritrabecular fibrosis (courtesy of Dr Gabriele Lehmann, Jena, Germany)

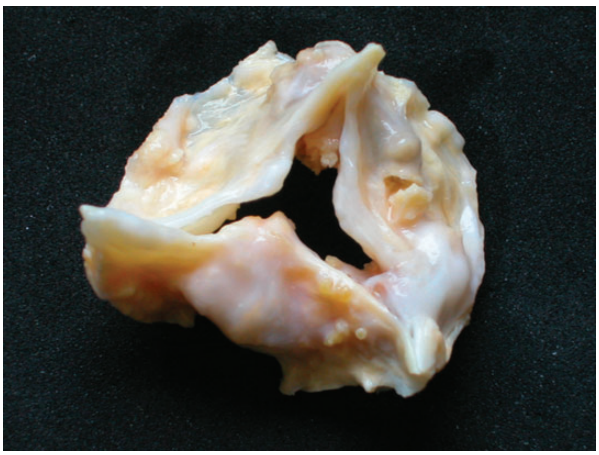

FIGURE 4: *Ex vivo* photograph of an explanted aortic valve due to severe calcific aortic valve stenosis revealing macroscopically areas of ulcerative calcification.

to reflect on why this qualification might be of importance in clinical practice. This may be illustrated by an example more close to nephrology than the metabolic syndrome, i.e. the nephrotic syndrome. It is clear that several glomerular diseases can underlie the nephrotic syndrome. For many of these glomerular diseases, the co-occurrence of a full-blown nephrotic syndrome is not a pre-requisite to establish the glomerular diagnosis. Nephrotic syndrome identifies a clinical situation of uniquely high risk for systemic (thrombosis) and renal complications (high risk of progression to ESKD) and per se dictates treatments that are independent of the cause(s) of the same syndrome, i.e. intensive use of diuretics and prophylactic anticoagulation in severe cases (serum albumin <2.0 or 2.5 g/dL). Thus, there are at least two good reasons why the nephrotic syndrome qualifies as a syndrome: prognosis and therapy. In parallel, diagnosing the co-occurrence of CKD-MBD

components, besides reduced renal function as reflected by declined GFR per se, may require specific interventions of its several components, that in itself may improve outcome.

However, to define CKD-MBD as a true 'syndrome', it is necessary to consider if it characterizes a specific complication of CKD, and we will try to do this by answering the following three questions.

The 'first question' is, whether MBD occurring in the framework of CKD is a special condition in terms of diagnosis, prognosis and treatment. According to its definition, the three components of CKD-MBD appear to be well defined and easily recognizable (see Figure 1). Therefore, while the diagnosis of CKD per se is straightforward and based on the recently reviewed international criteria of serum creatinine and albuminuria [3], this does not hold true for all components of CKD-MBD. While assessment of both mineral disorders (based on laboratory derangements in e.g. calcium, inorganic phosphorous, PTH, vitamin D, total and bone-specific alkaline phosphatases, and potentially also FGF23 and osteocalcin) and vascular or ectopic soft tissue calcification (based on instrumental tests) are easily attainable, bone disease is less easy to diagnose. Since CKD-MBD is defined by the presence of abnormalities in any of the three components by which it is defined, diagnosis can be regarded as relatively straightforward but easily missed when histological defined bone disease is the major or sole component. In contrast to the diagnosis of CKD-MBD, the correct prognosis and treatment of this putative syndrome is much more complex. Several large observational studies indicate the importance of serum phosphorus control during CKD and how its control leads to a favourable CKD-MBD prognosis [10–12]. Furthermore, the importance of monitoring serum phosphorus control has also been formally acknowledged in the recent KDIGO guidelines. Following a successful diagnosis of CKD-MBD, current therapeutic approaches in the later stages of CKD before dialysis include dietary phosphate restriction or oral phosphate binder use or 1,25D treatment to improve 1,25D deficiency and SHPT [13]. Use of phosphate binders and vitamin D activators has been well documented; however, evidence is mainly based on large epidemiological studies [14–18]. There is a concerning lack of randomized, controlled trials examining the effect of a specific therapy on prognostic and/or survival in this patient cohort [19]. In summary to the original question, while the diagnosis of CKD-MBD can be regarded as relatively simple, the prognosis and therapeutic management of these patients still remain a complex task.

The 'second question' is, whether there is an association between CKD and MBD in determining the risk for cardiovascular complications and CKD progression or bone outcomes. To address this, we need to establish whether the combined risk by CKD and MBD exceeds the risk predicted separately by the two components of the purported syndrome. From a clinical point of view, having the full-blown syndrome would intuitively be worse than having a single component. Numerous epidemiological studies associated all individual components of CKD-MBD (laboratory abnormalities, bone disease and cardiovascular disease) to clinical outcome parameters, including mortality, even after correcting for renal function using estimated GFR. Moreover, several basic research studies have provided compelling evidence on a mechanism that may underlie potential causality between CKD-MBD components and disturbed outcome. However, since the concept of CKD-MBD was launched, no study has attempted to verify the relationship between any quantifiable levels of all its individual components (as a composite risk score) with clinical outcome. Furthermore, derangements in either direction (above or below target range resulting in J-curve or U-curve associations) can imply an increase in relative risk, making it even more challenging to ascribe a weight to a single deranged component. Finally, the different components may indicate a different risk weight: would we count more for a fracture compared with raised serum phosphorous? Is the presence of a fracture worse with low or with high PTH levels? In summary, the question of added risk due to the presence of CKD-MBD is affirmative on a qualitative level, but is only based on historical cohort analyses. Currently, there is no clue that points to graded effects of more severe CKD-MBD. It is critical that we do not risk going down the road taken by the metabolic syndrome, where the existence of multiple definitions has led to confusion, resulting in many studies and research papers comparing the merits of each definition, as opposed to focussing on therapeutic management [6, 20].

A 'third question' is should the identification of each single component alone or in the setting of CKD-MBD affect therapeutic or clinical decision making? Treating each of the components separately (e.g. correcting hyperphosphatemia regardless of its effects on other components) is not expected to carry the most beneficial outcomes. This issue is even complicated by the fact that targeting one component, for instance the restoration of vitamin D deficiency, may aggravate another, such as phosphate burden. Rather, a well-balanced and CKD-MBD-multi-component-based approach is conceivably the best method to make optimal therapeutic strategies. As an example the approach to secondary hyperparathyroidism may be quite different if also circulating levels of mineral biochemical markers, vitamin D status, presence or absence of extra-skeletal calcifications, and bone histomorphometry are taken into account. So the answer to this third question appears to be affirmative, but evidence that such an approach improves outcome is lacking, and a challenging trial target for the future. Actually, almost all single-drug/single-intervention approaches in prospective studies on hard-outcomes in ESRD have not been successful so far, and a multi-faceted/combined CKD-MBD approach is probably needed. The only exception to this lack of evidence comes from studies targeting the disease entity formerly denominated.

DISCUSSION: WHERE DO WE STAND?

After the definition of CKD-MBD in 2006 [7], numerous guidelines have been published with recommended biochemical targets and therapeutic strategies aimed at obtaining a good clinical control of the condition [21]. Furthermore, almost every National Society of Nephrology considered it necessary to make its position statement on the subject

[22–24]. Thus, the overall impact of the introduction of the concept 'CKD-MBD' in the nephrology community has been both sustained and impressive. Not surprisingly, the resulting discussion has been centred on the applicability of the recommended biochemical targets, their reliability as surrogate markers of outcome and the probability that novel therapeutic approaches could actually result in the improvement of clinically important outcomes, such as cardiovascular complications and mortality. It is interesting, however, to note that few, if any, previous position statements have questioned the justification of the establishment and creation of a 'new' disease entity.

The European Renal Association–European Dialysis Transplantation Association (ERA-EDTA) has recently founded a scientific working group on CKD-MBD, because of the potential beneficial impact of increased awareness of these disturbed components, but also because ERA-EDTA recognizes the huge scientific efforts that are required to bridge enormous gaps in knowledge and bring this to the bedside of patients with CKD. As a scientific working group, we believe that CKD-MBD is most likely to be of importance in terms of added risk to CKD patients, and that this additional risk can be targeted. Indeed, as discussed above, in CKD patients, the presence of CKD-MBD can be defined by easily accessible diagnostic criteria (with the exception of bone biopsy). However, the proof that individual CKD-MBD components determine synergistically clinical outcomes is lacking (e.g. can the severity and presence of individual components of CKD-MBD assemble to a composite risk marker with additive predictive power). Moreover, it remains to be proven that treatment decisions based on sound biological principles and surrogate markers of CKD-MBD will translate into any detectable clinical benefit. Indeed, the recently published EVOLVE study [19] in which cinacalcet use was compared with conventional therapy, based mostly on vitamin D receptor activators (VDRA) in haemodialysis subjects with hyperparathyroidism, did not demonstrate a survival benefit in its primary unadjusted intention to treat analysis. In summary, our current opinion is, which CKD-MBD may have the potential to be defined as a true syndrome; however, it has not yet been demonstrated as having additive predictive value of its individuals components and still remains unproven that it is a modifiable risk factor.

CKD-MBD: HOW TO PROCEED?

As a working group, we would like to launch a call for prognostic and therapeutic studies that should be performed in order to progress on these issues, which may lead to CKD-MBD acquiring status as a syndrome. More important than this status would be the acknowledgement that specific targeting CKD-MBD improves outcome. Prior to that, a validated scoring system is required to quantify severity of CKD-MBD and its subsequent improvement after targeted CKD-MBD therapy.

The aim of this present paper was to recognize strengths and weaknesses of the concept of CKD-MBD and to discuss whether it should be considered a syndrome. The presence and diagnosis of CKD-MBD should prompt specific interventions targeted towards reducing the burden of CKD-MBD-related outcomes like fractures, calciphylaxis and arterial calcifications. In our opinion, clinical practice might benefit from moving from a single-risk factor therapeutic strategy to a multiple-risk factor or a single omni-comprehensive CKD-MBD score approach, but this position should be based on future clinical trials. This global–multiple therapeutic approach to treat several components of CKD-MBD, which is an additional argument to consider CKD-MBD as a syndrome, should be tested by new well-designed, randomized trials. Furthermore, the definition of a grading system for CKD-MBD may also provide opportunities for patient stratification (possible less heterogeneous subcategories of CKD-MBD) and improvement in design of future multi-target randomized clinical trials.

As a final note of caution, we must be aware that CKD-MBD is only one of several potential clinical syndromes associated with CKD and exacerbated cardiovascular risk. CKD-MBD is somehow unique in that either too low or too high derangements can have deleterious effects. The optimal metabolic balance to prevent cardiovascular risk remains to be defined and is expected to vary depending on CKD stage. Regardless, the corroboration of CKD-MBD as a distinct entity will likely increase our current knowledge in the field, promote early identification of patients exposed to CKD-MBD risk and ultimately generate more effective therapeutic strategies. Furthermore, the definition of CKD-MBD could next be refined in the future, by taking into account other components, like nutrition, inflammation, and/or other still incompletely understood endocrine functions of bone.

CONCLUSIONS

CKD-MBD does not currently fulfil all of the essential requirements of a true syndrome since the added value of the CKD-MBD definition compared with its individual parts is still undetermined. Moreover, additional work is warranted to demonstrate that it is truly a modifiable risk factor. However, there is a sound biological basis for the premise that CKD-MBD is a distinct complication that can accompany CKD and that it accelerates other comorbidities and leads to new complications that would not have occurred in the absence of CKD-MBD. Moreover, there is a striking consistency in epidemiological data supporting an independent role of CKD-MBD in the development of clinically relevant outcomes. We currently have several effective tools at our disposal, which can ameliorate or modify the metabolic disturbances of CKD-MBD. To conclude, since CKD-MBD may not presently meet all the criteria necessary for it to be accepted as a syndrome (but is definitely worthy of further research), we suggest that its continued currency adds significantly to clinical and experimental thinking and practice. Moreover, despite all we have learned about this putative syndrome, we have been left with hypotheses about how to treat patients. So a global–multiple therapeutic approach to treat simultaneously several components of CKD-MBD should be tested by specific new randomized trials.

CONFLICT OF INTEREST STATEMENT

Mario Cozzolino – Lecture honoraria from Abbvie, Shire, Amgen, Genzyme, Roche. Research Grants from Abbvie, Shire. Pablo Urena-Torres: honoraria from Abbvie, Amgen, Fresenius, Shire, Genzyme/Sanofi. Marc Vervloet: research grants from Dutch Kidney Foundation, Shire, Abbvie, Sanofi. Speaking fees form Amgen, Fresenius. Consultant fro Astellas, Amgen. Vincent Brandenburg:current Grants: AMgen, Bayer, Sanofi : Honoraria 2013: Bayer, Sanofi, Fresenius, Synlap Jordi Bover: speaking fees from Abbvie, Amgen, Sanofi/Genzyme, Shire. David Goldsmith: honoraria from Abbvie, Amgen, Fresenius, Keryx, Sandoz Tobias Larsson: part-time emplyee from Astellas Ziad Massy:speaking honoraria from Genzyme/Sanofi, Amgen, FMC, Vifor, Abbvie, Chugai; research grants from FMC, Baxter, Amgen, Genzyme/Sanofi. Sandro Mazzaferro–Lecture honoraria from Shire and Amgen.

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