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Expert panel appraisal of the treatment of chronic kidney disease-related mineral and bone disorders (CKD–MBD): an opinion-based approach

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INTRODUCTION

The Position Statement of the Work Group of the Portuguese Society of Nephrology on the treatment of chronic kidney disease-related mineral and bone disorders (CKD-MBD) published in this issue of the Portuguese Journal of Nephrology and Hypertension was the result of a thorough literature review according to explicit *a priori* criteria.

Much to our chagrin, the absence of solid evidence in this area has made the Statement quite meagre and, if anything, unable to provide clear guidance on most topics.

The Expert Panel felt that while waiting for further scientific evidence it might be useful to provide opinion-based guidance for clinical care, explaining how the Expert Panel approaches these questions and formulates treatment decisions in their daily practice.

It was felt that in the face of the extremely high cardiovascular risk of the CKD population it is not wise to wait for the best evidence from clinical trials to treat our patients. Our treatment decisions must be based on the best available evidence and this includes clinical trials, experimental studies, epidemiological data, expert opinion and our own experience.

BIOCHEMICAL TREATMENT TARGETS

Risks associated with abnormal serum phosphorus: target values for treatment

In dialysis patients, observational studies show an independent and consistent association between increasing serum phosphorus levels and adverse clinical outcomes. However, the range at which phosphorus is associated with adverse clinical outcomes varies from study to study, ranging from 5.0-5.5 mg/dl to >7.0 mg/dl[1-5].

However, the Expert Panel acknowledged that there are no randomised trials evaluating the effect of lowering serum phosphorus to a specific threshold

on patients' clinical outcomes. Therefore, the benefits of lowering phosphorus levels on patients' clinical outcomes (e.g. mortality, cardiovascular events, hospitalisation, and bone fracture) are currently unknown.

The Expert Panel believes that treatment should target thresholds beyond which there is most likely an increased risk for patient health. Therefore, clinicians should avoid phosphorus values that were associated with an increased risk of adverse outcomes in observational studies.

Recently published observational data showed that the risk of cardiovascular mortality was significantly greater for phosphorus levels greater than 6.0 mg/dl, with the greatest risk of mortality for phosphorus levels of 7.0 mg/dl or greater[5].

Risks associated with abnormal serum calcium: target values for treatment

In CKD stage 5D patients, observational studies show an independent and consistent association between increasing serum calcium levels and adverse clinical outcomes. However, the range at which calcium is associated with adverse clinical outcomes varies from study to study, ranging from >9.5 mg/dl to >11.4 mg/dl[1,3-5]. At the low end of serum calcium levels the evidence of an increased risk of adverse clinical outcomes is less consistent.

Additionally, the Expert Panel acknowledged that there are no randomised trials evaluating the effect of lowering serum calcium to a specific threshold (or avoiding high calcium levels, meaning above a specific threshold) on patients' clinical outcomes. Therefore, the benefits of lowering calcium levels (or avoiding high calcium levels) on patients' clinical outcomes are currently unknown.

The Expert Panel believes that in their pharmacologic intervention clinicians should avoid high calcium levels, meaning calcium levels that were associated with an increased risk of adverse outcomes in observational studies. Survival models based on observational data published recently identified categories with the greatest risk of mortality for calcium levels greater than 10.0 mg/dl[5].

Risks associated with abnormal serum parathyroid hormone (PTH): target values for treatment

In dialysis patients, observational studies showing an association between increasing PTH values and adverse clinical outcomes have been inconsistent. In all these studies, PTH analyses have been complicated by problems with assay methods and poor precision. Additionally, the range at which PTH is associated with adverse clinical outcomes varies from study to study, ranging from >400 pg/ml to >600 pg/ml[1,3-5].

Additionally, the Expert Panel acknowledged that there are no randomised trials evaluating the effect of lowering serum PTH to a specific threshold on patients' clinical outcomes. Therefore, the benefits of lowering PTH levels on patients' clinical outcomes are currently unknown.

The Expert Panel believes that treatment should target thresholds beyond which there is most likely an increased risk for patient health. Therefore, the Expert Panel believes that clinicians should avoid PTH values that were associated with an increased risk of adverse outcomes in observational studies. Survival models based on observational data published recently identified categories with the greatest risk of mortality for PTH levels greater than 600 pg/dl[5]. Additionally, the Expert Panel believes clinicians should take into account preceding values and long-term trends in PTH values.

In conclusion, the Expert Panel believes clinicians should lower phosphate and PTH levels, avoiding values that were associated with an increased risk of adverse outcomes in observational studies. Furthermore, in their pharmacologic intervention, the Expert Panel believes clinicians should avoid high calcium levels, meaning calcium levels that were associated with an increased risk of adverse outcomes in observational studies

SURROGATE ENDPOINTS: ARE THEY USEFUL FOR TREATMENT?

A surrogate endpoint is an endpoint that is intended to stand in for a clinical outcome in the evaluation of therapeutic efficacy in clinical trials.

Surrogate endpoints are statistically related with morbid events and are useful markers of the underlying disease. Amelioration of the surrogate marker as a result of an intervention is expected to be associated with an improvement in the underlying disease. However, in CKD patients, it has not yet been demonstrated that the effect of treatment on surrogate endpoints (biochemical endpoints – calcium, phosphorus and PTH, and intermediate endpoints – bone biopsy data or vascular calcification progression) will reduce the occurrence of patients' clinical endpoints (mortality, cardiovascular events, hospitalisations, fractures, quality of life), making them non-validated surrogate markers for patients' clinical outcomes.

It is important to remember that absence of evidence does not have the same meaning as evidence of absence. However, clinicians should be aware that although reliance on non-validated surrogate end points may, in some cases, be beneficial, there are several examples in the past in which it has been shown to be harmful.

Vascular Calcifications: a useful surrogate endpoint?

The association of vascular calcifications with lower survival is verified in predialysis and dialysis patients, and is considered to be a consistent association based on epidemiological studies.

In several clinical trials[6-8], the progression of vascular calcifications seems to be modified by the choice of phosphate binder; it is reduced in patients treated with sevelamer hydrochloride while progression is verified in the majority of patients treated with calcium-based phosphate binders. However, these are not consistent findings, as they were not observed in other studies[9,10]. Additionally, there are no studies evaluating whether altering the progression of calcification will impact on important patient outcomes.

Currently, there is no diagnostic method validated to stratify cardiovascular risk in CKD patients based on vascular calcification (plain X-ray, echocardiography, ultrasound or coronary Agatston score evaluated by computed tomography), and therefore systematic screening of vascular calcifications is not recommended. However, it is considered that knowledge of the presence of vascular calcifications may be used to individualise treatment in CKD patients. At this stage of knowledge, we can only interfere in a very small number of factors, mainly alterations in mineral metabolism.

EFFECT OF PHOSPHATE BINDERS ON BONE HISTOLOGY

Studies of the effect of phosphate binders on bone histology have been performed comparing sevelamer hydrochloride and lanthanum carbonate with calcium-based phosphate binders. Lanthanum carbonate[11,12] and sevelamer hydrochloride[13] do not cause adverse effects on bone. Sevelamer increases bone formation rate and ameliorates trabecular micro architecture. The clinical importance of these findings is currently unknown.

NOVEL EFFECTS OF VITAMIN D THERAPY?

Even though there is a lack of RCT data showing an improvement in patient clinical outcomes (all cause mortality, cardiovascular mortality, morbidity, hospitalisations, fractures), in CKD stages 3-5D patients treated with vitamin D, the Expert Panel considers the following aspects relevant for therapeutic decisions:

CKD patients frequently present not only $1,25(OH)_2$-D3 insufficiency/deficiency, but also 25(OH)-D3 insufficiency/deficiency[14-17].

Vitamin D is known to have pleiotropic extra-skeletal effects, including modulation of immune function, inflammatory responses, cell cycle regulation, insulin resistance and, in animal models, vascular smooth muscle cell hypertrophy and angiotensin system regulation[18-21].

In addition to the kidney, emerging data shows that 1-alpha hydroxylation occurs in many extra renal tissues such as cardiomyocytes, immune cells, and vascular smooth muscle cells[22,23].

25(OH)-D3 deficiency may play a direct role in many of the disturbances associated with lack of vitamin D[24]. 25(OH)-D3 deficiency / insufficiency has been associated with increased vascular calcification and arterial stiffness[25].

More than 130,000 patients were included in several observational retrospective and prospective studies, in which a reduction in all cause mortality and / or cardiovascular mortality was associated with the use of calcitriol or new vitamin D analogue therapy versus non-vitamin D therapy[3,26-28]. Although these findings were not present in all studies, they are relevant to point out testable hypothesis that need to be confirmed with RCT.

A distinction between "physiological" doses of vitamin D (to correct insufficiency / deficiency of vitamin D) and "pharmacological" doses of vitamin D, to control SHPT (secondary hyperparathyroidism), should be considered[28].

There are no studies comparing safety and efficacy of the different new vitamin D analogues.

The Expert Panel suggests:

Serum 25(OH)-D3 insufficiency/deficiency can be corrected with oral colecalciferol. A dose of 100 IU /day will increase, approximately, serum 25(OH)-D3 in 1 ng/ml[29,30].

As vitamin D intoxication has not been found for serum 25(OH)D3 levels ‹200 ng/ml and a daily intake below 10000 IU, a wide "safe therapy window," is observed[30].

Calcitriol and vitamin D analogues are effective in controlling SHPT, but the increase in serum calcium and serum phosphate frequently limits their use in high pharmacological doses. The association of vitamin D or vitamin D analogues with calcimimetics may be useful in the treatment of secondary hyperparathyroidism.

Based on the paucity of RCT, the Expert Panel cannot recommend the preferential use of calcitriol or a specific vitamin D analogue for treatment of SHPT.

SHOULD WE USE CALCIMIMETICS?

In observational studies, SHPT in chronic kidney disease stage 5D is associated with increased risk of bone fractures[1,31-33], proximal miopathy[34], unexplained bone pain[34] and mortality[1,35]. Also there is an association between hyperphosphataemia and hypercalcaemia with morbidity and mortality[1]. However, there are no RCT demonstrating a beneficial effect of controlling SHPT with calcimimetic agents on clinical outcomes such as fracture, bone pain, cardiovascular morbidity and mortality.

Treatment with the calcimimetic agent, cinacalcet, has been shown in RCT to be efficacious in suppressing parathyroid hormone secretion, with a simultaneous decrease in calcium and phosphorus levels[36-38].

A prospective, double-blind, placebo-controlled trial assessed the effects of cinacalcet on bone histology and serum markers of bone metabolism in dialysis patients with SHPT[39]. Treatment with cinacalcet lowered PTH, improved bone histology, and reduced bone turnover and tissue fibrosis among most dialysis patients with SHPT. However, the clinical importance of these findings is currently unknown.

The Expert Panel acknowledged that the risk of developing adynamic bone disease with cinacalcet treatment is low when used only in patients with evidence of high bone turnover and avoiding PTH oversuppression[39].

The Expert Panel believes that, in CKD stage 5D patients with SHPT, calcimimetic agents are highly specific therapeutic agents that effectively lower concentrations of plasma PTH and partially correct disturbances in mineral metabolism. However, there is a need for randomised controlled trials evaluating the impact of treating SHPT with calcimimetics on patient clinical outcomes such as fracture rate, cardiovascular morbidity and mortality. The EVOLVE trial is ongoing and this issue is to be reassessed after its publication.

Conflict of interest statements:

Dr. Teresa Adragão has received research grants from Amgen and Genzyme, lecture fees from Abbott, Amgen, Genzyme, and Novartis and consultancy fees from Abbott and Genzyme. Dr. Teresa Adragão receives fees from Diaverum.

Dr. Aníbal Ferreira has received research grants from Amgen, Genzyme, Shire and Abbott, lecture fees from Abbott, Amgen, Genzyme, and consultancy fees from Abbott, Amgen, Fresenius, Genzyme and Shire. Dr. Aníbal Ferreira receives fees from Fresenius Medical Care. **Prof. João M. Frazão** has received lecture fees from Amgen, Genzyme and Abbott and consultancy fees from Amgen and Genzyme. He participates in advisory board activities for Genzyme and Amgen. Prof. João Frazão receives fees from Diaverum.
Dr. Pedro Ponce is currently Country Medical Representative of Fresenius Medical Care – Portugal. Received lecture fees from Amgen and consultant fees from Amgen and Abbott.
Dr. José Vinhas has received lecture fees from Amgen and Roche, and consultancy fees from Amgen, Janssen Cilag and Roche. Dr. José Vinhas receives fees from Fresenius Medical Care.

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