REVIEW ARTICLE

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Position Statement of the Portuguese Society of Nephrology on the treatment of chronic kidney disease-related mineral and bone disorders

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INTRODUCTION

The Work Group (WG) believes that clinicians making treatment decisions should refer to methodologically strong clinical trials examining the impact of therapy on patient-level clinical outcomes. Accordingly, the Position Statement was based on a thorough evaluation of the evidence and was not the consensual position of an expert panel.

The WG considered as "patient clinical outcomes" the outcomes that are important to patients: mortality, hospital admission, cardiovascular events, bone fractures, bone pain. The WG also accounted for the effect of interventions for bone disease of chronic kidney disease on health-related quality of life.

This Position Statement is not intended to define standards of care and should not be construed as such.

METHODOLOGY

For the purpose of this statement, the WG used the following definitions:

1. Surrogate end point – a laboratory measurement or a physical sign used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions or survives[1];
2. Biochemical end point or biochemical treatment target – a characteristic that is measured and evaluated objectively as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention[2];
3. Patient clinical end point or clinical end point – a characteristic or variable that reflects how a patient feels or functions or how long a patient survives[2];
4. Intermediate end point – a characteristic that is intermediate in the causal pathway between an intervention and the clinical end point[2].

The WG acknowledged that intermediate end points (e.g. bone biopsy, bone mineral density and vascular calcification), and biochemical end points (e.g. serum phosphorus, calcium and PTH) can only be considered validated surrogate markers for patient clinical outcomes if there is a strong, consistent and independent association between the surrogate end point and patient clinical outcomes, found in observational studies, and if (more importantly) there is evidence from randomised trials using different drugs in the same setting that improvement in the surrogate end point has consistently led to improvement in the target outcome.

The WG understands that the use of surrogate end points is indispensable for drug evaluation in

phase 2 and early phase 3 trials geared to establish a drug's promise of benefit. However, the medical community should insist on trial evidence of effect on patient-level end points prior to adoption and full implementation of newer drugs. The WG strongly supports that funding agencies (both governmental and private) should invest resources to test efficacy of any agent on patient level end points in phase III and IV clinical trials.

In appraising the overall evidence, and in the absence of validated surrogate markers for patient clinical outcomes, the WG considered only patient outcomes: mortality, hospital admission, cardiovascular events, bone fractures, bone pain, and health-related quality of life.

Additionally, the WG acknowledged that intervention questions can only be addressed by randomised controlled trials. Unproven (or insufficiently proven) recommendations may expose patients to ineffective therapies and potential harms. Unanimously, the WG decided only to include a position statement when randomised controlled trial evidence or evidence from high quality systematic reviews of randomised trials were available. Accordingly, in the absence of randomised trials or high quality systematic reviews of randomised trials, the WG was unable to formulate a specific recommendation on therapeutic agents.

The WG chose to support the statements on the information provided by recently produced guidelines and recently published systematic reviews[3,4].

The WG defined all questions it intended to assess and developed the study inclusion criteria *a priori* in a meeting held in Lisbon on June 29, 2008.

INDEPENDENCE FROM FUNDING INDUSTRY

The Position Statement was funded by an unrestricted grant from Amgen to the Portuguese Society of Nephrology. However, funder played no role in selecting the expert panel, selecting the technical consultants, writing the Position Statement, or influencing the final document.

When panel members had any financial relationship with the funder or with industry with interests in the Position Statement, full and complete disclosure of relationships was stated.

Questions

WHAT SHOULD THE BIOCHEMICAL TREATMENT TARGETS BE?

The majority of existing data from observational studies show that increasing serum levels of phosphorus and calcium are associated with increased relative risk of adverse clinical outcomes. Observational studies show that abnormalities of circulating levels of calcium, phosphorus, PTH, and vitamin D metabolites are associated with increased mortality, hospital admission, vascular calcifications and/or fractures. In the case of phosphorus, there is a strong, independent, consistent association between this surrogate end point and patient clinical outcomes.

However, the WG acknowledged that there are no randomised trials comparing the use of threshold values of PTH, calcium, and phosphorus on patient clinical outcomes. Accordingly, the WG acknowledged that there is insufficient evidence for the recommendation of specific biochemical treatment targets.

The WG also considers that trials in which different targets for PTH, calcium and phosphorus are compared are not feasible nor needed immediately. Target trials have been performed in other settings (e.g. haemoglobin target trials, dialysis adequacy target trials) but historically various risk factors (blood pressure, cholesterol) have not been assessed in specific target trials. It is more feasible to run placebo-controlled trials and head-to-head trials of pharmacological interventions whose results can then be extrapolated to generate treatment targets, even though targets have not been formally evaluated. The rationale for favouring this type of trial against treatment target trials is that it seems unlikely that there is a true target range, but rather a need to treat with proper interventions with certain dose ranges. Unfortunately, trials to prove that existing

interventions for the management of bone disease of chronic kidney disease have an impact on patient clinical outcomes are still lacking.

In summary, the Work Group acknowledged that there is insufficient evidence to support the use of threshold values of calcium, phosphorus and PTH as performance measures in patients with CKD and that efficacy of drugs for this condition should be tested in placebo or head-to-head trials prior to assessing targets.

Question: What should the biochemical treatment targets – calcium, phosphorus and PTH be?
There are no randomised trials comparing the impact of targeting different thresholds of calcium, phosphorus and PTH on patient clinical outcomes. Therefore, no recommendations are possible based on the available evidence.
Additionally, the WG acknowledged that there is insufficient evidence to support the use of threshold values of calcium, phosphorus and PTH as performance measures in patients with CKD.
The WG suggests that, in the process of decision-making, physicians take into account their own expertise and experience, availability of resources, and patients' preferences.

ARE INTERMEDIATE END POINTS VALIDATED SURROGATE MARKERS FOR PATIENT CLINICAL OUTCOMES?

Cardiovascular calcifications and patient clinical outcomes

The diagnosis of CKD-MBD includes the presence of vascular calcifications. Existing data from observational studies show that patients with cardiovascular calcifications are at increased risk for cardiovascular events and mortality. However, in the CKD population, there is limited evidence showing that the reduction of arterial calcification progression influences patient mortality. No studies of adequate quality have reported on the relationship between cardiovascular calcification and bone outcomes in CKD patients. Furthermore, vascular calcification and bone disease are distinct entities that are not exclusive to CKD patients. In fact, age is the most consistent risk factor for severe or progressive calcification. Some studies showed an association between severe or progressive calcification and diabetes, time on dialysis, male gender, high serum iPTH and/or alkaline phosphatase levels, inflammation (CRP levels), calcium intake, hyperphosphataemia, and increased calcium x phosphate product. However, these were not consistent findings and these associations were not found in other studies.

The evidence for a connection between vascular calcification and mineral disturbances in the CKD population is not yet fully established, and the mechanisms of calcification may be multifactorial. Accordingly, and based upon absence of trial evidence that drugs which reduce vascular calcification reduce patient-level end points, the WG acknowledged that vascular calcification cannot be considered a validated surrogate marker for patient clinical outcomes, and should not be used as such.

Bone density and patient clinical outcomes (bone fractures and mortality)

The WG acknowledged that, in the CKD population, there is insufficient evidence to establish a link between bone density and bone fractures or mortality.

In CKD patients, there is no randomised controlled trial demonstrating a beneficial effect of treatment of low bone density on bone fractures or patient mortality. Accordingly, the WG acknowledged that bone density cannot be considered a validated surrogate marker for patient clinical outcomes, and should not be used as such.

Bone biopsies and patient clinical outcomes

In patients with CKD, there is no prospective study evaluating the impact of bone histomorphometric changes on the rate of fractures. There are no studies evaluating the impact of bone biopsy findings on mortality. Therefore, there is no evidence to show a relationship between findings on bone biopsies and clinical outcomes. Accordingly, the WG acknowledged that bone biopsy findings cannot be considered a validated surrogate marker for patient clinical outcomes, and should not be used as such.

Question: are intermediate end points validated surrogate markers for patient clinical outcomes?
Based on the available evidence, bone biopsy, bone mineral density and vascular calcification cannot be considered validated surrogate markers for patient clinical outcomes (mortality, hospital admission, cardiovascular events, bone fractures, bone pain, and health-related quality of life), and should not be used as such.

WHAT IS THE EFFECT OF VITAMIN D THERAPY ON BIOCHEMICAL MARKERS OF MINERAL METABOLISM AND PATIENT LEVEL OUTCOMES? IS THE PREFERENTIAL USE OF CALCITRIOL OR A SPECIFIC VITAMIN D ANALOGUE JUSTIFIED IN ALL PATIENTS OR IN A PARTICULAR SETTING?

In patients with CKD, severe hyperparathyroidism is associated with morbidity and mortality. Treatment options for lowering PTH include **calcitriol, vitamin D analogues** and calcimimetics. Compared with placebo, established vitamin D sterols may increase serum calcium and phosphorus levels, and are associated with an increased risk for hypercalcaemia and hyperphosphataemia. The use of calcitriol or vitamin D analogues is effective in decreasing serum PTH levels[3]. However, this is not a consistent finding, as a recently published meta-analysis concluded that established vitamin D compounds were not associated with a statistically significant reduction in PTH levels, although the point estimate and lower confidence bound suggest a possible reduction in PTH concentration at the end of treatment[4]. These results may be generally interpreted as resulting from reduced statistical power of existing studies. Nonetheless, they support the statement that evidence is insufficient for conclusive remarks.

The WG cannot recommend the preferential use of calcitriol or a specific vitamin D analogue for treatment of secondary hyperparathyroidism. In limited head-to-head testing, differences between these therapies have not been proven.

The WG acknowledged that there are no RCTs of patients with CKD designed to evaluate the effect of vitamin D compounds on patient clinical outcomes[3,4]. A meta-analysis of RCTs that were not designed to evaluate patient level outcomes has shown no significant difference for any patient-level outcome (all-cause mortality, cardiovascular outcomes, hospital admission, quality of life, fracture, bone pain, parathyroidectomy) between vitamin D and placebo, calcitriol and specific vitamin D analogues, or vitamin D administered by different routes of administration (oral *vs.* intravenous) and frequency of administration (single *vs.* multiple weekly administration)[4].

Question: should vitamin D compounds be used to prevent/treat secondary hyperparathyroidism?
Is the preferential use of calcitriol or a specific vitamin D analogue justified in all patients or in a particular setting?
In patients with CKD, there is a lack of RCTs evaluating the effect of vitamin D compounds on patient clinical outcomes. Therefore, there is no evidence showing that the effect of calcitriol or vitamin D analogues on PTH improves patient clinical outcomes (all-cause mortality, cardiovascular outcomes, hospital admission, quality of life, fracture, bone pain, parathyroidectomy), or properly describes potential harm. Direct comparisons found no clear differences between different vitamin D compounds.
Therefore, no recommendations are possible based on the available evidence.
The WG suggests that, in the process of decision-making, physicians take into account their own expertise and experience, availability of resources, and patients' preference.

WHAT IS THE EFFECT OF CALCIMIMETICS THERAPY ON BIOCHEMICAL MARKERS OF MINERAL METABOLISM AND PATIENT LEVEL OUTCOMES?

In patients with CKD, severe hyperparathyroidism is associated with morbidity and mortality. Treatment

options for lowering PTH include calcitriol, vitamin D analogues and **calcimimetics**.

Cinacalcet lowers serum PTH, calcium, phosphorus, calcium x phosphorus product, and bone alkaline phosphatase in patients with CKD Stage 5D.

However, the WG acknowledged that there are no RCTs of either moderate or high quality that demonstrate a beneficial or harmful effect of treatment with calcimimetics on mortality, cardiovascular disease, hospital admission, fractures, or quality of life. Therefore, there is insufficient comparative efficacy and safety evidence to make a recommendation for the use of calcimimetics in the CKD population.

Question: should calcimimetics be used to prevent/treat secondary hyperparathyroidism?
In patients with CKD, there is no evidence showing that the change in PTH with calcimimetics leads to improved clinical outcomes (mortality, fracture, quality of life, hospital admission, cardiovascular outcomes). Therefore, no recommendations are possible based on the available evidence.
The WG suggests that, in the process of decision-making, physicians take into account their own expertise and experience, availability of resources, and patients' preference.

WHAT IS THE EFFECT OF PHOSPHATE BINDER THERAPY ON BIOCHEMICAL MARKERS OF MINERAL METABOLISM AND PATIENT CLINICAL OUTCOMES?

Observational data have consistently shown an association between hyperphosphataemia and poor clinical outcomes in the CKD population. Reduction of phosphate in the diet, **treatment with phosphate binders**, and increased dialysis duration or frequency are effective measures for reducing phosphorus levels in CKD patients. Treatment with phosphate binders lowers serum phosphorus by reducing intestinal absorption.

However, there are no randomised trials evaluating the effect of lowering serum phosphorus to a specific threshold on patient clinical outcomes. Therefore, the benefits of lowering phosphorus levels on patients' clinical outcomes (e.g. mortality, cardiovascular events, hospital admission, and bone fracture) are currently unknown.

All medications currently used as phosphate binders (calcium salts, aluminum salts, magnesium salts, sevelamer hydrochloride and lanthanum carbonate) are effective in lowering serum phosphorus levels. The available data from RCTs do not allow recommendation of a specific phosphate binder. Studies of phosphate binders comparing sevelamer hydrochloride and calcium-based binders that have mortality as the primary end point have been inconsistent. Therefore, there is insufficient comparative efficacy and safety evidence to make a recommendation for the use of a specific binder for all patients.

The choice of pharmacologic agent in a particular patient should be influenced by clinicians' expertise and experience, availability of resources, and patients' preferences.

Question: should phosphate binders be used to prevent/treat secondary hyperparathyroidism? Is the preferential use of a specific phosphate binder justified in all patients or in a particular setting?
In patients with CKD, there is no evidence showing that the reduction in phosphorus level to a specific threshold with phosphate binders leads to improved clinical outcomes (mortality, fracture, quality of life, hospital admission, cardiovascular outcomes).
There are no RCTs showing the superiority of a specific phosphate binder in improving patient clinical outcomes. Therefore, there is insufficient comparative efficacy and safety evidence to make a recommendation for the use of a specific binder in a particular setting.
The Work Group suggests that, in the process of decision-making, physicians take into account their own expertise and experience, availability of resources, and patients' preference.

Research opportunities:

- The recognised gap in clinical knowledge in this area urges investigators to design and enrol patients in randomised controlled trials addressing the following issues:
- The effect of calcitriol and different vitamin D analogues on patient clinical outcomes;
- The effect of calcimimetics on patient clinical outcomes;
- The effect of different phosphate binders on patient clinical outcomes.
- Comparative head-to-head trials of different forms of vitamin D, different phosphate binders and different agents and therapeutic algorithms including more than one agent.

Conflict of interest statement:

Dr Teresa Adragao 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.
Prof. António Vaz Carneiro does not receive grants or consultancy fees from any institution (public or private), specifically the pharmaceutical industry. He heads an academic research centre in a State university that undertakes research and works with several health institutions in Portugal and abroad.
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 Anibal 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 M. Frazão receives fees from Diaverum.
Dr Pedro Ponce is currently Country Medical Representative of Fresenius Medical Care-Portugal. He has received lecture fees from Amgen and consultant fees from Amgen and Abbott.
Dr Giovanni Strippoli is currently the Head of Diaverum Medical--Scientific Office.
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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