Author’s response to reviews

Title: Age dependent parathormone level and different CKD-MBD treatment practice of dialysed patients in Hungary - results from nationwide clinical audit

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Author’s response to reviews:

Dear Editor and Reviewers,

First of all, we thank the editor and the reviewers for their thorough work and suggestions in improving the quality of the manuscript. We have incorporated the suggestions made by the editor and the reviewers. In addition, the manuscript has been extensively edited by an English speaking colleague in order to improve the grammatical quality of the text.

We would also like to include an additional author, C. Ambrus who contributed to the revision of the manuscript.

We hope you will find this revision suitable for publication in BMC Nephrology.

Kind regards,

Istvan Kiss

Point-by-point responses to editor’s comments:

Please format your manuscript to IforA guidelines for research articles.

We have reformatted the manuscript and also we added a separate section for Conclusions.

Please remove the summary from the Title page and the figures from the main manuscript.
The Summary has been removed and Figure 1 is now attached in a separate file.

Please use the recommended text for Competing Interest Section and move the list of sub-investigators to Acknowledgement section.

Corrected.

Point-by-point responses to reviewer’s comments:

Reviewer BM:

What type of assays for iPTH have been used during the study period. If there are several different assays, please elaborate on the effects the may have had on study results.

The vast majority of samples were analyzed by either the Elecsys (Roche) intact PTH assay or the Architect (Abbot) intact PTH assay. Unfortunately, the “gold standard” Nichols Allegro assay is no longer available, however, the Elecsys assays has a very high correlation with the Nichols assay. [Reichel et al Nephrol Dial Transplant, 2003 (18): 759].

Cavalier et al showed that the Architect assay was somewhat more likely to classify patients to higher PTH ranges compared to the Elecsys assay. [Cavalier et al, Nephrol Dial Transplant. 2012 May;27(5):1950] However, the normal range in this work was based on earlier guidelines too tight, between 150 and 300 pg/ml. We do not have individual data about the assay for each patient. However we believe that the difference between the two assays in this regard could not largely influence our results and conclusions.

Patients were stratified in three age groups (I <65; II 65-80; III > 80 years of age). Why were these cut-offs chosen? Please repeat the analysis with ten year strata (< 50, 50-60, 60-70, 70-80 and >80). Does this affect the relationship between age and PTH?

Based on the other reviewer’s comment we stratified our patients into two groups (<65 and 65+) and reported the results accordingly, please see it in the manuscript.

In addition, we repeated the analysis of the association between age, diabetes and PTH with ten year strata as suggested. This new analysis further confirmed the previously reported relationship. This was also incorporated into the manuscript and shown in table 2 and figure 1

One of the main findings of the study is that PTH on average is lower in elderly patients. Please add a section in the discussion elaborating on potential explanations for this finding.

We added an additional paragraph to the discussion with potential explanations.

What are the main findings of ref 14? Please confirm that the current manuscript is not a translation of ref 14.
The main findings in reference 14 are that only a minority of dialyzed patients reach KDOQI targets and while all possible medication is in use in Hungary, the drug coverage very limited, not following current guidelines. Although this study used similar dataset, we confirm that the current manuscript is not a translation of reference 14.

The 2 final sentences read as: the higher the age, the lower the DM prevalence. I think you meant: DM = lower PTH levels.

Corrected.

P5, line 7: hypertonia needs to be changed in hypertension

Corrected.

P5, line 14: non-sentence: ...the mean value of PTH we give median value...

Please rephrase.

This sentence was deleted.

Ref 10. Replace KIDIGO with KDIGO

Corrected.

Reviewer WQ:

Abstract:

The abstract narrative does not discuss specific results on which the conclusions were made. i.e. It is not clear if the percentage of achieved laboratory targets was significantly (need P-value) higher in group II than other age groups and that achievements of target ranges and the clinical practice were dependent on patients’ age.

The abstract was corrected accordingly. Instead of narrative description we added some results and significance levels were also marked.

Introduction:

Not focused. I would delete the reference to the CasR and VDR as well as to whether clinical practice guidelines are definitive or not.

In order to be more focused, the referenced parts have been removed from the revised manuscript, and the introduction has been shortened.

Patients and methods:

Data were collected from the database of each dialysis unit. It would be helpful to mention whether the database is electronic or paper medical records. I suggest removing a repetitive reference to the fact that “Data was collected from the database of each dialysis unit”.

Patient demographics and all laboratory data were captured from electronic
databases of the dialysis providers. Data regarding bone abnormalities and vascular calcification were collected additionally using a survey that was filled out electronically by dialysis physicians.

Repetitive references were removed from the text.

The statistical methods used were appropriate but did not utilize multivariable logistic regression analysis. Authors should state the reasons for using the geometric means.

Since PTH follows non normal but log-normal distribution, the geometric mean was used for its description. The geometric mean is based on log-transformation of data and it is thought to be a better measure of average and more appropriate in this situation than the median since the latter is based on only one or two central values.

A new table was added (Table 2) to the manuscript so that we present the significant and independent association among age, DM and serum iPTH level with two-way ANOVA analysis. In this work we do not examine other determining factors of PTH. We used subgroup analysis based on diabetes and that way reduced the number of variables; therefore, we did not need multivariate logistic regression analysis.

It would have been cleaner to just focus on hemodialysis patients

We divided patients by dialysis modality into two groups and then we compared peritoneal and hemodialysis patient groups. There was no relevant difference in epidemiological or laboratory parameters between these patient groups. The prevalence of diabetes was similar (32.7 %), however, bone disease (39.9 % vs. 29.2 %) and soft tissue calcification (52.7 % vs. 35.5 %) were more frequent (p<0.001) in hemodialysis than peritoneal dialysis. Separate analyses were conducted for the two patient groups that lead to similar result; therefore, we reported only results for the whole patient population. This paragraph was added to the discussion.

Since the vast majority of the patients were in group I. (n=2413) and group II (n=2116), they should consider dividing their patients into 2 groups only. < 65 and 65 or older.

We repeated the analyses according to the reviewer’s suggestion. As a result, the previous three age groups have been removed and they were merged into two age groups. The new results are presented in the tables and the text was changed accordingly.

How bone disease and calcification were documented is not stated in the manuscript.

Dialysis physicians completed an electronic survey for each patient about the existence of bone abnormalities defined as any radiologically documented bone fracture or other bone abnormality and vascular calcification or tissue calcinosis detected by any imaging study.
This clarification was added to the manuscript.

Results:

Manuscript adheres to the standards for reporting

The results are mentioned in a diffuse manor. I suggest that the authors divide the results sections into patient demographics, parameters of CKD-MBD and treatment given.

The results section has been extensively edited and made clearer.

Discussion:

Hypercalcemia was seen in 18% of their patients yet they explain what they perceived as “low” incidence to the high frequency use of non-calcium binders, calcimimetics and low calcium dialysate. Unfortunately, they did not elaborate on these issues. For example, it is important to know what the concentration of calcium in the dialysate was.

Hypercalcemia is usually defined as Ca > 2.6 mmol/l, however, we used 2.4 mmol/l as it was the upper limit of normal range. Taking this difference into consideration, we believe that an 18 % prevalence was relatively low. Unfortunately, dialysate calcium content was not available and uniformly captured for all patients. As a result, we do not have patient-level information about this factor. Overall, around 65 % of patients were treated with 1.5 mmol/l and around 20 % with 1.75 mmol/l Ca dialysate.

In their discussion, they should make distinction between nutritional vitamin D supplement versus use of active vitamin D analogues.

This distinction was made clear in the whole manuscript, additional details of vitamin D usage was added to the text and also tables 1 and 5.

Vitamin D and calcimimetic agent were used in 60 % and 20% of their patients with PTH level> 540 pg/ml respectively. They stated that more calcimimetics should be used without stating the reasons.

The relatively low percentage of calcimimetics in this group could be explained by the strict and very limiting rules of financial drug coverage by the National Health Insurance. We believe that in patient with hyperparathyroidism and high Ca levels, calcimimetics would be much better or often additional treatment option than/to active vitamin D analogs.

Other:

The language is a serious impediment to understanding the study and therefore the manuscript should be extensively edited.

The manuscript has been extensively edited.
There is no reason to list the causes of kidney disease in the abstract.

This was deleted from the abstract.

Please remove from the discussion section comments about the cause of ESRD which is not relevant to the aims of the study except for the association of diabetes with lower PTH level and calcification.

This was also deleted from the discussion.