Reviewer's report

Title: Vitamin D Resistance In Chronic Kidney Disease (CKD)

Version: 2

Date: 23 November 2013

Reviewer: Bjorn Meijers

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The manuscript entitled “Vitamin D resistance in chronic kidney disease” by Parikh et al. describes a retrospective study to elucidate potential factors determining vitamin D resistance in CKD. For this purpose, patients are retrospectively compared with respect to presence or absence of response to cholecalciferol supplementation. Their main findings are that vitamin D treatment response is associated with initial eGFR and progression of renal function loss, proteinuria, and albumin levels.

Although the study has limitations inherent to its retrospective design, its purpose and findings are interesting and of certain relevance. However, the authors should address some comments before this manuscript can be considered for acceptance.

Major Essential Revisions

Both patients with CKD and patients post kidney transplantation have been included for analysis. I don’t follow the reasoning of the authors that these patients have comparable pathophysiology. Especially in the early (< 1 year) post transplant period there are major fluctuations in several variables (PTH, FGF-23) that may be of relevance to explain vitamin D resistance. Please redo the analyses including only CKD patients without transplantation. The authors may consider performing separate analyses of patients post-transplantation.

As this is a retrospective study, how sure can we be that the treatment protocol for titration of cholecalciferol based on 25-OH vitamin D serum concentrations was identical during the study period? Were stepwise dose increments always identical and how was this ascertained? we seasonal differences taken into account.

Was the same assay for 25-OH vitamin D used throughout the study period? In addition, was follow-up and determination of 25-OH vitamin D levels with possible cholecalciferol dosing adjustment standardized, e.g. once every 3 month/…?

It would be interesting to calculate the cumulative dose of cholecalciferol supplements given in both the responder vs. non-responder group (for example amount of IU adjusted for months of follow-up).

Figure 1: This figure is slightly puzzling. Why are patients with a short follow up not excluded before stratification in responders and non-responders? I don’t
understand why you exclude 8 patients with the statement “8 had last final 25vitD < 40”, as these may be considered to be non-responders?

Figure 2 and text P 9: How do you explain your number of patients of 240, the same for figure 3, why 212 patients? Why is it different from the numbers in figure 1? Missing values? The same question for Table 1 vs. Table 2, as mean values for variables such as eGFR are not completely identical.

Additive to the univariate comparisons of responders vs. non-responder, I would suggest building a logistic multivariate model to also obtain significant determinants after multivariate adjustment? E.g., is proteinuria or albumin still significantly different after adjustment for differences in eGFR?

Figure 4 and text P 9: The authors state that proteinuria increases for 11 months in the non-responders, and decreases for 21 months in the responder group. Was this difference significant?

Discussion page 10: “one of the aims of this study was to test whether cholecalciferol is a more potent vitamin D precursor therapy than ergocalciferol in patients with CKD…..” Please delete this part of the discussion, as there are no data whatsoever on ergocalciferol.

Discussion P 12, 3rd alinea to P 14, 1st alinea: this section is too extensive and needs to be shortened

Conclusions (P 15): The conclusion section doesn’t really cover the findings of this study. Please rephrase

Minor Essential Revisions

Please add citations in the text (not reference list) uniformly and following journal guidelines (e.g., citation 3 before full stop, citation 4 after full stop)

I would suggest changing Vitamin D into vitamin D (leave out capital letter).

P10, line 3 in discussion. “Target…kidney function”, this sentence may not be entirely incorrect.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.