Reviewer's report

Title: Tubular reabsorption and local production govern urine hepcidin-25 excretion

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Reviewer: Michael MH Haase

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In this study the authors aimed to assess the role of tubular reabsorption and local production of hepcidin-25 in 30 patients with chronic renal disease as well as in 19 patients who underwent cardiopulmonary bypass surgery.

I would recommend considering several major and minor issues:

- What was the rationale/objective of the study? Please add this information under “Introduction”.

-“urine beta2-MG was only measured in urine with a urinary pH>6.0”. Please provide the information in how many patients beta2-MG was measured in the urine as for example in other large cardiac surgery cohorts >35% of patients had a preoperative urine pH of # 5.5 (Haase et al. Crit Care Med 2009).

Also, please, acknowledge the limitation that beta2-MG is not stable under aciduric conditions and why alpha1-MG was not chosen.

-The number of patients being operated was very small. Were patients enrolled in a consecutive manner? What were the inclusion and exclusion criteria? How can the authors exclude selection bias in this regard?

-Why did the authors choose to measure urine and serum markers in 8 patients 1-2 hours after CABG and in 13 patients 12-24 hours after CABG? In how many patients, markers were measured at both time points? What was the rationale not to use the same, predefined sample time-point in all 19 cardiac surgery patients?

-Please also be more specific in the information on the timing: “CABG, 1-2 hours after surgery”. Does this correspond with a) 1-2 hours after end or start of cardiopulmonary bypass (CPB) or b) 1-2 hours after end of surgery?

- Were all 19 CABG patients operated “on pump”? Please add duration of CPB in Table 1.

-How many patients developed acute kidney injury after cardiac surgery?

-Please add a section in the discussion on strength and limitations as well as on potential clinical implications.

-The article would further benefit from a stronger discussion section as currently the majority of the discussion deals with results from other studies. How did your findings add to the literature? How did you interpret your findings? Did you consider evidence against the potential local production and tubular reabsorption of hepcidin?
Abstract:
- “Following cardiac surgery, FE of hepcidin-25 increased despite a decline in FE of beta2MG……” Please add e.g. “potentially indicating local production at 12-24 hours”
- Conclusions: “…increased urine hepcidin-25 level may reflect tubular dysfunction.”
Consider to be more precise and change “tubular dysfunction” into “reduction in tubular hepcidin uptake”.

Results:
- Please add Spearman correlation coefficients in Figure 3.
- Please be more precise “…there was no evidence of tubular threshold (Figure 3)”. How did you analyze the potential existence of such a threshold? Please, add this information to the statistical analysis section.

Minor point:
Animal experiments
-“In order investigate…” Please add “to”.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I received lecture fees from Abbott Diagnostics and Alere Inc. Both companies are involved in the development of neutrophil gelatinase-associated lipocalin (NGAL) as renal biomarker.