

Reviewer Comments

Reviewer 1

In the legend of Fig. 1 the last part of the sentence is lost. "Figure adapted from...???" –

Author Response: This has been corrected

Chapter "Synthesis, function and degradation of copeptin", the table cited in the sentence "As summarised in Table 2, the precursor peptide..." is wrong, therefore must be substituted with table 1.

Author Response: This has been corrected

In the Chapter "Advantages and disadvantages of copeptin measurement in the laboratory", Authors describe possible disadvantages for the copeptin measurement in clinical laboratories mainly in terms of costs. In my opinion, this description is incorrect because, as underline the Authors, there are insufficient clinical evidence for the use of copeptin as ADPKD marker. Therefore, the clinical use of copeptin is still too far.

Author Response: We agree with Reviewer #1. The emphasis on cost has been eliminated and more importance is placed on the absence of sufficient clinical evidence.

Are there evidences of copeptin plasma level variations in ADPKD patients treated with Tolvaptan? The reduction or the slowed increase in copeptin plasma levels could indicate a "good" response to Tolvaptan treatment.

Author Response: We agree with Reviewer #1. There is no published data regarding this, and this is discussed in the Chapter entitled: "Is serum copeptin a predictive biomarker or treatment response to vasopressin receptor antagonists or prescribed fluid intake"

Reviewer #2

In introduction, please also include for information regarding use of Copeptin measurement in various other clinical indications, e.g., including the diagnosis of diabetes insipidus and the monitoring of sepsis and cardiovascular diseases.

Author Response: We agree with Reviewer #2 and have added an extra sentence (with supporting references) in the introduction regarding the use of copeptin in other conditions.

Case control study by Corradi et al is an important one, I agree. The reference for citation #28 is not correct; should be Corradi et al, not Zitteima et al. Corradi et al. recently demonstrated that glomerular filtration affects copeptin to a greater extent rather than its correlation to AVP [28].

Author Response: Thank you for detecting this error. The correct reference has been cited.

Suggest discussing the findings by Nakajima et al. Association of arginine vasopressin surrogate marker urinary copeptin with severity of autosomal dominant polycystic kidney disease (ADPKD). PMID: 25715868

Author Response: Thank you for this advice, and we have included this in the sections (*Is serum and urinary copeptin levels are correlated with markers of disease severity? and Are there any confounding factors that influence the interpretation of serum copeptin in ADPKD? .*

Reviewer #3

Expression of copeptin is 'multifactorial' (i.e., some situations have some effects on the result). This point should be mentioned.

Author response: We agree with Reviewer #3 and have added an extra sentence (with supporting references) in the introduction regarding the use of copeptin in other conditions.

Reviewer #4

Minor language polishing required.

Author response: We agree with Reviewer #4 and have proof-read and corrected grammatical errors

