

Re: Manuscript NO:75346 - Performance of Dexcom-G5 and Freestyle Libre tested simultaneously in persons with type 1 or 2 diabetes and advanced chronic kidney disease.

Dear Editors in chief

Thank you for considering the above mentioned study for publication in World Journal of Clinical Cases. We have addressed the comments from the editors and reviewers point by point and made changes in the manuscript accordingly using track changes. A clean copy of the manuscript has also been submitted.

We are grateful for the thorough review and believe our adjustments have improved the manuscript. We hope you will find the study of interest for publication. Do not hesitate to contact me for further questions.

Regards

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Reviewer #1: The authors tried to assess the accuracy of Dexcom-G5 and Freestyle Libre tested simultaneously in persons with type 1 or 2 diabetes and advanced chronic kidney disease (CKD). This paper is well organized and may provide useful information about clinical experience of continuous glucose monitoring (CGM) in diabetic patients with advanced CKD. There are several methodological concerns and I wrote some comments below:

1.Methods a) This study was designed prospectively. However, there is no information on how 40 patients were included in this study. If it is a pre-planned number, please provide evidence more in detail.

Response: Thank you for your comment. We have now added a text in the statistics section and in the supplement detailing the power analysis.

b) Please provide a detailed information of inclusion & exclusion criteria in this study, especial exclusion criteria.

Response: We have now added this information to the manuscript on page 5 in “study procedures”

c) When abbreviations used, they should be defined where first used, followed by the abbreviation in parentheses. e.g., “FAS” in “Abstract - Methods”.

Response: thank you for pointing out this mistake. We have now corrected this

d) It's better to clarify how to calculate MAD and MD.

Response: Thank you for this comment, we have now clarified this in the statistics session page 7

2. Results a) The study included 40 participants, 33 met the criteria for data analysis, please tell the reasons for exclusion of the other 7 participants.

Response: We have now clarified why the other 7 participants did not meet the criteria in the first paragraph of the results section page 9. Two patients chose to terminate their participation and 5 did not managed to operate the HemoCue system effectively.

b) In sub-group analyses, MARD and MAD were significantly different between Dexcom-G5 and Freestyle Libre test, could you please provide grouped results by type of diabetes?

Response: It is interesting to see the difference between these two groups and we have now added this into the post-hoc analysis section for the results on p.12 of the manuscript although these results should be interpreted with caution as these sub-groups small sample size.

c) How to define patients as glucose ranges below 3.9 mmol/l, between 3.9 and 10 mmol/l or above 10 mmol/l ?

Response: We have now clarified that the ranges were based on the HemoCue values and have clarified this in the statistics section on page 8 which now reads "All analyses for different glucose ranges were based on HemoCue values within respective range."

3. Table 2 Generally, normally distributed variables are expressed as means \pm SD and/or means (95% CIs). Other skewed distributed variables are expressed as medians (interquartile ranges). Why variables in table 2 expressed in such ways?

Response: Thank you for pointing this out, we have now made appropriate changes in the table.

4. Discussion Earlier studies with similar methodology have shown that the Freestyle libre had a MARD of 13.2% in type 1 diabetes. But in this study, the MARD seemed to be much higher (20.9%) in patients with CKD, what could be the possible mechanism?

Response:

This comment is well taken. Possible mechanism behind greater accuracy of the Freestyle Libre in type 1 diabetes in earlier studies compared with our finding is beyond the scope of the present study. However, it is well-established that patients with advanced CKD frequently experience wide glycemic alterations of both hypoglycemia and hyperglycemia owing to different pathophysiological mechanism including altered glucose and insulin metabolism by advanced CKD (reference 9). Thus, it is feasible to speculate that more frequent glycemic alternations in diabetic patients with advanced CKD, at least in part, reduced the accuracy of the Freestyle Libre compared to data from patients without advanced CKD. In line with this notion, the Freestyle Libre had a MARD between 13-22% depending on the glycemic range in diabetic patients during hemodialysis (reference 10).

Furthermore, one could speculate that fluctuations in the interstitial fluid during dialysis including fluid volume shift, alteration in uremic toxins and acid-base status may have a

potential impact on the performance of the Freestyle libre in dialysis subgroup and hence reduced its overall accuracy in advanced CKD. However, the MARD values for Freestyle libre in dialysis and non-dialysis patients were comparable 19.3% (95% CI 15.3-23.2%) and 22.5% (95% CI 17.6-27.4%) respectively. Hence, our subgroup analysis does not support this notion, albeit these results should be interpreted with caution due to small sample size.

Evidently, further studies are needed to elucidate other possible factors that might interfere with the accuracy of the Freestyle Libre in advanced CKD. We have not added a comment about this in the discussion section p13.

Reviewer #2: This unblinded clinical study compared the application of the two devices in chronic kidney disease, although preliminary conclusions were reached. However, it relies on subjective index evaluation, which is lack of credibility and innovation.

Response:

These studies are not possible to blind and have not been blinded in earlier (reference 14 and 15). We are aware that the questionnaire is not validated but no questionnaire with these specific questions is validated. It would be of interest in future studies to validate the questionnaire. We have now noted this is limitation section of the article.