

Peer Review File

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Reviewer A

The non invasive measurement of blood glucose has been pursued by many techniques. All so far have failed. The spectrum of glucose is quite smooth making it difficult to narrow a search of wavelengths to associate to concentration. Other techniques have failed due to the similarity of glucose to other 6 carbon molecules. The authors have focused on nine publications out of a huge number of attempts and identified salivary glucose and breath glucose as possible surrogate measures. They also mention efforts on the skin. As they show the accuracy of these measures is far too low to serve any clinical value. Nonetheless their review is interesting and should be reworked to cover all the techniques that have been attempted and then to explain why to date there has been failure. The manuscript as it stands is excessively verbose and must be rendered succinct and to the point for each procedural technique they describe.

Response:

Thank you for your suggestions. We have reviewed the article and revised it to convey the points concisely and clearly.

We present the non-invasive techniques that we retrieved based on the selection criteria of this review in the results section (Page: 6, line: 186). Additionally, because of addressing the reviewer's query, we have included in the discussion section under section 4.1 Promising non-invasive approaches (Page: 13, line: 394), the non-invasive techniques that have been attempted. We have also mentioned a few encountered challenges in section 4.2 Challenges in non-invasive approaches (Page: 13, line: 411).

They should also certainly cover the minimally invasive interstitial fluid devices which are in everyday use in continuous glucose monitors.

Response: We have included a paragraph in the introduction section mentioning the use of continuous glucose monitoring devices, their benefits, and associated challenges (Page: 3, line: 76). Additionally, in section 4.1 Promising non-invasive approaches (Page: 13, line: 394) we have discussed the commercially available minimally invasive devices.

Reviewer B

The manuscript has described three non-invasive methods for diabetes managements. However, none of them has provided clear information or mechanism.

Also, a comparison of the methods for diabetes will be much helpful to target the main objective of the paper.

Response: We have now added more detailed information regarding the non-invasive blood glucose monitoring mechanisms in the revised paper. Section 3 (Page: 6, line: 186) presents the three non-invasive methods identified in this study for diabetes management. Table 2 (Page: 6, line: 191) presents the characteristics of the included studies, including participant demographic details, diabetes type, and the invasive blood glucose method used for validating the non-invasive recordings. Sub-section 3.1 (Page: 7, line: 235) details the non-invasive screening, including saliva, skin, and breath. The mechanism followed to measure blood glucose is presented in detail. In the revised paper, we have now included a comparison of methods in Table 3 (Page: 9, line: 257). Table 3 details the non-invasive technologies, including device, technology, parameters, and procedure duration for each study.

Reviewer C

The authors provide an overview of non-invasive glucose monitoring technologies, as well as in-depth considerations regarding the accuracy of these technologies in predicting blood glucose levels.

Major

1. The authors indicate that the innovation progress for non-invasive glucose monitoring is slow, and attribute that partly to misalignment with regulatory approval (lines 27-31; 96:97). While they do describe the aspects of accuracy, they hardly mention the aspect of safety. For several of those technologies, e.g., iontophoresis, safety may be a bigger issue than accuracy. With their frame on regulatory approval, safety needs more attention.

Response: Thank you for the suggestion. We have included section 4.3 safety and regulatory approvals of non-invasive approaches (Page: 14, line: 422).

2. One of the well-known technologies in blood glucose monitoring is continuous glucose monitoring. I do assume this was not included in the systematic overview, since CGM is still minimally invasive (although very well appreciated by end-users with diabetes). However, it must be mentioned at least in the introduction to provide a more complete picture of the glucose monitoring field. Also, a lot of lessons learned for CGM regarding regulatory approval can be applied to other non-invasive glucose monitoring technologies.

Response: The objective of this article is to review the non-invasive technologies validated against individuals' blood glucose levels. CGMs are minimally invasive

devices that automatically and constantly measure the glucose concentration in the interstitial fluid; although it is widely used it is plagued with safety and accuracy concerns due to painful insertion, skin/adhesive problems, the necessity of calibration by fingerstick glucose, the need of avoiding calibration timing after eating, and limited glucose levels readings. Since a non-invasive blood glucose monitoring system could overcome these challenges we did not include CGM studies in this review.

In the revised paper, we have included a paragraph in the introduction section mentioning the use of continuous glucose monitoring devices, their benefits, and associated challenges (Page: 3, line: 76). Additionally, in section 4.1 Promising non-invasive approaches (Page: 13, line: 394) we have mentioned the commercially available minimally invasive devices. Further, in section 4.3, we have highlighted the safety and accuracy concerns associated with CGMs (Page: 14, line: 422).

Minor

3. The parameter that is used to compare CGM, and that is also used for the regulatory approval process, is the Mean Absolute Relative Difference (MARD). It can be helpful to, where possible, use this parameter to compare the different technologies on their ability to predict blood glucose.

Response: Only one study had presented the MARD recording (Page: 12, line: 340), which we have included. Unfortunately, the other studies have not specified MARD recordings.

4. What is the reason to exclude studies with participants below 18 years (table 1)? Many people with T1D are below 18.

Response: Since the studies used non-invasive technologies that are under development and would need informed consent, we considered studies with adult participants (Page: 5, line: 138).

5. Table 1 describes the inclusion and exclusion criteria. It is not clear if these were applied to select titles or to select full texts

Response: We have detailed the Study selection process in section 2.3 in the revised paper (Page: 6, line: 144).

The first level screening was performed by reading the title and abstract of the article. We excluded reviews and editorials, studies undertaken on those younger than 18 years, non-human subjects, and research tool evaluation and development. Further, we excluded studies irrelevant to the objective of this review, such as research proposals, descriptive surveys, clinical protocols, research methods, conceptual papers, undertaken among non-diabetic participants, hardware and algorithm improvement studies, clinical measurement technology to access and analyse secondary data,

prototypes, simulations, application of machine learning algorithms to predict diabetes, data modelling and statistical analysis of diabetes detection, and diabetes risk prediction. We obtained 88 articles for further full-text review at the end of this stage.

At the second level of screening, we read the entire article and eliminated studies undertaken in non-adults, less than 20 participants, and those irrelevant to the objective of this review. We then had 9 articles that we considered for this review.

6. For the non-invasive BG monitoring technologies on the skin, there is a large area of research on Raman spectroscopy (e.g., from MIT) that could be touched upon.

Response: We have included it under section 4.1 Promising non-invasive approaches (Page: 13, line: 394) also presenting other non-invasive techniques that have been attempted.

Reviewer D

In this theoretical study, the authors are discussing non-invasive glucose measurements in diabetic patients. The authors paid significant attention to the comparison of different detection approaches such as for glucose levels in saliva measurements and considered different parameters of glucose measurements including the age and gender of patients. The strong side of the research is that the authors discussed different approaches for glucose level evaluation even those contactless, by temperature fluctuation which is widening the understanding of the temperature-diabetes relation. The major limitation of the study is the small number of publications selected for the discussion and the lack of discussion on 1-3 generations of electrochemical biosensors (meaning non-invasive on-skin detection). Other questions and comments addressed to the authors are below:

Response: In the revised manuscript, we have explained in section 2.2 Study selection criteria (Page: 4, line: 118) the criteria applied to select articles. In section 2.3 Study selection process (Page: 6, line: 144), we have explained the stepwise process as to how we have finally obtained 9 articles for this study. In the revised paper in section 4.5 Limitations of this review (Page: 16, line: 493), we have acknowledged that this study has considered only nine studies due to the applied selection criteria in addition to the other limitations.

Additionally in the revised article, in the discussion section under section 4.1 Promising non-invasive approaches (Page: 13, line: 394) we have presented the non-invasive techniques that have been attempted. We have also mentioned a few encountered challenges in section 4.2 Challenges in non-invasive approaches (Page: 13, line: 411).

1. A keyword means one single word; 2 and more words like "type 1 diabetes" have to

be replaced with, for example, juvenile diabetes, etc.

Response: The keywords are revised as Diabetes, T1DM, T2DM, non-invasive, technology, screening, management, smartphone, mobile solutions, usability, and chronic disease (Page: 2, line: 47).

2. Line 82. The abbreviation SMBG must be deciphered.

Response: We have deciphered SMBG (Page: 3, line: 69).

3. Line 100. Please pay attention to the grammar (a recent review evaluating).

Response: We have checked the entire manuscript for grammar, and addressed the mentioned comment (Page: 4, line: 98).

4. Line 146. I would rather put dots between name and surname (JCM - J.C.M.).

Response: We have addressed (Page: 6, line: 164).

5. Figure 1. It is interesting why did you select only 9 articles? Are those from open-access journals?

Response: The 9 studies were selected as they met all the inclusion criteria specified in section 2.2 Study selection criteria (Page: 4, line: 118). The article selection process followed the method specified in section 2.3 Study selection process (Page: 6, line: 144).

6. Line 189. Please specify the acronym HbA1c.

Response: We have specified the acronym at the first instance in the text (Page: 5, line: 133).

7. Lines 261-272. Units of measure have to be specified (e.g. NBR: 87.4 ± 1.7 of what ?)

Response: Thank you. NBR is a performance evaluation measure and is represented in %. We have updated the text (Page: 9, line: 261).

8. Line 274. Saliva definitely can not be the tool as mentioned here: "potential role of saliva as a diagnostic tool", it rather is a material or sample.

Response: Thank you. We have rewritten it (Page: 9, line: 270).

9. A section on non-invasive electrochemical sweat glucose sensors should be added.

Response: In the discussion section under section 4.1 (Page: 13, line: 394) we have presented the non-invasive techniques and a few encountered challenges in section 4.2 (Page: 13, line: 411).

Reviewer E

Jeban Chandir Moses et al. in the manuscript showed non-invasive blood glucose monitoring technology in diabetes management. In the presented work, the Authors focused on showing non-invasive methods of glucose detection and their comparison. Herewith I added a few comments that will help the Authors to improve the current manuscript:

1. Introduction should be enriched with examples of optical or electrochemical glucose detection methods, based on the latest works, for example, doi.org/10.1016/j.snb.2020.128832; doi.org/10.3390/s20185247; doi.org/10.1007/s00604-022-05256-y; doi.org/10.1016/j.bioelechem.2022.108071.

Response: Thank you for the suggested four articles. In the revised manuscript we have included an article on electrochemical glucose detection methods that is relevant to this study in the introduction section (Page: 3, line: 88).

2. In my opinion, the manuscript lacks a comparison and reference to commercial glucose testing methods.

Response: In the revised manuscript in section 4.1 we have discussed the promising non-invasive technologies and the commercially available systems (Page: 13, line: 394). Currently, two commercial systems, namely, FreeStyle Libre and Dexcom provide continuous glucose measurement; however, both use minimal-invasive technology resulting in disadvantages, such as infection risk, pain for the patient, and the cost of sensor replacement.

3. There are already reviews in the literature on non-invasive glucose detection methods (doi.org/10.3390/bios12110965; doi.org/10.3390/s20051251; doi.org/10.3390/s22020638), what is the superiority of the review presented by the Authors?

Response: We have included the mentioned studies in the revised article in addition to other non-invasive glucose reviews that we had presented earlier (Page: 4, line: 93). However, the studies had different objectives. For example, they were focused on specific non-invasive technology such as impedance spectroscopy, sweat-based wearable electrochemical sensors and CGM, salivary diagnostics, and optical, electrical, and breath acetone. A review highlighted the clinical significance of non-invasive methods in glucose monitoring and presented the progression of these methods for potential diabetes management. Another review evaluated the scope of non-invasive technologies in increasing adherence towards checking BG.

In our review, we systematically reviewed the non-invasive technologies (considering all non-invasive approaches) validated against individuals' blood glucose levels to

update the current knowledge of reliable biomarkers, devices, data analysis methods, and factors to be considered in decision-making (Page: 4, line: 102).

4. In section 2.2. the Authors state that they chose the years in the period 2000-2020, why did the Authors not analyze the latest sensor developments for the years 2021 and 2022? A review should concern the latest knowledge, therefore, in my opinion, it should be enriched with the literature.

Response: We have explained the reason for selecting the time in section 2.2 in the revised article (Page: 4, line: 124). We limited the article search timeframe to June 2020 due to COVID-19. During this period, with recommendations regarding social isolation to minimise the spread of COVID-19, telehealth was the most utilised healthcare delivery method. Hence, we have considered studies in the period January 2000 to June 2020.

However, we have included recent studies in the introduction and discussion section.

5. Why did the Authors focus on only 9 studies (Chapter 3) when originally found 2336?

Response: The 9 studies were selected as they met all the inclusion criteria specified in section 2.2 Study selection criteria (Page: 4, line: 118). Section 2.3 Study selection process (Page: 6, line: 144) explains the stepwise process followed to obtain the 9 articles for this study.

6. Chapter 4.2.1 should be expanded to show trends and a broader future perspective in the field of non-invasive glucose sensors.

Response: Thank you. In the revised paper we have included section 4.1 Promising non-invasive approaches (Page: 13, line: 394). In this section, we have presented the non-invasive techniques that have been attempted. We have also mentioned a few encountered challenges in section 4.2 Challenges in non-invasive approaches (Page: 13, line: 411) in the revised article. We have included section 4.3 Safety and regulatory approvals of non-invasive approaches (Page: 14, line: 422).

7. In the conclusions, the Authors state that a statistical relationship was observed between the comparison of glucose and the clinical measurement. What is this conclusion? In my opinion, it should be highlighted in the manuscript.

Response: Thank you. We have rewritten the manuscript to reflect the findings. In section 4.4 (Page: 14, line: 450) we suggest that non-invasive methods could have potential clinical use after further research. Although statistical relationships were observed between non-invasive recordings and clinical measurements, in section 4.3 (Page: 14, line: 422) we highlighted the importance of following safety and regulatory guidelines while developing non-invasive systems.