Meta-analysis and Cross-validation of a Hyperglycemic Status Predictor Model based on Salivary Glucose

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Review

Early screening of type 2 *diabetes mellitus* (DM), a hyperglycemic status associated condition, is essential for preventive treatment and effective delay of diabetes clinical complications [1]. However, testing for hyperglycemic status often requires invasive and painful blood testing, limiting its large-scale usefulness. To overcome this constraint salivary glucose assays have recently being studied with the purpose of screening hyperglycemia and type 2 DM [2]. Literature results regarding blood and salivary glucose relationship in diabetics or in healthy individuals are controversial. On the other hand, to the best of our knowledge no validation has been done on type 2 DM / hyperglycaemia detection models based on salivary glucose. We have performed a systematic review and meta-analysis on those studies and cross-validated a type 2 DM / hyperglycemic status predictor model based on salivary glucose.

Experimental Methods

We conducted a meta-analysis of peer-reviewed published articles that reported data regarding mean salivary glucose levels for type 2 DM and non-diabetic individuals combined with our own results [3]. Furthermore, we used our blood and salivary glucose data from type 2 diabetics and healthy individuals to build type 2 DM / hyperglycemia status prediction models. These logistic models were cross-validated against external data (Brazil and India) and accuracy was evaluated through ROC curve analysis.

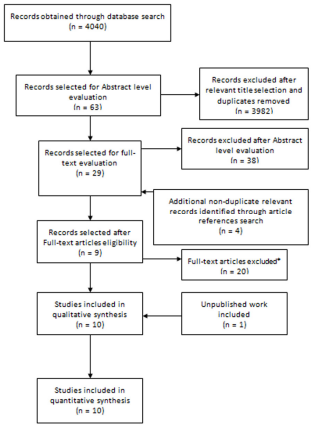

Figure 1 - Flow of study selection for mean salivary glucose levels. *Studies were excluded unless contained salivary glucose data (means, standard deviations and sample size) obtained from strictly diabetes mellitus type 2 patients and non-diabetic controls unstimulated whole saliva collected after a minimum fast period of 2 hours. Were also excluded if the full-text article were not available and the author(s) failed in sending a copy after contact request or failed in giving back supplementary required data inexistent in the original article. Records containing data already published in other article were also excluded.

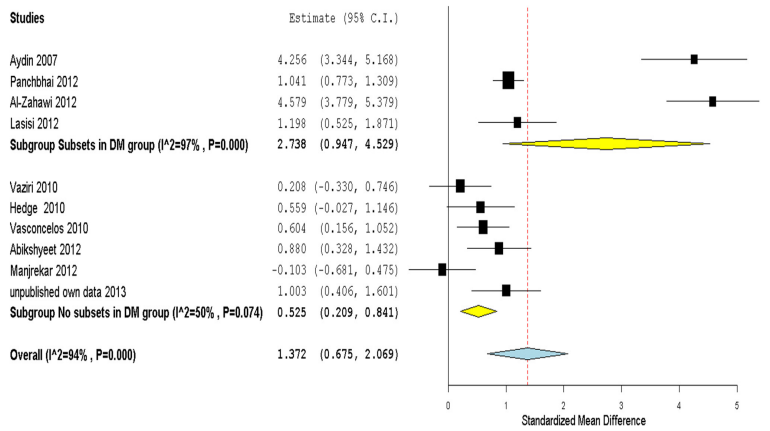

Figure 2 - Subgroup forest plot of type 2 DM mean salivary glucose levels studies. Studies have been grouped according to the type 2 DM group allocation: with or without subsets. Hedge's *g* (standardized mean difference) effect size estimates have been calculated with 95% confidence intervals and are shown in the figure. Area of squares represents sample size, continuous horizontal lines and diamonds width represents 95% confidence interval. Yellow diamonds center indicates the subgroup pooled estimates while the blue diamond center and the vertical red dotted line both point to the overall pooled estimate.

Results

- On our global meta-analysis of standardized mean differences on salivary glucose levels results show an overall large positive effect of type 2 DM over salivary glucose (Hedge's $g > 1$).
- The logistic models showed a good accuracy on our sample predicting both hyperglycemia (81,0%) and type 2 DM (84,5%), while in the external data cross-validation accuracy was lower (65,5% and 69,0%, respectively). While our prediction models are well fitted for our Portuguese sample, cross-validation results using both Brazilian and Indian data showed a significant decrease on accuracy, suggesting that hyperglycemia status / type 2 DM prediction from salivary glucose should only be based on region specific models.

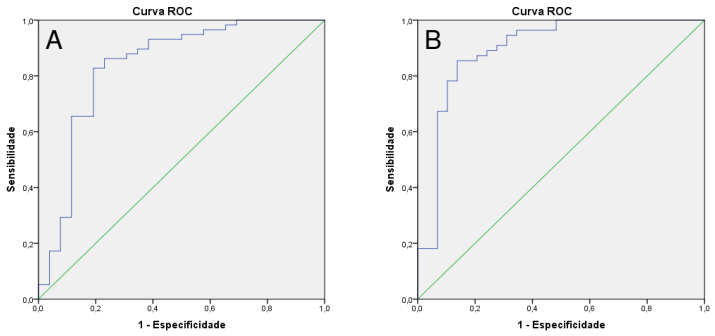

Figure 3 – **A**: ROC curve for hyperglycemia status prediction with a logistic model based on salivary glucose trained with the Portuguese sample set ; **B**: ROC curve for type 2 DM status prediction with a logistic model based on salivary glucose trained with the Portuguese sample set.

Conclusion

Our results show that salivary glucose has potential to be used as type 2 DM biomarker. If associated with the development of sensitive portable technology to measure salivary glucose this will allow a less painful and invasive method for type 2 DM screening in large cohorts. Even if at present, due to several limitations, salivary glucose *per se* may not show enough cross-validation performance to be used as an global and autonomous DM type 2 biomarker, our results suggest that it provides valuable information, and in the future may be combined with other salivary biomarkers to create an effective high sensitivity/specificity DM type 2 large-scale screening system.

References

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- [3] Mascarenhas P, Fatela B, Barahona I (2014) Effect of Diabetes Mellitus Type 2 on Salivary Glucose – A Systematic Review and Meta-Analysis of Observational Studies. PLoS ONE **9(7)**: e101706

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