CLINICAL MODEL-BASED ASSESSMENT OF INSULIN SENSITIVITY – FEWER MEASUREMENTS AND HIGH RESOLUTION

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Introduction: Insulin resistance (IR), or low insulin sensitivity, is a major risk factor in type 2 diabetes and cardiovascular disease. Current tests are either very labour intensive (Euglycaemic clamp, IVGTT) or have too low resolution (HOME, fasting glucose/insulin). A simple, high resolution assessment of IR would enable earlier diagnosis and more accurate monitoring of intervention effects. This research is based on a previously validated model-based method for measuring insulin sensitivity (S_I) which is highly correlated to the gold-standard clamp. The prior work utilises both insulin and glucose measurements approximately every 5 minutes as well as Cpeptide measurements. The protocol is of short duration (<1 h), is a simple protocol, has low cost and high repeatability. This paper improves the accuracy of model-parameter identification for the insulin kinetics with little to no added computational cost. It also significantly reduces the number of insulin measurements required to identify S_I, and shows that the removal of Cpeptide measurements has little effect on the accuracy of S_I.

Methods: Clinical data is used from a prior study which included 46 insulin sensitivity short IGVTT tests and with ethics approval granted by the Upper South A Regional Ethics committee. A full data set of glucose, insulin and Cpeptide measurements is first assumed, and a new extended iterative integral-based parameter identification is implemented to identify insulin kinetics. Once the insulin kinetics are obtained, insulin sensitivity is obtained using a previously derived one iteration integral method. The new iterative integral method uses an approximate analytical solution to the non-linear saturated kinetic equations and requires very minimal computation. This method, first assumes there is no saturation to obtain an approximate insulin curve. This approximate insulin curve is then substituted into the saturated part of the insulin kinetics differential equations, to enable an approximate solution to the full saturation equations. For the insulin kinetics analysis, the accuracy of the method is compared to the previous one iteration integral method. An analysis is then done, to find the minimal data set required for accurate insulin sensitivity measurement. This analysis includes removing Cpeptide measurements, followed by insulin measurements. All glucose measurements are kept. The baseline for comparison is the S_I value from the full data set.

Results: The new iterative integral method is found to converge very rapidly with very little more computational time required. The percentage model insulin response errors are typically 3-5% compared to 7-15% for the one iteration integral method. A similar iterative integral method applied to the glucose response was not used as simulation showed it only gave a small reduction in error (<2%). The removal of Cpeptide measurements had only a very small effect on S_I (<1%). The use of one basal insulin measurement I_{basal}, one insulin measurement 10-15 minutes after the bolus I_{bolus}, and a near steady state insulin measurement after 1 hour I_{ss}, was also shown to have only a small effect on S_I (up to ~5% error). With the removal of I_{bolus}, the fitting routine was reformulated. The approach was to treat the unknown measurement as another fitting parameter. This parameter was optimized using a line search, where for each parameter update, the objective optimization function was the error in the glucose measurements. In principal, the correct I_{bolus} value should give the best match to the glucose measurements after adjusting S_I. This algorithm gave quite good results, with up to ~15% error in the accuracy of S_I. For the case of the removal of I_{basal}, this parameter was also treated as an unknown (and optimized based on the glucose response) but was only allowed to vary from $0.5I_{ss}$ to $0.9I_{ss}$. The results were similar to when I_{basal} was included in the analysis.

Discussion: With the addition of I_{ss}, S_I could be obtained quite accurately. These results suggest a much simpler and cost effective test for the future. However, if pancreatic function is required, more insulin measurements must be used and/or Cpeptide. Note that without a I_{basal} measurement there were significant trade offs in the unknowns so that the accuracy of S_I deteriorated quite significantly up to ~50% error in some cases. However, quite a strong relationship (r>0.7) between a diffusion population parameter n_I in the model and I_{basal} was found over all patients. Some initial tests also show that after utilizing this parameter, the accuracy of S_I was improved to ~20-30% error. which may be potentially suitable for a reasonably rough and quick insulin sensitivity measurement. The advantage of this approach is that no lab measurements are required of insulin, which reduces both cost and time. This approach, however would need many more trials to prove robustness, and is left to future work.

Conclusion: The model-based assessment of insulin sensitivity proved to be accurate even with only a minimal number of insulin measurements. As expected as the number of insulin measurements was reduced the accuracy of SI was also reduced, but the accuracy remained sufficiently good for diagnostic purposes. Further trials are required for validation.