Closed loop control for type 1 diabetes

Shows promise in a research setting, but needs further development in practice

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In the linked randomised crossover studies, Hovorka and colleagues compare the safety and efficacy of overnight closed loop insulin delivery with conventional insulin pumps in adults with type 1 diabetes.[1] Automated closed loop control, known as an "artificial pancreas," has the potential to greatly improve the health and lives of people with type 1 diabetes. The idea is not new—it can be traced back to developments that took place decades ago, when studies using intravenous glucose measurement and infusion of insulin and glucose showed that external blood glucose regulation was possible.[2 3] Although these systems resulted in excellent glucose control, they were cumbersome and unsuitable for long term or outpatient use.[4 5]

With the advent of minimally invasive subcutaneous continuous glucose monitoring, research and drug company efforts have been focused on the development of subcutaneous artificial pancreas systems. These systems link a continuous glucose monitor and a subcutaneous insulin infusion pump via a control algorithm, which retrieves continuous glucose monitoring data in real time (for example, every five minutes) and uses a mathematical formula to compute insulin delivery rates that are then transmitted to the insulin pump.[6] So far, several studies have reported encouraging results.[7-10] Almost all of the studies reported that closed loop control was better than standard insulin infusion pump treatment in terms of three outcomes: increased time within a target range, reduced incidence of hypoglycaemia, and better overnight control.

Hovorka and colleagues report two randomised crossover clinical trials that looked at 24 adults with type 1 diabetes to compare the safety and efficacy of overnight closed loop insulin delivery with that of conventional insulin pump therapy. The two protocols used a medium sized meal (60 g carbohydrate) or a large size meal (100 g carbohydrate plus alcohol). As in previous studies, closed loop insulin delivery significantly increased the time that plasma glucose was in the target range (3.91-8.0 mmol/L). In the context of ongoing research these trials have several new features:

Firstly, the randomised crossover trial design is virtually unique in the field of closed loop control. Because this design is the gold standard for clinical research, the results set a benchmark for future studies. The only other randomised controlled trial of closed loop control was recently presented at the 4th International Conference on Advanced Technologies and Treatments for Diabetes.[11] This study recruited 24 adults and adolescents with type 1 diabetes in the United States and in France and achieved results similar to those reported by Hovorka and colleagues—more time within the target range of 3.9-10 mmol/L and a threefold reduction in hypoglycaemia.

Secondly, the control algorithm used by Hovorka and colleagues belongs to an advanced class of closed loop control technologies known as model predictive control. Algorithm designs for closed loop control have generally used either proportional-integral-derivative control[6 7] or model predictive control.[8-10] Proportional-integral-derivative control algorithms are reactive, responding to changes in glucose levels with adjustment in insulin delivery. Model predictive control algorithms are built over a model of the human metabolic system. Such algorithms are therefore proactive and insulin can be delivered in anticipation of changes in glucose concentrations. This compensates partially for the time delays inherent in subcutaneous glucose control (the time delay in insulin action, which can amount to 60 minutes or more). For this reason, model predictive control has become the approach of choice more recently. The algorithm developed by Hovorka and colleagues has certain distinct features, such as real time adaptation of the underlying model to changing patient parameters implemented as a selection from several predefined models. However, because details have not been given in this or in previous publications,[8] this potential advantage remains to be evaluated.

Thirdly, this is one of the first studies to test realistic meal scenarios and challenge the participants with a large dinner that included alcohol. As such, the study is a clear advance in the quest for an ambulatory artificial pancreas.

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Artificial pancreas systems link a glucose monitor and a subcutaneous insulin infusion pump via a control algorithm

However, as the authors admit, one limitation is the exclusively manual control of the closed loop control system. The closed loop control system relied on study personnel to transmit data manually from the continuous glucose monitor to the computer running the closed loop control, and to transmit insulin injection recommendations from the computer to the insulin pump. In fully automated systems these processes are handled by data transmission and pump control devices, respectively. The authors used manual control in their previous trials for well known reasons, including technological and regulatory barriers.[8] However, manual transfer of continuous glucose monitoring data and manual control of the insulin pump place human factors into the closed loop control system and limit the investigation to testing only the control algorithm, not the closed loop control system as a whole. The testing of other key components, such as sensor-pump communication and error mitigation, would require much more effort and thorough system validation. Studies using fully automated systems have already been reported and offer hope for the future of ambulatory systems.[6 7 11 12]

Finally, despite the sophistication of the control algorithm and the significant reduction in nocturnal hypoglycaemia, four episodes of severe hypoglycaemia (<3mmol/L) occurred, three of which the authors thought were attributable to the preceding prandial insulin dose and could not be prevented by the closed loop suspending insulin delivery. This finding reinforces the recently proposed idea that a dedicated hypoglycaemia safety system—a separate algorithm responsible solely for the assessment and mitigation of the risk of hypoglycaemia—may need to accompany closed loop control.[12] Such safety systems already exist, and have proved useful.[11 12]

In conclusion, closed loop control is in its infancy, with the first in-clinic studies now being reported. Preliminary results have been promising—the most notable improvement is in overnight control of type 1 diabetes, with improvements in safety and a reduction in nocturnal hypoglycaemia being reported. These improvements result from the fine adjustment of insulin delivery provided by closed loop control overnight being superior to a generally fixed basal rate and less likely to cause hypoglycaemia. The first application of closed loop control is therefore likely to be in glucose regulation overnight, a step that has the potential to improve dramatically the safety of insulin delivery during crucial, generally unsupervised, periods.

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Clinical risk prediction of pre-eclampsia

A helpful tool, but not reliable enough to replace traditional methods of detection

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Pre-eclampsia remains a leading cause of maternal and perinatal mortality and morbidity worldwide.[1] In the linked study, North and colleagues present a predictive model for pre-eclampsia that is based on routine clinical data.[2]

The study used data from 3529 "healthy" nulliparous women with a singleton pregnancy participating in the Screening for Pregnancy Endpoints (SCOPE) study.[3] The SCOPE study is a large international undertaking that makes an important contribution towards assessing potential risk markers, individually and in combination. North and colleagues have identified nine clinical predictors of pre-eclampsia: one protective (miscarriage at ≤10 weeks' gestation with the same partner) and eight associated with increased risk (younger maternal age, higher mean arterial blood pressure, higher body mass index, family history of pre-eclampsia, family history of coronary heart disease, the woman having a lower birth weight, vaginal bleeding for at least five days during early pregnancy, and duration of sexual relationship six months or less). All can be collected easily in routine clinical practice, and each of their associations with pre-eclampsia is consistent with the published literature.[4]

The SCOPE model has an area under the receiver operating curve (AUC ROC) of 0.71 whether or not uterine artery Doppler data (bilateral notching or mean resistance index) are included. This AUC ROC is on the cusp of the threshold that defines a clinically useful test (0.70). The point of the AUC ROC curve that optimises sensitivity and specificity is associated with a false positive rate of 30-40%. Only about

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half of the women with pre-eclampsia would be detected using the information provided in the paper. In a healthy nulliparous woman, the pre-test probability of pre-eclampsia would be 5%. This figure would increase using the model proposed by North and colleagues, but only to 10%. Also, the model seems to underestimate pre-eclampsia at rates greater than 10%.

It is questionable whether the most clinically relevant end points are prediction of "any pre-eclampsia" or "pre-eclampsia resulting in delivery at less than 37 weeks' gestation." It is increasingly clear that pre-eclampsia that develops early and results in delivery before 34 weeks' gestation has a higher maternal mortality and morbidity than pre-eclampsia that develops later and results in delivery at or near term.[4 5] Further recruitment to the cohort may allow for sufficient numbers to evaluate early severe pre-eclampsia (with delivery at less than 34 weeks) as an end point, in addition to others, such as intrauterine fetal growth restriction or placental abruption.

Importantly, North and colleagues did not include the results of first or second trimester serum screening, which can be used to stratify the risk of placental disease (such as pre-eclampsia or fetal growth restriction) without assessing the risk of aneuploidy in families not interested in prenatal diagnosis. Although the authors clearly state their future plan to include biomarkers that may improve the performance of the model, those markers collected in routine clinical practice should have been included in this initial pragmatic modelling study to reflect what clinicians have to work with at the present time.

How should clinicians interpret these results? The authors wisely conclude that their model needs external validation before clinical application, and we agree. However, there are three important take home messages.

Firstly, although all historical risk factors can be routinely collected and are supported by published data, three are less well known yet were found to be influential in North and colleagues' model: family history of pre-eclampsia, family history of coronary heart disease, and vaginal bleeding for at least five days during early pregnancy.

Secondly, the model cannot accurately predict who will not develop pre-eclampsia, so absence of the risk markers must not be used to justify a decrease in the intensity of antenatal care.

Thirdly, North and colleagues' model can identify some but not most of the woman who will develop pre-eclampsia. If one or more of the model's risk factors is (are) identified in early pregnancy, the clinician could consider taking one or more of the following actions: providing specific education about the signs and symptoms of pre-eclampsia to facilitate early diagnosis, increasing materno-fetal surveillance, introducing low risk interventions that decrease the risk of pre-eclampsia in other "at risk" populations (such as low dose aspirin), or enrolling women in pre-eclampsia prevention trials for which they are eligible.

In summary, the SCOPE study model is a step forward in formalising ideas early on in pregnancy about the risk of pre-eclampsia. If North and colleagues' model is externally validated and particularly if it incorporates serum screening, we will have a new tool for identifying some women who will develop pre-eclampsia and its complications. Even then, much of antenatal care will need to be devoted to the detection of pre-eclampsia, most of which cannot be predicted.

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Putting evidence into practice

Revised levels of evidence help to find the best evidence, in real time

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In 1998 the Centre for Evidence Based Medicine (CEBM) published its levels of evidence, which were designed to help clinicians and decision makers have a clearer understanding of bias within clinical research and be able to look at the fewer articles with higher validity. Recently the levels of evidence were revised in light of new concepts and data (table).[1]

Not all that is published is true. Although this may not matter too much for some publications, when it comes to clinically relevant ones it can be a matter of life or death. Consequently, there is a clear need for a scientific approach to clinical evidence. Not every test or treatment will be completely accurate or effective in every person. Moreover, study results usually come with confidence intervals that provide a range of possibilities for what happens in a wider population and can help clinicians explain uncertainty when making decisions with individual patients.[2] In addition to the confidence interval a scientific study will have layers of information that help the reader gauge the likely bias and subsequent validity of the study.[3 4] Critical appraisal is time consuming and requires practice so selecting the "best" article is important when time is limited.

In the early 1990s the first descriptions of levels of evidence seemed to help clinicians identify scientifically robust articles from the rapidly expanding body of medical literature.[5] Since their introduction, levels of evidence have been a red flag to some people who decry the emphasis on systematic reviews.[6]

At that time, systematic reviews and meta-analyses were being developed, and the often quoted example of the meta-analysis of streptokinase for patients having heart attacks was used to promote their development.[7] In that example, the evidence from small individual randomised

Oxford Centre for Evidence Based Medicine 2011 levels of evidence[1]

Question	Step 1 (level 1*)	Step 2 (level 2*)	Step 3 (level 3*)	Step 4 (level 4*)	Step 5 (level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances†	Local non-random sample†	Case-series†	Not applicable
Is this diagnostic or monitoring test accurate? (diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards†	Case-control studies, or "poor or non-independent reference standard"†	Mechanism based reasoning
What will happen if we do not add an intervention? (prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomised trial†	Case-series, case-control studies, or poor quality prognostic cohort study†	Not applicable
Does this intervention help? (treatment benefits)	Systematic review of randomised trials or n-of-1 trials	Randomised trial or observational study with dramatic effect	Non-randomised controlled cohort/follow-up study†	Case-series, case-control studies, or historically controlled studies†	Mechanism based reasoning
What are the common harms? (treatment harms)	Systematic review of randomised trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomised trial or (exceptionally) observational study with dramatic effect	Non-randomised controlled cohort/follow-up study (postmarketing surveillance) provided there are sufficient numbers to rule out a common harm (for long term harms the duration of follow-up must be sufficient)†	Case-series, case-control, or historically controlled studies†	Mechanism based reasoning
What are the rare harms? (treatment harms)	Systematic review of randomised trials or n-of-1 trial	Randomised trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (screening)	Systematic review of randomised trials	Randomised trial	Non-randomised controlled cohort/follow-up study†	Case series, case-control or historically controlled studies†	Mechanism based reasoning

*Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO (Patient or Problem, Intervention, Comparison, Outcome) does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; level may be graded up if the effect size is large or very large.

†As always, a systematic review is generally better than an individual study.

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control trials was not large enough to reach clinical significance. A meta-analysis in 1992 showed that the systematic combination of the trial evidence was clinically significant. Levels of evidence are not just about the need for systematic reviews and they are not levels of recommendation. The levels include case series and thereby acknowledge the importance of these in highlighting new problems. The appearance of AIDS with the description of eight cases is an example of the effectiveness of this method of research.[8] Levels of evidence do not help readers appraise the literature, which may be performed with a variety of tools,[9 10] but they guide the search for evidence.

The original table of levels of evidence has been updated and is now accompanied by a clear and concise guide on its use. It is described as a search short cut for busy clinicians and patients to use in real time rather than a strict hierarchy of evidence. With that in mind, the table has been simplified in several ways. For example, levels 1a, 1b, and 1c in the original table have been replaced with simply level 1. All the relevant terms are now defined in an extensive glossary, and the definitions are precise, accurate, and easily understood. The intent is that these become more widely used in practice.

How does the table work in practice? If, for example, a mother asks about a new diagnostic test for their child's seasonal allergy and presents an article from a website, by finding the row labelled, "Is this diagnostic or monitoring test accurate?," the doctor can quickly see that this article relates to a test developed on the basis of "mechanism based reasoning." This would indicate that either other articles are more likely to represent the truth or that this has yet to be tested using more advanced scientific methods. Levels of evidence help doctors by giving a quick reference and, for example, reminding them that retrospective studies in which the gold standard test was not applied are less valid than prospective studies that applied the gold standard to everyone. It does not tell the doctor what to say to the patient but may help provide a more scientific basis for the discussion. It will also guide clinicians in their search for articles that may tackle the diagnostic question.

The weakness of the table is that it does not directly provide the evidence for its own statements. For teachers, clinicians, and patients the provision of evidence for distinguishing the levels of evidence would be helpful. However, in the accompanying guide many areas, such as making sure the reader realises that levels of evidence are not recommendations for treatment, are tackled in a constructive manner. These new levels of evidence are an important tool for scientific reasoning. They appear easier to use, more practical, and should have a positive effect on healthcare as we deal with the increasing complexity and volume of evidence.

Patient decision support is a new science, where even the categories of support are still being determined.[11] The next step is to evaluate how well, and in what circumstances, these new levels of evidence work to help patients make informed decisions.

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