In this issue:

- Cost-effectiveness of individualised glycemic control
- Weight management for remission of type 2 diabetes
- Life satisfaction protective against type 2 diabetes in men
- SGLT-2 inhibitors and risk of lower extremity amputation
- Myo-inositol lowers risk of gestational diabetes
- High vs. low carbohydrate diet in type 2 diabetes
- Trial of implanted continuous glucose sensor
- Haemoglobin glycation index and risk of complications
- Semaglutide and diabetic retinopathy risk
- Novel subgroups of adult-onset diabetes

Abbreviations used in this issue:

- BMI = body mass index
- GLP = glucagon-like peptide
- HbA1c = hemoglobin A1c
- HbA1c = hemoglobin A1c
- HbA1c = hemoglobin A1c
- HDL = high-density lipoprotein
- LDL = low-density lipoprotein
- MMI = number of medication items
- NNT = number needed to treat
- OEMT = oral glucose tolerance test
- OR = odds ratio
- QALY = quality-adjusted life-year
- RCT = randomized controlled trial
- RR = relative risk
- SGLT = sodium glucose cotransporter
- SLN = sentinel lymph node

Welcome to issue 104 of Diabetes Research Review.

First up we review an interesting US study on the cost-effectiveness of individualised glycaemic control in patients with type 2 diabetes and discover that individualised control was cost-saving and generated more quality-adjusted life-years (QALYs) compared with uniform intensive control. Following on, a primary care-led weight management intervention for remission in type 2 diabetes shows promising findings. Also in this issue we address the topics of life satisfaction and protection against type 2 diabetes in men, SGLT-2 inhibitors and risk of lower extremity amputation, myo-inositol lowering the risk of gestational diabetes, high versus low carbohydrate diet in type 2 diabetes, a trial of an implanted continuous glucose sensor, haemoglobin glycation index and risk of complications, semaglutide and diabetic retinopathy risk, and identifying novel subgroups of adult-onset diabetes.

Kind Regards,

Associate Prof. Neale Cohen
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Individualized glycemic control for U.S. adults with type 2 diabetes: A cost-effectiveness analysis

Authors: Laiteerapong N et al.

Summary: The cost effectiveness of individualised versus uniform intensive type 2 diabetes control (target HbA1c level <7%) was evaluated for ~17.3 million patients with type 2 diabetes from the US National Health and Nutrition Examination Survey 2011–2012. A patient-level Monte Carlo-based Markov model was used to estimate the lifetime cost effectiveness from the perspective of the healthcare sector. A base-case analysis revealed that compared with uniform intensive glycaemic control, individualised control was associated with lower costs ($US$105,307 vs. $US$118,854), due primarily to lower medication costs ($US$34,521 vs. $US$48,763), but decreased life expectancy due to an increase in complications (20.63 vs. 20.73 years), despite more QALYs (16.68 vs. 16.58) due to fewer hypoglycaemic events and reduced medications. A sensitivity analysis revealed that compared with uniform intensive glycaemic control, individualised control was cost-saving and generated more QALYs, except where the disutility associated with receiving diabetes medications was decreased by ≥60%.

Comment (PL): Control of blood glucose is an absolute requirement for the treatment of patients with type 2 diabetes, with the imperative of hitting targets needing to be moderated by minimising the induction of hypoglycaemia. Hyperglycaemia is only one of multiple risk factors occurring in many patients, so the concept of individualised medicine would dictate that targets might be modified and concurrent metabolic factors and conditions (complications) taken into account. This rather sophisticated study used multiple models to analyse data for almost 20,000,000 adults with type 2 diabetes. The trade-off in the analysis is reduced medication use versus increased complications, and in this study relaxing targets saved over $US$10,000 per patient over the lifetime. Most of the measures were not greatly altered. The authors reflected on the emergence of new antihyperglycaemic medications that might be more efficacious in relation to pleiotropic actions, which could impact on the analysis.


Abstract
Primary care-led weight management for remission of type 2 diabetes (DiRECT)

Authors: Lean MEJ et al.

Summary: Patients aged 20–65 years diagnosed with type 2 diabetes in the prior 6 years, who had a BMI of 27–45 kg/m² and were not receiving insulin, were randomised by general practice to a weight management intervention of withdrawal of anti-diabetic and antihypertensive drugs, total diet replacement (825–853 kcal/day for 3–5 months), stepped food reintroduction (2–8 weeks) and structured support for long-term weight maintenance, or best practice care (evaluable n=149 per group) in the open-label DIRECT trial. Compared with the best practice control group, the intervention was associated with: i) a greater proportion of participants losing ≥15kg of bodyweight at 12 months (24% vs. 0% [p<0.0001]); ii) a greater rate of diabetes remission (46% vs. 4% [p<0.0001]), with the proportion achieving remission increasing as the amount of bodyweight loss increased; iii) greater mean bodyweight loss (10.0 vs. 1.0kg [p<0.0001]); and iv) a significant improvement in QoL (p=0.0012). The adverse event rates were 4% and 1% in the intervention and control groups, respectively. There were no study withdrawals due to serious adverse events, although one participant experienced both biliary colic and abdominal pain potentially related to the intervention.

Comment (PL): The big problem in diabetes (type 2) prevention has been translating clinical trials to the real-world environment. This UK primary-care setting study randomly assigned subjects to either a weight management programme or best practice care by guidelines. The subjects were relatively recently diagnosed, with BMI of 27–45 kg/m² and were not on insulin. The study recruited 300 subjects. Just one interesting statistic was that 36 (24%) of the intervention group lost 15kg or more, whereas not one participant in the control group lost this much weight. Somewhat amazingly (at least to this commentator) was that almost 50% of the intervention group attained a non-diabetic status and were off anti-diabetic medications at the end of the intervention. The resources required to implement the medical intervention are not clear and will possibly be the subject of a future publication. The study provides proof of principle for the approach and the possibility of modulating the course of type 2 diabetes, which is in line with several other recent reports.

Reference: Lancet 2018;391:541–51

Life satisfaction is a protective factor against the onset of type 2 diabetes in men but not in women: findings from the MONICA/KORA cohort study

Authors: Picu AM et al.

Summary: Associations between a high level of life satisfaction and incident type 2 diabetes were explored separately in 3664 men and 3443 women from the population-based MONICA/KORA survey cohort. Compared with medium or low levels of life satisfaction, both men and women with a higher life satisfaction level had lower crude incidence rates of type 2 diabetes (57 vs. 73 and 37 vs. 48 per 10,000 person-years, respectively). Men with a high level of life satisfaction were at a significantly reduced risk of incident type 2 diabetes after adjustment for sociodemographic, behavioural and clinical risk factors (HR 0.73 [95% CI 0.56–0.94]), but statistical significance was lost on further adjustment for depressed mood (0.79 [0.61–1.03]). No significant association was seen between life satisfaction and incident type 2 diabetes in women.

Comment (PL): It is quite easy to overlook the impact of mental health status (depression) on all aspects of general health. This German study looked at indices of life satisfaction with incident type 2 diabetes in men and women. The top line finding was that high life satisfaction was associated with the modestly lower incidence of type 2 diabetes in men and there was no such association for women. The association in men occurred after adjusting for multiple parameters but was lost, as implied above, when depression was added to the model. Lifestyle, life satisfaction and mental health are just some of the factors that need to be considered when counselling men and women at risk of type 2 diabetes.


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Risk of lower extremity amputations in people with type 2 diabetes mellitus treated with sodium-glucose co-transporter-2 inhibitors in the USA

Authors: Yuan Z et al.

Summary: The incidence of below-knee lower extremity amputation was investigated in a retrospective cohort of 118,018 patients with type 2 diabetes started on SGLT-2 inhibitors, including 73,024 starting canagliflozin specifically, compared with 226,623 patients starting other classes of antihyperglycaemic agents. The respective crude incidence rates of below-knee lower extremity amputation for SGLT-2 inhibitor, canagliflozin and non-SGLT-2 inhibitor antihyperglycaemic agent users were 1.22, 1.26 and 1.87 events per 1000 person-years. There was no significant difference in the incidence rates of below-knee lower extremity amputations between 63,845 canagliflozin users and the same number of matched non-SGLT-2 inhibitor antihyperglycaemic agent users (1.18 vs. 1.12 events per 1000 person-years [p=0.95]).

Reference: Diabetes Obes Metab 2018;20:582–9

Myo-inositol lowers the risk of developing gestational diabetic mellitus in pregnancies

Authors: Guo X et al.

Summary: This was a systematic review and meta-analysis, with trial sequential analysis, of four RCTs (n=586) comparing myo-inositol with placebo in pregnant women at risk of gestational diabetes mellitus. Compared with placebo, myo-inositol supplementation was associated with a significantly lower risk of developing gestational diabetes (RR 0.44; 95% CI 0.32–0.62) without heterogeneity (I²=0% [p=0.99]); this was confirmed by trial sequential analysis, with an NNT of 6.2. Myo-inositol had no significant impact on birthweight (p=0.31) with significant heterogeneity (I²=52% [p=0.12]), but this was not confirmed by trial sequential analysis. Significant relationships were seen between myo-inositol supplementation and lower fasting, 1-hour and 2-hour OGTT results and the incidence of preterm delivery; no difference was seen between myo-inositol and placebo for the incidences of other complications.

Comment (PL): Drugs are drugs (says this pharmacist) and we have seen many surprises (and some not so surprising outcomes) when apparently safe agents have been given to huge numbers of subjects. Patients with diabetes account for the majority of all cases of lower extremity amputation, creating a situation of high sensitivity to a drug either directly (drug effect) or indirectly (as a consequence of its action) inadvertently having a negative impact on this extremely debilitating comorbidity. The SGLT-2 inhibitor canagliflozin gave some negative signals in early use (CANVAS) for increased lower extremity amputations, mainly of the toe in middle foot. This very recent study looked at data for over 100,000 users of SGLT inhibitor (including canagliflozin) and in a similar group given alternative antihyperglycaemic medications. The bottom line was that there was no difference, or hint of a difference, in any of the patient groups, so canagliflozin would appear to be not exceptional in relation to the complications.

Reference: J Diabetes Complications 2018;32:342–8

Abstract

Myo-inositol lowers the risk of developing gestational diabetic mellitus in pregnancies

Authors: Guo X et al.

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Comment (PL): Gestational diabetes is increasing throughout the world; diagnosis and treatment is the topic of considerable controversy even amongst peak bodies and international opinion leaders. For a current and full analysis of this situation, see our paper, Gray et al. J Diabetes 2018, which was accepted for publication this week. Obviously any medical intervention in gestational diabetes or hyperglycaemia in pregnancy needs to be ultra safe. Myo-inositol is a naturally occurring substance, which has the biochemical potential to enhance insulin signalling. This micro-systematic review analysed four studies and 500 patients. In raw data there were 102 events (gestational diabetes) in controls and 38 in those on myo-inositol. In agreement, those on myo-inositol had lower values in OGTTs. This is a very important area, and perhaps some larger groups will undertake a substantial study of the potential efficacy of this presumably safe intervention.

Reference: J Diabetes Complications 2018;32:342–8

Abstract
Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial

Authors: Tay J et al.

Summary: This study involving 115 overweight and obese patients with type 2 diabetes (mean BMI 34.6 [SD 4.3] kg/m²; age 58 [7] years; HbA₁c 7.3 [1.1]% examined whether a low-carbohydrate, high-unsaturated/low-saturated fat diet (LC) improves glycemic control and cardiovascular risk factors. Patients were randomised to receive either the LC diet (14% energy as carbohydrate, 28% as protein, 58% as fat [<10% saturated fat]) or a low-fat, high-carbohydrate, low-glycaemic index diet (HC); 53% energy as carbohydrate, 17% as protein, 30% as fat [<10% saturated fat]) combined with aerobic/resistance exercise (1 hour, 3 days per week); for 12 weeks, the diets were energy matched and hypocaloric. A total of 61 patients (LC n=33; HC n=28) who completed the study, reductions were seen in weight (LC estimated marginal mean -6.8 kg [95% CI -8.8 to -4.7]; HC -6.6 kg [-8.8 to -4.5]), body fat (LC estimated marginal mean -4.3 kg [-6.2 to -2.4]; HC -6.4 kg [-6.6 to -2.7]), blood pressure (LC estimated marginal mean -2.0 mmHg [5.9 to 1.8]/-1.2 mmHg [-3.6 to 1.2]; HC -3.2 mmHg [-7.3 to 0.9]/-2.0 mmHg [-4.5 to 0.5]), HbA₁c (LC estimated marginal mean -0.6% [-0.9 to -0.3]; HC -0.9% [-1.3 to -0.5]) and fasting glucose (LC estimated marginal mean 0.3 mmol/L [-0.4 to 1.0]), HC -0.4 mmol/L [-1.1 to 0.4]). All of the observed reductions were similar between groups (p>0.09). While changes in LDL-C (LC 0.2 mmol/L [95% CI -0.1 to 0.5]; HC 0.1 mmol/L [-0.2 to 0.4]; p=0.05), brachial artery flow mediated dilatation (LC -0.5% [1.5, 0.5]; HC -0.4 [-1.4, 0.7]; p=0.73), albuminuria and eGFR were similar between the two groups, LC recipients experienced greater reductions in diabetes medication use (medication effect score LC -0.5 units [95% CI -0.6 [-0.3]; HC -0.2 units [-0.4 to -0.02]; p=0.03). Gastrointestinal events were more common in LC group (29% vs HC 16%; p=0.04). When adjusted for covariates, HbA₁c was a stronger predictor than HC, as a predictor. This suggests that either HGI is not a good surrogate for rate of glycation, or that glycation is not a key mechanism in the pathophysiology of diabetic complications.

Comment (NC): Intensive lifestyle remains a key ingredient in the management of type 2 diabetes. There are now a range of dietary macronutrient recommendations that mostly have had limited long-term scientific analysis. This important 2-year trial looked at a high-carbohydrate versus low-fat diet in overweight or obese patients with type 2 diabetes. Results broadly showed equal reductions in HbA₁c, and body weight in both groups, with reduced glycemic variability and marginally improved lipid profile in the low-carbohydrate compared with high-carbohydrate groups. What seems fairly conclusive from this and other previous studies is that clinically meaningful benefits of low-carbohydrate diets in type 2 diabetes are small compared with the more traditional high-carbohydrate diet.

Reference: Diabetes Obes Metab 2018;20(4):858–71

Abstract

A prospective multicenter evaluation of the accuracy of a novel implanted continuous glucose sensor: PRECISE II

Authors: Christiansen MP et al.

Summary: The prospective, nonrandomised, blinded, single-arm PRECISE II study examined the use of an implantable continuous glucose monitoring system (CGM; Eversense) in 90 adult patients with type 1 diabetes or type 2 diabetes mellitus. Overall, mean absolute relative difference was 6.8% (95% CI 8.1–9.3) versus Yellow Springs Instrument (YSI) reference measurements (glucose values 40–400 mg/dL) over 90 days after insertion, and was lower than a pre-specified 20% performance goal for accuracy (p<0.0001); 93% were within 20/20% of reference values. Clarke Error Grid analysis indicated 99.3% and was lower than a pre-specified 20% performance goal for accuracy (p<0.0001); a RESEARCH REVIEW publication

Haemoglobin glycation index and risk for diabetes-related complications in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial

Authors: van Steen SC et al.

Summary: Data from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (n=11,083) were used to test whether haemoglobin glycation index (HGI; difference between observed Hba₁c, and predicted Hba₁c, [linear regression of Hba₁c on fasting plasma glucose]) was predictive of diabetes-related complications and adverse outcomes during intensive glucose lowering. Intensive glucose control reduced mortality risk only in high HGI participants (HR 0.74; 95% CI 0.61–0.91, p=0.003); there was no difference in participants with high Hba₁c, An increase of one standard deviation in HGI was associated with a microvascular and macrovascular disease and mortality risk increase of 14–17%. When adjusted for covariates, Hba₁c, was a stronger predictor than HGI.

Comment (NC): Hyperglycaemia is associated with the development of microvascular and macrovascular disease in patients with diabetes. It is thought that glycation of proteins plays a major role; however, there is no direct measure of protein glycation currently. Hba₁c is a measure of mean blood glucose; however, it is also a product of glycation. It has been proposed that patients who are rapid glycators may be more at risk of diabetes-related complications, and may also have higher Hba₁c values than might be expected from mean glucose levels. The HGI is a measure of the difference between expected Hba₁c and measured Hba₁c, and a surrogate for rate of glycation. This analysis from the ADVANCE study did show an association of HGI with microvascular and macrovascular outcomes; however, this was not better than Hba₁c, as a predictor. This suggests that either HGI is not a good surrogate for rate of glycation, or that glycation is not a key mechanism in the pathophysiology of diabetic complications.


Abstract

Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy

Authors: Vlitsell T et al.

Summary: This was an analysis of diabetic retinopathy data from across the SUSTAIN trials and a post hoc analyses of the SUSTAIN 6 data. The SUSTAIN programme evaluated the efficacy and safety of semaglutide, a glucagon-like peptide-1 analogue for the treatment of type 2 diabetes. SUSTAIN 6 was a 2-year, pre-approval cardiovascular outcomes trial that demonstrated an association between semaglutide and a significant increase in the risk of diabetic retinopathy complications compared with placebo. Data analysis revealed no imbalance in diabetic retinopathy adverse events across the SUSTAIN 1 to 5 and Japanese trials. The authors concluded that the majority of the effect on risk of diabetic retinopathy with semaglutide in SUSTAIN 6 may possibly be due to the magnitude and rapidity of Hba₁c, reduction during the first 16 weeks of treatment in patients who had pre-existing diabetic retinopathy and poor glycaemic control at baseline, and whom received insulin.

Comment (NC): Semaglutide is a new once-weekly GLP1 agonist that is highly effective glucose-lowering agent. A cardiovascular outcome trial SUSTAIN 6 showed a reduction in major adverse cardiac events compared with placebo, however, there was an adverse signal for diabetic retinopathy with a 76% increase in retinal adverse events. This post hoc analysis looked at glycaemia and the association with retinal outcomes. It appears that the rate of improvement in Hba₁c, was associated with this adverse outcome rather than semaglutide itself. Initial deterioration in retinopathy with rapid glucose lowering has been described in previous studies like the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study, and this seems a plausible explanation. Nevertheless systematic and complete retinal data collection was not part of SUSTAIN 6, and more studies are needed in this space. Regardless, the risk/benefit ratio would seem to be well in favour of semaglutide considering the glycaemic, weight and cardiovascular benefits of this impressive agent.


Abstract

RESEARCH REVIEW — The Australian Perspective Since 2007
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Authors: Ahlqvist E et al.

Summary: This data-driven cluster analysis (k-means and hierarchical clustering) in patients with newly-diagnosed diabetes (n=6980) from the Swedish All New Diabetics in Scania cohort was undertaken in order to identify different subgroups within type 2 diabetes. Clusters were identified based on six variables (glutamate decarboxylase antibodies, BMI, age at diagnosis, HbA\(_1c\), and homoeostatic model assessment 2 estimates of \(\beta\)-cell function and insulin resistance). These were then related to prospective data from patient records on development of complications and prescription of medication, and repeated in three independent cohorts: the Scania Diabetes Registry (n=1466), All New Diabetics in Uppsala (n=844), and Diabetes Registry Vaasa (n=3485). Overall, five replicable clusters of patients with significantly different patient characteristics, disease progression and risk of diabetic complications were identified. Striking findings were that individuals in cluster 2, the group most resistant to insulin, exhibited a significantly higher risk of diabetic kidney disease compared to individuals in clusters 4 and 5, however, they had been prescribed similar diabetes treatment. Furthermore, those in cluster 2 (insulin deficient) had the highest risk of retinopathy. The genetic associations in the clusters differed from those seen in traditional type 2 diabetes.

Comment (NC): Traditional classification of diabetes has largely focused on differentiating between type 1 and type 2 diabetes because of the dramatically different patient phenotypes and therapies involved. This important study from Swedish databases looked at clusters of patients with adult-onset diabetes on the basis of autoimmunity, age of onset, BMI, insulin resistance, insulin deficiency and HbA\(_1c\). It identified five distinct phenotypes and associated outcomes and genetic links. The most dramatic findings were in the SIDD (severe insulin resistant diabetes) group who had much higher rates of renal disease, and the SIDD (severe insulin deficiency diabetes) group with high rates of retinopathy. This work does not define pathophysiology, or guide us as to optimal therapy in these subgroups, it is the first attempt to reclassify what is currently a heterogeneous group of disorders resulting in hyperglycaemia. There are potential benefits that can now be explored in terms of more targeted therapies in these subgroups.

Reference: Lancet Diabetes Endocrinol 2018;Mar 1 [Epub ahead of print]

Abstract

This 7-year data set is the longest follow-up of patients with Type 2 Diabetes treated with a GLP-1RA in phase 3 clinical trials.

"HbA\(_1c\) reductions vs. baseline over 7 years for patients receiving BYDUREON."

Open-label, controlled extension study in patients given BYDUREON
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