In this issue:

- Insulin pumps vs. MDIs with structured education in type 1 diabetes
- Liraglutide for reducing progression risk in prediabetes
- Basal-bolus fast-acting insulin aspart for type 1 diabetes
- Basal-bolus fast-acting insulin aspart for type 2 diabetes
- Nocturnal glycaemia with insulin analogues vs. human insulin
- ADA recommendations for pharmacological type 2 diabetes treatment
- Screening frequency for retinopathy in type 1 diabetes
- Mortality and CV disease in types 1 and 2 diabetes
- Birth season affects type 2 diabetes risk in adulthood
- Gestational diabetes and adverse perinatal outcomes

Abbreviations used in this issue:

- CV = cardiovascular
- GLP = glucagon-like peptide
- HbA1c = glycosylated haemoglobin
- HR = hazard ratio
- MDI = multiple daily injection

Welcome to issue 96 of Diabetes Research Review.

This issue begins with a cluster randomised controlled trial comparing insulin pumps with MDIs (multiple daily injections) in patients with type 1 diabetes, when both groups received equivalent training in flexible insulin treatment. Results from the ONSET 1 and 2 trials of the impact of fast-acting insulin aspart versus regular insulin aspart on glycaemic control in patients with types 1 and 2 diabetes, respectively, are included. The latest evidence-based recommendations from ADA (American Diabetes Association) for the pharmacological management of type 2 diabetes are discussed. There is also an N Engl J Med paper from the DCCT/EDIC Research Group presenting a rational screening frequency for retinopathy.

We hope you enjoy these and the other research papers selected for this issue. Please don’t hesitate to send us your feedback and suggestions.

Kind Regards

Prof. Peter Little AM
peter.little@researchreview.com.au

Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes

Authors: The REPOSE Study Group

Summary: The REPOSE trial allocated adults with type 1 diabetes to places on 46 established group courses that taught flexible intensive insulin treatment, and the course groups were randomly allocated to either insulin pump therapy (n=156) or MDIs (n=161); 119 and 116 participants from the respective pump and MDI groups had baseline HbA1c levels ≥7.5%. Both groups had improvements in glycaemic control and severe hypoglycaemia rates, with the pump group having a trend for a greater mean reduction in HbA1c level at 2 years compared with the MDI group (–0.85% vs. –0.42% [p=0.10]). No significant between-group differences were seen for most psychosocial measures assessed, but the pump group reported greater treatment satisfaction and improvements in dietary freedom and daily hassle at 12 and 24 months.

Comment (NC): Insulin pump therapy in type 1 diabetes has been associated with improved outcomes, including HbA1c level lowering and reduction in hypoglycaemia. However, there is debate regarding the long-term benefits, their clinical significance and to what extent these relate to patient motivation and clinician contact. This study is consistent with other literature showing modest HbA1c level benefit when compared with structured education, in this case DAFNE, in a randomised 2-year trial. There was surprisingly no difference in most quality of life measures or hypoglycaemia rates. This study confirms what most clinicians now accept, that pump therapy is not indicated as a treatment for all adult type 1 diabetes. However, it does not assess important subgroups, including those with disabling hypoglycaemia or glycaemic variability, and it is likely that targeted pump therapy is of great importance in these groups.

Reference: BMJ 2017;356:j1285

Abstract
3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes

Authors: le Roux CW et al. for the show SCALE Prediabetes NN8022-1839 Study Group

Summary: Adults with prediabetes and a body mass index of ≥30 kg/m², or ≥27 kg/m² with comorbidities, were randomised to receive subcutaneous liraglutide 3.0mg (n=1503) or placebo (n=749) once daily as an adjunct to a reduced-calorie diet and increased physical activity; the completion rate for the 16-week study was 50%. The respective rates of a diabetes diagnosis by week 160 in the liraglutide and placebo arms were 2% and 6%, and taking diagnosis frequencies into account, liraglutide was associated with a 2.7-fold longer time to diabetes onset than placebo (HR 0.21 [95% CI 0.13–0.34]). Liraglutide was also associated with a significantly greater reduction in bodyweight than placebo at week 160 (–6.1% vs. –1.9%; p=0.0001]). The respective serious adverse event rates in the liraglutide and placebo arms were 15% and 13%.

Comment (NC): Liraglutide is one of the rapidly growing class of GLP-1 agonists that was initially approved as a glucose-lowering drug for use in type 2 diabetes. Its well documented weight loss benefit is an added bonus, and it is now the only GLP-1 agonist with an obesity indication. This further analysis of the SCALE trial looked at patients within the trial with prediabetes, and showed around an 80% reduction in progression to diabetes over 3 years compared with placebo. This is comparable with other therapeutics in diabetes prevention trials; however, it is one of the highest risk reductions we have seen. Tolerance and cost remain the biggest issues with these agents and will continue to limit their use.

Abstract

Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes

Authors: Russell-Jones D et al.

Summary: The 26-week ONSET 1 trial randomised adults with type 1 diabetes to receive mealtime fast-acting insulin aspart (n=381), insulin aspart (n=380) or open-label postmeal fast-acting insulin aspart (n=382), each with insulin detemir. The treatment groups had reductions in HbA₁c level, with noninferiority confirmed for both mealtime and postmeal fast-acting insulin aspart versus insulin aspart (respective estimated treatment differences –0.15% [95% CI –0.23 to –0.07] and 0.04% [–0.04 to 0.12]). Mealtime fast-acting insulin aspart was also associated with significantly lower 1- and 2-hour postprandial plasma glucose level increments, with significant superiority confirmed versus insulin aspart for the 2-hour increment. Severe or blood glucose-confirmed hypoglycaemic episodes and safety profiles were similar among the treatments.

Comment (NC): Rapid-acting insulin analogues have been developed to allow for more rapid absorption of insulin, with the aim to reduce postmeal glucose elevations. The latest insulin in this field is the Novo Nordisk product fast-acting insulin aspart. This large type 1 diabetes study showed a small HbA₁c level benefit (0.15%) compared with standard aspart insulin without any increase in hypoglycaemia. There was also a group in which the ultrafast aspart was administered postmeal, and this showed noninferiority compared with premeal aspart. These outcomes are small and somewhat disappointing, and there will be the need for discussions around cost and cost effectiveness of this new insulin if it is to be used in this setting.

Reference: Diabetes Care; Published online March 29, 2017
Abstract

Faster aspart versus insulin aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes

Authors: Bowering K et al.

Summary: In the ONSET 2 trial, adults with type 2 diabetes treated with basal insulin and oral antidiabetic agents were recruited and randomised to 26 weeks of mealtime fast-acting insulin aspart (n=345) or insulin aspart (n=344), titrated using a simple daily patient-driven algorithm and with insulin glargine 100U and metformin. Fast-acting insulin aspart and insulin aspart were associated with respective reductions in HbA₁c level of 1.36 and 1.36 percentage points, with noninferiority confirmed for fast-acting insulin aspart versus insulin aspart. While postprandial plasma glucose control was improved in both arms, the improvement was significantly better in the fast-acting insulin aspart arm after 1 hour (p=0.0198), but not after 2–4 hours. There was no significant between-group difference for change from baseline in fasting plasma glucose level, bodyweight or overall severe/blood glucose-confirmed hypoglycaemia rate, but postmeal hypoglycaemia over 0–2 hours was greater with fast-acting insulin aspart than with insulin aspart (2.27 vs. 1.49 per patient-year; rate ratio 1.60 [95% Cl 1.13–2.27]).

Comment (NC): This is the type 2 equivalent of the ONSET 1 trial. This study examined patients with type 2 diabetes on basal insulin and commenced them on basal bolus with either aspart or faster aspart insulin. Apart from a 0.59 mmol/L decrease in 1-hour postmeal plasma glucose level with faster aspart, there was no difference between the two groups. Although safety has been demonstrated, there would appear to be no clinical advantage identified for this new insulin in type 2 diabetes when used in a basal-bolus setting.

Reference: Diabetes Care; Published online May 8, 2017
Abstract
Comparing effects of insulin analogues and human insulin on nocturnal glycaemia in hypoglycaemia-prone people with type 1 diabetes

Authors: Kristensen PL et al.

Summary: These researchers analysed data from nights during treatment with insulin detemir/insulin aspart and from nights during treatment with human NPH insulin/human regular insulin for 72 participants with type 1 diabetes from the HypoAna trial, a 2-year randomised, crossover trial of these treatments, to assess the hypoglycaemia risk in participants with recurrent severe hypoglycaemia. Compared with human insulin treatment, treatment with an insulin analogue was associated with a significantly higher mean nocturnal plasma glucose level (10.6 vs. 8.1 mmol/L), with no difference in fasting plasma glucose level, and a lower proportion of nights with nocturnal hypoglycaemia recorded (16% vs. 41%; HR 0.26 [95% CI 0.14–0.45]).

Comment (NC): Insulin analogues have been available for over 10 years and are widely used for type 1 diabetes management. They are more expensive than other insulins, and their value has been questioned. This study in patients with type 1 diabetes and recent severe hypoglycaemia demonstrated that, firstly, nocturnal hypoglycaemia is frequent and often asymptomatic. It also showed a marked reduction in nocturnal hypoglycaemia with analogue insulin compared with human insulin, with a risk ratio of 0.26. While the clinical significance of this is not certain, there is growing evidence that recurrent hypoglycaemia has associations with adverse outcomes such as hypoglycaemia unawareness, prolonged QT-interval and cardiac arrhythmia. Insulin analogues have perhaps not changed the world, but they have provided an important advance in safety for the management of type 1 diabetes.


Abstract

Pharmacologic therapy for type 2 diabetes: synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes

Authors: Chamberlain JJ et al.

Summary: This paper reported a synopsis of the recommendations from the 2017 annual update of the ADA’s (American Diabetes Association’s) Standards of Medical Care in Diabetes on pharmacological treatment of glycaemia in type 2 diabetes. After describing the process for the development and grading of evidence for the guidelines, the paper highlights initial pharmacological management with metformin. It also describes other agents that can be considered for patients not tolerating or with a contraindication for metformin, and also the role of insulin therapy, and emphasises the use of a patient-centred approach. Clinical trial evidence for the recommendations is also summarised.

Comment (PL): One of the most interesting areas of modern therapeutics has been the medical treatment of the high blood glucose in type 2 diabetes, especially when the cause of the primary molecular defect, insulin resistance, is unknown. Therapy is transitioning from the reliance on insulin and a small number of the agents to the current revolution based around GLP-1 agonists and SGLT1 (sodium glucose cotransporter)-2 inhibitors and other emerging agents. The pre-eminent authority in this area is the ADA, and it released its first standards of care documents in 1989 – almost 30 years ago, but some 66 years after the discovery of insulin. Prescribing clinicians will make themselves familiar with the guidelines, but some key points are: therapy begins with metformin; for patients not achieving glycaemic goals “insulin therapy should be instituted without delay”; and finally adding agents to or replacing metformin when not tolerated should be done with a ‘patient-centred approach’. This is all about glycaemia, so it is noted that the benefits of treating other CV risk factors is greater in people with diabetes (compared with those without diabetes).


Abstract

Frequency of evidence-based screening for retinopathy in type 1 diabetes

Authors: The DCCT/EDIC Research Group

Summary: A rational screening frequency for retinopathy was developed by analysing retinal photographs obtained from DCCT/EDIC study participants. The likelihood of progression to proliferative diabetic retinopathy or clinically significant macular oedemas was limited to ~5% for retinal screening intervals of 4 years, 3 years, 6 months and 3 months for participants with no retinopathy, mild retinopathy, moderate retinopathy and severe nonproliferative diabetic retinopathy, respectively. A close relationship was seen between progression from no retinopathy to proliferative diabetic retinopathy or clinically significant macular oedema and mean HbA1c level, with a 1.0% risk over 5 years for an HbA1c level of 6% versus a 4.3% risk over 3 years for an HbA1c level of 10%. Compared with routine annual retinopathy screening, these researchers’ schedule was associated with a 58% lower frequency of eye examinations over a 20-year period with substantial resultant lower costs.

Comment (PL): Several recent commentaries in Diabetes Research Review have reflected on the safety, efficacy and status of screening – screening is probably going to increase in coming years and a more sophisticated approach to when, how and what to do with the results is required. The data here are from the DCCT/EDIC study covering 30 years of follow-up of people with type 1 diabetes and published in N Engl J Med, so clearly a gold standard reference point. The risk of progression to proliferative retinopathy (from any starting point) was closely related to the mean HbA1c level, clearly indicating the relationship between glycaemia and microvascular disease. Based on a changed paradigm of more frequent (evidence-based) screening with worsening retinopathy versus a default standard annual screening protocol, the recommended frequency of screening produces 60% less screening (with no diminution of outcomes) giving a very substantial cost saving, thus releasing funds for use elsewhere. We will follow developments in the broad area of screening closely in the coming period.


Abstract
Mortality and cardiovascular disease in type 1 and type 2 diabetes

Authors: Rawshani A et al.

Summary: Long-term trends in excess mortality and CV outcome risks were reported for Swedish registry patients with type 1 or 2 diabetes enrolled between 1998 and 2012, and followed until 2014. The patients were matched to controls from the general population. Patients with type 1 and type 2 diabetes had the following respective absolute changes in incidence rates of sentinel outcomes per 10,000 person-years: ~31.4 and ~69.6 for all-cause death, ~26.0 and ~110.0 for CV disease-related death, ~21.7 and ~91.9 for coronary heart disease-related death, and ~45.7 and ~203.6 for CV disease-related hospitalisation. Compared with controls, patients with types 1 and 2 diabetes had ~40% and ~20% greater reductions in CV outcomes, respectively, whereas reductions in fatal outcomes were similar between patients with type 1 diabetes and controls, but smaller for patients with type 2 diabetes than for controls.

Comment (PL): Last month I commented on CV disease in young people with type 1 diabetes or type 2 diabetes and noted the greater risk accompanying type 2 diabetes. This study was based on data in the Swedish National Diabetes Register and covered the last 20 years. This study looked at changes (reductions) in the rate of death and less severe events in people with type 1 diabetes and type 2 diabetes compared with the changes in the same parameters in matched people without diabetes, i.e., the relative rate of change due to the presence of diabetes. Selecting some relevant data bites, in the normal population, death fell by 14 cases per 10,000 people years in controls and by 31 in people with type 1 diabetes. For type 2 diabetes, the match numbers were 74 for type 2 diabetes and matched controls 135 deaths. The rate of change in deaths did not differ significantly in people with type 1 diabetes, but was 13% greater amongst controls than patients with type 2 diabetes. Basically, rates of death were lowered in people with and without diabetes, so all sorts of changes in interventions and the environment are working. It is noted that this paper is in N Engl J Med, and the introduction reflecting briefly on the aetiology of diabetes makes no mention of inflammation or chronic inflammatory disease as you see used so widely elsewhere.


Abstract

Season of birth and the risk of type 2 diabetes in adulthood

Authors: S J et al., on behalf of the China Kadoorie Biobank Collaborative Group

Summary: The association between season of birth and risk of type 2 diabetes in adulthood was prospectively explored in a cohort of 189,153 men and 272,058 women from China. There were 68,74 incident cases of type 2 diabetes recorded over a median 3.3 million person-years of follow-up. Compared with individuals born during summer months, those born during spring, autumn and winter were at increased likelihood of developing type 2 diabetes (respective adjusted HRs 1.09 [95% CI 1.02–1.16], 1.08 [1.02–1.15] and 1.09 [1.02–1.15]); these associations were consistent in men and women and across subgroups defined by residence locality and lifestyle factors later in life.

Comment (PL): This paper starts off telling us that the rate of diabetes in China reached a staggering 9.7% in 2010 (and is undoubtedly still rising) – this represents well over 100 million people. It follows that diabetes is a major current and future issue for China, so much research of all types is justifiably urgently needed. The study was done by various Chinese groups in collaboration with a major university at the University of Oxford in the UK. The researchers used seasonality of birth as a surrogate measure of changing environmental factors – a clear advance on simply looking at the effects of famine – where relevant parameters might be duration of sunlight, exercise, food availability, eating habits, etc. The study covered half a million people across wide areas of China. With 3000 cases of type 2 diabetes in men and 5000 cases in women over 7 years, the season of birth was statistically significantly associated with the risk of incident type 2 diabetes. Compared with the lowest rates in summer, rates were increased by 9%, 8% and 9% for those born in spring, autumn and winter, respectively. The effects are quite small and the authors explained that findings in this area are not consistent, and even some of their own earlier data are not consistent, with the current work.

Reference: Diabetologia 2017;60(8):836–42

Abstract

Participants may claim credentialling points for self-directed study

(1 point per hour) Valid until April 2017

Click here for credentialling applications.
Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012

Authors: Billionnet C et al.

Summary: This research from France reported adverse perinatal outcomes for 796,346 deliveries, including 57,629 mothers with gestational diabetes; mother-infant linkage was obtained for 705,198 deliveries. Compared with pregestational diabetes, gestational diabetes was associated with lower risks of adverse outcomes. For deliveries after 28 weeks, women with gestational diabetes versus nondiabetics had higher risks of preterm birth (odds ratio 1.3 [95% CI 1.3–1.4]), Caesarean delivery (1.4 [1.4–1.4]), pre-eclampsia/eclampsia (1.7 [1.6–1.7]), macrosomia (1.8 [1.7–1.8]), respiratory distress (1.1 [1.0–1.3]), birth trauma (1.3 [1.1–1.5]) and cardiac malformations (1.3 [1.1–1.4]), particularly in women with insulin- versus diet-treated gestational diabetes. The risk of perinatal mortality was also increased when the analysis was limited to term deliveries. When women suspected of having undiagnosed pregestational diabetes were excluded, the risk remained moderately increased only for women with diet-treated gestational diabetes (odds ratio 1.3 [95% CI 1.0–1.6]).

Comment (PL): As mentioned in earlier issues of Diabetes Research Review, gestational diabetes is increasing, so the focus on it and its implications is also increasing. This study in France looked at the adverse outcomes of gestational diabetes. Some findings were that the risk of adverse outcomes was much lower for gestational diabetes compared with pre-existing diabetes and furthermore, higher risks were observed for insulin-treated gestational diabetes compared with diet-treated gestational diabetes. The conclusion is that gestational diabetes is associated with adverse pregnancy outcomes and the risks are higher for women with insulin-treated gestational diabetes. The database did not allow for a deeper analysis of the data. This is a difficult area to research and interpret, but research is of considerable value.

Reference: Diabetologia 2017;60(4):636–44

Abstract

Independent commentary by Professor Peter Little, AM and Associate Professor Neale Cohen

Professor Peter Little, AM, is Head of the School of Pharmacy (Pharmacy Australia Centre of Excellence) at the University of Queensland. Peter is a past national President of Diabetes Australia. For full biography please click here.

Associate Professor Neale Cohen is a physician specialising in diabetes and endocrinology, and is the General Manager of Diabetes Services at the Baker IDI Heart and Diabetes Institute. He is an Adjunct Associate Professor at University of Queensland School of Pharmacy.