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 Obesity Prediabetes NN8022-1839 Study Group

**Summary:** Adults with prediabetes and a BMI of ≥30 kg/m², or ≥27 kg/m² with comorbidities, were randomised to receive subcutaneous liraglutide 3.0mg (n=1505) or placebo (n=749) once daily as an adjunct to a reduced-calorie diet and increased physical activity; the completion rate for the 160-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:** There is no doubt that effective treatments for preventing the progression of prediabetes to diabetes are required. The benchmark for this remains intensive diet and lifestyle intervention, which was shown to be so effective in the Diabetes Prevention Study and Diabetes Prevention Program studies; however, the translation and implementation of these into real-world clinical settings has proven difficult and largely ineffective. Therefore the focus has again turned to pharmaceutical options. In this trial, liraglutide induced greater weight loss than placebo with greater delay in progression to diabetes. However, the effect was very modest, with a marginal benefit in bodyweight of 4% and a 4% difference in progression to diabetes after 3 years. In the Diabetes Prevention Program study, metformin had similar results and is a fraction of the cost of liraglutide. Therefore it would be extremely difficult to justify the widespread promotion of liraglutide for this indication. This trial was also majorly compromised by an almost 50% dropout rate by the end of the study. It is a bit hard to see how it got published in the Lancet!

**Reference:** Lancet 2017;389(10,077):1399–409
**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 oedema 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 associated with a 58% lower frequency of eye examinations over a 20-year period with substantial resultant lower costs.

**Comment:** The use of retinal photography for screening for retinopathy in diabetes has revolutionised the accuracy, efficiency and effectiveness of screening. However, it is a costly service and with blanket rules for screening interval, there is a lot of wasted resource in repeat screening of low-risk individuals in order to not miss those who do progress quickly. This paper reports a stratified approach to screening interval based on data from the DCCT and follow-up EDIC studies. The use of existing retinopathy status and glycaemic control reduced the scan frequency by 58%. This is highly relevant for NZ. These data come from people with type 1 diabetes, and cannot necessarily be directly translated to those with type 2 diabetes; however, it is likely that a similar effect would be seen.


**Cardiac effects of sulfonylurea-related hypoglycemia**

**Authors:** Middleton TL et al.

**Summary:** Thirty patients receiving sulfonylureas for type 2 diabetes underwent 48 hours of concurrent continuous glucose monitoring and ambulatory ECG recordings in this research, with ventricular repolarisation and QT dynamics analysed during periods of hypoglycaemia versus periods of euglycaemia and hyperglycaemia combined. The mean HbA1c level was 52 mmol/mol (6.9%). Nine participants experienced episodes of hypoglycaemia, 67% of which occurred at night and 73% of which were asymptomatic. Five of these participants had associated corrected QT-interval prolongation, with a large variation in individual responses. Compared with participants who did not experience hypoglycaemia, those who did had higher QT dynamics nocturnally (0.193 vs. 0.159 [p=0.01]), which persisted after the hypoglycaemic event. There was a nonsignificant trend for ventricular and supraventricular ectopy rates to increase during hypoglycaemia. The findings were similar in an insulin-treated cohort.

**Comment:** Hypoglycaemia is one of the side effects of sulfonylureas, but seen much less frequently with the newer shorter acting agents that are almost universally prescribed in NZ now. However, this study suggests that unrecognised nocturnal hypoglycaemia in those on sulfonylureas may be considerably more common than we appreciate. Furthermore, this can be associated with cardiac abnormalities in QT-interval, which may result in a more sinister rhythm disturbance. These data add weight to the increasing demand for funding of the newer diabetes drugs, which do not cause hypoglycaemia and, particularly in the case of the SGLT (sodium glucose cotransporter)-2 inhibitors, result in reduced cardiovascular events.

Reference: *Diabetes Care* 2017;40(5):663–70

**Abstract**

**Independent commentary by Associate Professor Jeremy Krebs.**

Associate Professor Krebs is an Endocrinologist with a particular interest in obesity and diabetes. He trained in Endocrinology at Wellington Hospital in New Zealand and then did his doctorate with the Medical Research Council - Human Nutrition Research unit in Cambridge England. His thesis was on the impact of dietary factors on obesity and insulin resistance. Assoc Prof Krebs returned to New Zealand in 2002 to take up a consultant Endocrinology post at Wellington Hospital, where he is Clinical Leader of Endocrinology and Diabetes. He is an Associate Professor with the University of Otago, and former Director of the Clinical Research Diploma at Victoria University - which he established. As well as clinical and teaching activities, Assoc Prof Krebs maintains active research interests in the area of obesity and diabetes, with a focus on nutritional aspects, bariatric surgery and diabetes service delivery.
Behaviours, thoughts and perceptions around mealtime insulin usage and wastage among people with type 1 and type 2 diabetes mellitus

Authors: Van Brunt K et al.

Summary: This cross-sectional online survey assessed mealtime insulin usage and wastage behaviours in adults with type 1 (n=120) or type 2 (n=280) diabetes treated with >20 U/day of mealtime insulin via 100 U/mL prefilled pens/cartridges for ≥1 month (mean duration 8.6 years). The respondents reported administering 3.7 ±5.9 injections per day with meals, using 11.3 ±18.0 prefilled pens/cartridges per month. Splitting a full dose across two prefilled pens/cartridges was reported by 63.5%, 15.0% reported that they underdosed themselves only with what was remaining in their current pen and 36.3% reported using a new pen when there was insufficient insulin remaining in an already-used pen/cartridge, resulting in a mean of 5.5 prefilled pens/cartridges per month discarded, with each containing a mean 8.8U of insulin. The respondents who reported such insulin wastage also reported that they found it frustrating, time-consuming and painful to inject twice.

Comment: Isn’t it interesting to discover what people really do compared with what we prescribe and think they do! With the increasing use of disposable insulin pens, it is perhaps not surprising that when the remaining amount of insulin in that pen is less than the dose prescribed, that people either dispose of the pen and start a new one, or just give what is left and not top up from the next pen. The disposable nature of the device perhaps creates a reduced sense of importance or significance of the dose regimen. The practice of disposing pens still containing insulin is wastage of resources, over and above the pen itself, and ultimately costly to the funder. You can tell I’m not a big fan of these disposable devices and the throwaway society that they reinforce.


Podiatry impact on high-low amputation ratio characteristics

Authors: Schmidt BM et al.

Summary: The effect of the addition of a limb salvage and diabetic foot programme involving podiatry on amputations in a single centre’s diabetic population was explored in this 16-year retrospective study. Compared with the period prior to the limb salvage and diabetic foot programme being introduced, there were significant reductions in the annual limb salvage rate (−0.11% vs. −0.36% [p<0.01]) and the high-low amputation ratio (0.60 vs. 0.89) during the period following its introduction, with around 40 major lower extremity amputations avoided each year (p<0.05).

Comment: Both patients and health professionals alike can easily overlook the foot complications of diabetes. Whilst directly related to glycaemic control, there are many other factors such as smoking that contribute. Furthermore, simple screening practices for individuals, such as regular inspection of the feet, can also make a big difference. However, it has also been recognised that a structured approach to foot screening and then a systematic, multidisciplinary team approach to managing those with ‘at risk’ feet can significantly reduce the rates of lower limb amputations. This paper provides further evidence to support this. Wherever possible, diabetes teams should be encouraged to try to establish a structured multidisciplinary approach.


Impact of accelerometer and pedometer use on physical activity and glycaemic control in people with type 2 diabetes

Authors: Baskerville R et al.

Summary: This was a systematic review and meta-analysis of trials evaluating the use of pedometers (nine trials) or accelerometers (three trials) to promote physical activity in a total of 1458 individuals with type 2 diabetes. Pooled data showed that intervention groups had an overall increase in physical activity (standardised mean difference 0.57 [95% CI 0.24, 0.91]), with similar effect sizes seen for accelerometers and pedometers, but there was no evidence of significant benefits in terms of HbA1c level, BMI, blood pressure or lipid profile.

Comment: Use of wearable technology to monitor physical activity has become very popular. Various devices either within mobile phones or worn as wristwatches can monitor activity, heart rate, sleep, etc. Use of such devices might be expected to increase physical activity, and therefore improve parameters of glucose control and cardiovascular risk factors. However, the results of this systematic review of studies comparing either simple pedometers or accelerometers with controls are sadly disappointing. Whilst measures of physical activity were increased, this did not translate to other benefits in those with type 2 diabetes. Given the evidence of benefits of increasing activity from highly controlled studies, the lack of effect observed may be due to the intensity or duration of the increases observed. I still believe these devices have potential to be effective, but more research is required to establish the best way to harness them.


Friends and social contexts as unshared environments: a discordant sibling analysis of obesity- and health-related behaviors in young adolescents

Authors: Salvy S-J et al.

Summary: These researchers recruited 40 pairs of same-sex biological weight-discordant siblings aged 13–17 years and their best friends to explore contribution of the friends’ weight and the peer social context on weight and health behaviours. The best predictor of the participants’ BMI z-score was their best friends’ BMI z-score, even when controlling for the child’s birth weight. The friends’ BMI z-score was also a predictor of participants’ sugar-sweetened beverage intake and time engaged in sedentary behaviours. A positive association was seen between the participants’ overall activity score and being active with their friends, whereas time spent alone was negatively associated with siblings’ adiposity.

Comment: The old adage that you can pick your friends but you can’t pick your parents may have even more importance than we thought! This sibling study with a twist sheds an interesting light on the issue of nature and nurture. Here, the apparent effect of the weight of a best friend had an important impact on weight of an individual over and above the effect of genetics as assessed by comparison with a sibling. This does make intuitive sense, and would suggest that lifestyle interventions to increase physical activity and modify dietary patterns may be more effective if targeted at groups of friends rather than at individuals. Either that or only make friends with slim people! (I can hear the outrage now…).


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Long-term incidence of microvascular disease after bariatric surgery or usual care in patients with obesity, stratified by baseline glycaemic status

Authors: Carlsson LMS et al.

Summary: This post hoc analysis of SOS (Swedish Obese Subjects) study data investigated the effects of bariatric surgery on microvascular complication incidence in participants with obesity stratified according to normal blood glucose level (n=2838), prediabetes (n=591), screen-detected diabetes (n=246) and established diabetes (n=357) at baseline; median follow-up was 19 years. Compared with the SOS control group, bariatric surgery was associated with a lower incidence of microvascular disease (HR 0.56 [95% CI 0.48, 0.66]), with respective unadjusted HRs for participants with baseline prediabetes, screen-detected diabetes, established diabetes and normoglycaemia of 0.18 (0.11, 0.30), 0.39 (0.24, 0.63), 0.54 (0.40, 0.72) and 0.63 (0.48, 0.81) (p=0.0003 for interaction). Bariatric surgery reduced the incidence of microvascular events in individuals with prediabetes at baseline irrespective of whether they went on to develop diabetes.

Comment: A common question I am asked is whether people with type 2 diabetes who undergo bariatric surgery and have ‘resolution’ of their diabetes with no requirement for medication can come off the register for annual laboratory testing. Ban devices from the bedroom! Good luck to those with teenagers associated with important hormonal changes that then may drive appetite and food consumption. The strong signal is the use of mobile technology in the bedroom overnight being associated with increased risk of developing diabetes complications. Until recently we have had very few data to answer that question. This report from the SOS study adds to the information, although I am curious about the classification system used to define baseline glycaemic status. Nevertheless, two things are clear. First, bariatric surgery and associated improvements in glucose metabolism reduce the risk of microvascular complications. Second, despite this, these complications do still occur. Therefore people with existing diabetes at the time of surgery should continue to have screening for these after successful weight loss. Furthermore, these data also support the current focus on prevention of diabetes in those with prediabetes.


Sleep duration and obesity in children

Authors: Li L et al.

Summary: This was a systematic review and meta-analysis of twelve prospective cohort studies in fifteen distinct populations reporting relevant data on the association between sleep duration and obesity in children. A significant association was evident between short sleep duration and obesity (relative risk 1.45 [95% CI 1.14, 1.85]), and this association remained significant when two cohorts that substantially affected the heterogeneity were excluded (1.30 [1.20, 1.42]) and in subgroup analyses. The association between short sleep duration and obesity (relative risk 1.45 [95% CI 1.14, 1.85]), with respective unadjusted HRs for participants with baseline prediabetes, screen-detected diabetes, established diabetes and normoglycaemia of 0.18 (0.11, 0.30), 0.39 (0.24, 0.63), 0.54 (0.40, 0.72) and 0.63 (0.48, 0.81) (p=0.0003 for interaction). Bariatric surgery reduced the incidence of microvascular events in individuals with prediabetes at baseline irrespective of whether they went on to develop diabetes.

Comment: The association between poor sleep patterns and obesity has been observed in a number of studies. This meta-analysis of sleep duration and obesity in children confirms this. One of the difficulties in this field has been the accuracy of measuring sleep outside of strictly controlled laboratories. However, there is overwhelming consistency in the evidence to date that short sleep has important effects on bodyweight. Exactly why and how remains to be determined, but one strong signal is the use of mobile technology in the bedroom overnight being related to sleep disturbance. There is emerging evidence that disturbed sleep is associated with important hormonal changes that then may drive appetite and food consumption. Ban devices from the bedroom! Good luck to those with teenagers who haven’t had that rule from day 1.


Pathways to reduce diabetic ketoacidosis with new onset type 1 diabetes

Authors: Gunn ER et al., on behalf of the Starbase Diabetes Working Group

Summary: This NZ study evaluated potentially modifiable antecedents of diabetic ketoacidosis in children with new-onset type 1 diabetes. Data for 263 children aged <15 years who presented with new onset type 1 diabetes in 2010–2014 were reviewed; 61% of the children were NZ European, 14% were Māori, 13% were Pacifica and 11% were ‘other’. Diabetic ketoacidosis at presentation was documented for 27% of the patients (31 mild, 20 moderate and 20 severe). Diabetic ketoacidosis was associated with no family history of type 1 diabetes, higher HbA1c levels, self-presenting to secondary care, healthcare professional contacts in the month prior to final presentation and greater deprivation. A <48-hour delay in referral from primary care for laboratory testing was also associated with an increased risk of diabetic ketoacidosis.

Comment: With the incidence of type 1 diabetes increasing, it is important that all healthcare professionals are aware and alert to the potential diagnosis. Early detection can avert the development of ketoacidosis and make the initial presentation and experience for the child and their family considerably less traumatic. These NZ data show that there may be some potential to improve on this. There is scope to improve general population health literacy and suspicion of the diagnosis, which would reduce delays in presentation, but also systematic improvements in health systems to do the same and to reduce delays in laboratory testing once the diagnosis is suspected.

Reference: Pediatr Diabetes; Published online Oct 11, 2016

Abstract

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