News from the Diabetes UK Professional Conference 2021. Part 2

The annual Diabetes UK Professional Conference returned in a virtual format in 2021, having been cancelled the previous year at the beginning of the COVID-19 pandemic. This year, the conference was held from 19th to 30th April, and the three-track multidisciplinary programme took place over lunchtime and late afternoon slots to ensure it offered flexibility for learning opportunities, supported by an on-demand option. In part 2 of this report, Pam Brown highlights key learning points from the conference and their application to practice.

Expert debate: The best way to achieve type 2 diabetes remission

This debate was expertly chaired by Barbara McGowan (Guy's and St Thomas' NHS Foundation Trust, London), who began proceedings by taking a vote, in which 66% of the audience supported intentional weight loss, 19% low-carbohydrate diets and 15% gastric bypass surgery. The speakers then proceeded to make the case for the respective interventions.

Intentional weight loss

Mike Lean (University of Glasgow) began by reminding the audience that having type 2 diabetes shortens life expectancy by a mean of 7 years, but that 15 kg of weight loss in early studies has demonstrated a return to normal life expectancy (Lean et al, 1990). Among people who achieved remission following bariatric surgery, 83% had achieved weight loss of ≥15% (equivalent to 15 kg).

The goal of the DiRECT study was to use a very-low-calorie diet (VLCD) to achieve a 15 kg weight loss, aiming for a diabetes remission rate of at least 22% in the intervention group, who received 12–20 weeks of VLCD soups and shakes containing around 850 kcal/day. The participants were typical of a primary care population with early type 2 diabetes: average age 54 years, BMI 35 kg/m^2, HbA_{1c} 59 mmol/mol, diabetes duration 3 years and not yet on insulin. Remission was defined as HbA_{1c} <48 mmol/mol whilst off all glucose-lowering medication. Remission of type 2 diabetes was achieved in 46% of the intervention group at 1 year and 36% at 2 years.

Amongst those achieving and maintaining >15 kg weight loss, remission rates were 86% and 82% at 1 and 2 years, respectively, and those who lost 10–15 kg also had good outcomes, with remission rates of 62% and 79% at 1 year and 2 years, respectively. Significant reductions were seen in blood pressure, which fell by around 10 mmHg whether people had been on treatment or not, as was recently reported by Leslie et al (2021).

At 24 months, comparing those in the intervention group with controls, weight was on average 8 kg lower; HbA_{1c} was lower, with fewer requiring glucose-lowering medication; blood pressure was lower, with fewer on medication; cardiovascular risk, as calculated using QRISK, was lower; and medical costs were lower and quality of life improved. By 5 years, it is expected that the cost of the intervention will be fully compensated by the cost savings from, for example, medication.

Professor Lean summarised the key study outcomes looking at remission with different dietary/lifestyle interventions, including low- or high-carbohydrate diets. For example, although the Virta study demonstrated impressive weight loss (Athinarayanan et al, 2019), it did not have a control arm and participants were encouraged to continue with metformin, so they could not be said to be truly in remission. Other nutritionally complete diets, using local ingredients, at no cost, have been used to assist with weight loss and could potentially help achieve remission (e.g. the Nepali Diet or the Scottish NoDoubtsDiet), but there is as yet no formal evidence to support this.

Remission in the DiRECT study occurs in those who lose fat from the liver and pancreas, while non-responders do not decrease their ectopic fat. Roy Taylor and colleagues published an elegant study in 2020, which demonstrated that the shape, size and function of the pancreas returns to normal by 24 months in those who achieve remission (Al-Mrabeh et al, 2020).

Professor Lean concluded that it is ideal to encourage self-help with the patient's choice of diet first, then to follow with a more structured programme of intentional weight loss with full team support, such as was used in the DiRECT study, if remission is not achieved, as this has no short- or long-term side effects yet is capable of achieving significant remission rates. If further weight loss is needed, a glucagon-like peptide-1 receptor agonist (GLP-1 RA) or referral for bariatric surgery could be considered.

Low-carbohydrate diets

Nicola Guess (University of Westminster, London) began by agreeing with Professor Lean that bariatric surgery is the number one way to achieve diabetes remission; therefore, she would not argue that low-carbohydrate diets are the only way to achieve remission. However, she sought to demonstrate that, as a replacement for surgery, they are better than other diets in terms of achieving and maintaining remission. She started by defining low- and very-low-carbohydrate diets and reminding the audience that most are high in protein, and that if the carbohydrate level is very low then such diets can also be ketogenic. Low-carb is known to be as good as other food-based approaches in achieving weight loss and diabetes remission. However, she reminded the audience that weight loss is the easy part, and it is weight maintenance which is the challenge.

Dr Guess proposed that the main reason why we should consider low-carb is that it does not just have weight-loss and weight-maintenance benefits, but it also has independent effects, the most important of which is that low-carb diets may help people regain their first-phase insulin response. She described how dietary amino acids are a potent stimulus for insulin secretion from the pancreas, and this can be demonstrated even in long-standing type 2 diabetes, when the beta-cells are no longer capable of responding to glucose stimulation.

Whatever method of weight loss used, it is vital to minimise the pathophysiological processes which led to type 2 diabetes in the first place. Dr Guess highlighted that some of the achievements with a VLCD, such as decreasing liver fat and maintaining weight loss, can also be achieved with a low-carb diet. Maintaining glucose levels as low as possible may not only protect the beta-cells in the short term but may also assist in achieving long-term remission, as can be achieved using short-term insulin to achieve near-normal glucose levels.

High-quality studies have shown that a ketogenic, very-low-carbohydrate diet can result in 95% of people with type 2 diabetes eliminating or reducing their medication, compared to only 62% with a higher-carb diet, and other studies have demonstrated significant reductions in insulin requirements. Although limited by the fact that participants stayed on metformin, a lack of randomisation and the fact that remission rates were lower than in DiRECT, the Virta study demonstrated that people could significantly reduce their medications, and that this effect was maintained at 2 years (Athinarayanan et al, 2019). Perhaps most exciting is that people in this study needed less insulin at 2 years than at 1 year.

Dr Guess concluded by reminding the audience that a low-carb diet helps address the underlying pathophysiology of type 2 diabetes and does not just rely on weight loss, but lowers liver fat and promotes a robust insulin response, and for these reasons could offer hope even for people who have type 2 diabetes of longer duration than those in the DiRECT study, as well as being useful after bariatric surgery.

Bariatric surgery

Carel le Roux (Imperial College London) began by reminding the audience of Sisyphus, who spent his afterlife pushing a boulder to the top of a hill, only for it to roll down before he had to push it back up again – this is exactly what our patients with obesity tell us about their weight loss efforts. Surgery in effect removes the repeated effort and should therefore be recognised as the best way to achieve weight loss and type 2 diabetes remission. Although people do not need to choose surgery and many will choose to try diets and medication first, surgery remains the option against which all others should be compared. Throughout his talk, Professor le Roux reminded the audience that there are many ways to achieve remission, and that we need more dietary, medical and surgical options which can make remission happen.

Do we want to practice "eminence-based medicine" or evidence-based medicine? If the latter, then there is not a single randomised controlled trial which has shown that non-surgical approaches achieve higher remission rates than surgery. Thirteen randomised controlled trials have compared surgical outcomes with those achieved in the best medical treatment trials and, however good the drugs or diets, whatever the ages of the patients and whether their BMIs are below or above 35 kg/m^2, surgery has achieved the highest remission rates.

Optimising quality of life (QoL) and minimising complications from diabetes is important and, according to recent studies, surgery significantly outperforms medical treatment for both these parameters at 10 years (Mingrone et al, 2021). It is hardly surprising that 90% of people have improved QoL given that their diabetes complications decrease so significantly and they are functionally much improved.

The MOMS (Microvascular Outcomes after Metabolic Surgery) trial compared medication or surgery plus medication, looking at the impact on urinary albumin:creatinine ratio and chronic kidney disease (CKD) outcomes (Cohen et al, 2020). More than 80% of people in the gastric bypass group had remission of their CKD, as well as significant weight loss and high rates of diabetes remission.

Exploring the weight loss and remission benefits of surgery, Professor le Roux highlighted that GLP-1 levels postprandially are three times higher after surgery than before, with significant changes also in levels of other gut hormones, as well as changes in bile acid levels and the microbiome which may all contribute to improved health. Insulin needs decrease rapidly immediately after

surgery – unlike during the postoperative period for other types of surgery – again confirming this is not all about weight loss.

Surgery should be seen as having a scattergun approach, whereby it impacts so many different mechanisms to achieve not just weight loss but also diabetes remission. So although we need more and better drugs and diets, we also need to ensure that more surgery happens as services recover from the pandemic.

Finally, Professor le Roux explored mortality benefits, which are considerable. Overall, 60–80% of those undergoing surgery will achieve remission at 1 year, whereas for medication or diet the rate is much lower: around 20%, which is not good enough. Although surgery has high up-front costs, it provides long-term benefits such as 30% weight loss maintained for 10 years. This is significant. Although we have excellent new drugs for obesity, over a 10-year window surgery still outperforms medication; 50% of patients are in remission at 10 years in the long-term studies, compared with only 25% of those treated with medication. However, he concluded, the most important option is to understand how we can combine the different options for most impact.

In their opening and summing-up statements, all three speakers were broadly in agreement that there is a place for diets, drugs and surgery to achieve type 2 diabetes remission, and that people should be supported to choose where they want to start. Combinations of drugs, diets and surgery are likely to offer the best benefits in terms of diabetes remission, reduction of complications and improved mortality. There should be increased discussion of surgery as an option.

In the post-debate vote, intentional weight loss attracted 54% of the votes (down from 66%), low-carbohydrate diets 18% (down slightly from 19%), and bypass surgery 28% (up from 15%).

Dorothy Hodgkin Lecture: Genes, drugs and diabetes

Although the Dorothy Hodgkin lecture focuses on basic science, Ewan Pearson's presentation was very relevant to primary care, as it shed new light on the mechanisms of action of commonly used drug classes. Professor Pearson (University of Dundee) focused on insights from genetics to help answer three key questions regarding commonly prescribed medications:

- How does metformin work?
- How do sulfonylureas work and are we using them correctly?
- Why is glycaemic response variable with GLP-1 RAs?

Metformin

Metformin's mode of action was previously thought to only involve a reduction in hepatic glucose production. Professor Pearson highlighted that the mechanisms underlying the benefits on glucose metabolism and effects on diabetes-related complications are complex and still not fully understood. Around 8% of people have a genetic variant which results in no uptake of metformin into the liver, yet these people continue to benefit from the glucose-lowering effects of the drug. Recent evidence demonstrates that only doses of ≥2.5 g of metformin reduce glucose output by the liver (Natali and Ferrannini, 2006). Furthermore, in those with new-onset type 2 diabetes, metformin does not decrease liver glucose production and may increase it (Gormsen et al, 2019), yet this is when the drug is most commonly initiated, with good glucose-lowering efficacy.

Recent studies demonstrate that effects of metformin in the gut may be significant (Rena et al, 2017), not only in triggering gastrointestinal side effects but also in achieving beneficial metabolic effects. Changes to the microbiome seen in those with type 2 diabetes may be related to metformin rather than the underlying disease.

More recent evidence suggests other beneficial effects of metformin on the heart, kidney, brain and nervous system, which may be mediated via lactate production and utilisation at lower levels than would be seen in the lactic acidosis which occurs very rarely with metformin use (Giaccari et al, 2021).

Professor Pearson concluded that metformin is a complex drug which works not only in the liver to decrease glucose production but also has multiple other sites of action, including the gut, where it increases glucose utilisation, increases GLP-1 levels and alters the microbiome.

Sulfonylureas

Sulfonylureas (SUs) have been available since the 1940s but are falling out of favour due to hypoglycaemia, weight gain, lack of durable effects and lack of cardiovascular benefit (and the misbelief that they increase cardiovascular risk). They work by closing the potassium ATP (K_{ATP}) channel, activating the triggering pathway on beta-cells, resulting in insulin secretion. Studies in people with K_{ATP} mutations causing neonatal diabetes have demonstrated that these people do not experience severe hypoglycaemia on SU treatment despite tight glycaemic control.

This led Professor Pearson and his team to explore whether this could be extrapolated to people without the variant. In those with normal K_{ATP} channels, standard-dose SUs cause complete channel closure, which in turn results in insulin secretion occurring even when glucose levels are low. However, low-dose gliclazide (20 mg) lowers glucose by augmenting insulin secretion via a glucose-dependent mechanism, including an incretin effect. Low-dose gliclazide has been demonstrated to lower glucose more than sitagliptin, and continuous glucose monitoring has confirmed that it does not increase hypoglycaemia when used alone or when combined with a dipeptidyl peptidase-4 inihibitor. However, it works

better in men than in women, and in the non-obese.

Dr Pearson shared unpublished data from a population-based study of ambulance call-outs for severe hypoglycaemia in his area between 2008 and 2016, which demonstrated that gliclazide MR 30 mg had only 9% of the call-out rates of glibenclamide (the SU with the highest rates of severe hypoglycaemia), compared to 42% with standard gliclazide 80 mg.

Professor Pearson therefore advocated that SUs have historically been used at too high a dose, causing harm. Low-dose SUs, (including gliclazide MR 30 mg or lower) are cheap, effective drugs and at this dose cause minimal hypoglycaemia, so if we have to use an SU then this should be our first choice. This represents a significant difference in prescribing from current practice. When using low-dose SUs, we should be aware that they are not as effective in females or those with obesity, but the mechanism for these differences in effects is unclear. Normal doses of SUs also work better in men than in women, which has been recognised only recently, although it could be seen when previous clinical trials were re-analysed. It is not clear why this was not identified earlier.

GLP-1 RAs

It has long been recognised that the response to GLP-1 RAs is highly variable between individuals, with some people being termed "non-responders". GLP-1 receptor and *ARRB1* genetic variants have been identified which influence the glucose-lowering effects of GLP-1 RAs in different individuals. For example, one *ARRB1* variant results in GLP-1 RA recycling to the beta-cell membrane, which in turn results in increased glucose-lowering effects. It is not yet known how these variants impact the cardiovascular benefits of GLP-1 RA drugs, and work is ongoing to explore this further.

Professor Pearson concluded that within his laboratory and collaborations, information from exploration of genetics has been used to good effect in clarifying some of the important questions in relation to commonly used drugs, but ongoing work is required to fully understand many of these mechanisms.

Type 1 diabetes and disordered eating (T1DE)

This session introduced the concept of type 1 diabetes and disordered eating (T1DE), including anorexia, bulimia, binge eating disorder and insulin omission to reduce weight. T1DE is not yet recognised as either a medical or a psychological disorder. However, while the term "diabulimia" is more widely used, it is insufficient to describe the wide array of phenotypes and clinical presentations of type 1 diabetes-associated disordered eating.

Outlining the work of the NHS England-funded ComPASSION (Combined Pathway for Assessment and Support for the Syndrome of Insulin OmissioN) project, Carla Figueiredo and Nicola Stacey (Dorset Healthcare NHS Trust and Royal Bournemouth Hospital) provided a working definition to diagnose T1DE (*Box 1*). They went on to describe the work of the ComPASSION project in creating multispecialist teams using joined-up working between diabetes and eating disorder multidisciplinary teams.

Marietta Stadler (King's College London) spoke about the STEADY (Safe management of people with Type 1 diabetes and EAting Disorder studY) programme to develop novel interventions for people with T1DE. To date there is no evidence-based intervention to improve glycaemic control in this population.

Through a collaboration between people with type 1 diabetes, healthcare professionals, psychologists and dietitians, the STEADY team has developed a toolkit that draws on cognitive behavioural therapy and diabetes education, and which can be tailored to the needs of individual patients (Poster P238). As a next step, the toolkit will be tested in a feasibility randomised control trial to compare it with standard care and to refine it.

Conducting difficult diabetes consultations

Marilyn Ritholz (Joslin Diabetes Center, Boston, MA, USA) outlined the latest research on the interactions between healthcare professionals and people with diabetes, paying particular attention to the difficult task of explaining the need to

Box 1. Working diagnosis of type 1 diabetes and disordered eating (T1DE).

People with type 1 diabetes who present with all three of these criteria:

1. Disturbance in the way in which one's body weight or shape is experienced, or intense fear of gaining weight or becoming overweight (note: T1DE typically occurs in people with a normal BMI).
2. Recurrent inappropriate restriction of insulin, either directly or indirectly (the latter meaning reduced insulin need or use due to dietary restriction), and/or other compensatory behaviour (self-induced vomiting, laxative use, dietary restriction or excessive exercise) in order to prevent weight gain.
3. Insulin restriction, eating or compensatory behaviours that cause at least one of the following:
   - Harm to health.
   - Clinically significant diabetes distress.
   - Impairment in areas of functioning.

prevent microvascular complications such as retinopathy and renal disease. The key implications for practice were:

- Conduct individualised and compassionate conversations that include thorough and complete information and specific self-care guidance.
- Avoid messages of fear, blame and judgement, and do not use scare tactics.
- Find the right balance of being open and honest but also providing hope that complications can be avoided with successful self-care.
- Promote active self-care as soon as possible after diagnosis, but taking into account the individual's (or their family's in the case of children and young people) capacity to handle simple versus complex information.
- Inquire about and address the individual's social and emotional needs.

Circadian rhythms and type 2 diabetes

The gene–environment interactions that affect the risk of obesity and type 2 diabetes are complex. There is evidence that timing of exercise and dietary interventions may have a significant impact on potential benefits, and it has been postulated that synchronising exercise and dietary interventions to the body's circadian clock could be beneficial. Juleen Zierath (Karolinska Institutet, Stockholm) reviewed the latest evidence on the body clock and type 2 diabetes, and the effects of exercise and meal timings on metabolic health.

Exercise timing and glycaemia

Is there an optimal time of day to exercise to improve insulin sensitivity and blood glucose control in people with type 2 diabetes? Using continuous blood glucose monitoring, Savikj et al (2019) found that men with type 2 diabetes had improvements in blood glucose if they undertook a high-intensity exercise session in the afternoon, whereas the same session undertaken in the morning increased blood glucose levels. There appeared to be a metabolic memory effect, as these effects on glucose persisted up to 24 hours later, on rest days. Muscle biopsies taken 36–48 hours after the last bout of training demonstrate that increased insulin sensitivity persists for 24 hours. The time of day appears to amplify the metabolic impact of exercise training, so timing of exercise may prove to be a valuable therapy for people with metabolic disorders (Sato et al, 2019).

Professor Zierath concluded that exercise training improves insulin sensitivity in muscle, even in those with type 2 diabetes, and is therefore a positive benefit at any time of day. However, timing of the exercise rewires different metabolic pathways and systemic energy effects, and thus exercise may be more effective in the early afternoon.

Time-restricted eating and glycaemia

Satchidananda Panda (Salk Institute for Biological Studies, San Diego, CA, USA) answered questions on the effects of meal timing on circadian rhythms and health. Studies of time-restricted eating (TRE), in which meals were either confined to an 8-hour period (no eating before 10 AM or after 6 PM) or to a 15-hour period (7 AM to 10 PM), revealed that TRE reduced nocturnal glucose levels and improved insulin profiles throughout the day in overweight and obese men (Parr et al, 2020). TRE alters lipid and amino acid rhythms but does not change the expression of genes underlying the circadian clock (Lundell et al, 2020). In those with type 2 diabetes, the mechanisms may relate to changes in the inner mitochondrial membranes.

Is there an effect of TRE on weight loss and the weight set point? All the studies have been small to date, so it is premature to answer that. Effects may be different in men and women, and between pre- and post-menopausal women. Women appear to achieve metabolic benefits, with improved blood pressure and blood glucose, but some do not lose weight with TRE. Many lifestyle intervention studies have focused on weight reduction, and many of the health outcomes observed are linked to weight loss. However, in many TRE studies, health benefits are often disproportionate to weight loss, and some benefits of TRE (e.g. on hypertension) occur without weight loss. Therefore, when looking at TRE, it may be better to focus on other health outcomes rather than weight loss.

There have been few studies exploring TRE beyond one year. What is clear is that if a person is allowed to select their 10-hour eating window, they are more likely to sustain the habit, due to improvements in sleep, gut health and energy levels. The benefit of TRE over calorie restriction is that there is no sense of deprivation.

The question was raised whether TRE could slow one's metabolism by, for example, skipping breakfast. By definition, the first meal of the day is "breakfast", and currently there are no data to support a slowing of metabolism. However, as yet there has been too little research in humans to draw firm conclusions.

Professor Panda finished by pointing out that timed exercise or timed eating interventions could have a greater effect than a single medication, and that the effects are independent of ethnicity, gender and income level.

Age, gender and ethnicity barriers to FreeStyle Libre access

Analysis of the FreeStyle Libre audit conducted by the Association of British Clinical Diabetologists suggests that, among people with type 1 diabetes, older people, men and people of non-white ethnicity are less likely to be using the

flash glucose monitoring device than their counterparts (Poster P211).

Compared with the type 1 diabetes population in the National Diabetes Audit (NDA), in the Libre audit, men were significantly under-represented (48.1% vs 56.5% in the NDA), as were black people (0.2% vs 2.7%) and Asian people (2.0% vs 4.3%). People with a shorter diabetes duration and those over 60 years of age were also under-represented.

As uptake of the Libre audit is not uniform across the country, it is possible that these findings merely reflect regional variation in type 1 diabetes populations; however, it seems likely that these groups face barriers to taking up flash monitoring. Given the potential impact on glycaemia, hospitalisation and diabetes distress that the technology has, it is important to overcome these barriers. ■

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