Highlights from the 2021 EASD Annual Meeting. Part 2

The *57th European Association for the Study of Diabetes Annual Meeting* was held from 27 September to 1 October. The EASD virtual meeting again provided a platform for experts to showcase the latest developments in the diabetes field. In the second of our two-part coverage, we summarise more of the key presentations from a primary care perspective.

Care of people with diabetes post COVID-19 in primary care

Both people with diabetes and delivery of diabetes care have suffered during the COVID-19 pandemic, and it is now time to take action to clear the backlog and prioritise care for those who need it most, highlighted Professor Kamlesh Khunti (University of Leicester) in his "Care of people with diabetes post COVID-19 in primary care" session at the *57th EASD Annual Meeting*.

Direct impact of COVID-19 on people with diabetes

Of those admitted to hospital with COVID-19, 11–15% had diabetes, often alongside other comorbidities. In those suffering serious consequences from the virus, the two commonest comorbidities were diabetes and hypertension. The combination of diabetes and chronic kidney disease (CKD) was also particularly dangerous, resulting in a 5-times higher risk of severe COVID-19 outcomes than in those without chronic disease.

For those hospitalised with COVID-19, there is significant ongoing morbidity and mortality after discharge back into the community. From a population of 47 780 people hospitalised with COVID-19 compared with matched controls, there was significant increase in new diabetes, new major adverse cardiovascular events, CKD and chronic lung disease (Ayoubkhani et al, 2021). Nearly 30% were re-admitted and an additional 12.3% died.

Several potential mechanisms (K. Khunti, personal communication, 2021) that may contribute to an increased risk of type 2 diabetes following COVID-19 have been postulated. These include stress hyperglycaemia; direct effects of the virus on the pancreas increasing beta-cell dysfunction; pre-existing, but undiagnosed, type 2 diabetes; and treatment with in-hospital steroids. Exact mechanisms remain to be elucidated.

Professor Khunti encouraged the audience to try out the updated QCOVID® validated calculator, which takes into account vaccination status (https://qcovid.org) and can be used to identify those at highest risk of serious consequences from COVID-19 infection, so that people with diabetes and clinicians may be motivated to improve modifiable risk factors, such as poor glycaemic control.

Indirect impact of COVID on people with diabetes

Professor Khunti shared data previously published and presented by other speakers during the EASD conference that demonstrated the size of the impact of the pandemic on delivery of services by primary care. In one study, a 70% decrease in diagnoses of type 2 diabetes in a cohort of 14 million people translated to 40 000 missed or delayed diagnoses (Carr et al, 2021). Testing rates for HbA_{1c} decreased by 77–84% during April 2020, while data from the National Diabetes Audit demonstrated that the number of people receiving all eight care processes fell from 58.5% in the 2019/20 figures to 19.2% from January to September 2020 (NHS Digital, 2020). Primary care, therefore, faces a huge challenge and Professor Khunti warned that the indirect effects of disruption to normal care were likely to be greater and more long-lasting than the direct impacts (hospitalisations and deaths).

Implications for services

Previous studies have demonstrated the impact that a year of delay in achieving tight glycaemic control will have on development and progression of complications, particularly early in the course of disease. This includes a 67% increased risk of myocardial infarction, 64% increased risk of heart failure, 51% increase in stroke and 62% increased risk of a cardiovascular composite of events (Paul et al, 2015). Nephropathy, neuropathy and retinopathy cumulative incident increase by 16%, 8% and 7% respectively.

Significant increases in mental health problems are occurring and, in relation to diabetes, good mental health is a core requirement supporting improved control, and facilitating adherence with medication and self-management, so helping people with mental health problems also needs to be a priority (Forde et al, 2021).

85% of those with diabetes have other significant comorbidities, so it is not just their diabetes care that is likely to have been suboptimal throughout the pandemic, but management of all their chronic diseases. Much can be learned from the short- and long-term impacts

of previous natural disasters, such as earthquakes and hurricanes, on chronic disease, including type 2 diabetes. Even short durations of disrupted care have demonstrated significant consequences for people with diabetes. The COVID-19 pandemic disruption has already lasted much longer than any natural disaster, so the impact on UK health and the people we look after with diabetes is likely to be larger and longer lasting. Shielding and isolation for clinically vulnerable people has had both physical and mental health implications, as has suspension of routine review appointments and redeployment of specialist healthcare staff to deal with acute care, meaning that specialist advice and input to diabetes care has not been possible.

How to move diabetes care forward while the pandemic is ongoing

Professor Khunti reminded primary care teams that they need to both prioritise people for appointments and decide what care they need, so they can be stratified between face-to-face or virtual appointments. Any of the many prioritisation tools, such as the one from the PCDS (Brown and Diggle, 2020), can be used to identify those most at risk of both serious outcomes from COVID-19 and from complications of diabetes, as these people need to be managed early. Likewise, those with a new diagnosis of type 2 diabetes will benefit from being prioritised. Identifying people with multiple risk factors, even if they are in the amber (moderately poorly controlled) rather than the red (severely uncontrolled) group, should lead to an increase in the prioritisation. For example, black and Asian groups, and those with higher BMI, are at risk of higher mortality and serious disease if they develop COVID-19 and are also at risk of rapid progression of their diabetes complications, including cardiovascular risk.

Rises in BMI during the pandemic are well documented, including in those with non-diabetic hyperglycaemia for whom average weights that are 2–3 kg higher than in preceding years have been recorded in populations referred to the NHS Diabetes Prevention Programme (Valabhji et al, 2021).

Clinicians then need to decide, for each individual, whether a face-to-face appointment for data collection and/or blood sampling is needed, or if follow-up can be managed with virtual reviews, which may be a time-efficient way to deliver some diabetes care. For example, those needing foot assessment or with ulceration will need face-to-face review, while those wishing to discuss their mental health or who have had recent data collection may prefer the convenience of a virtual discussion.

For the priority groups, we already have the guidelines we need to improve diabetes care – we just need to implement them again, while remembering that COVID-19 may also leave a significant legacy of new heart disease and other chronic health problems that will complicate diabetes care.

As we move into the COVID and flu booster campaign, tight glycaemic control is also important to optimise the effects of COVID-19 vaccination (Marfella et al, 2021). Although the long-COVID risk is now being quantified, there are, as yet, no data specifically on whether the risk will be influenced by diabetes.

From a primary care perspective, if we paused routine diabetes reviews, we need to restart these as well as encouraging people with diabetes to attend for blood tests and retinopathy screening when these are possible. We need secondary care services up and running to provide support to primary care – including urgent specialist reviews, inpatient diabetes services, pregnancy services, foot-care services and retinopathy screening (Hartmann-Boyce et al, 2020). Professor Khunti finished with a clear call for action – primary care teams need to help people manage their diabetes and tackle their practice backlog as soon as possible, despite other ongoing workload. Although we cannot change the historical impact of the direct effects of COVID-19 in people with diabetes, we have an ongoing, important role in helping people take control of their modifiable risks, and to try to manage the indirect consequences from care delayed or missed during the pandemic. Sadly, the indirect impacts of the pandemic on the care of people with diabetes are likely to be much larger than the direct effects, and will continue to play out on physical and mental health over the next 5 years, at least.

ReTUNE trial: Intensive weight loss can achieve type 2 diabetes remission even in those with a normal BMI

Previously, the landmark DiRECT (Diabetes Remission Clinical Trial) study showed that an intensive weight loss programme delivered by GPs can put type 2 diabetes into remission in people who are overweight. Now, preliminary results from the ReTUNE (Reversal of Type 2 Diabetes upon Normalisation of Energy Intake in the Non-obese) trial indicate that the programme can also reverse the condition in people of normal weight.

Twelve people with type 2 diabetes despite having a normal BMI (<27 kg/m²; mean, 24.5 kg/m²) followed an 800 kcal/day soups-and-shakes diet for two weeks, followed by 4–6 weeks in which they received support to maintain their new weight. They completed up to three rounds of this diet/maintenance cycle until they had lost 10–15% of their body weight. Eight of the 12 participants (67%) achieved type 2 diabetes remission (HbA$_{1c}$ <48 mmol/mol whilst off any diabetes medication). Average weight fell by 8.2 kg (11.9%), while total body fat fell from 33.1% to 27.4%.

The participants were also compared with 11 control subjects without diabetes, matched for age, sex and (post-weight-loss) BMI. Following weight loss, their

levels of body fat, liver and pancreatic fat, and plasma triglycerides had all fallen significantly and were similar or approaching levels seen in the controls.

In the population at large, approximately 10% of people with type 2 diabetes have what is viewed as a healthy BMI. Professor Roy Taylor (Newcastle University), one of the lead authors of the ReTUNE and DiRECT studies, commented: "These results, while preliminary, demonstrate very clearly that diabetes is not caused by obesity but by being too heavy for your own body. It's due to having too much fat in your liver and pancreas, whatever your BMI."

A new focus on obesity management in type 2 and type 1 diabetes

Speaking at the shared EASD/*Lancet* symposium on obesity, Ildiko Lingvay (UT Southwestern Medical Center, Dallas, TX, USA) and colleagues spoke of a need to focus on weight loss of at least 15% as the cornerstone of management for the majority of people with type 2 diabetes. Although managing glycaemia and cardiovascular/renal risk will inevitably be a key part of management also, it was argued that focusing on significant weight loss early would have a cascade of benefits on insulin resistance and subsequent diabetes complications.

The authors argued that data from DiRECT and ReTUNE show that intensive dietary interventions can result in "double-digit" weight loss and even type 2 diabetes remission, and recent advances in drugs with weight-lowering effects mean that this weight loss is now more achievable than previously. Thus, they concluded:

"The time is right to consider the addition of substantial (i.e. double-digit %) weight loss as a principal target for the treatment of many patients with type 2 diabetes. This approach would address the pathophysiology of the disease process for type 2 diabetes; recognise adipose tissue

pathology as a key underlying driver of the continuum of obesity, type 2 diabetes, and cardiovascular disease; and reap metabolic benefits far beyond blood sugar control. Such a change in treatment goals would recognise obesity as a disease with reversible complications and require a shift in clinical care."

Dr Lingvay added, "Healthcare providers, especially those managing people with diabetes routinely, should be trained and become experienced in all aspects of obesity management. Support staff should be trained to support patients through their weight-loss journeys, and practices should consider the need for specialised staff to deliver the educational component of the new treatment strategies that are proposed."

More in-depth discussion of the proposals is available in *Diabetes Distilled* here.

Type 1 diabetes and obesity management

Later in the same symposium, Bart Van der Schueren (University Hospitals Leuven, Belgium) and colleagues argued that we should not forget to address the issue of obesity in people with type 1 diabetes, who are also being hit by the global obesity pandemic; indeed, there is some evidence that obesity rates are growing more quickly in this group than in the general population. Not only are exogenous insulin injections likely to result in more weight gain than normal physiological insulin secretion, but people with type 1 diabetes may often feel the need to consume superfluous calories in order to avoid hypoglycaemia when undertaking certain activities and exercise. Following calorie-restricted diet plans for weight loss may also be more difficult if hypoglycaemia is a concern.

Unfortunately, specific goals and strategies do not yet exist regarding weight management in people with type 1 diabetes. One of the most effective strategies for preventing weight gain has proven to be the provision of

additional nutrition education, which allows for more accurate tailoring of insulin doses to levels that mimic physiological levels. However, resources to provide such education are lacking in many settings. Adjunct therapies, such as metformin, GLP-1 receptor agonists, SGLT2 inhibitors and the amylin analogue pramlintide, may also play a helpful part. However, they can have side effects which must be taken into consideration. Obesity surgery was also discussed; however, while this can massively reduce the complications of obesity in people with type 1 diabetes, it can also increase the risk of hypoglycaemia and substance abuse.

The authors call for more research to get a better grasp of the exact prevalence of the abnormal and/or excessive accumulation of body fat in people living with type 1 diabetes, which eventually leads to overweight and obesity, to understand if and how these processes differ from people in the general population.

Common osteoporosis drug may reduce risk of type 2 diabetes

Data from Denmark suggest that the widely used osteoporosis drug alendronate reduces the risk of developing type 2 diabetes. Alendronate is a bisphosphonate and is used first-line to help strengthen bones and reduce the risk of a fracture in people with osteoporosis.

Dr Rikke Viggers (Aalborg University Hospital, Denmark) conducted a retrospective, case–control study using Danish national registry records and compared 163 588 people with type 2 diabetes and 490 764 matched controls without the condition. Over a 10-year follow-up period, the crude odds ratio (OR) of developing type 2 diabetes after alendronate use was 0.93 (95% confidence interval [CI], 0.90–0.96). After adjustment for other factors associated with type 2 diabetes, including smoking, obesity and steroid therapy, the OR reduced further to 0.64 (95% CI, 0.62–0.66).

The adjusted risk was reduced by 53% in those with more than 8 years of alendronate use, and there was evidence of a dose–response relationship between longer effective use of alendronate and lower risk of type 2 diabetes.

While it is not yet clear how alendronate reduces the risk of developing type 2 diabetes, one hypothesis is that the drug reduces low-grade inflammation and oxidative stress, two processes thought to be central to the development of insulin resistance.

The material has been peer reviewed by the congress selection committee. It has been submitted to a medical journal but the full paper is not yet available.

Almost 4 million HbA$_{1c}$ tests likely to have been missed or delayed during the pandemic

Estimates extrapolated from test sites across the UK suggest that there were 3.9 million fewer HbA$_{1c}$ tests conducted over the first 6 months of the pandemic compared with the average over the same time period in previous years. This includes 2.5 million diagnostic tests, which likely led to 213 000 cases of prediabetes and 68 500 cases of diabetes going undiagnosed.

Among people with pre-existing diabetes, an estimated 1.4 million monitoring tests were missed or delayed, including over 500 000 in people with high blood glucose levels. Results suggest that this delay in monitoring was linked to an average increase in HbA$_{1c}$ of 2–3 mmol/mol. Commenting on the findings, the lead study author, David Holland (Director, The Benchmarking Partnership), said:

"Even now, in September 2021, HbA$_{1c}$ test volumes are only just starting to reach the levels we would typically expect to see. The impact may last well beyond the crisis, potentially creating long-term health repercussions and placing new demands on an already overburdened NHS. The healthcare system urgently needs to find a way to test and review the most at-risk [people with diabetes] before the increased risks they face to their long-term health become a reality."

COVID-19 lockdown associated with differing impacts on type 1 and type 2 diabetes

Data from 33 observational studies (25 studies involving 2881 people with type 1 diabetes, 8 studies involving 1823 people with type 2 diabetes) identified by a systematic search of the literature published in English and German, identified improvements in HbA$_{1c}$ in those with type 1 diabetes and deterioration in those with type 2 diabetes over lockdown.

Lockdown was associated with improved glycaemic control in those with type 1 diabetes. 18 studies of people with type 1 diabetes demonstrated significant improvements in glycaemic control, 4 showed no change and 3 studies demonstrated deterioration. A meta-analysis of the data in those with type 1 diabetes demonstrated a mean HbA$_{1c}$ reduction of 0.05% (0.5 mmol/mol) across 11 of the 25 studies, and 3.75% increased time in range in 11 of the studies (Eberle and Stichling, 2021).

In those with type 2 diabetes, 4 of the 8 studies demonstrated deterioration in glycaemic control during lockdown, with only 2 studies showing some improvement. Overall, there was an average increase in HbA$_{1c}$ of 0.14% (1.5 mmol/mol) over lockdown. Three studies reported non-significant increases in weight and BMI, which the authors attributed to people having developed unhealthy habits, such as increased snacking, more screen time and less activity, during lockdown conditions. Lack of sleep and increased stress and anxiety were also postulated to have contributed.

The authors concluded that the improvements in glycaemic control in those with type 1 diabetes were likely to have been due to positive changes in self-care and availability of digital diabetes management, and that further research is required to better understand what was involved. Likewise, it is important to understand contributing factors for the deterioration in control in those with type 2 diabetes, particularly as this was a smaller group in this study.

In the UK, it appears that many people with type 2 diabetes have gained weight over the last 18 months, including during lockdown, and the weight gain has been associated with deterioration in glycaemia despite maintenance of drug treatment. How much of this is due to the lack of reviews versus the natural history of type 2 diabetes progression is unclear.

The study was presented at the *57th EASD Annual Meeting* and published in *Diabetology & Metabolic Syndrome*. Click here to read the study in full. ∎

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