Highlights from the 59th Annual Meeting of the European Association for the Study of Diabetes

The *59th European Association for the Study of Diabetes Annual Meeting* was held on 2–6 October in Hamburg, Germany. In this brief report, we summarise the key presentations from a primary care perspective.

Worldwide audit shows benefits of testosterone replacement therapy in men with type 2 diabetes

Real-world data from an ongoing international audit of testosterone deficiency in men with type 2 diabetes was presented at the meeting and suggests that testosterone replacement therapy (TRT) improves glycaemic control for up to 2 years.

The audit, led by the Association of British Clinical Diabetologists (ABCD), allows anonymised data input from new and retrospective patients who have commenced on TRT as well as those with testosterone deficiency who are not treated. The aim is to determine the real-world benefits and safety of TRT on symptoms, glycaemic control, obesity and other cardiometabolic risk factors, and on cardiovascular events and diabetes complications. In total, 34 centres in eight countries, including 428 patients (average age 71 years) have so far joined the audit.

The TRT formulations included gels and long-acting injections. The researchers evaluated HbA_{1c} on paired data after 3, 12 and 24 months. Early data demonstrated reductions in HbA_{1c} at all of these time points:

- At 3 months (*N*=81): 4.9 mmol/mol.
- At 12 months (*N*=121): 9.6 mmol/mol.
- At 24 months (*N*=101): 15.4 mmol/mol.

These results were likely to be due to the ongoing effect of testosterone on insulin resistance and fat reduction.

Estimates suggest that around 40% of men with type 2 diabetes have symptomatic testosterone deficiency. Testosterone deficiency is linked with adverse effects on cardiovascular risk factors, osteoporosis and psychological wellbeing, and is associated with double the risk of death in men with type 2 diabetes.

TRT has previously been shown to reduce insulin resistance, HbA_{1c}, cholesterol, obesity and mortality in men with type 2 diabetes and testosterone deficiency. However, many diabetologists are unaware of the association between testosterone and diabetes, and uptake of TRT has been slow in practice due to conflicting findings on cardiovascular risks. A recent multicentre randomised controlled trial on the cardiovascular safety of TRT, however, found no difference in major adverse cardiovascular events between the TRT and placebo groups (Lincoff et al, 2023).

Commenting on the present findings, the study lead, Professor Hugh Jones (Barnsley Hospital), said that the ongoing audit would allow for more and longer-term data to determine which individuals would be likely to respond to TRT. He added that, "These findings will also form the evidence basis for general practitioners and endocrinologists to proactively ask patients with type 2 diabetes about their symptoms and investigate and diagnose testosterone deficiency appropriately and treat them with testosterone where indicated."

Click here to learn more about the ABCD audit.

Tirzepatide effective in people with early-onset type 2 diabetes

The dual GIP/GLP-1 receptor agonist tirzepatide appears to be as effective at treating early-onset type 2 diabetes (EOT2D) as it is at treating type 2 diabetes diagnosed later in life, according to data presented at the meeting.

EOT2D, defined as type 2 diabetes diagnosed before the age of 40 years, has a more aggressive disease course than the later-onset variety; the insulin-producing beta-cells deteriorate more quickly and there is often a lesser response to glucose-lowering drugs in people with EOT2D than in those with later-onset diabetes.

In this *post hoc* analysis, data from the SURPASS programme of phase 3 trials of tirzepatide was used to compare the effect of tirzepatide on glycaemic control, body weight and cardiometabolic markers in people with EOT2D (*N*=873) and later-onset diabetes (*N*=3394) after 40 or 52 weeks of treatment. Despite being younger, those with EOT2D had higher blood glucose, BMI and lipid levels than those with later-onset diabetes.

Tirzepatide was found to be equally effective in young- and later-onset type 2 diabetes, with similar improvements in HbA_{1c} (approximately 25 mmol/mol) and body weight (up to a ~14% reduction from baseline) between the two groups at follow-up. Waist circumference, triglycerides and HDL cholesterol, and systolic blood pressure also improved to similar extents in both groups.

Commenting on the results, the study lead, Professor Melanie Davies (University of Leicester) concluded: "Early-onset type 2 diabetes is not only more aggressive, it usually responds less well to drugs, which means our findings are really encouraging. Further research is now needed to evaluate whether starting treatment with tirzepatide and similar drugs early improves long-term outcomes in this important group."

Dapagliflozin meets primary endpoint in paediatric type 2 diabetes study

Findings from the T2NOW phase 3 trial suggest that dapagliflozin results in clinically meaningful improvements in HbA_{1c} for children and adolescents with type 2 diabetes compared with placebo.

In the 26-week study, children aged 10–17 years with type 2 diabetes and an HbA_{1c} of 48–91 mmol/mol were randomised to receive dapagliflozin (*N*=81), saxagliptin (*N*=88) or placebo (*N*=76). Participants in the active treatment groups with an HbA_{1c} ≥53 mmol/mol at week 12 were further randomised 1:1 at week 14 to continue the dose or up-titrate to a higher dose (10 mg of dapagliflozin or 5 mg of saxagliptin).

At week 26, HbA_{1c} fell by 7 mmol/mol in the dapagliflozin group and by 2 mmol/mol with saxagliptin, and increased by 4 mmol/mol with placebo. Compared with placebo, dapagliflozin significantly reduced HbA_{1c}, whereas the difference did not reach significance when comparing dapagliflozin with placebo.

Safety was evaluated over a total of 52 weeks, and the results were consistent with those seen in adults with type 2 diabetes. The most common adverse event was headache, which occurred in 14.8% of dapagliflozin recipients versus 5.3% of placebo recipients. Most events were mild and none were considered serious or resulted in discontinuation.

Dapagliflozin is not currently licensed for treatment of type 2 diabetes in children and adolescents. Approved therapies in those aged 10 years and over are metformin, insulin and liraglutide.

These results were simultaneously published in *NEJM Evidence*; click here to access.

Metabolically healthy obesity: fact or fiction?

Professor Matthias Blüher (University of Leipzig, Germany) discussed the concept of "metabolically healthy obesity" (MHO) and whether it could truly be defined as healthy.

"Some 15–20% of people living with obesity have none of the metabolic complications we associate with the condition, namely abnormal blood sugar control and blood fats, high blood pressure, type 2 diabetes and other signs of cardiovascular disease," he explained. This absence of risk factors is likely to be a result of where fat is stored, with visceral fat deposition associated with higher metabolic risk than subcutaneous deposition, and of how the fatty tissue behaves, with enlarged adipocytes and inflamed adipose tissue leading to greater risk compared to people with normal-sized adipocytes.

In people with adipose tissue dysfunction, this can lead to damaged tissue, fibrosis, and secretion of proinflammatory and adipogenic molecules that subsequently contribute to end-organ damage. As an example, adipokines (fat-released hormones) may act directly on the cells of the vascular system and lead to atherosclerosis. In addition, metabolites such as fatty acids may impair the function of liver or beta-cells.

On the key question as to whether or not MHO can genuinely be described as healthy, Professor Blüher explained that, compared to people of normal weight with no metabolic comorbidities, people living with obesity but no metabolic comorbidities still have a 50% increased risk of coronary heart disease. He concluded that MHO is a transient phenotype only and that cardiometabolic risk remains increased. In the past, obesity without increased cardiometabolic risk factors has been given a low priority for treatment; however, Professor Blüher argued that timely and personalised treatment for obesity is required to reduce cardiometabolic risk in the future.

New international consensus on DKA and HHS set for imminent publication

An international committee outlined the details of a new, updated consensus report on the diagnosis and management of hyperglycaemic emergencies, including diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS). The new guideline is the joint work of a number of diabetes societies, including the EASD, the American Diabetes Association and the Joint British Diabetes Societies for Inpatient Care (JBDS-IP).

Hyperglycaemia cut-offs for diagnosing DKA have been standardised internationally at ≥11.1 mmol/L, in line with the present JBDS-IP advice. However, in people who already have a diabetes diagnosis, the cut-off has been eliminated entirely, reflecting the increasing recognition of euglycaemic DKA, particularly in people taking SGLT2 inhibitors.

Regarding management, the report includes individual algorithms for management with intravenous fluids, insulin, and potassium, and there is a new emphasis on preventing recurrence and readmission. It calls for close follow-up (including remotely) within 2–4 weeks of discharge, and for consideration of possible causes (including mental health disorders and social determinants of health). It also calls for delivery of "structured" education (causes, problem solving, sick day rules,

insulin dosing and injection technique, ketone testing and glucose monitoring) at discharge. Patients should be provided with an adequate supply of insulin, along with contact information for healthcare professionals who can assist them. Social service professionals can be helpful for patients who lack reliable access.

The document will be published soon.

Risk factors for sudden cardiac arrest in type 2 diabetes

Sudden cardiac arrest (SCA) is responsible for 50% of cardiac mortality and 20% of total mortality in the EU and is twice as common in people with diabetes versus those without the condition; however, it is difficult to predict. Peter Harms (Amsterdam University Medical Centers) presented data from a case–control study designed to identify risk factors for SCA in people with type 2 diabetes.

The authors used data from national primary care and SCA databases in the Netherlands to compare people with type 2 diabetes who experienced SCA and matched individuals with diabetes who did not have an SCA. Analyses revealed a number of factors, all routinely recorded in primary care electronic records databases, that were associated with increased risk of SCA. These were:

- Arrhythmia.
- Use of insulin therapy.
- Use of drugs that prolong QTc interval, including domperidone, macrolides, fluoroquinolones, quetiapine, olanzapine and citalopram.

In people with established cardiovascular disease (CVD), albuminuria (moderate, severe or unknown) and history of heart failure were associated with increased SCA risk. In those without CVD, fasting blood glucose <4.5 mmol/L, systolic blood pressure >180 mmHg, HDL cholesterol <1 mmol/L, LDL cholesterol >2.6 mmol/L, QTc-prolonging antipsychotics and antibiotics were associated with increased risk.

Clinical systems warn of QTc-prolonging effects of medications. These findings raise the question of whether alternative drugs could be used to reduce the risk of SCA.

SURPASS-6: Tirzepatide versus insulin lispro added to basal insulin in type 2 diabetes

Results from the phase 3 SURPASS-6 study suggest that adding weekly tirzepatide leads to superior glycaemic control compared to adding meal-time insulin in people with type 2 diabetes inadequately controlled with basal insulin.

In the open-label study, 1428 adults with a mean HbA_{1c} of 73 mmol/mol and taking daily insulin glargine were randomised to receive once-weekly tirzepatide or prandial thrice-daily insulin lispro. At 52 weeks, the estimated mean reduction in HbA_{1c} from baseline was 23 mmol/mol (2.1%) in the tirzepatide group, compared with 12 mmol/mol (1.1%) with insulin lispro, a significant difference. Furthermore, the tirzepatide group had a mean body weight reduction of 9.0 kg, while the insulin lispro group had an increase of 3.2 kg.

Hypoglycaemia rates were 0.4 per person-year with tirzepatide and 4.4 per person-year with lispro. The most common adverse events with tirzepatide were mild to moderate gastrointestinal symptoms (nausea: 14–26% depending on dose; diarrhoea: 11–15%; vomiting: 5–13%).

The study was simultaneously published in *JAMA*; click here to access.

Diabetes screening in A&E

Emergency department screening could detect thousands of undiagnosed prediabetes and diabetes cases, a study in a UK hospital suggests.

The study included patients visiting the A&E department at Tameside and Glossop Integrated Care NHS Foundation Trust, all without a diabetes diagnosis and selected at random, who were given an HbA_{1c} test at admission. Prediabetes was defined as HbA_{1c} 39–47 mmol/mol (a lower cut-off point than the 42–47 mmol/mol typically used in the UK) and diabetes as HbA_{1c} 48 mmol/mol or higher.

Of the 1388 inpatients screened, 848 (61%) had normal blood glucose levels; however, 420 (30%) were found to have prediabetes (mean HbA_{1c} 41 mmol/mol, mean BMI 28.6 kg/m²) and a further 120 (9%) were diagnosed with type 2 diabetes (mean HbA_{1c} 51 mmol/mol, mean BMI 31.2 kg/m²). People of South Asian and other ethnic-minority backgrounds were twice as likely to be diagnosed with prediabetes or diabetes as Caucasians.

Identifying new cases of diabetes earlier could allow the delay or prevention of diabetes complications, whilst identifying people with prediabetes would allow referral to the NHS Diabetes Prevention Programme (if in England) before the condition fully develops. ■

Lincoff AM et al; TRAVERSE study investigators (2023) Cardiovascular safety of testosterone-replacement therapy. *N Engl J Med* **389**: 107–17

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