Abstract Highlights

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The following highlights showcase key research presented at the European Association for the Study of Diabetes (EASD) Annual Meeting 2025. Featured studies explore innovations across the spectrum of diabetes research, from long-term real-world benefits of hybrid closed-loop systems and genetic insights into maturity onset diabetes of the young, to the predictive value of single glutamate decarboxylase autoantibody (GADA) positivity for disease progression. Other investigations reveal how rare mitochondrial mutations contribute to insulin resistance, the vascular advantages of exercise over pharmacotherapy in weight maintenance, and the distinct metabolic effects of low-carbohydrate diets on hepatic glucose handling. Together, these findings highlight the expanding frontiers of diabetes science and its growing emphasis on personalisation, prevention, and the interplay between genetics, behaviour, and technology.

Long-Term Real-World Data Supports Hybrid Closed-Loop Use in Adults with Type 1 Diabetes

A BELGIAN multi-centre study, presented at EASD 2025, revealed compelling new data on the 24-month outcomes of the Control-IQ system (Tandem Diabetes Care, Inc., San Diego, California, USA) in adults with Type 1 diabetes (T1D). The study showed persistent improvements not only in glycaemic control but also in quality of life and work participation, with over 93% of participants continuing to use the system for 2 years after initiation.[1]

Hybrid closed-loop insulin delivery systems have emerged as transformative tools in the management of T1D, offering automated glucose regulation with reduced patient burden. While RCTs have demonstrated short-term efficacy, long-term real-world evidence remains crucial to understanding the sustained impact of these technologies.

This prospective observational study recruited all adults with T1D who began using Control-IQ between October 2021–December 2022 across 13 diabetes centres in Belgium. Participants underwent routine evaluations every 4 months up to 24 months post-initiation. Glycaemic metrics were collected alongside person-reported outcomes using validated questionnaires, and the incidence of severe hypoglycaemic events and work absenteeism was self-reported. Data were analysed using mean values with SDs or least-squares means with 95% CIs.

Of the 473 adults enrolled, 442 (93.4%) continued Control-IQ for the full 24 months. The cohort had a mean age of 38.5±13.1 years, with 57.3% female, and a mean diabetes duration of 20.0±12.6 years. Time in range (70–180 mg/dL) increased significantly from 58.8% at baseline to 71.0% at 12 months ($p<0.001$) and was maintained at 70.7% at 24 months ($p<0.001$). Improvements in HbA1c, time in tight range (70–140 mg/dL), and reductions in hypo- and hyperglycaemia were sustained throughout. Reported severe hypoglycaemic events dropped from 40.9 to 15.0 events per 100 person-years. Work absenteeism fell from 126 to 69 days per 100 person-years over the same period. Participants also reported sustained reductions in diabetes distress and fear of hypoglycaemia, alongside increased treatment satisfaction.

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These findings highlight the long-term benefits of Control-IQ in routine clinical practice, extending beyond glycaemic metrics to include psychosocial and functional outcomes. Limitations include the observational design, reliance on self-reported data for some endpoints, and the absence of a control group. Nonetheless, the high retention rate and consistency of benefits across multiple domains support the system's enduring value in everyday diabetes care.

Understanding Maturity Onset Diabetes of the Young and Its Clinical Implications

A RECENT study, presented at EASD 2025, explored the prevalence, penetrance, and mortality associated with maturity onset diabetes of the young (MODY) in a population sample of 454,275 individuals from the UK Biobank, providing insights into the broader implications for clinical practice.[2]

MODY is relatively prevalent in the general population and exhibits variable penetrance, with low penetrance genes being more common in non-clinical cohorts. Exome sequencing was performed on 454,275 UK Biobank participants, with a mean age of 57 years, to identify pathogenic variants in 10 known MODY genes. The prevalence of a MODY pathogenic variant was found to be 0.095%, and the prevalence increased to 0.63% among individuals with diabetes. For those diagnosed with diabetes before the age of 30 years, the prevalence rose to 2.13%. The most common MODY gene variants were *GCK* (37.7%), followed by *RFX6* (22.0%), and *HNF4A* (22.0%). Interestingly, variants in low-penetrance genes accounted for 31% of identified cases in the population, though these genes contribute less than 2% in clinical settings. *GCK* variants showed high penetrance, with average HbA1c 8.8 mmol/mol higher than controls, and 94.5% of carriers had prediabetes or diabetes. However, these variants did not increase all-cause mortality (hazard ratio: 0.94; p=0.79). In contrast, non-*GCK* variants showed lower penetrance, with *RFX6*, *HNF4A*, and *HNF1A* having penetrance rates of 12.0%, 32.9%, and 60.6%, respectively, by the age of 60 years. These variants did not increase mortality risk either (hazard ratio: 0.81; p=0.32).

The findings demonstrate that MODY is more prevalent in the general population than previously recognised, with varying penetrance depending on the genetic variant. This highlights the importance of refining screening strategies for MODY, particularly for low-penetrance genes. The lack of increased mortality in individuals with *GCK*-MODY supports the current clinical practice of discontinuing follow-up for these patients, suggesting that ongoing monitoring may be unnecessary for those with this variant. Future research should focus on refining clinical guidelines to incorporate these findings, optimising management for patients with MODY based on genetic aetiology.

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Single Glutamate Decarboxylase Autoantibody Positivity Predicts Diabetes Progression in Adults

A NEW study presented at EASD 2025 has provided new insights into diabetes risk among adults who test positive for glutamate decarboxylase autoantibodies (GADA).[3]

Around 80% of people diagnosed with autoimmune diabetes have detectable autoantibodies, and single GADA positivity is the most common finding in adults at diagnosis. With growing interest in diabetes prevention and immunotherapy, understanding the risk for adults identified as single GADA positive has become increasingly important.

Researchers analysed data from 6,115 adult relatives of people with autoimmune diabetes, with a median follow-up period of nearly 11 years. Among them, 199 individuals (3%) were GADA positive, and 53 of these (27%) developed diabetes during the study period. The risk of diabetes progression varied markedly depending on the number and level of autoantibodies present.

As expected, those with multiple autoantibody positivity were at the highest risk, showing a 41% chance of developing diabetes within 10 years. However, even adults who were single GADA-positive faced a substantially elevated risk compared to those testing negative for autoantibodies (12% versus 2% over 10 years). Importantly, higher GADA levels were found to significantly increase the likelihood of diabetes progression within this group. Participants with GADA levels ≥450 DK U/mL had a 39% 10-year risk, while those with lower levels had only a 9% risk.

> **Overall, being single GADA positive was associated with a sixfold higher 10-year risk of developing diabetes compared with individuals who were autoantibody-negative**

Overall, being single GADA positive was associated with a sixfold higher 10-year risk of developing diabetes compared with individuals who were autoantibody-negative. The study highlights that adults with high GADA levels may have a similar risk profile to those with multiple autoantibody positivity. These findings provide useful evidence for clinicians and researchers designing screening programmes and immunotherapy trials. Adults identified as single GADA positive, particularly those with high antibody levels, may benefit from closer monitoring and could be prioritised for inclusion in Type 1 diabetes prevention studies.

Rare Mitochondrial DNA Mutation Provides New Insight into the Origins of Insulin Resistance

A PIONEERING study presented at EASD 2025 has shed new light on how mitochondrial abnormalities contribute to insulin resistance in humans. The research focused on individuals carrying a rare pathogenic mitochondrial DNA mutation, m.3243A>G, offering a unique human model to dissect the causal role of mitochondria in metabolic disease.[4]

Led by an international team of researchers, the case-control study compared 15 carriers of the m.3243A>G mutation with healthy participants matched for age, sex, and physical activity level. Using advanced physiological and metabolic techniques, including the hyperinsulinaemic-euglycaemic clamp, femoral arteriovenous balance, glucose tracer infusion, and muscle biopsies, the team assessed insulin sensitivity across skeletal muscle, liver, and adipose tissue, as well as β-cell function and mitochondrial integrity.

The results revealed that skeletal muscle insulin sensitivity was 45% lower in carriers of the mutation compared to controls, despite normal liver and adipose tissue insulin sensitivity. This suggests that mitochondrial dysfunction exerts a tissue-specific effect, predominantly impairing muscle glucose uptake. Carriers also exhibited a 65% reduction in β-cell function, indicating that mitochondrial defects may contribute to both insulin resistance and impaired insulin secretion.

Muscle analyses showed reduced mitochondrial content, as evidenced by lower citrate synthase activity, and diminished oxidative phosphorylation capacity per unit of tissue. However, when corrected for mitochondrial abundance, intrinsic mitochondrial function and reactive oxygen species production appeared largely preserved, suggesting that insulin resistance stems from a quantitative rather than qualitative mitochondrial deficit.

These findings point to a direct link between reduced mitochondrial content and skeletal muscle insulin resistance, independent of systemic factors or intrinsic mitochondrial dysfunction. The study team noted that ongoing analyses of plasma and muscle samples will further clarify the molecular pathways involved.

By isolating the mitochondrial contribution to insulin resistance in humans, this research provides critical insight into the pathophysiology of Type 2 diabetes and highlights potential avenues for the development of mitochondria-targeted therapies aimed at restoring metabolic health.

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Exercise Outperforms Glucagon-Like Peptide-1 Agonist in Reducing Atherosclerosis Progression

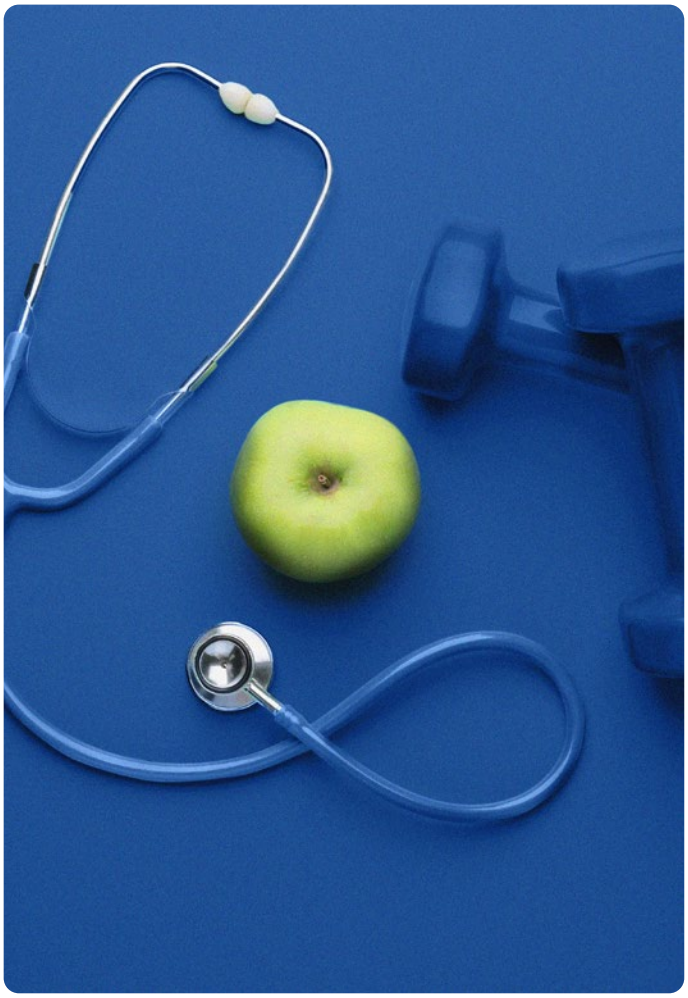
EXERCISE, but not treatment with a glucagon-like peptide-1 (GLP-1) receptor agonist, reduces the development of atherosclerosis during weight loss maintenance in adults with obesity, according to new research presented at EASD 2025.[5]

Obesity is a major contributor to systemic inflammation, endothelial dysfunction, and subsequent atherosclerosis, which remains the leading cause of cardiovascular disease. Whilst weight reduction strategies such as low-calorie diets, pharmacotherapy, and exercise are known to reduce cardiovascular risk, their relative effectiveness in preventing vascular changes after weight loss is not fully understood. Incretin-based therapies, such as GLP-1 receptor agonists, have gained popularity for weight management, but their direct effects on vascular health compared with exercise remain to be clarified.

This randomised, controlled, two-by-two factorial trial enrolled 215 adults with obesity and without diabetes. Following an 8-week low-calorie diet, 195 participants who achieved an average weight loss of 13.1 kg were randomly assigned to 52 weeks of maintenance therapy with exercise and/or the GLP-1 receptor agonist liraglutide 3.0 mg/day, or placebo. Circulating biomarkers of inflammation, including IL-6 and interferon-γ (IFN-γ), and markers of endothelial function (intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion molecule 1 [VCAM-1], and tissue plasminogen activator [tPA]) were measured, along with carotid intima-media thickness as an indicator of atherosclerosis.

Participants in the exercise group demonstrated significant reductions in IL-6 by 21% (95% CI: −34–−10; p=0.012), IFN-γ by 27% (−46–−1; p=0.044), and VCAM by 6% (−12–−0.1; p=0.046). Small but favourable trends were also noted for ICAM (−8%; p=0.058) and tPA (−1.08 ng/mL; p=0.036). Carotid intima-media thickness was reduced by 0.024 mm (−0.044–−0.005; p=0.015) in exercising participants, while no significant vascular or inflammatory changes were observed in those receiving liraglutide.

These findings demonstrate that exercise, but not incretin-based therapy, reduces atherosclerosis development during weight loss maintenance, beyond weight loss alone, improving vascular structure and inflammatory status. In clinical practice, structured exercise should remain a central component of obesity management strategies aimed at preventing atherosclerosis.



New Insights into How Low-Carb Diets Affect Blood Sugar Control

A KEY FINDING in data presented at EASD 2025 showed that a low-carbohydrate diet (LCD) led to a more effective suppression of liver-derived glucose production following a glucose load, independent of weight loss.[6]

The effects of LCDs on weight loss and blood glucose control are well established, but their influence on organ-specific glucose handling remains less clear, particularly when changes in body weight are accounted for. Researchers have now compared an LCD with a Mediterranean-style diet (MED), both energy-matched and mildly hypocaloric, to examine how each affects glucose metabolism at a physiological level in people who are overweight and without diabetes.

In the randomised cross-over study, 20 participants with a BMI over 27 kg/m² (average age: 53.5 years; 55% female) completed two 4-week dietary interventions: an LCD (20% carbohydrate, 50% fat, 30% protein) and an energy-matched MED (50% carbohydrate, 20% fat, 30% protein). Glucose metabolic fluxes were measured using dual-isotope oral glucose tolerance tests after each diet, supported by continuous glucose monitoring and food diary assessments to ensure compliance.

Both diets led to a comparable, modest weight reduction (LCD: −2.8±2.3 kg; MED: −2.7±2.4 kg; p=0.398). However, glucose metabolism differed in key areas. Suppression of endogenous glucose production was significantly greater following LCD compared to MED (area under the curve: 1,437±341 versus 1,553±250 µmol/min/kg x min; p=0.041), indicating improved hepatic insulin sensitivity. Endogenous glucose production adjusted for insulin secretion also favoured LCD (area under the curve: 113±43 versus 125±41 µmol/min/kg x nmol/m² x min; p=0.026). Additionally, glucose absorption was delayed on a LCD, as shown by later time to peak appearance of oral glucose (30±12 versus 21±7 min; p=0.001), although overall absorption was similar (p=0.303). There were no significant differences in peripheral glucose clearance or insulin-adjusted clearance between diets.

These findings suggest that short-term carbohydrate restriction can beneficially alter hepatic and intestinal glucose handling, potentially offering postprandial glycaemic benefits without affecting peripheral insulin sensitivity. In clinical practice, LCDs may be particularly useful in managing glucose profiles in individuals at risk of metabolic disease. However, limitations include the short study duration, small sample size, and lack of longer-term outcomes. Further research is needed to determine whether these effects persist and translate into long-term clinical benefit.

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