Article published online: 2023-01-23

58th EASD Annual Meeting from 19 to 23 September 2022, Stockholm, Sweden (Virtual)

Wiam I. Hussein[1] Mohammed Hassanein[2,3,4]

[1] Department of Diabetes and Endocrinology, Royal Bahrain Hospital, Manama, Bahrain
[2] Department of Diabetes and Endocrinology, Dubai Hospital, Dubai, United Arab Emirates
[3] Department of Medicine, College of Medicine, Gulf Medical University, Ajman, United Arab Emirates
[4] Department of Medicine, College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates
[5] Postgraduate Diabetes Education, Cardiff University, Cardiff, United Kingdom

Address for correspondence Wiam I. Hussein, MD, Department of Diabetes and Endocrinology, Royal Bahrain Hospital, Manama, Bahrain (e-mail: drwiam@outlook.com).

J Diabetes Endocrine Practice 2022;5:126–131.

Abstract

The 58th European Association for the Study of Diabetes (EASD) Annual Meeting was held between 19 and 23 September 2022 in Stockholm, Sweden. It was also fully streamlined online. The authors attended the conference, giving a narrative commentary on what they felt were the highlights of the meeting. Several interesting lectures were presented. The ADA-EASD hyperglycemia management consensus was among the landmark presentations. The development of a particular model that could predict severe hypoglycemia risk in people with type 2 diabetes (T2D) was interesting. The remission of T2D data from the ReTUNE analysis backs the "personal fat threshold" concept was very promising. Interestingly, a link between autoimmunity degree and latent autoimmune diabetes in adults' cardiovascular disease (CVD) risk was proposed. A benefit of high-intensity exercise for people with impaired hypoglycemia awareness was demonstrated. The CLOuD, namely, early and sustained closed-loop therapy does not stave off β-cell decline, data were shared. Also, subjective energy levels were shown to predict CV events in T2D. Also, C-peptide may be better than C-reactive protein for predicting CV risk in T2D. Furthermore, a fatty liver index may predict mortality and CVD risk in people with T1D. New data suggest that topical esmolol hydrochloride might aid in the healing of diabetic foot ulcers. Finally, microalbuminuria in pregnancy forecasts adverse outcomes. We hope this short account helps those who did not attend the conference to get a glimpse of the program.

Keywords
- cardiovascular
- diabetes
- diagnosis
- hypoglycemia
- management

DOI https://doi.org/10.1055/s-0042-1759707.
ISSN 2772-7653.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

The European Association for the Study of Diabetes (EASD) and ADA annual congresses are the most prominent meeting in the world of diabetes. They are prime events to release guidelines and landmark diabetes trials. This year the 58th EASD Annual Meeting was held between 19 and 23 September in Stockholm, Sweden. It was also fully streamlined online. The authors attended the conference, giving a narrative commentary on what they felt were its highlights. We have selected to comment on the following presentation: (a) The ADA-EASD hyperglycemia management consensus was among the landmark presentations. (b) Development of a certain Model could predict severe hypoglycemia risk in people with type 2 diabetes (T2D). (c) Remission of T2D data from the ReTUNE analysis backs the "personal fat threshold" concept. (d) Degree of autoimmunity impacts cardiovascular disease (CVD) risk in latent autoimmune diabetes in adult (LADA), (e) high-intensity exercise may be beneficial for people with impaired hypoglycemia awareness. (f) CLOuD: Early and sustained closed-loop therapy does not stave off β-cell decline. (g) Subjective energy levels predict CV events in T2D. (h) C-peptide may be better than C-reactive protein (CRP) for predicting CV risk in T2D. (i) Fatty liver index (FLI) may predict mortality and CVD risk in people with T1D. (j) Topical esmolol hydrochloride may aid in the healing of diabetic foot ulcers. (k) Microalbuminuria in pregnancy forecasts adverse outcomes

The ADA-EASD Hyperglycemia Management Consensus

The latest update to the ADA and EASD hyperglycemia management consensus report strongly emphasizes holistic, person-centered care for T2D. The experts reviewed 346 references in the manuscript published up to June 2022. Overall, the particular needs of patients with diabetes, such as lowering the risk of first or subsequent CV or renal events, managing high glucose levels, or losing weight, continue to dictate pharmacologic care heavily. The list of alternatives for decreasing blood sugar and losing weight now includes recently approved drugs like tirzepatide. Notably, the statement no longer advises metformin as the standard first-line treatment for T2D, acknowledging that other options would be preferable in cases where there is a pressing need to lower CV and/or renal risk or lose weight. Indeed, upfront combination therapy may be explored for young people with T2D that progresses quickly and has high CV risk, as in the VERIFY experiment. The authors also stress how crucial it is for patients with T2D to change their daily and night physical habits, including taking frequent breaks from prolonged sitting, walking more, and doing resistance training in addition to aerobic activity. Another newly included element is sleep—quality and quantity—in which people's natural chronotypes should be considered.

Communication between people with T2D and healthcare team members is at the core of integrated care. Clinicians need to understand the importance of language. The language used in diabetes treatment should be fact-based, courteous, strengths-based (emphasizing what is working), neutral, and devoid of stigma. It should also promote teamwork and be person-centered. People living with diabetes should not be referred to as "diabetics," described as "noncompliant," or blamed for their health condition.

Averting symptomatic hyperglycemia leads to a significant and long-lasting decrease in microvascular problems. Twenty-five percent fewer in the UK Prospective Diabetes Study with hemoglobin A1c (HbA1c) 7 vs. 7.9%, and 50–76% less in the Diabetes Control Complications Trial with HbA1c 7% vs 9% with the most significant advantage from lowering at higher HbA1c levels.

HbA1c test performance is excellent in accredited laboratories, with limitations in situations affecting red blood cell turnover and in specific racial and ethnic groups. Monitoring of glucose monitoring blood sugar is helpful for T2D to control their condition, especially when taking insulin. People with T2D, especially those using insulin, may find continuous glucose monitoring (CGM) advantageous since it provides additional information.

Model Could Predict Severe Hypoglycemia Risk in People with T2D

In persons with T2D treated with insulin or sulfonylureas, various conditions are linked to an increased risk of severe hypoglycemia. Using these variables, a clinical prediction method that might be used to identify those at high risk was developed.

In Scotland's Tayside and Fife districts, 23,016 persons with T2D treated with insulin or sulfonylureas between 2008 and 2016 were included in the retrospective cohort research. Severe hypoglycemia was more common in people on insulin than those on sulfonylureas, with incidence rates of 17.9 versus 5.5 per 1,000 person-years. When the sulfonylureas were examined independently, individuals taking glibenclamide (13.6 per 1000 person-years) had the highest incidence of severe hypoglycemia, and those taking gliclazide modified release had the lowest incidence (1.66 per 1,000 person-years). For individuals taking glimepiride, gliclazide, or glipizide, the incidence varied from 4.38 to 6.32 per 1,000 person-years. These results imply that sulfonylureas, even at low sustained concentrations, are protective against severe hypoglycemia. After examining risk variables for severe hypoglycemia in people using sulfonylurea, the research team discovered that past episodes of severe hypoglycemia were "a potent predictor of future events," with an incidence rate ratio (IRR) of 1.82. Higher body mass index (BMI), male sex, and use of modified-release gliclazide were significant predictors of reduced risk. In contrast, older age, longer diabetes duration, and lower HbA1c levels were significant predictors of greater risk for severe hypoglycemia among those on sulfonylureas.

On the other hand, men were considerably more likely than women to experience severe hypoglycemia in T2D treated with insulin. Although to a lower extent than those using sulfonylurea, prior severe hypoglycemia was related to a significantly

higher risk in the insulin-treated population (IRR = 1.02). Significant indicators of higher extreme hypoglycemia risk in insulin-treated individuals included older age, longer diabetes duration, and lower HbA1c. Incorporating these variables into a model was done to forecast a person's yearly risk for severe hypoglycemia. Although this clinical prediction tool needs further validation, it could have practical clinical applications in primary and secondary care.

Remission of T2D: ReTUNE Analysis Backs "Personal Fat Threshold" Concept

According to the ReTUNE study, even those who are only marginally overweight can reverse T2D by significantly reducing weight. People with T2D typically have greater body fat regardless of their BMI. Because of this, losing weight is "a valid therapeutic alternative" for those with low BMIs.

ReTUNE sought out individuals with T2D whose BMI ranged from 21 to 27 kg/m2, with 24.8 kg/m^2 being the norm. The average BMI was roughly 35 kg/m2 in the DiRECT experiment, which conclusively demonstrated that T2D might be cured with diet-induced weight loss. As in DiRECT, the ReTUNE participants had a diabetes duration of fewer than 6 years (an average of 2.8 years). The researchers initially recruited 24 participants. The participants undertook 2 to 3 weeks of consuming 800 kcal/day in the form of meal replacements and vegetables, aiming to lose 5% of their starting body weight, followed by 5 to 6 weeks of weight loss maintenance, with this cycle repeated up to three times. Dramatic lowering of HbA1c from an average of 7.1 to 6.4% resulted in remission of T2D in 70% of the patients, with just eight needing all three cycles of weight loss. Over 12 months of follow-up, body weight decreased from an average of 71.8 to 64.1 kg, and BMI decreased from 24.8 to 22.4 kg/m^2. After losing weight, the cohort's average body fat decreased from 32.1 to 27.6%, falling within the range of 20 controls matched for age, sex, and BMI. However, it should be pointed out that only the male participants reached normalization. The average waist circumference decreased dramatically from 90.0 to 79.7 cm, returning to normal in men but not women. Additionally, liver fat decreased from 4.1 to 1.5%, with most reduction occurring after the first cycle of weight loss.

If we evaluate what would be considered a normal liver fat content, the baseline liver fat level does not appear to be increased. However, it was 2.5 times in the controls, similar to the increase reported in those with higher BMIs. Despite having their diabetes under control, participants' visceral fat levels remained "markedly increased" compared with matched controls during magnetic resonance imaging scans.

Degree of Autoimmunity Impacts CVD Risk in LADA

The risk of CVD is higher in people with LADA and high levels of glutamic acid decarboxylase antibodies (GADA) than it is in people with lower levels of autoantibodies, according to research presented at the annual meeting. The population-based study included 521 Swedish participants with newly diagnosed LADA, 1,639 participants with newly diagnosed T2D, and 2,165 participants who were population controls. During a median follow-up of 6 years, 322 participants in the population controls experienced their first CVD event—ischemic heart disease, stroke, or heart failure. When people in the LADA group were categorized according to GADA levels, those with high levels of autoimmunity (GADA $\geq$250 IU/mL) had a significantly elevated risk for CVD relative to population controls (hazard ratio [HR] = 1.67), which was similar in magnitude to the increased risk seen in people with T2D (HR = 1.53 vs controls). On the other hand, people with LADA and low levels of autoimmunity (GADA <250 IU/mL) had a comparable CVD risk to the population controls.

Regardless of the type of diabetes, the percentage of people achieving goal glycated hemoglobin levels of less than 53 mmol/mol (7%) grew significantly following a diabetes diagnosis. However, they then started to fall (with time). It was observed that during the study period, patients with LADA, especially those with a high level of autoimmunity, had worse glycemic control than people with T2D. The researchers analyzed the baseline characteristics of the various diabetes groups. They discovered that those with LADA and high autoimmunity had lower rates of CVD history (6.7 vs. 14.9 and 18.1%, respectively) and insulin resistance than those with common autoimmunity and T2D. Since high autoimmunity and LADA are both associated with raised CVD risk, this association may account for the gradual rise in CVD risk over time. It was found that to "assist with more efficient and customized LADA management," persons with LADA might be divided into two disease trajectory groups depending on GADA levels.

High-Intensity Exercise May Be Beneficial for People with Impaired Hypoglycemia Awareness

Findings from the HIT4HYPOS trial suggest that a high-intensity exercise program may improve hormonal and symptomatic responses to hypoglycemia among people with T1D and impaired awareness of hypoglycemia (IAH). Prior exposure to hypoglycemia is the leading risk factor for IAH, implying that habituation (i.e., a decrease in responsiveness to a stimulus due to repeated exposure) could be a good target for management. Eighteen people with a median age of 27 years, T1D, and indications of recurrent hypoglycemia on flash or continuous glucose monitoring were enrolled in the current study (CGM). After a 4-week run-in period for insulin optimization, participants were randomly assigned to participate in the 4-week exercise program. This comprised three cycling sessions per week to reach an intensity corresponding to at least 90% peak heart rate—alongside real-time (rt) CGM or to receive rtCGM alone. They underwent a 90-minute hyperinsulinemic hypoglycemic clamp at 2.5 mmol/L, with hormonal counterregulatory responses measured before and after the intervention. Compared with those in the control group, participants in the exercise

group exhibited average increases in glucagon levels of 16.2 versus 0.9 ng/L during hypoglycemia.

According to the presentation, the epinephrine response to hypoglycemia in the exercise group "somewhat increased," but there was "little difference" with hypoglycemia in the control arm. In the exercise group, norepinephrine levels were kept steady during hypoglycemia, but they significantly dropped in the control group. According to these results, analysis of symptom awareness as determined by Edinburgh Hypoglycemia Symptom ratings revealed that participants who had engaged in the high-intensity exercise had maintained their awareness of hypoglycemia. However, the control group's awareness significantly decreased.

Although the exact processes by which high-intensity exercise restores hypoglycemia awareness are unknown, it has been hypothesized that they may entail an autonomic nervous system response, increased adrenergic receptor sensitivity, or increased glucagon release from the central nervous system.

Cloud: Early and Sustained Closed-Loop Therapy Does Not Stave Off β-Cell Decline

The drop in young people's C-peptide levels over the following 12 months is not slowed by starting them on closed-loop insulin delivery within 21 days of receiving a T1D diagnosis, according to the CLOuD researchers. After this point, 51 trial participants randomly assigned to receive closed-loop therapy had a geometric mean of 0.35 pmol/mL for the C-peptide area under the curve during a mixed-meal tolerance test. The study demonstrated that the equivalent value in the 46 patients getting standard care and several daily injections were 0.46 pmol/L and did not differ substantially from that in the closed-loop group. The participants began their randomized treatment an average of 9.5 days after diagnosis and ranged in age from 10.0 to 16.9 years (average age 12.0 years, 44% female). By month 12, 10% of those receiving conventional care had begun using an insulin pump, and 57% had switched to intermittently scanned or continuous glucose monitoring.

After 12 months, adolescents in the closed-loop group had an average time in range (70–180 mg/dL; 3.9–10.0 mmol/L) of 64%, which was significantly higher than the 54% achieved in the standard care group. Adolescents in the closed-loop group used the entire system on average for 76% of the time and continuous glucose monitoring for 81%.

C-peptide levels decreased in both groups during the trial period and the whole 24-month follow-up, with no discernible differences. When the analysis was limited to people who used the closed-loop system at least 60% of the time versus those in the standard care group who did not begin insulin pump therapy, there were no differences in C-peptide levels between the groups. It is possible that a more remarkable improvement in glucose control with the attainment of normoglycemia could stop the decline in C-peptide secretion, the researchers note, even though the differences in glycemic control between the two treatment approaches "did not reach the prespecified significance thresholds." It might be too soon to rule out that greater glucose management or approaching normoglycemia might decrease the loss of remaining β-cell activity.

Subjective Energy Levels Predict Cardiovascular Events in T2D

Can a vitality questionnaire help persons with T2D predict major adverse cardiovascular events (MACE)? When all items from the Short Form Surbey-36 quality of life questionnaire were included in the same model, the study discovered that only the item "rarely having much energy" remained significantly related to the risk for MACE. After controlling for variables like age, sex, the length of the patient's diabetes, glycated hemoglobin, blood pressure, and diabetes type, they found three of the four items from the vitality domain and one of the five from the emotional wellbeing domain were related to MACE.

The 756 participants with T2D who participated in the study had a 20 to 30% higher chance of MACE if they gave negative answers to these items. Sixteen percent of these individuals experienced MACE over a median follow-up of 11.6 years. To provide patients with T2D with more predictive data about their risk of CVD and death, the investigators propose that this question be added to any future risk algorithms used in clinical practice for CV risk stratification.

C-Peptide May Be Better Than CRP for Predicting Cardiovascular Risk in T2D

The researchers examined the DD2 Danish cohort of patients with recently diagnosed T2D and no prior history of hospitalization for CV events to examine the relationship between C-peptide and CRP and unfavorable outcomes. C-peptide levels, which show the degree of insulin resistance, were assessed in 5,765 people, while baseline serum high-sensitivity CRP levels were measured in 7,301 people.

After adjusting for potential confounders and C-peptide levels, participants were divided into three groups based on CRP levels. Those in the highest group (CRP >3 mg/L) had a significantly higher risk for CV events during a median follow-up of 4.8 years than those in the lowest group (CRP 1 mg/L), with rates of 5.4 versus 4.4% and a HR of 1.39.

CRP levels were also closely related to mortality risk; an adjusted HR of 2.40 was obtained because 8.2% more participants with the highest CRP levels died throughout the research than did 4.1% of those with the lowest levels.

To evaluate the joint impact of the two biomarkers on the risk for CV events and mortality, they categorized the cohort into four groups according to whether they had high (>3 mg/L) or low (≤ 3 mg/L) CRP levels and high (≥ 1.47 nmol/L) or low (<1.47 nmol/L) C-peptide levels.

When people with low CRP and low C-peptide were used as the reference group, the highest risk for CV events was seen in people with high levels of both biomarkers (HR $= 1.61$). However, people with elevated C-peptide alone (HR $= 1.54$) had a greater risk increase than those with elevated

CRP alone (HR = 1.37). The largest risk increase for all-cause death was likewise observed in individuals with increased CRP and C-peptide (HR = 2.36 vs. those with low levels of both biomarkers). However, persons with elevated CRP alone had a bigger risk increase than those with elevated C-peptide alone (HR = 1.90 vs. 1.15), which is in contrast to the findings for CV events. CRP is a better diagnostic of an increased risk of all-cause death, but C-peptide is a more robust marker of future risk of CVD.

Fatty Liver Index May Predict Mortality and CVD Risk in People with T1D

A higher mortality risk and CVD are linked to hepatic steatosis, as determined by the FLI, among individuals with T2D. Seven-hundred seventy-four patients with T1D (mean age 40 years; 53% men) were studied to determine this association. Of these, 11.6% had an FLI of 60 or higher, suggesting hepatic steatosis, while 66.5% had an FLI below 30, indicating no hepatic steatosis, and the remaining 21.8% had an intermediate FLI. At baseline, there was a significant negative inverse connection between FLI and the estimated glucose disposal rate, pointing to a link between hepatic steatosis and insulin resistance. About 7.4% of the group died during an average follow-up of 11.6 years. With hepatic steatosis, the mortality rate was highest at 22.2%, which dropped to 10.1% in the intermediate FLI group, and was lowest in those without hepatic steatosis at 3.9%.

Regression analysis demonstrated that people with hepatic steatosis had a significant 6.07-fold higher mortality risk than those without. This risk was attenuated to 2.51 to 3.04-fold but remained statistically significant in additional analyses adjusting for prior CVD and CV risk factors and diabetes-related variables included in the Steno Type 1 Risk Engine and EURODIAB Risk Score models.

According to these findings, those with hepatic steatosis had the highest incidence of major CV events during the follow-up period (17.2 vs. 3.5%), while those without did not. Hepatic steatosis was linked to a substantial 5.41-fold higher risk of CV events, which was reduced to a significant 2.25 to 2.98-fold in the analyses with adjustments. The research team noticed a consistent pattern of outcomes for coronary events. Together, these results show that hepatic steatosis is a significant independent predictor of major CV, coronary events, and all-cause mortality in type 1 diabetic group.

Topical Esmolol Hydrochloride May Aid in the Healing of Diabetic Foot Ulcers

The use of esmolol hydrochloride in adults with diabetic foot ulcer may constitute a novel treatment option for diabetic foot ulcers. A phase 3 study comprised people with diabetes from 27 sites in India. They had total thickness, noninfected diabetic foot ulcers that had been present for more than 4 weeks and ranged in size from 2 to 15 cm^2. Esmolol hydrochloride 14% gel plus standard of care was administered to 68 individuals, while the standard of care alone was given to 72. At 60.3 versus 41.7%, with an odds ratio (OR) of 2.12, the proportion of patients receiving full wound closure during the 12-week treatment phase was substantially greater in the esmolol group than in the standard of care group. The 24-week study was completed by 57 participants in the esmolol group and 63 in the standard of care group. Similarly, the proportion of participants who had achieved target ulcer closure at the end of week 24 was significantly higher in the esmolol group than in the standard of care group, at 77.2 versus 55.6% (OR = 2.70). In addition, a subgroup analysis revealed that regardless of the location and size of the ulcer, esmolol was superior to the standard of care group (57 individuals).

Safety-wise, 13.2% of individuals who received esmolol and 18.4% of those who received standard treatment alone (adverse events) occurred adverse events. The bulk of the adverse events ($n = 21$) and all significant adverse events ($n = 1$) in the esmolol arm were unrelated to the drug, showing a favorable safety profile.

Microalbuminuria in Pregnancy Forecasts Adverse Outcomes

Seventy-five of the 191 women in the research cohort who had T1D during their first pregnancy also had microalbuminuria. These women's glycemic control and duration of diabetes were comparable to those with normoalbuminuria at baseline, but when tested during the first trimester, 18.6% versus just 6.8% of the women had retinopathy. Women with baseline microalbuminuria experienced considerably more significant rates of macroalbuminuria and retinopathy throughout the third trimester than those with normoalbuminuria, at 14.6 versus 2.4% and 20.0 versus 8.6%, respectively. In addition, preterm birth rates were substantially higher in women with microalbuminuria than in those without, at 14.6 versus 5.1%, and preeclampsia and perinatal mortality rates were slightly higher (8.0 vs. 1.7% vs 6.6 vs. 0.5%). Their incidences of infant hypoglycemia (10.6 vs. 5.1%) and neonatal respiratory distress syndrome (14.6 vs. 3.4%) were significantly greater.

The pattern of significantly worse outcomes persisted in pregnant women who had microalbuminuria. At 13 years, these women had a retinopathy rate of 50.6%, compared with a normoalbuminuria rate of 14.6%, and a macroalbuminuria rate of 32.0%, compared with a normoalbuminuria rate of 10.3%. Stage 3, 4, and 5 chronic kidney disease were present in 30.6, 38.8, and 18.4% of the women who acquired macroalbuminuria, respectively, while 5.5% required a kidney transplant and 5.5% passed away.

Conclusions

This was a quick resume of the highlights of the EASD congress 2022. We hope it gives a short summary of the event. Furthermore, we hope it stimulates those who missed it to use the on-demand facilities to review the full presentations.

Authors' Contribution
Equal authorship.

Compliance with Ethical Principles
Ethical approval is not required for the conference highlights type of study.

Funding and Sponsorship
None.

Conflict of Interest
None declared.

