HIGHLIGHTS

EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (EASD) 2015 SCIENTIFIC MEETING

Introduction

The recent European Association for the Study of Diabetes (EASD) 51st annual scientific meeting in Stockholm, Sweden, lived up to expectations and was attended by more than 17 000 delegates. It delivered excellent plenary sessions, posters and oral abstracts in addition to industry symposia.

I have selected a few highlights from this conference to share with you. The interpretation of the data is entirely my own and I am happy to discuss or debate any points of disagreement and provide further explanation where it is needed.

KEY MESSAGES

- The SGLT2 inhibitor, empagliflozin, has shown cardiovascular safety in the EMPA-REG study
- Pre-diabetes and the role of adipocytes offer opportunities to understand type 2 diabetes progression
- Adipose tissue signalling from different sites presents new targets for drug development and research

The results of the Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME) in type 2 diabetes mellitus patients

The investigators who presented this much-anticipated trial included B Zinman, S Inzucchi, D Fitchett and JM Lachin and the results were critiqued by HC Gerstein. The EMPA-REG OUTCOME trial was designed to assess the cardiovascular safety in high-cardiovascular-risk type 2 diabetes patients where an SGLT2 inhibitor was combined with standard of care vs placebo added to usual care. Patients were treated at 590 sites in 42 countries, including South Africa; 7 020 patients were randomised into three groups – placebo, empagliflozin 10mg and empagliflozin 25mg.

A summary of this trial, which was published in the New England Journal of Medicine in September 2015, highlights a significant HbA1c reduction in the active group, significant weight loss in the actively treated arm, reduced systolic blood pressure and no tachycardia.

The most significant result was an unexpected benefit with the three-point MACE HR of 0.86, CI 0.76-0.99, \( p = 0.0382 \) accompanied by early divergence of the curves at three months. Even more dramatic was the cardiovascular mortality benefit with a HR of 0.62, CI 0.49-0.77, \( p = 0.0001 \), which translated into a reduction in all-cause mortality of 38%. This was driven by a heart failure reduction of 35%.

There was an increase in urinary tract infections as well as genital infections vs placebo with withdrawals due to side effects, but these were not significantly different from those seen with placebo.
There are many discussion points further to these results being made available, as they surprised even the investigators. Different subgroups will need to be evaluated in respect of a number of questions, e.g. what drove the reduction in heart failure and was it due to a diuretic effect of the SGLT2 inhibitor? The most important question – that of the cardiovascular safety of the highly selective SGLT2 inhibitor, empagliflozin – was answered, however.

Pre-diabetes – the phenotype that will progress

Adipose tissue and the role of the adipocyte in diabetes progression and management were important topics during the congress. Hans-Ulrich Huding presented the lecture on this topic in which he discussed the pre-diabetic phenotype and how to identify those patients who would progress to type 2 diabetes.

The major risk groups include those with gestational diabetes and a family history of diabetes and obesity. In the Tubingen Family Study, his team studied over 3,000 patients, assessing insulin activity and insulin sensitivity in the brain, pancreas, liver, adipose tissue and skeletal muscle. Several genes were identified, specifically those affecting incretin secretion and insulin receptor signalling. Unfortunately, no specific gene could be identified for this ‘at risk’ phenotype.

He went on to discuss different ectopic sites of fat deposition and how we can better understand the metabolically unhealthy visceral fat. Firstly, in the liver, the fat may be benign or malignant depending on the genetic predisposition of the individual. In malignant cases, the lipotoxicity results in dysregulation of hepatokines with lipid-induced insulin resistance via the endogenous ligand of TLR4, a toll-like receptor.2

In the pancreas, ectopic fat in the pre-diabetic individual may result in normal glucose tolerance or impaired glucose tolerance. In the impaired glucose tolerance (IGT) group, a C-peptide based index of insulin secretion shows significant impairment thereof. In these patients, clusters of fat cells are in direct contact with the islets in more than 50% of cases. This finding is associated with macrophage concentration in the islets, which supports the hypothesis that perivascular fat cells express IL-6, IL-8, MCP-1 and other chemo-attractants with an inflammatory reaction that causes beta cell dysfunction. There is therefore crosstalk between the fatty liver and pancreatic fat cells.

The third organ of interest is the brain. There are clearly insulin-sensitive areas in the brain as well as insulin-resistant areas in some obese patients. The fusiform gyrus and frontal areas are involved in object recognition, processing and reward, as well as positive emotion. The hypothalamus is the central regulator of whole-body energy homeostasis and the control of food intake.

The pre-frontal area is concerned with integration of sensory information and inhibits the control of eating. The hippocampus acts as the memory bank. The ectopic deposition of malignant or ‘bad’ fat in these areas affects their functioning and results in dysregulation.

A tantalising possibility is that in utero signals to the foetal brain, in mothers with or without gestational diabetes, may influence later metabolic signals. There are also phenotypes that determine the glycaemic response to lifestyle intervention. This has to do with the efficiency of fuel oxidation, with around 50% responding to exercise by reducing liver fat. However, up to 25% are non-responders in whom exercise does not improve liver fat deposition or bring about any significant weight loss.3

Importance of adipose tissue in diabetes and beyond

In the subsequent Minkowski lecture by Matthias Bluher, University of Leipzig, a certain deficiency of adipose tissue metabolism in patients with lipodystrophy was discussed. In these patients, it is associated with type 2 diabetes and fatty liver, insulin resistance, hypertriglyceridaemia and poor fasting glucose tolerance. The researchers in this field evaluated signals from adipose tissue which regulate multiple processes, e.g. the immune system (immune cell attraction, systemic inflammation and wound healing); the brain (appetite, satiety and energy expenditure);
the vascular bed (blood pressure, endothelial function and heart muscle contractility); the adipose tissue (triglyceride storage, insulin sensitivity glucose and lipid transport, adipokine secretion, differentiation and cell growth, fat distribution and ‘browning’); the liver (insulin sensitivity, lipid accumulation, hepatokine secretion, lipid metabolism and growth factors); the pancreas (insulin secretion, glucagon secretion and insulin sensitivity); skeletal muscle (insulin sensitivity, myokine secretion and lipid storage) and, finally, the gut (resorption, incretin secretion and metabolite absorption).

The complexity of stimulation by adipose tissue makes this an interesting area for research and offers possible targets for treatment and intervention.

**Clinical News**

**Second-line treatment with sulphonylureas compared to DPP-4 inhibitors is associated with risk of cardiovascular disease, all-cause mortality and severe hypoglycaemia**

In a Swedish study of type 2 diabetes patients, second-line treatment with a sulphonylurea compared to a DPP-4 inhibitor was associated with an increased risk of subsequent cardiovascular events, all-cause mortality and severe hypoglycaemia. Ongoing and future randomised trials will be important in elucidating possible causal relationships between treatments and the reported complications.

**Three-year efficacy and safety of exenatide once weekly: a pooled analysis of three trials**

Long-term exenatide once-weekly (QW) treatment improved multiple outcomes in a large, pooled cohort of patients. Exenatide QW was associated with weight loss and a lower risk of hypoglycaemia than the reference insulin glargine treatment, but was accompanied by a higher incidence of gastrointestinal and injection-site events.

**Dapagliflozin modulates SGLT1 and GLUT2 expression and glucagon secretion in a SGLT2-independent manner in murine alpha cells**

Dapagliflozin acutely upregulates SGLT1 and downregulates GLUT2 expression in pancreatic α-cells, while SGLT2 was not detectable in these cells. In addition, glucagon was significantly reduced after long-term (12-hour) treatment with dapagliflozin. These data suggest that the glucagon increase reported in type 2 diabetes patients treated with dapagliflozin does not reflect the direct action of this molecule on pancreatic α-cells.

**EASD virtual meeting available for all**

A useful resource is available at: easdvirtualmeeting.org – it supplies full audio and some slides from oral talks. It also has a search facility.
References


Declaration

Dr Adri Kok’s attendance at this meeting was sponsored by AstraZeneca, which paid for an economy class flight, hotel and registration fees.