Registry-based randomised clinical trials: a remedy for evidence-based diabetes care?

Jan W. Eriksson, Björn Eliasson, Louise Bennet, Johan Sundström

Over recent years, registry-based randomised clinical trials (RRCT) have been used in some clinical conditions, for example within cardiology and orthopaedic surgery. In both type 1 and type 2 diabetes, there are several examples of observational studies based on registries or established cohorts that evaluate treatment effects; however, to date, no RRCTs have been performed. In this issue, Eriksson et al (https://doi.org/10.1007/s00125-022-05762-x) review how pragmatic large-scale clinical trials could be applied in the diabetes area. The authors propose that both academic and industry sponsors should consider this highly cost-effective and robust design for future large-scale diabetes trials. Following allocation to randomised treatment, the participants’ outcome data are collected from established healthcare registries or potentially from other well-defined cohort databases. The authors outline the pros and cons of RRCTs compared with traditional RCTs. The first RRCT in diabetes is briefly described, namely the ongoing SMARTTEST trial, which is evaluating the effects of monotherapy with a sodium–glucose cotransporter 2 (SGLT2) inhibitor vs metformin to prevent macro- and microvascular events and premature death in patients with early-stage type 2 diabetes. The authors conclude that RRCTs in diabetes could enable the rapid recruitment of large cohorts with broad coverage of both geographical and disease subgroups and provide robust endpoint data at very low cost. The figures from this review are available as a downloadable slideset.

Intestinal lipid absorption and transport in type 2 diabetes

Bruno Vergès

The intestine plays an important role in the dyslipidaemia observed in type 2 diabetes and particularly in postprandial hyperlipidaemia, which is known to promote atherosclerosis and increase the incidence of cardiovascular disease. In this issue, Bruno Vergès (https://doi.org/10.1007/s00125-022-05765-8) reviews disorders of intestinal lipid metabolism in type 2 diabetes, which include increased chylomicron production by enterocytes and delayed catabolism of chylomicrons and chylomicron remnants. He outlines how overproduction of chylomicrons is secondary to increased expression of microsomal triglyceride transfer proteins, higher stability and availability of apolipoprotein B-48 and increased de novo lipogenesis. He goes on to discuss how reduced activity of lipoprotein lipase is a major factor responsible for reduced catabolism of chylomicrons in type 2 diabetes. Interestingly, some glucose-lowering treatments significantly influence intestinal lipid metabolism, particularly glucagon-like peptide-1 agonists. Vergès concludes that a better understanding of intestinal lipid metabolism should help to define interesting therapeutic targets for improving postprandial lipid metabolism in type 2 diabetes. The figures from this review are available as a downloadable slideset.
Islet amyloid polypeptide aggregation exerts cytotoxic and proinflammatory effects on the islet vasculature in mice

Joseph J. Castillo, Alfred C. Aplin, Daryl J. Hackney, Meghan F. Hogan, Nathalie Esser, Andrew T. Templin, Rehana Akter, Steven E. Kahn, Daniel P. Raleigh, Sakeneh Zraika, Rebecca L. Hull

Aggregation of islet amyloid polypeptide (IAPP) is a pathologic feature of several forms of diabetes, including type 2 diabetes. Aggregated IAPP accumulates in the islet extracellular matrix between beta cells and the islet vasculature and is well known to be cytotoxic to islet beta cells. However, whether IAPP aggregation is also detrimental to the islet vasculature, an important modulator of beta cell function/survival, has not previously been examined. In this issue, Castillo et al (https://doi.org/10.1007/s00125-022-05756-9) use cell- and animal models to show that IAPP elicits a cytotoxic and pro-inflammatory response from cultured islet microvascular endothelial cells. In pancreases from transgenic mice, the authors found that aggregated IAPP (amyloid deposits) exerts specific, localised effects to increase capillary diameter and increase the number of neuron-glial antigen 2 (NG2)-positive islet pericytal structures. The authors conclude that, together, these findings demonstrate that the islet vasculature is a target of the cytotoxic and proinflammatory effects of IAPP, which is likely to contribute to beta cell failure in diabetes.

Three weeks of time-restricted eating improves glucose homeostasis in adults with type 2 diabetes but does not improve insulin sensitivity: a randomised crossover trial

Charlotte Andriessen, Ciarán E. Fealy, Anna Veelen, Sten M. M. van Beek, Kay H. M. Roumans, Niels J. Connell, Julian Mevenkamp, Esther Moonen-Kornips, Bas Havekes, Vera B. Schrauwen-Hinderling, Joris Hoeks, Patrick Schrauwen

Time-restricted eating (TRE) is a form of intermittent fasting whereby food intake is limited to a pre-defined time window during the day. Previous studies in healthy, overweight/obese adults showed that 6–8 h TRE regimes were successful in improving metabolic health. In this issue, Andriessen et al (https://doi.org/10.1007/s00125-022-05752-z) investigated the effect of a more accessible 10 h TRE intervention in adults with type 2 diabetes. Three weeks of TRE resulted in lower fasting glucose and 24 h glucose levels, as well as more time spent in the normal glucose range as compared with spreading habitual food intake over at least 14 h per day. The study did not find changes in insulin sensitivity, hepatic glycogen or substrate oxidation. The authors conclude that these findings highlight the therapeutic potential of TRE in adults with type 2 diabetes. They recommend that more studies are conducted to investigate the underlying mechanisms and long-term effects of TRE.

Glucose-mediated insulin secretion is improved in FHL2-deficient mice and elevated FHL2 expression in humans is associated with type 2 diabetes

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FHL2, the gene encoding the four and a half LIM domains 2 (FHL2) protein, contains DNA methylation marks, which forensic studies have consistently found to be correlated with the age of an individual. Hypermethylation of these CpG loci causes an increase in FHL2 expression. In this issue, Habibe and Clemente-Olivo et al (https://doi.org/10.1007/s00125-022-05750-1) show that individuals with type 2 diabetes also express higher FHL2 levels in their pancreatic islets compared with healthy individuals. Furthermore, the authors demonstrate that, compared with their wild-type littermates, Fhl2-deficient mice clear glucose faster, whereas insulin sensitivity is similar for both strains of mice. Isolated pancreatic islets from mice that are deficient for Fhl2 show increased glucose-induced insulin secretion, which the authors suggest may be explained, at least partially, by enhanced expression of the glucose-transporter GLUT2. In line with this, FHL2 gain of function is detrimental to insulin secretion of cultured beta cells due to a reduced uptake of glucose and enhanced levels of reactive oxygen species. The authors conclude that inhibition of FHL2 in human transplant islets may improve transplant function in vivo.

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