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Up front

Competition for publication in *Diabetologia* continues to grow, and less than 20% of papers are accepted. Of all the high-quality papers that appear in this month's issue I want to draw your attention to five articles that I think are particularly interesting. The articles are summarised here. Our publisher, Springer, has kindly made the full text of each of these papers freely available.
I hope you enjoy reading them!

Sally M. Marshall, Editor

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PCSK9 inhibition: the dawn of a new age in cholesterol lowering?

David Preiss, Marion Mafham

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating enzyme that plays a key role in the metabolism of LDL-cholesterol. Since the complementary discoveries that individuals with gain-of-function *PCSK9* mutations develop a severe form of familial hypercholesterolaemia while those with diminished PCSK9 have lower LDL-cholesterol levels and a reduced risk of coronary heart disease, various medicines have been developed to reduce PCSK9 levels. In this issue, Preiss and Mafham discuss the biology of PCSK9 and describe the lipid-modifying effects and safety of available PCSK9-lowering agents in individuals with and without diabetes. Monoclonal antibodies to PCSK9 lower circulating LDL-cholesterol by over 50% and are currently being evaluated in major cardiovascular endpoint trials, which will soon report their findings. Alternative modalities such as adnectin-based polypeptides and small interfering RNA are under investigation in earlier phase trials. The review concludes with a discussion of the potential benefit of monoclonal antibodies to PCSK9 and their position in clinical practice in the future.

Detection of enteroviruses in stools precedes islet autoimmunity by several months: possible evidence for slowly operating mechanisms in virus-induced autoimmunity

Hanna Honkanen, Sami Oikarinen, Noora Nurminen, Olli H. Laitinen, Heini Huhtala, Jussi Lehtonen, Tanja Ruokoranta, Minna M. Hankaniemi, Valérie Lecouturier, Jeffrey W. Almond, Sisko Tauriainen, Olli Simell, Jorma Ilonen, Riitta Veijola, Hanna Viskari, Mikael Knip, Heikki Hyöty

Enteroviruses have been found in the pancreatic islets of people with type 1 diabetes and are associated with an increased risk of the disease in epidemiological studies. In this issue, Honkanen et al explore this association in a large cohort of children followed from birth in the prospective Type 1 Diabetes Prediction and Prevention (DIPP) study in Finland. Enterovirus infections were detected by analysing the presence of viral nucleic acids in longitudinal stool samples. Infections were more common in the case group, who developed islet autoantibodies, compared with the control group. This excess of infections occurred several months before islet autoantibodies appeared, at which time case children had three times more infections than control

children. The study supports the concept that enterovirus infections could contribute to the initiation of the beta cell-damaging process. Together with other evidence, this study encourages further exploration of whether some incidences of type 1 diabetes could be preventable by antiviral interventions, such as enterovirus vaccines or antiviral drugs.

Loss of prohormone convertase 2 promotes beta cell dysfunction in a rodent transplant model expressing human pro-islet amyloid polypeptide

Jaques A. Courtade, Evan Y. Wang, Paul Yen, Derek L. Dai, Galina Soukhatcheva, Paul C. Orban, Bruce Verchere

The beta cell peptide islet amyloid polypeptide (IAPP or amylin) forms toxic aggregates in both type 2 diabetes and islet transplants, although the underlying mechanism remains unknown. The IAPP precursor, proIAPP, is processed by prohormone convertases PC1/3 and PC2 in rodent beta cells. In this issue, Courtade et al show, in a mouse model of PC2 deficiency in islet transplantation, that defective beta cell prohormone processing accelerates islet graft failure. Interestingly, lack of PC2 did not accelerate formation of detectable amyloid, leaving open the possibility that precursors of mature IAPP may form toxic oligomeric aggregates. These findings point to a potential mechanism for beta cell loss in type 2 diabetes and islet transplantation, involving defects in proIAPP processing.

Breaking sitting with light activities vs structured exercise: a randomised crossover study demonstrating benefits for glycaemic control and insulin sensitivity in type 2 diabetes

Bernard M. F. M. Duvivier, Nicolaas C. Schaper, Matthijs K. C. Hesselink, Linh van Kan, Nathalie Stienen, Bjorn Winkens, Annemarie Koster, Hans H. C. M. Savelberg

Structured exercise is one of the cornerstones of type 2 diabetes treatment, but adherence to exercise guidelines is frequently poor and the time spent sitting is increasing in modern society. In this issue, Duvivier et al report that breaking sitting time with light activities is a promising alternative to structured exercise in sedentary adults with type 2 diabetes. When energy expenditure was matched, standing and light walking had, after 4 days, the same beneficial effect on 24 h glycaemic control as a daily bout of moderate-to-vigorous intensity cycling. Moreover, insulin sensitivity improved to a greater extent with standing and walking. Hence, decreasing sitting time seems to improve insulin sensitivity independent of energy expenditure. These findings provide further support for recommending less sitting and more light activity in adults with type 2 diabetes. This article is the subject of a commentary in this issue by Dempsey et al.

Empagliflozin decreases myocardial cytoplasmic Na^+ through inhibition of the cardiac Na^+/H^+ exchanger in rats and rabbits

Antonius Baartscheer, Cees A. Schumacher, Rob C. I. Wüst, Jan W. T. Fiolet, Ger J. M. Stienen, Ruben Coronel, Coert J. Zuurbier

The EMPA-REG OUTCOME trial revealed the long-awaited possibility of pharmacologically combatting the cardiovascular complications of type 2 diabetes, reducing cardiovascular death and hospitalisation for heart failure. How the kidney-targeted medicine, empagliflozin, reduced cardiac complications is, however, an enigma, as the molecular target (SGLT2) is absent in heart. It is known, however, that raised cardiac cellular sodium is often an early driver of cardiovascular death and heart failure. In this issue, Baartscheer, Schumacher et al demonstrate that empagliflozin does work directly on cardiac cells in animal models, lowering cellular sodium through inhibition of the Na^+/H^+ exchanger. In addition, they show that hyperglycaemia itself raises cellular sodium and that lowering cellular sodium directly improves mitochondrial activation status. This work suggests that empagliflozin's effects against diabetes, cardiovascular death and heart failure relate to its capacity to combat two important metabolic phenomena in our current society: cellular overload of sodium and glucose. This article is the subject of a commentary in this issue by Vettor et al.