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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 stand out in some regard and are very 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!

Hindrik Mulder, Editor

Patient-reported outcomes for people with diabetes: what and how to measure? A narrative review

Caroline B. Terwee, Petra J. M. Elders, Marieke T. Blom, Joline W. Beulens, Olaf Rolandsson, Alize A. Rogge, Matthias Rose, Nicola Harman, Paula R. Williamson, Frans Pouwer, Lidwine B. Mokkink, Femke Rutters

Patient-reported outcomes (PROs) are important for shared decision making and standardisation of outcomes in research. However, in the field of diabetes, the use of PROs and associated patient-reported outcome measures (PROMs) is heterogeneous. A core outcome set for clinical trials and an International Consortium for Health Outcomes Measurement (ICHOM) standard set for clinical practice have been developed, but they, as well as other initiatives, recommend different PROs and PROMs. Standardisation of relevant outcomes and outcome measures is therefore needed. In this issue, Terwee et al (https://doi.org/10.1007/s00125-023-05926-3) provide recommendations on the selection of relevant PROs and PROMs for use in clinical practice and research in people with diabetes. The figure from this review is available as a downloadable slide

100 years of glucagon and 100 more

Nicolai J. Wewer Albrechtsen, Jens J. Holst, Alan D. Cherrington, Brian Finan, Lise Lotte Gluud, Danielle Dean, Jonathan E. Campbell, Stephen R. Bloom, Tricia M.-M. Tan, Filip K. Knop, Timo D. Müller

More than 100 years ago, scientists were on the path to discovering a central novel metabolic regulator, now known as glucagon. Although the role of glucagon in diabetes has been studied intensively, its place in physiology and pathophysiology is still debated. In this issue, Wewer Albrechtsen et al (https://doi.org/10.1007/s00125-023-05947-y) capture the fundamentals of glucagon biology and its role in metabolic diseases. Key questions on how glucagon secretion is controlled, not only by glucose but also by amino acids and lipids, are addressed. In addition, the authors discuss how a new concept, termed 'glucagon resistance', may explain the diabetogenic hyperglucagonaemia observed in metabolic diseases. The authors propose that future glucagon research may help to uncover the molecular backbone of inter-organ dysfunction in individuals with diabetes and liver disease. They conclude that, as well as treating hypoglycaemia, glucagon-based therapies may also provide benefits for weight loss and the treatment of fatty liver disease. The figures from this review are available as a downloadable slideset

Umbilical cord-derived mesenchymal stromal cells preserve endogenous insulin production in type 1 diabetes: a Phase I/II randomised double-blind placebo-controlled trial

Per-Ola Carlsson, Daniel Espes, Sofia Sisay, Lindsay C. Davies, C. I. Edvard Smith and Mathias G. Svahn

Mesenchymal stromal cells (MSCs) have been shown to modulate the immune system and dampen inflammatory and autoimmune responses in numerous diseases. In this issue, Carlsson et al (https://doi.org/10.1007/s00125-023-05934-3) report their findings from a Phase I/II dose escalation and double-blind placebo-controlled clinical trial investigating

the Wharton's jelly MSC drug product, ProTrans, for the treatment of new-onset type 1 diabetes. In the dose escalation safety study, the authors demonstrate that ProTrans can be safely administered intravenously with no serious adverse events. A fixed dose of 200 million MSCs preserved the production of endogenous insulin and reduced exogenous insulin replacement compared with placebo 1 year after treatment. The authors conclude that a single treatment with ProTrans could potentially delay type 1 diabetes disease progression, thereby reducing the associated complications and improving quality of life.

Inhibition of the type 1 diabetes candidate gene *PTPN2* aggravates TNF-α-induced human beta cell dysfunction and death

Arturo Roca-Rivada, Sandra Marín-Cañas, Maikel L. Colli, Chiara Vinci, Toshiaki Sawatani, Lorella Marselli, Miriam Cnop, Piero Marchetti, Decio L. Eizirik

TNF-α inhibition delays the progression of type 1 diabetes and circulating TNF-α is associated with aggressive forms of the disease. In this issue, Roca-Rivada et al (https://doi.org/10.1007/s00125-023-05908-5) describe the molecular mechanisms triggered by TNF-α that lead to human beta cell dysfunction and death when the type 1 diabetes candidate gene *PTPN2* is silenced. Cells silenced for PTPN2 are more susceptible to the deleterious effect of TNF-α and IFN-α, showing increased beta cell apoptosis. The authors demonstrate that beta cell apoptosis is abolished by the parallel blocking of Bcl-2-like protein 2 (BIM) or c-Jun N-terminal kinase (JNK1), indicating an unexpected common pathway between TNF-α and IFN-α. They further identify JNK1 as a substrate for PTPN2 in beta cells. The authors conclude that people with type 1 diabetes carrying risk-associated *PTPN2* polymorphisms may benefit from therapies that inhibit TNF-α.

Disruption of cortical cell type composition and function underlies diabetes-associated cognitive decline

Karis Little, Aditi Singh, Angel Del Marco, María Llorian-Salvador, Maria Vargas-Soria, Mireia Turch-Anguera, Montse Solé, Noëlle Bakker, Sarah Scullion, Joan X. Comella, Ingeborg Klaassen, Rafael Simó, Monica Garcia-Alloza, Vijay K. Tiwari, Alan W. Stitt, on behalf of the RECOGNISED consortium

People with type-2 diabetes are at higher risk of cognitive decline and dementia; however, the cellular changes that occur in the brain as type 2 diabetes progresses remain poorly understood. In this issue, Little, Singh and Del Marco et al (https://doi.org/10.1007/s00125-023-05935-2) describe using single-cell RNA sequencing to investigate changes to the neurovascular unit (NVU) within the cerebral cortex in a mouse model of type 2 diabetes. The authors identified distinct transcriptional signatures in a number of key neuronal, glial vascular and immune cells, demonstrating that metabolic and inflammatory processes are dysregulated in the cortical glia of diabetic mice. In parallel, they report that neuronal maturation was significantly affected in the type 2 diabetes cortex, with these changes occurring alongside evident cognitive decline and vascular damage. They further demonstrate that post-mortem cortex from individuals with type 2 diabetes showed comparable changes to what was observed in the mouse model. The authors conclude that altered metabolic function, neuroinflammation and changes to neuronal maturation may play an integral role in NVU damage and thus cognitive decline in type 2 diabetes.

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