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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 some 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

Incretins: turning the venom into the antidote

In this issue, we feature a series of reviews that focus on incretin-based therapies. These drugs were developed following the discovery of a peptide, exendin-4, in the Gila monster's venom in the 1990s. Being structurally similar to the incretin hormone glucagon-like peptide-1 (GLP-1), exendin-4 was found to mimic the glucose-regulating effects of incretins. The decades following this discovery have seen the generation of several incretin-based therapies and, in this issue of *Diabetologia*, we are excited to include eight reviews summarising the state-of-the-art knowledge about these agents. Drucker and Holst (https://doi.org/10.1007/s00125-023-05906-7) start by describing the function of GLP-1, namely glucose-dependent potentiation of insulin secretion and glucoregulatory actions, appetite reduction and cardioprotection. Nauck and Müller (https://doi.org/10.1007/s00125-023-05956-x) go on to discuss another incretin hormone: glucose-dependent insulinotropic polypeptide (GIP). GIP was not initially considered an obvious drug candidate; however, a novel drug, tirzepatide, has demonstrated that dual agonism of GLP-1 and GIP receptors produces more substantial reductions in HbA_{1c} and body weight than selective GLP-1 receptor agonists. Tirzepatide is but one example of a novel incretin-based therapy, with this and other advances in incretin pharmacology and drug development being summarised in the review by Tschöp et al (https://doi.org/10.1007/s00125-023-05929-0). These therapies, old and new, not only have therapeutic potential in type 2 diabetes, but also may be beneficial in other types of diabetes. In their review, Mathieu and Ahmadzai (https://doi.org/10.1007/s00125-023-05980-x) discuss the evidence for the beneficial effects of incretin-based therapies in type 1 diabetes, monogenic forms of diabetes and other conditions leading to hyperglycaemia. In terms of diabetic complications, Solini et al (https://doi.org/10.1007/s00125-023-05973-w) delve into the cardiovascular protection offered by incretin-based therapies, while Goldney et al (https://doi.org/10.1007/s00125-023-05988-3) discuss their effects on microvascular complications. Andreasen et al (https://doi.org/10.1007/s00125-023-05966-9) highlight the use of these drugs in the treatment of other metabolic diseases, specifically obesity and non-alcoholic fatty liver disease (NAFLD). Thus, the potential benefits of incretin-based therapies are clearly extensive. In contrast, however, as discussed by Karagiannis et al (https://doi.org/10.1007/s00125-023-05962-z), their uptake is restricted due to socioeconomic factors, such as affordability, accessibility, health literacy and provider bias. To extend their benefits at a societal level, a concerted effort must be made to address these issues. Looking ahead, the future holds great promise for incretin-based therapies to expand the treatment options available for individuals with metabolic disorders, offering new avenues for effective management and improved quality of life. This review set is accompanied by an editorial by Krook and Mulder (https://doi.org/10.1007/s00125-023-05987-4).

SGLT2i and GLP-1 RA therapy in type 1 diabetes and reno-vascular outcomes: a real-world study

Matthew Anson, Sizheng S. Zhao, Philip Austin, Gema H. Ibarburu, Rayaz A. Malik, Uazman Alam

The beneficial extra-glycaemic effects of SGLT2i and GLP-1 RA on weight, renal protection and major adverse

cardiovascular events are well established and make them attractive therapies in type 2 diabetes compared with other more traditional glucose-lowering agents. People with type 1 diabetes share many of the same cardiovascular risk factors as those with type 2 diabetes. Such novel agents are not approved for type 1 diabetes but are still prescribed off-label, with a paucity of robust data underpinning their safety and efficacy in this cohort. In this issue, Anson et al (https://doi.org/10.1007/s00125-023-05975-8) undertake a retrospective analysis of individuals with type 1 diabetes adjunctively treated with either an SGLT2i or a GLP-1 RA, with outcomes analysed 5 years after initiation of therapy. The authors show that individuals treated with an SGLT2i had a reduced risk of developing heart failure and chronic kidney disease and of being hospitalised for any cause compared with those adjunctively treated with a GLP-1 RA, despite an increased risk of diabetic ketoacidosis. They conclude that the findings suggest a net overall benefit of SGLT2i in type 1 diabetes compared with GLP-1 RA therapy and that dedicated long-term randomised trials are warranted to validate these findings.

Strength training is more effective than aerobic exercise for improving glycaemic control and body composition in people with normal-weight type 2 diabetes: a randomised controlled trial

Yukari Kobayashi, Jin Long, Shozen Dan, Neil M. Johannsen, Ruth Talamoa, Sonia Raghuram, Sukyung Chung, Kyla Kent, Marina Basina, Cynthia Lamendola, Francois Haddad, Mary B. Leonard, Timothy S. Church, Latha Palaniappan

Previous studies in people with overweight/obesity and type 2 diabetes have shown that a combination of aerobic and resistance training is superior to either type of exercise alone for lowering HbA_{1c} levels. In this issue, Kobayashi et al (https://doi.org/10.1007/s00125-023-05958-9) describe the STRONG-D study, which aimed to determine the impact of different exercise regimens on glycaemic control in people with 'normal-weight type 2 diabetes' (BMI <25 kg/m²). The study compared strength training alone, aerobic training alone, and combined strength and aerobic training. In contrast to previous trials in individuals with overweight/obesity, the authors show that strength training alone was more effective at reducing HbA_{1c} levels than aerobic training alone, with combination training showing intermediate effects. The authors highlight that increased lean mass relative to fat mass, observed only in the strength training group, independently predicted lower HbA_{1c} levels. The authors emphasise the significance of strength training for managing type 2 diabetes in normal-weight individuals and highlight the importance of considering body composition in exercise recommendations for this population. They conclude that these findings could contribute to personalised care for different diabetes phenotypes.

Hyperglucagonaemia in diabetes: altered amino acid metabolism triggers mTORC1 activation, which drives glucagon production

Yael Riahi, Aviram Kogot-Levin, Liat Kadosh, Bella Agranovich, Assaf Malka, Michael Assa, Ron Piran, Dana Avrahami, Benjamin Glaser, Eyal Gottlieb, Fields Jackson III, Erol Cerasi, Ernesto Bernal-Mizrachi, Aharon Helman, Gil Leibowitz

Diabetes is characterised by hyperglucagonemia as well as insulin deficiency, making it a dual hormone disease; however, the mechanisms involved in alpha cell dysfunction are unclear. In this issue, Riahi et al (https://doi.org/10.1007/s00125-023-05967-8) highlight the nutrient sensor mammalian target of rapamycin complex 1 (mTORC1) as a key player in diabetes-related hyperglucagonemia. They show that mTORC1 activity was increased in alpha cells from type 1 and type 2 diabetes models, and its inhibition by inducible *Rptor* knockout in alpha cells from a type 1 diabetes model dampened glucagon secretion and ameliorated diabetes. Metabolomics, metabolic flux and gene expression studies revealed that alpha cell exposure to hyperglycaemia enhanced glucose-derived amino acid synthesis and transport, culminating in increased glutamate, branched-chain amino acid and methionine cycle activity, all contributing to stimulation of mTORC1 activation. The authors highlight that prolonged high glucose exposure therefore alters amino acid metabolism, which may drive persistent mTORC1 activation and subsequent excessive glucagon secretion. They conclude that early normalisation of blood glucose levels is crucial to prevent alpha cell dysfunction in diabetes and suggest targeting nutrient(s) metabolism and mTORC1 signalling in alpha cells as an appealing avenue for diabetes treatment.