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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 four 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

Epidemiology of heart failure in diabetes: a disease in disguise

Anna G. Hoek, Elisa Dal Canto, Eva Wenker, Navin Bindraban, M. Louis Handoko, Petra J. M. Elders, Joline W. J. Beulens

Heart failure (HF) and type 2 diabetes are closely linked, and concomitantly pose an increased risk of morbidity and mortality. In this issue, Hoek et al (https://doi.org/10.1007/s00125-023-06068-2) present a comprehensive review of the epidemiology of HF in people with type 2 diabetes using both a narrative and systematic review approach. In their systematic review/meta-analysis, the authors reveal that there is a higher prevalence of left ventricular diastolic dysfunction (LVDD; 43%) and HF with preserved ejection fraction (HFpEF; 17%) in type 2 diabetes, as compared with left ventricular systolic dysfunction (LVSD; 6%) and HF with reduced ejection fraction (HFrEF; 7%). Furthermore, HFpEF incidence (7%) was shown to surpass HFrEF incidence (4%), emphasising the predominance of LVDD/HFpEF in type 2 diabetes. For LVDD, when assessed by grade (grade I, II or II) or by classification (indeterminate vs definitive), grade I and indeterminate LVDD were highly prevalent; this indicates that there is a large pre-clinical group with early LVDD that could be targeted for early disease detection, to reduce disease burden. The authors conclude that there is a need for easily accessible and reliable tools for diagnosing HF. They outline how the introduction of uniform and accessible guidelines for diagnosing HF (published by the European Society of Cardiology [ESC] in 2021) and the use of sodium–glucose cotransporter 2 inhibitors may lead to more effective treatment of HF in type 2 diabetes. The figures from this review are available as a downloadable slideset.

Remission of type 2 diabetes: always more questions, but enough answers for action

Amy Rothberg, Michael Lean, Blandine Laferrère

The concept of type 2 diabetes remission is gaining wide public and professional attention. In this issue, Rothberg, Lean and Laferrère (https://doi.org/10.1007/s00125-023-06069-1) discuss how substantial and sustained intentional weight loss can result in durable remission, especially if implemented early in the onset of the disease, preferably at the stage of prediabetes (defined in Europe, Australasia and Canada [and most of the world] as HbA_{1c} ≥42 mmol/mol and <48 mmol/mol [≥6.0% and <6.5%], and in the USA as HbA_{1c} ≥39 mmol/mol and <48 mmol/mol [≥5.7% and <6.5%]). Effective weight management also improves all features of the metabolic syndrome and reduces complications. The authors highlight that, although newer medications, such as glucagon-like peptide-1 receptor agonists and sodium–glucose cotransporter-2 receptor inhibitors, represent a formidable leap forward in the treatment of type 2 diabetes and associated obesity, and for the prevention

of cardiovascular complications, their cost and side effects are still prohibitive for many. They conclude that affordable intensive lifestyle management should be provided as first-line therapy for the treatment of type 2 diabetes. According to the authors, the greatest research challenges are to improve adherence to a healthy lifestyle and long-term weight loss maintenance, and to define cost-effective approaches tailored to the preferences and needs of people living with type 2 diabetes. The figure from this review is available as a downloadable slide.

Genetic engineering of regulatory T cells for treatment of autoimmune disorders including type 1 diabetes

Karoliina Tuomela, Megan K. Levings

Advanced genetic engineering approaches are transforming cell therapies across a number of fields, from cancer to autoimmunity. In this issue, Tuomela and Levings (https://doi.org/10.1007/s00125-023-06076-2) discuss the role and potential of immunosuppressive regulatory T cells (Tregs) in type 1 diabetes, focusing on the opportunities presented by the genetic engineering of these cells in this context. The authors highlight that although Tregs have demonstrated excellent safety in clinical trials, there has been a clear need for improved efficacy and consideration for the unique challenges in type 1 diabetes. Fortunately, genetic engineering has led to significant advancements in the areas of Treg manufacture, antigen specificity and in vivo survival, leading to promising pre-clinical results. As a result, engineered Treg therapies are on the verge of entry into clinical trial for the treatment type 1 diabetes. Nevertheless, the authors conclude that questions remain regarding the optimal strategy for designing Tregs that effectively suppress immune responses in the pancreatic islet environment. The figure from this review is available as a downloadable slide.

Skeletal muscle TET3 promotes insulin resistance through destabilisation of PGC-1α

Beibei Liu, Di Xie, Xinmei Huang, Sungho Jin, Yangyang Dai, Xiaoli Sun, Da Li, Anton M. Bennett, Sabrina Diano, Yingqun Huang

Skeletal muscle insulin resistance is a critical component of the pathogenesis of type 2 diabetes. Decreased expression of PGC-1α is among the many mechanisms implicated in insulin resistance; however, how this dysregulation occurs is yet to be elucidated. In this issue Liu, Xie, Huang et al (https://doi.org/10.1007/s00125-023-06073-5) report increased expression of ten-eleven translocation 3 (TET3) in skeletal muscle of individuals with type 2 diabetes as compared with individuals without diabetes. They show that TET3 interacts with and reduces the abundance of PGC-1α in myocytes. Specifically, TET3 was found to form protein complexes with PGC-1α, preventing its phosphorylation on sites known to promote protein stability and activity. It is proposed that this results in decreased mitochondrial respiration and insulin sensitivity in myocytes. Consistent with this theory, the authors showed that mice with skeletal muscle-specific TET3 deficiency exhibited increased PGC-1α abundance, and enhanced muscle and whole-body insulin sensitivity. Moreover, these animals remained insulin sensitive under high-fat diet challenge. The authors conclude that these findings hold promise for developing novel, TET3-targeting therapeutic agents for insulin resistance and type 2 diabetes.