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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

Embracing complexity: making sense of diet, nutrition, obesity and type 2 diabetes

Nita G. Forouhi

Diet and nutrition are critical for the prevention and mitigation of type 2 diabetes. However, the research evidence and its implementation have been challenging, partly because of the plethora of information and apparently conflicting dietary strategies. In this issue, Nita Forouhi (https://doi.org/10.1007/s00125-023-05873-z) reviews the evidence on the role of dietary components in the prevention and management of type 2 diabetes and obesity. The review cuts through the complexity of, and challenges of measuring, diet and investigates the impact of diet using robust study designs. The author concludes that it is unhelpful to play off one nutrient against another, such as favouring a low-fat or a low-carbohydrate diet. Instead, the review suggests the importance of nutrient type or quality, nutrient food sources in food-based guidelines and the relevance of overall dietary patterns, as well as taking into account dietary adherence and longer term effects. Important areas of consensus on effective dietary strategies are highlighted and future directions are considered. The figure from this review is available as a downloadable slide.

Causal factors underlying diabetes risk informed by Mendelian randomisation analysis: evidence, opportunities and challenges

Shuai Yuan, Jordi Merino, Susanna C. Larsson

Exploration of causal factors underlying diabetes is of great importance not only for the development of more effective prevention strategies but also to provide insight into the molecular processes underlying disease risk. Mendelian randomisation is an epidemiological method that can strengthen causal inference based on the use of genetic variation. In this issue, Yuan et al (https://doi.org/10.1007/s00125-023-05879-7) summarise the evidence on potential causal risk factors for diabetes by integrating published Mendelian randomisation studies on type 1 and 2 diabetes, and reflect on future perspectives of Mendelian randomisation studies on diabetes. The authors highlight that, despite the influence of genetics on type 1 diabetes, few Mendelian randomisation studies have been conducted to identify causal exposures or molecular processes leading to increased disease risk. For type 2 diabetes, Mendelian randomisation analyses support causal associations of somatic, mental and lifestyle factors with development of the disease. The authors discuss how studies on circulating protein biomarkers, metabolites and gut

microbiota provide valuable data to better understand disease pathophysiology and explore potential therapeutic targets. They conclude that more Mendelian randomisation studies in multi-ancestry cohorts are needed to examine the role of different types of physical activity, dietary components, metabolites, protein biomarkers and gut microbiome in diabetes development The figure from this review is available as a downloadable slide.

Separate and combined effects of semaglutide and empagliflozin on kidney oxygenation and perfusion in people with type 2 diabetes: a randomised trial

Søren Gullaksen, Liv Vernstrøm, Steffen S. Sørensen, Steffen Ringgaard, Christoffer Laustsen, Kristian L. Funck, Per L. Poulsen, Esben Laugesen

Diabetes mellitus is the leading cause of chronic kidney disease. Kidney hypoxia has been suggested as a unifying pathophysiological pathway in the development of chronic kidney disease in diabetes. Renoprotective effects have been documented for the sodium–glucose cotransporter 2 inhibitor empagliflozin whereas positive effects for the glucagon-like peptide-1 receptor agonist semaglutide await confirmation in dedicated kidney outcome trials. The underlying mechanisms of action of the two drugs are unclear, but it has been suggested that they may improve kidney oxygenation. In this issue, Gullaksen et al (https://doi.org/10.1007/s00125-023-05876-w) report that treatment with empagliflozin for 32 weeks, in contrast to previous assumptions, decreases kidney medullary oxygenation in people with type 2 diabetes. Semaglutide did not affect kidney medullary oxygenation nor was there any additional effect on oxygenation with combination therapy. The authors suggest that empagliflozin-induced medullary hypoxia may stimulate erythropoietin production, leading to kidney protection. They conclude that these findings improve our understanding of the differential kidney protective effects of empagliflozin and semaglutide.

Presence of immunogenic alternatively spliced insulin gene product in human pancreatic delta cells

René van Tienhoven, Maria J. L. Kracht, Arno R. van der Slik, Sofia Thomaidou, Anouk H. G. Wolters, Ben N. G. Giepmans, Juan Pablo Romero Riojas, Michael S. Nelson, Françoise Carlotti, Eelco J. P. de Koning, Rob C. Hoeben, Arnaud Zaldumbide, Bart O. Roep

In type 1 diabetes, insulin-producing beta cells in the pancreatic islets of Langerhans contribute to their own demise in various ways. Under stress, beta cells can generate so-called neoantigens that result from misreads from insulin mRNA (e.g. insulin defective ribosomal product [INS-DRiP]) and which strongly provoke the immune system. In this issue, van Tienhoven et al (https://doi.org/10.1007/s00125-023-05882-y) report on the surprising finding that an antibody generated against these new beta cell stress proteins selectively stains delta cells. The authors show that the target of this antibody is another insulin gene product, resulting from alternative splicing of insulin mRNA (referred to as INS-splice), that partly overlaps with INS-DRiP. Islet delta cells express this insulin gene product, INS-splice, which contains important targets of diabetes-causing T cells. The authors highlight that this finding may point to some delta cells being potential targets of autoimmunity. The authors conclude that insulin splicing may also play a role in islet development and senescence.

Chaperonin counteracts diet-induced non-alcoholic fatty liver disease by aiding sirtuin 3 in the control of fatty acid oxidation

Shao-Wen Weng, Jian-Ching Wu, Feng-Chih Shen, Yen-Hsiang Chang, Yu-Jih Su, Wei-Shiung Lian, Ming-Hong Tai, Chia-Hao Su, Jiin-Haur Chuang, Tsu-Kung Lin, Chia-Wei Liou, Tian-Huei Chu, Ying-Hsien Kao, Feng-Sheng Wang, Pei-Wen Wang

Heat shock protein 60 (HSP60) is a mitochondrial chaperonin that plays an important role in escorting unfolded proteins. Mice deficient in HSP60 develop mitochondrial dysfunction and insulin resistance; however, the biological role of this chaperonin in nutrient metabolism and the development of non-alcoholic fatty liver disease (NAFLD) remains unclear. In this issue, Wang et al (https://doi.org/10.1007/s00125-023-05869-9) report that HSP60 deficiency was correlated with severe steatosis in human NAFLD biopsies. In contrast, transgenic mice overexpressing Hsp60 (*Hsp60*-Tg) developed less body fat, showed amelioration of dyslipidaemia, hepatic steatosis and M1/M2 macrophage dysregulation and exhibited lower levels of insulin resistance than wild-type mice when fed a high-fat diet. The respiratory quotient profile indicated that fat in *Hsp60*-Tg mice may be metabolised to meet energy demands. The authors demonstrate that, mechanistically, HSP60 promoted fatty acid oxidation by preserving sirtuin 3 (SIRT3)/AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor α (PPARα) signalling. The authors conclude that gain of mitochondrial HSP60 function may be a promising avenue for the development of therapeutic interventions for NAFLD and type 2 diabetes.