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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

Interpreting global trends in type 2 diabetes complications and mortality

Mohammed K. Ali, Jonathan Pearson-Stuttard, Elizabeth Selvin, Edward W. Gregg

Trends in diabetes complications and mortality rates convey the health impacts of diabetes and serve as a barometer of whether clinical practice, intervention programmes and policies are achieving their intended goals. In this issue, Ali et al (https://doi.org/10.1007/s00125-021-05585-2) review recent published data to characterise patterns in type 2 diabetes complications and mortality in adults since 2015, noting stark disparities between different populations. For example, while the burden of diabetes in high-income countries is declining, complications and mortality rates are increasing in low- and middle-income countries. Ali and colleagues discuss how data sources and definitions may be influencing rates and trends observed, and recommend four critical areas of investment to harmonise and bridge the data divide: (1) increasing investments in data collection systems; (2) standardising case definitions and approaches to ascertainment; (3) strengthening analytical capacity; and (4) developing and implementing structured guidelines for reporting of data.

Lipotoxicity-induced circGlis3 impairs beta cell function and is transmitted by exosomes to promote islet endothelial cell dysfunction

Li Xiong, Li Chen, Liting Wu, Weiman He, Dubo Chen, Zishan Peng, Jin Li, Xiaonan Zhu, Lei Su, Yanbing Li, Yingying Gong, Haipeng Xiao

Circular RNAs (circRNAs) play important roles in regulating beta cell function, and exosomes are essential mediators of intercellular communication. However, the role of exosomal circRNAs in type 2 diabetes is poorly understood. In this issue, Xiong et al (https://doi.org/10.1007/s00125-021-05591-4) report that circGlis3 (Gli-similar 3) participates in the development of type 2 diabetes in two different ways. In a conventional way, circGlis3 exerts deleterious effects on beta cells by inhibiting cell survival and insulin secretion. In an unconventional way, by acting as a mediator of intercellular crosstalk, beta cell-derived exosomal circGlis3 promotes islet endothelial cell dysfunction through the glucocorticoid modulatory element-binding protein 1 (GMEB1)/heat shock protein 27 (HSP27) signalling pathway. They also demonstrate that exosomal circGlis3 is upregulated by lipotoxicity and is found at higher levels in mouse models of diabetes and in the serum of participants with type 2 diabetes. The authors conclude that this study provides new insights into the pathogenesis of type 2 diabetes and suggests the significance of circGlis3 as a potential biomarker and therapeutic target for the disease.

Impaired postprandial skeletal muscle vascular responses to a mixed meal challenge in normoglycaemic people with a parent with type 2 diabetes

Ryan D. Russell, Katherine M. Roberts-Thomson, Donghua Hu, Timothy Greenaway, Andrew C. Betik, Lewan Parker, James E. Sharman, Stephen M. Richards, Stephen Rattigan, Dino Premilovac, Glenn D. Wadley, Michelle A. Keske

Blood flow increases in skeletal muscle after a mixed nutrient meal to promote nutrient storage. In individuals who

are obese or have type 2 diabetes, this vascular response is impaired. However, it is unclear if this vascular impairment is present in apparently healthy people at risk of type 2 diabetes. In this issue, Russell and Roberts-Thomson et al (https://doi.org/10.1007/s00125-021-05572-7) report that people with normal glucose tolerance but with at least one first-degree relative with type 2 diabetes have impaired skeletal muscle vascular responses to a mixed nutrient meal compared with individuals without a family history. The authors suggest that the impaired postprandial skeletal muscle vascular response is an early feature of insulin resistance. The authors conclude that these findings indicate that the skeletal muscle vasculature may be a therapeutic target for early intervention to prevent development of type 2 diabetes.

Sex differences in intraorgan fat levels and hepatic lipid metabolism: implications for cardiovascular health and remission of type 2 diabetes after dietary weight loss

Aaron Jesuthasan, Sviatlana Zhyzhneuskaya, Carl Peters, Alison C. Barnes, Kieren G. Hollingsworth, Naveed Sattar, Michael E. J. Lean, Roy Taylor, Ahmad H. Al-Mrabeh

The cardiovascular risks associated with type 2 diabetes are increased to a greater extent in women compared with men. The metabolic basis for this sex difference is not known. In this issue, Jesuthasan et al (https://doi.org/10.1007/s00125-021-05583-4) report that women without diabetes have lower levels of triacylglycerol in their liver compared with men, but this difference is lost in individuals with diabetes. The authors also report levels of plasma insulin, a driver of hepatic de novo lipogenesis, which are normally lower in women than men, were as high in women with diabetes as in men with diabetes. Higher levels of fat in the liver leads to higher rates of VLDL secretion. As the most atherogenic lipid particles (small dense LDL) are derived from VLDL particles after release of triacylglycerol, the authors propose that the relatively greater cardiovascular risk in women is directly linked to the greater increase in intrahepatic fat during type 2 diabetes. The authors conclude that management of type 2 diabetes by substantial weight loss is particularly important for cardiovascular health in women.