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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 are particularly 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!

Sally M. Marshall, Editor

Type 2 diabetes: a multifaceted disease

Ewan R. Pearson

Type 2 diabetes is a complex disease which, in the broader sense, can be considered a composite of 'missed' cases of monogenic and other forms of diabetes, as a result of poor diagnostics, and true polygenic type 2 diabetes. In this issue, Ewan Pearson (https://doi.org/10.1007/s00125-019-4909-y) summarises the recent advances in dissecting the aetiological processes that drive the development of diabetes using measures of phenotype and genotype, including partitioned polygenic scores. Consideration of these aetiological processes can provide insight into the variation in diabetes progression, drug response and risk of complications, supporting a precision medicine approach to diabetes care. ⬇ The figure from this review is available as a downloadable slide.

Neprilysin inhibition: a new therapeutic option for type 2 diabetes?

Nathalie Esser, Sakeneh Zraika

Neprilysin is a peptidase that hydrolyses oligopeptide substrates, such as glucagon-like peptide-1, which are known to regulate glucose homeostasis. Recent studies in humans with diabetes have demonstrated that a new class of drug for heart failure, which combines a neprilysin inhibitor with an angiotensin receptor blocker, improves glycaemic control, enhances insulin sensitivity and reduces the need for initiation of insulin therapy. In this issue, Esser and Zraika (https://doi.org/10.1007/s00125-019-4889-y) summarise these data, with an emphasis on neprilysin inhibition as the principal contributor to these positive clinical outcomes. The authors also review supporting data from preclinical studies to make the case that neprilysin inhibition may be a novel therapeutic approach for the treatment of type 2 diabetes. Potential mechanisms underlying beneficial glycaemic effects are discussed, as well as possible deleterious effects that may limit the clinical use of neprilysin inhibitors. Beyond its beneficial impact on glycaemic control, neprilysin inhibition could also exert favourable effects in treating complications of diabetes.
⬇ The figures from this review are available as a downloadable slide.

The impact of diabetes on productivity in China

Thomas R. Hird, Ella Zomer, Alice Owen, Lei Chen, Zanfina Ademi, Dianna J. Magliano, Danny Liew

Diabetes can cause reduced workforce participation and productivity whilst at work. However, current estimates of the economic burden of diabetes in China do not incorporate diabetes-related productivity loss. In this issue, Hird et al (https://doi.org/10.1007/s00125-019-4875-4) used life table modelling to estimate productivity-adjusted life years (PALYs) lost among those with diabetes over the working lifetime of the Chinese population. Among the 56.4 million people with diabetes of working age in China in 2017 with simulated follow-up to retirement age, diabetes was predicted to reduce years of life lived by 22.7 million (3.7%). Taking into account diabetes-related labour force dropout, absenteeism, presenteeism (reduced efficiency at work) and premature mortality, diabetes also caused the loss of 75.8 million PALYs (15.1%). This equates to an estimated Chinese ¥17.4 trillion

(US$2.6 trillion) loss in gross domestic product (GDP) over the working lifetime of the cohort, highlighting the long-term economic consequences of diabetes in the Chinese population. The authors state that, given the considerable economic impact of these productivity losses, prevention of diabetes and its complications should be considered an investment with potentially large economic benefits in the longer term.

Glucose controls glucagon secretion by directly modulating cAMP in alpha cells

Qian Yu, Hongyan Shuai, Parvin Ahooghalandari, Erik Gylfe, Anders Tengholm

Despite the importance of glucagon in glycaemic control, it remains unclear how glucose regulates glucagon secretion from pancreatic alpha cells. In this issue, Yu et al (https://doi.org/10.1007/s00125-019-4857-6) investigate the role of the intracellular messenger cAMP in alpha-cell-intrinsic glucose regulation of glucagon release. The authors report that glucose-induced alterations of glucagon release are paralleled by changes in subplasmalemmal cAMP concentration in alpha cells. In support of a regulatory role for cAMP, glucose-induced suppression of glucagon release was prevented by imposed elevations in cAMP, while inhibition of protein kinase A (a mediator of the effects of cAMP) mimicked the suppressive effect of glucose on glucagon. Yu and colleagues provide evidence that glucose acts directly on alpha cells to regulate glucagon secretion independent of paracrine signalling from insulin or somatostatin. The authors conclude that these findings point to a new mechanism for glucose control of glucagon release and indicate that the counter-regulatory glucagon response to hypoglycaemia could be enhanced by agents that increase cAMP concentration in alpha cells.

Metformin increases endogenous glucose production in non-diabetic individuals and individuals with recent-onset type 2 diabetes

Lars C. Gormsen, Esben Søndergaard, Nana L. Christensen, Kim Brøsen, Niels Jessen, Søren Nielsen

Although metformin is the endorsed first-line glucose-lowering drug for individuals with type 2 diabetes, the exact mechanisms by which the drug exerts its effects are still debated. Studies in individuals with poorly controlled diabetes have indicated that the main site of action is the liver, through reduced hepatic gluconeogenesis, whereas others have demonstrated that the drug may increase intestinal glucose uptake. In this issue, Gormsen et al (https://doi.org/10.1007/s00125-019-4872-7) report that 3 months of metformin treatment lowered blood glucose as expected but, surprisingly, it increased endogenous glucose production. This effect was observed both in individuals with recent-onset type 2 diabetes and age-matched non-diabetic healthy individuals. The authors suggest that the primary glucose-lowering effect of metformin may, thus, be extra-hepatic, at least in healthy individuals and patients with recent-onset diabetes.

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