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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 Iwant 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

Utility of genetic risk scores in type 1 diabetes

Amber M. Luckett, Michael N. Weedon, Gareth Hawkes, R. David Leslie, Richard A. Oram, Struan F. A. Grant

Advances in genetic research have greatly expanded our understanding of the genetic contribution to type 1 diabetes, facilitating the development of genetic risk scores (GRSs) for type 1 diabetes risk. In this review, Luckett et al (https://doi.org/10.1007/s00125-023-05955-y) summarise the utility of type 1 diabetes GRSs, specifically for disease classification and prediction. They highlight how progression from simplistic models to models that incorporate HLA interactions have allowed us to capture disease risk and discriminate type 1 diabetes from other forms of diabetes. Alongside other factors, such as family history and autoantibody status, GRSs have been integrated into combined risk scores for type 1 diabetes onset prediction. Within newborn population screening, type 1 diabetes GRSs have the potential to identify infants at risk of future presentation of the disease so that they can receive additional clinical care. The authors conclude that the integration of GRSs into healthcare has huge potential for identifying and informing treatment in individuals with type 1 diabetes. The figures from this review are available as a downloadable slideset

Genetics of diabetes-associated microvascular complications

Valeriya Lyssenko, Allan Vaag

The diabetes epidemic has resulted in an epidemic of diabetes-associated complications. Systemic monitoring of individuals with diabetes and new insights into biological mechanisms leading to the progression of complications are necessary to halt this escalation. In this issue, Lyssenko and Vaag (https://doi.org/10.1007/s00125-023-05964-x) summarise state-of-the-art discoveries in the genetic predisposition to kidney, eye and nerve damage in individuals with diabetes. They also provide a critical view on the existing gaps in the current clinical definitions of organ damage that might hinder discovery of genomic factors that trigger or cause associated disease. Knowledge about environmental perinatal exposures may shed light on adaptive changes responsible for the intrauterine programming of metabolic mechanisms that may underlie organ vulnerability. Profiling genetic susceptibility to diabetes-associated metabolic risk factors, including high blood glucose levels, impaired insulin secretion and action, obesity, hypertension, reduced liver function and dysregulated immune system, may aid in pathophysiology-based classification of complications and identification of individuals at high risk for these complications for early prevention in individuals with diabetes. The figure from this review is available as a downloadable slide

Plasma proteomic signatures of a direct measure of insulin sensitivity in two population cohorts

Daniela Zanetti, Laurel Stell, Stefan Gustafsson, Fahim Abbasi, Philip S. Tsao, Joshua W. Knowles, RISC Investigators, Björn Zethelius, Johan Ärnlöv, Beverley Balkau, Mark Walker, Laura C. Lazzeroni, Lars Lind, John R. Petrie, Themistocles L. Assimes

The euglycaemic–hyperinsulinaemic clamp (EIC) is a reference standard for directly assessing insulin sensitivity

but is invasive and time-consuming. In this issue, Zanetti et al (https://doi.org/10.1007/s00125-023-05946-z) assess the incremental value of high-throughput plasma proteomic profiling, using the proximity extension assay, in developing signatures that correlate with the *M* value derived from the EIC. The authors use two cohorts, the Relationship between Insulin Sensitivity and Cardiovascular disease (RISC) and the Uppsala Longitudinal Study of Adult Men (ULSAM), to show that plasma proteomic signatures of up to 67 proteins substantially improve the cross-sectional estimation of the *M* value over routinely available clinical variables. A smaller subset of proteins afforded much of this improvement, especially when considering predictive models applied across both cohorts. IGF-binding protein 2 was the single most consistently selected protein across all analyses and models. Zanetti and colleagues state that their approach provides opportunities to improve the identification of individuals at risk of adverse health consequences related to insulin resistance.

Low birthweight is associated with a higher incidence of type 2 diabetes over two decades independent of adult BMI and genetic predisposition

Rasmus Wibaek, Gregers S. Andersen, Allan Linneberg, Torben Hansen, Niels Grarup, Anne Cathrine B. Thuesen, Rasmus T. Jensen, Jonathan C. K. Wells, Kasper A. Pilgaard, Charlotte Brøns, Dorte Vistisen, Allan A. Vaag

Over the past three decades, longitudinal studies have consistently found lower birthweight to be associated with higher risk of type 2 diabetes, but prospective data on diabetes incidence are lacking. In this issue, Wibaek et al (https://doi.org/10.1007/s00125-023-05937-0) used data on objectively measured birthweight from original midwife records dating back to 1939–1971, and in a large sample of middle-aged to older adults examined the influence of birthweight on age- and sex-specific incidence of type 2 diabetes over two decades, from 1999–2020. The authors show that type 2 diabetes incidence rate increased with age, was higher in male participants, and that the absolute rate of increase was markedly higher in individuals born with lower birthweight compared with higher birthweight in a dose–response manner. Altogether, birthweight, genetic susceptibility of type 2 diabetes and adult adiposity (BMI) were found to be strong and independent risk factors for type 2 diabetes. The authors conclude that, within the era of precision medicine, birthweight holds strong potential to be used as a feasible marker to guide clinical care and treatment in type 2 diabetes.

Cholesterol crystal formation is a unifying pathogenic mechanism in the development of diabetic retinopathy

Sandra S. Hammer, Tim F. Dorweiler, Delaney McFarland, Yvonne Adu-Agyeiwaah, Natalia Mast, Nicole El-Darzi, Seth D. Fortmann, Sunil Nooti, Devendra K. Agrawal, Irina A. Pikuleva, George S. Abela, Maria B. Grant, Julia V. Busik

With the advancement of spectral-domain optical coherence tomography imaging, hyperreflective crystalline deposits have been identified in retinal pathologies, including diabetic retinopathy. In this issue, Hammer and Dorweiler et al (https://doi.org/10.1007/s00125-023-05949-w) uncover the nature of crystalline deposits in retina from human donors with diabetes as cholesterol crystals. Using cell culture- and animal model-based studies, cholesterol crystals were shown to recapitulate all major pathogenic mechanisms leading to diabetic retinopathy, including inflammation, cell death and breakdown of the blood–retinal barrier. Fibrates, statins and α-cyclodextrin effectively dissolved cholesterol crystals and prevented endothelial pathology. The authors conclude that the formation of cholesterol crystals represents a unifying pathogenic mechanism in the development of diabetic retinopathy and strategies for removal of cholesterol crystals may have therapeutic value in the treatment of diabetic retinopathy.