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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

Consortium-based approach to receiving an EMA qualification opinion on the use of islet autoantibodies as enrichment biomarkers in type 1 diabetes clinical studies

Stephen R. Karpen, Jessica L. Dunne, Brigitte I. Frohnert, Marjana Marinac, Claudia Richard, Sarah E. David, Inish M. O'Doherty, on behalf of the Type 1 Diabetes Consortium

Enriching a clinical trial for individuals with a higher likelihood of experiencing a clinical event can greatly increase the statistical power of that trial, potentially leading to smaller, shorter, and more feasible clinical trials. Because of significant individual heterogeneity, currently available enrichment techniques are insufficient in clinical trials of medical products intended to prevent or delay progression to type 1 diabetes diagnosis in high-risk populations. In this issue, Karpen et al (https://doi.org/10.1007/s00125-022-05751-0) discuss how the Critical Path Institute's Type 1 Diabetes Consortium undertook a global data-sharing initiative and acquired individual-level data from three longitudinal observational studies (TEDDY, DAISY and TN01). These data informed a modelling analysis of islet autoantibodies, plus additional clinical features, as enrichment biomarkers. The European Medicines Agency has now issued a positive qualification of the islet autoantibodies, a first-of-its-kind success in type 1 diabetes, supporting the design of more efficient trials with optimised trial populations. The figures from this review are available as a downloadable slideset.

Cardiovascular outcomes in type 1 and type 2 diabetes

Annika Rosengren, Pigi Dikaiou

A typical adult with type 1 diabetes is different from adults with type 2 diabetes, with respect to mean age, duration of diabetes and body size. While individuals with type 2 diabetes are generally older and have higher levels of other cardiometabolic risk factors, those with type 1 typically have longer exposure to high plasma glucose levels. In this issue, Rosengren and Dikaiou (https://doi.org/10.1007/s00125-022-05857-5) discuss why both types of diabetes face increased risk of cardiovascular disease. The authors highlight that in each type of diabetes, absolute risk and excess risk, compared with the general population, vary depending on the control of other factors. However, few studies have formally compared the two types, and those studies that have done so have reached different conclusions. Accordingly, there is as yet no consensus on which type of diabetes fares worse with respect to cardiovascular disease. The authors conclude that future studies in large, unselected populations are needed, taking other risk factors into account. The figures from this review are available as a downloadable slideset.

Exercise as a non-pharmacological intervention to protect pancreatic beta cells in individuals with type 1 and type 2 diabetes

Alexandra Coomans de Brachène, Corentin Scoubeau, Anyïshai E. Musuaya, Jose Maria Costa-Junior, Angela Castela, Julie Carpentier, Vitalie Faoro, Malgorzata Klass, Miriam Cnop, Decio L. Eizirik

Exercise training is known to reduce diabetes risk. In this issue, Coomans de Brachène et al (https://doi.org/10.1007/s00125-022-05837-9) report that serum obtained from 82 individuals after 8–12 weeks of exercise training protects human pancreatic beta cells against apoptosis induced by the endoplasmic reticulum stressor thapsigargin, compared with serum obtained from the same individuals before training. The protective effect was observed regardless of the type of exercise training, or sex, age, BMI, ancestry or diabetes status (type 1, type 2 or non-diabetic) of the individuals. The study points to a role for muscle-released clusterin in this protective effect, and other exerkines may also be involved. The authors highlight the unexpected potential to preserve beta cell health by exercise training and suggest that exercise could be tested as a non-pharmacological approach to preserve beta cell mass in the early stages of diabetes.

High-throughput genetic clustering of type 2 diabetes loci reveals heterogeneous mechanistic pathways of metabolic disease

Hyunkyung Kim, Kenneth E. Westerman, Kirk Smith, Joshua Chiou, Joanne B. Cole, Timothy Majarian, Marcin von Grotthuss, Soo Heon Kwak, Jaegil Kim, Josep M. Mercader, Jose C. Florez, Kyle Gaulton, Alisa K. Manning, Miriam S. Udler

Genome-wide association studies (GWAS) have identified hundreds of loci associated with type 2 diabetes; however, clinical translation of findings has been challenging. In this issue, Kim et al (https://doi.org/10.1007/s00125-022-05848-6) describe a high-throughput pipeline using GWAS summary statistics to perform physiologically informed clustering of 323 independent type 2 diabetes loci and identified ten genetic clusters. These clusters represent subsets of diabetes risk variants that are most similar to each other based on their associations with disease-related traits. The ten clusters included both previously captured and novel clusters, and displayed tissue-specific enrichment of epigenomic marks. Cluster-based polygenic scores were associated with distinct clinical outcomes. The authors also demonstrated application of the pipeline to two other metabolic diseases. They conclude that their high-throughput clustering approach can produce robust findings and identify potential genetic subtypes of disease.

CCR2-positive monocytes contribute to the pathogenesis of early diabetic retinopathy in mice

Aicha Saadane, Alexander A. Veenstra, Martin S. Minns, Jie Tang, Yunpeng Du, Fatima Abubakr Elghazali, Emma M. Lessieur, Eric Pearlman, Timothy S. Kern

Inflammation has been implicated in the pathogenesis of the early stages of diabetic retinopathy but the molecular mechanisms are unclear. In this issue, Saadane et al (https://doi.org/10.1007/s00125-022-05860-w) report that deletion of CC chemokine receptor 2 (CCR2)-positive cells (largely monocytes) in a mouse model of diabetes or generation of chimeric mice lacking *Ccr2* only from myeloid cells significantly inhibited the diabetes-induced increase in retinal capillary degeneration. The authors highlight how these results in monocytes reflect previous studies that have shown that neutrophils have direct cytotoxic effects on retinal endothelial cells, thus providing at least one mechanism by which leucocytes contribute to diabetes-induced vascular damage in diabetes. They conclude that abnormalities in multiple cell types in the innate immune system contribute to the development of the early stages of diabetic retinopathy, providing potential therapeutic targets for inhibiting retinopathy.