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Diabetologia

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

When therapeutic drugs lead to diabetes

Bruno Fève and André J. Scheen

Drug-induced diabetes is not a novel concern, and this is examined in this issue by Fève and Scheen (https://doi.org/10.1007/s00125-022-05666-w). The archetype of this iatrogenic complication is glucocorticoid-induced diabetes, which remains the most frequently encountered one in clinical practice. However, we should not overlook the high prevalence of diabetes caused by antipsychotics, in particular by second generation compounds. The pharmacopoeia of antiretrovirals has greatly improved since the first classes of these drugs became available at the end of the 1980s; however, there is still a residual metabolic toxicity of several new generation molecules. Even more recently, the advent of immunotherapies in oncology has been accompanied by the emergence of diabetes cases that are reminiscent of the phenotype of type 1 diabetes. This short review is focused on these four families of diabetogenic drugs, and provides information on the prevalence of this complication, the main clinical presentations and the key pathophysiological mechanisms, before addressing the management and prevention of these chemically induced forms of diabetes. The figure from this review is available as a downloadable slide.

Epigenome-wide association study of incident type 2 diabetes: a meta-analysis of five prospective European cohorts

Eliza Fraszczyk, Annemieke M. W. Spijkerman, Yan Zhang, Stefan Brandmaier, Felix R. Day, Li Zhou, Paul Wackers, Martijn E. T. Dollé, Vincent W. Bloks, Xīn Gào, Christian Gieger, Jaspal Kooner, Jennifer Kriebel, H. Susan J. Picavet, Wolfgang Rathmann, Ben Schöttker, Marie Loh, W. M. Monique Verschuren, Jana V. van Vliet-Ostaptchouk, Nicholas J. Wareham, John C. Chambers, Ken K. Ong, Harald Grallert, Hermann Brenner, Mirjam Luijten, Harold Snieder

Epigenetics may play a role in the development of type 2 diabetes, and predictive DNA methylation markers have been identified in single-cohort epigenome-wide association studies. Combining results from several prospective cohorts may identify additional markers. In this issue, Fraszczyk et al (https://doi.org/10.1007/s00125-022-05652-2) report 76 DNA methylation markers from the meta-analysis of five European cohorts, of which 63 were novel for incident type 2 diabetes. The authors suggest that epigenetics has the potential to elucidate new biological pathways underlying the development of type 2 diabetes, and predictive DNA methylation markers could ultimately be useful in type 2 diabetes prevention efforts.

Spatial and transcriptional heterogeneity of pancreatic beta cell neogenesis revealed by a time-resolved reporter system

Shugo Sasaki, Michelle Y. Y. Lee, Yuka Wakabayashi, Luka Suzuki, Helena Winata, Miwa Himuro, Taka-aki Matsuoka, Iichiro Shimomura, Hirotaka Watada, Francis C. Lynn, Takeshi Miyatsuka

Although endocrine pancreas development has been investigated by many researchers, the beta cell developmental niche, or precisely where and when beta cells arise in vivo, remains less well described. Part of the reason for this is that there have been no methods to readily detect newly generated beta cells in situ. In this issue, Sasaki et al (https://doi.org/10.1007/s00125-022-05662-0) describe a novel time-resolved mouse model, which was developed to distinguish newborn beta cells from more differentiated beta cells. The authors report that this model provides the first in vivo evidence that beta cells arise from two distinct regions: ductal or blood vessel niches. Using this model, the authors also show that single-cell transcriptional heterogeneity during beta cell genesis correlates with the spatial heterogeneity. Furthermore, single-cell mRNA profiles of human embryonic stem cell-derived beta-like cells demonstrated a transcriptional similarity with the data from newborn beta cells in mice. The authors conclude that this work provides insight for the future development of regenerative therapies for diabetes.

Early DNA methylation changes in children developing beta cell autoimmunity at a young age

Inna Starskaia, Essi Laajala, Toni Grönroos, Taina Härkönen, Sini Junttila, Roosa Kattelus, Henna Kallionpää, Asta Laiho, Veronika Suni, Vallo Tillmann, Riikka Lund, Laura L. Elo, Harri Lähdesmäki, Mikael Knip, Ubaid Ullah Kalim, Riitta Lahesmaa

DNA methylation changes associated with type 1 diabetes were previously detected in individuals clinically diagnosed with the disease. Recently, using array-based methods, these changes were also detected in whole blood samples from individuals before they developed diabetes. In this issue, Starskaia et al (https://doi.org/10.1007/s00125-022-05657-x) use genome-wide reduced representation bisulphite sequencing to detect cell type-specific DNA methylation changes associated with type 1 diabetes before clinical diagnosis, and even before the appearance of autoantibodies. The authors conclude that the early epigenetic changes associated with type 1 diabetes identified in this study may contribute to pathogenesis and provide basis for the early detection of diabetes.

Endothelial glycocalyx is damaged in diabetic cardiomyopathy: angiopoietin 1 restores glycocalyx and improves diastolic function in mice

Yan Qiu, Stanley Buffonge, Raina Ramnath, Sophie Jenner, Sarah Fawaz, Kenton P. Arkill, Chris Neal, Paul Verkade, Stephen J. White, Melanie Hezzell, Andrew H. J. Salmon, M.-Saadeh Suleiman, Gavin I. Welsh, Rebecca R. Foster, Paolo Madeddu, Simon C. Satchell

Diabetic cardiomyopathy is a serious and under-recognised complication of diabetes. The first sign is diastolic dysfunction, which progresses to heart failure. Endothelial glycocalyx plays multiple vital roles in the microcirculation and whilst it is known to be compromised in diabetes, it has not previously been studied in the coronary microcirculation in diabetes. In this issue, Qiu et al (https://doi.org/10.1007/s00125-022-05650-4) report that, in mouse models of diabetes, diastolic dysfunction is associated with glycocalyx loss from coronary microvascular endothelial cells and increased microvascular permeability. The authors also show that endothelial glycocalyx damage is sufficient to impair cardiac function. They provide evidence for increased matrix metalloproteinase activity as a potential mechanism of endothelial glycocalyx damage. They go on to demonstrate that angiopoietin 1 restores the endothelial glycocalyx and ameliorates diastolic dysfunction in diabetes. The authors conclude that these findings identify coronary microvascular endothelial glycocalyx damage as a contributor to the development of diabetic cardiomyopathy and, therefore, as a therapeutic target for heart failure in people with diabetes.

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