The best-laid schemes o’ mice an’ men gang aft agley (To a Mouse, Robert Burns, 1785). We planned this series of mini-reviews in Diabetologia to coincide with the 2020 Olympic Games. Instead, I hope the articles will provide a timely stimulus to us all, to increase our activities again as we emerge from COVID-19 lockdown.

Regular exercise is known to improve insulin sensitivity and metabolic health in people with type 1 and type 2 diabetes, but how exactly does it do this and how should these individuals exercise? In this issue, we have commissioned a mini-series of reviews to try to answer these questions. Gemmink et al (https://doi.org/10.1007/s00125-020-05170-z) begin this series by providing a muscle-centred view on the beneficial impact of exercise on fat metabolism and, consequently, insulin sensitivity. The authors explain how regular exercise may alter lipid droplet characteristics in the human muscle (and liver) in insulin-resistant individuals, resulting in an ‘athlete-like’ phenotype that is associated with improved insulin sensitivity. Other than the muscle, the liver, adipose tissue, vasculature and pancreas also play a role in the beneficial effects of exercise. Thyfault and Bergouignan (https://doi.org/10.1007/s00125-020-05177-6) explain how exercise activates metabolic changes in these non-skeletal-muscle tissues and how the adaptations can protect against metabolic diseases. So, it is clear that exercise is beneficial for individuals with diabetes, but how in practice should exercise be carried out? In their review, Riddell and colleagues (https://doi.org/10.1007/s00125-020-05183-8) specifically focus on the competitive athlete with type 1 diabetes. They explain the challenges that athletes with type 1 diabetes face in trying to maintain normal glucose levels during training, travel and competition, and how these challenges may be overcome, such as with the use of insulin pumps and continuous glucose monitors. In addition, they discuss how adjustment of carbohydrate intake can improve performance in athletes with type 1 diabetes. Exercise training can also improve glycaemic control in individuals with type 2 diabetes, but it is not known which training regime is likely to elicit the most benefit with regards to this. In their review, Savikj and Zierath (https://doi.org/10.1007/s00125-020-05166-9) discuss how exercise type, intensity and modality affects the impact of exercise on glycaemic control in individuals with type 2 diabetes. They also discuss the impact of nutritional status on exercise-associated benefits, indicating that training with low carbohydrate availability may improve cardiorespiratory function and skeletal muscle oxidative capacity vs conventional training. They conclude that, just like competitive athletes, individuals with type 2 diabetes should be encouraged to adopt training regimens that improve fitness and metabolism.

The figures from these reviews are available as downloadable slideset: Gemmink et al slideset; Thyfault and Bergouignan slideset; Riddell et al slideset; Savikj and Zierath slideset.
Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study

Bertrand Cariou, Samy Hadjadj, Matthieu Wargny, Matthieu Pichelin, Abdallah Al-Salameh, Ingrid Allix, Coralie Amadou, Gwénaëlle Arnault, Florence Baudoux, Bernard Bauduceau, Sophie Borot, Muriel Bourgeon-Ghittori, Olivier Bourrou, David Bouteille, France Cazenave-Roblot, Claude Chaumeil, Emmanuel Cosson, Sandrine Coudol, Patrice Darmon, Emmanuel Disse, Amélie Ducet-Boiffard, Bénédicte Gaborit, Michael Joubert, Véronique Kerlan, Bruno Laviolle, Lucien Marchand, Laurent Meyer, Louis Potier, Gaëtan Prevost, Jean-Pierre Riveline, René Robert, Pierre-Jean Saulnier, Ariane Sultan, Jean-François Thébaut, Charles Thivolet, Blandine Tramunt, Camille Vatier, Ronan Roussel, Jean-François Gautier, Pierre Gourdy, for the CORONADO investigators

Diabetes has been shown to be a major comorbidity that affects the severity of Coronavirus disease-2019 (COVID-19). However, precise data regarding diabetes characteristics and their prognostic relevance in inpatients with COVID-19 are still lacking. In this issue, Cariou, Hadjadj, Wargny et al (https://doi.org/10.1007/s00125-020-05180-x) report the first results from the CORONADO study, an observational, multicentric (68 centres), French nationwide study. With a prespecified design and protocol, the CORONADO study aims to explore the phenotypes of diabetic individuals with COVID-19. The authors found that patients with diabetes requiring hospital admission for COVID-19 were more likely to be elderly (mean age, 70 years; 38% ≥75 years old) and male (65%), and more commonly had type 2 (90%) than type 1 diabetes (3%). One in ten patients (10.3%) died by day 7 following hospital admission; age and advanced diabetic complications were independently associated with mortality on day 7 of admission. Thus, people with this profile should follow all rules to avoid infection with severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2). In addition, severe forms of COVID-19 were associated with macrovascular complications, as indicated previously, and also microvascular complications, as established for the first time by this study. Long-term glycaemic control (HbA1c) showed no obvious association with prognosis; however, increased BMI appeared to be an independent prognostic factor for COVID-19 severity and, hence, the authors suggest that individuals with a high BMI require special attention.

Complex interaction of fasting glucose, body mass index, age and sex on all-cause mortality: a cohort study in 15 million Korean adults

Mi-Hyang Jung, Sang-Wook Yi, Sang Joon An, Beverley Balkau, Jee-Jeon Yi, Hyeongsu Kim

Lean diabetes (diabetes in people with a low BMI [<25 kg/m²]) is emerging as a pathological condition that is associated with a higher mortality risk than excessive weight or grade I obese diabetes. However, it is not clear whether low BMI and hyperglycaemia have a joint effect on mortality and whether combined associations of fasting glucose levels and BMI with mortality differ by age and sex. In this issue, Jung et al (https://doi.org/10.1007/s00125-020-05160-1) use a Korean cohort study to report that: (1) the adverse effects of hyperglycaemia on mortality risk are more marked in leaner than more overweight individuals, particularly in young men and middle-aged women; and (2) the interpretation of mortality risk associated with fasting blood glucose–BMI subgroups is not straightforward because of complex interactions between fasting glucose, BMI, age and sex. For example, people with a fasting glucose level of 6.1–6.9 mmol/l and a lower normal weight (BMI 20–22.4 kg/m²) had similar or higher mortality risk than people with a fasting glucose level of 7.0–9.9 mmol/l and BMI ≥22.5 kg/m², while obese people with diabetes had higher mortality risk than overweight people with diabetes. The authors state that this study calls for sophisticated management of patients according to the detailed metabolic profiles of each individual, including fasting glucose and BMI, as well as sex and age, to achieve better health outcomes.

Islet pericytes convert into profibrotic myofibroblasts in a mouse model of islet vascular fibrosis

Luciana Mateus Gonçalves, Elizabeth Pereira, João Pedro Werneck de Castro, Ernesto Bernal-Mizrachi, Joana Almeida

Vascular fibrosis is a very common lesion in islets from individuals with type 2 diabetes but its aetiology has not yet been determined. Until now, mouse models that enable us to study the role of dysfunctional islet microvasculature in diabetes pathogenesis have not been available. In this issue, Mateus Gonçalves et al (https://doi.org/10.1007/s00125-020-05168-7) report that a transgenic mouse model of beta cell expansion (the AktTg mouse) exhibits an increased deposition of extracellular matrix proteins around islet blood vessels, allowing for the study of cellular mechanisms that
lead to islet vascular fibrosis and its functional consequences. They found that islet pericytes proliferated extensively in this model and were converted into profibrotic myofibroblasts. Vascular alterations were associated with diminished islet blood perfusion and impaired islet vascular responses to noradrenaline and glucose, which led to a decrease in glucose-stimulated insulin secretion per beta cell unit in these transgenic mice. The authors conclude that the AktTg mouse model can now be used to conduct studies aimed at elucidating the role of insulin or other beta cell secretory products in determining the number, phenotype and function of islet pericytes. They state that elucidating the crosstalk between pericytes and beta cells is necessary to fully understand the pathogenesis of islet adaptation in diabetes.

Innate immune stimulation of whole blood reveals IFN-1 hyper-responsiveness in type 1 diabetes

Kameron B. Rodrigues, Matthew J. Dufort, Alba Llibre, Cate Speake, M. Jubayer Rahman, Vincent Bondet, Juan Quiel, Peter S. Linsley, Carla J. Greenbaum, Darragh Duffy, Kristin V. Tarbell

Although type 1 IFN (IFN-1) has been implicated in the early stages of type 1 diabetes pathogenesis, less is known about key innate immune alterations in individuals with established type 1 diabetes. In this issue, Rodrigues, Dufort et al (https://doi.org/10.1007/s00125-020-05179-4) report findings from their study, which used ex vivo whole blood immune stimulation to show that individuals with type 1 diabetes display higher IFN-1 responses after innate immune stimulation. Furthermore, they show that IFN-γ- and IL-1β-driven responses were not significantly different. Monocytes from NOD mouse models, a strain that develops autoimmune diabetes, also displayed increased IFN-1 responses after treatment with CpG, which stimulates the innate immune system. These findings indicate that increased responsiveness to IFN-1 is a feature of both mouse autoimmune diabetes and human established type 1 diabetes. The authors suggest that a stimulated IFN-1 gene signature could be used as a potential biomarker to identify individuals with type 1 diabetes who may be successfully treated with therapies targeting the IFN-1 pathway.

Sex-specific associations of insulin resistance with chronic kidney disease and kidney function: a bi-directional Mendelian randomisation study

Jie V. Zhao, C. Mary Schooling

Chronic kidney disease (CKD) contributes substantially to the global burden of morbidity and mortality. Notably, CKD has a sexual disparity that is not fully understood. To provide further insight, in this issue Zhao and Schooling (https://doi.org/10.1007/s00125-020-05163-y) contextualise these differences within evolutionary biology theory, which suggests a sex-specific growth and reproduction trade-off against longevity. As such, insulin, a key driver of this trade-off, may have different roles in men and women. Given fasting insulin, fasting glucose and HbA1c are related, the authors used the novel Mendelian randomisation-Bayesian model-averaging (MR-BMA) method to identify the best-fitting model and most influential exposure, followed by univariable or multivariable Mendelian randomisation, as appropriate. Fasting insulin was selected as the most likely exposure by both overall and sex-specific MR-BMA. Genetically predicted insulin was associated with CKD and unfavourable kidney function in men but not women. The authors suggest that clarifying the underlying pathways by which insulin has these sex-specific renal effects could provide new insights for prevention and treatment strategies for CKD.

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