The numbers are grim. According to the American Diabetes Association, in the United States, ~29 million individuals have diabetes and an additional 86 million are prediabetic. In 2010, diabetes was listed as the underlying cause of ~70,000 deaths and a contributing factor to an additional >230,000 deaths. It is clear that heart pathology is a major complication of diabetes. In 2004, the most recent year for which statistics are available, heart disease was noted in ~70% of diabetes-related deaths among people ≥65 yr old, and heart disease mortality rates are two to four times higher in adults with diabetes than adults without diabetes.

Researchers need adequate models of diabetes to address the cardiac complications of diabetes, as well as to test therapeutic interventions. Broadly defined, diabetes is a disorder of metabolism, where, in response to a meal and the resultant rise in plasma glucose, the pancreas produces little or no insulin [type 1 diabetes (T1D)] or cells do not respond appropriately to the insulin that is produced [type 2 diabetes (T2D)]. T1D results from an autoimmune destruction of the pancreatic β-cells, accounts for 5–10% of diabetes, and is characterized by excessive urination, hunger, and weight loss. In contrast, T2D accounts for >90% of the cases of diabetes and is characterized by older age of onset, obesity (80% of cases), and physical inactivity (4).

In this issue of *American Journal of Physiology-Cell Physiology*, Pham et al. (7) assess the impact of a single, high dose of the pancreatic β-cell toxin streptozotocin in rats, a model of T1D, on the myocardium and subsequent alteration of mitochondrial function. Using state-of-the-art high-resolution mitochondrial respirometry coupled to purpose-built fluorometers, oxygen flux was linked to ATP synthesis, reactive oxygen species generation, or mitochondrial membrane potential in heart tissue homogenates. The use of multipurpose sensors for simultaneous detection of two parameters and use of tissue homogenates in place of isolated mitochondria provide an elegant approach to assess the implication of T1D on heart mitochondria. A key observation was that ATP consumption under anoxic states was similar in T1D and control hearts, which in turn leads to increased susceptibility of the diabetic heart to ischemic injury. Application of such techniques to other models of metabolic disease and diabetes has great potential.

Although high-resolution analysis of various parameters suggested these dramatic deficits with T1D, limited severity of cardiac pathology in the streptozotocin model was observed at the whole heart level, which poses two main questions: 1) does diabetic cardiomyopathy exist (especially in rodent models) independent of secondary factors, and, if so, 2) can this be adequately modeled in rodents to move research forward? Controversy exists as to whether cardiac events associated with diabetes are a consequence of underlying coronary artery disease and/or hypertension. There is growing evidence suggesting that diabetes results in pathological cardiac function and structure independent of vascular pathology in humans and animal models, supporting the notion that diabetic cardiomyopathy does in fact exist (1). T1D models exhibit diastolic (i.e., prolongation of relaxation and increased left ventricular end-diastolic pressure) (2) and systolic (i.e., heart rate, systolic blood pressure, and fractional shortening) (2) dysfunction, and such findings are also observed in humans (1). The molecular mechanisms proposed for diabetic cardiomyopathy are diverse (9); however, it is not clear if the pathology of T1D and T2D is linked to a common mechanism or if the two syndromes diverge.

So, how best to model diabetic cardiomyopathy? Rodents provide specific advantages with respect to cost, genetic manipulation, ease of maintenance and breeding, and experimentation (8); however, it has been suggested that muscle organization and function in mice may be structurally distinct from humans, limiting the use of mice as ideal candidates for modeling human disease (3). A variety of factors and their combination can influence the extent of diabetic cardiomyopathy (i.e., age, diet vs. genetically induced disease, sex, and duration of induction), with the human condition a likely consequence of interplay of genetic, epigenetic, and environmental factors that co-mingle over decades to produce a complex phenotype. So how does one accelerate the phenotype and compress it into a model system that can be studied and manipulated and also extrapolated to the human condition?

Rodent models for T1D, as employed in the study of Pham et al. (7), are routinely used in biomedical research and involve a high-dose single injection or low-dose multiple injections of streptozotocin or alloxan, which are toxic to pancreatic β-cells. A limitation of the study of Pham et al. and many reported in the literature is that the T1D model develops rapidly in rodents with glucose intolerance as quickly as 2 days following toxin treatment, and within 8 wk, when end-point analyses are performed, the mice are quite moribund. In the current study this 8-wk duration resulted in mild cardiac effects. Also, in the clinical setting, there are no diagnosed T1D patients who have...
not initiated insulin therapy, yet in animals models, insulin therapy is largely absent, bringing into question what disease pathology is actually being studied. Additionally, such models ignore autoimmune, which is a classic feature of the human condition. A number of genetic models of T1D that have an autoimmune component have been described, but these are limited by the fact that the immune response is different between rodents and humans. Generation of humanized rodent models that account for such limitation may be a means forward to integrate complexity and create a better T1D model.

Appropriate models and studies, such as those described by Pham et al. (7) that apply highly sensitive techniques to mitochondrial analysis, are necessary to help researchers tackle the looming pandemic of T2D on the horizon. Although a variety of genetic models exist for T2D, a review of rodent models for metabolic syndrome research by Panchal and Brown (6) concluded that normal rodents chronically fed a diet high in both carbohydrates and fats provided a model that mimicked the complications in humans with metabolic syndrome. It will be interesting to see if the mitochondrial complications associated with diabetes are similar in T1D and T2D, thus providing a common therapeutic target for management of cardiac complications associated with diabetes.

An analysis for the Global Burden of Disease Study 2013 (5) estimates that 2.1 billion people worldwide are overweight or obese (nearly one-third of the world’s population), whereas three decades ago the number was closer to 800 million, hallmarks an echo from the past. It shows us that, for all our attempts to lead healthier lives, with healthier diets and more physical activity, here we are 30 years later, more overweight and obese, with a myriad of health epidemics looming for the young and aged alike. Can mouse save man?

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

H.H.P. drafted the manuscript; H.H.P. and A.A.M. edited and revised the manuscript; H.H.P. and A.A.M. approved the final version of the manuscript.