Helping to stop diabetic cardiac complications | Mountain/West

**Occupation:** Chief, Division of Endocrinology and Metabolism, University of Utah School of Medicine, Salt Lake City, Utah

**Professional Focus:** Cardiac dysfunction in diabetes, Regulation of myocardial growth and metabolism by insulin signaling

**Outside Interests:** Family, church, travel, photography

**Research Funding:** ADA-Takeda Cardiovascular Postdoctoral Fellowship
"Molecular Pathogenesis of Diabetic Cardiomyopathy"

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**Evan Dale Abel, MD, DPhil**

What does the face of diabetes look like? Diabetes touches everyone, either directly or indirectly. Therefore, the face of diabetes is simply the human face—regardless of age, gender, ethnicity or background.

There are many misconceptions about diabetes, including what types of people are diagnosed, particularly with type 2. Increasing the dissemination of information about risk factors for diabetes might serve to reduce the number of new cases. Meanwhile, for those individuals who already have this illness, encouraging them to be mindful of potential complications of diabetes will help their quality of life and the healthcare system in general.

As the American Diabetes Association works to promote awareness, one of my jobs as Chief of the Endocrinology and Metabolism Division at the University of Utah is to focus my research on the risk factors and complications that make diabetes one of the deadliest diseases in our society.

Until about ten years ago, many research funding opportunities focused on the development of the disease (pathogenesis) and the classic types of diabetic complications, such as neuropathy, nephropathy and retinopathy. These still remain serious and deadly consequences of diabetes. However, until recently, another set of complications remained relatively unaddressed: cardiovascular events, like heart attacks, strokes and heart failure. Cardiovascular complications represent the major causes of death in individuals with diabetes.

This growing revelation encouraged groups like the American Diabetes Association and its Research Foundation to dedicate funding opportunities to address this critical area of diabetes science. In 2006, the Association and Takeda Pharmaceuticals, Inc. decided to fund the education of upcoming diabetes researchers who specialize in this area of diabetes science. Through the "ADA-Takeda Cardiovascular Complications in Diabetes Postdoctoral Fellowship Program," the Association hopes to foster research and clinical initiatives that will improve diabetes care in general and specifically cardiovascular disease.

I have had the privilege of being funded by an ADA-Takeda Cardiovascular Postdoctoral Fellowship Award for the last year and a half.
Every dollar spent on diabetes research is an immense investment in our future—in healthcare dollars and, most importantly, in lives.

This competitive grant supports the education of my post-doctoral fellow, Sandra Sena, PhD, who is one of five fellows in our laboratory. Dr. Sena is an excellent example of the available talent in this upcoming generation of researchers, which must not be lost. With the diabetes landscape changing so quickly, it is especially important to train this group of researchers in my lab, as they will continue to discover better ways to prevent and treat heart disease in people with diabetes. The goal of the ADA-Takeda award is to provide Dr. Sena with a strong environment to receive the training necessary to become a leading contributor to this goal.

Our project entitled "Molecular Pathogenesis of Diabetic Cardiomyopathy" increases our understanding of the ways in which diabetes leads to heart muscle damage. Dr. Sena is conducting experiments to further understand how diabetes results in malfunctioning mitochondria in the heart. Mitochondria are the cellular organelles responsible for the production of cellular energy.

Through our experiments, Dr. Sena and other members of the laboratory are focusing on: 1) understanding the role that insulin resistance plays in the regulation of mitochondrial function in the heart, particularly in the context of cardiac hypertrophy and cardiac ischemia; 2) identifying novel roles for insulin signaling in the heart that may contribute to cardiac muscle injury in diabetes; and 3) understanding how increased dietary lipid might lead to cardiac dysfunction in diabetes.

Ultimately, we hope these discoveries might lead to new treatments aimed at preventing heart failure in people who have diabetes or are obese and/or insulin-resistant. I am pleased to report that, so far in the last 18 months, we have found that decreased insulin signaling in the heart, as occurs in diabetes, impairs the function of mitochondria. Therefore, treatments designed to increase the heart's sensitivity to insulin might improve mitochondrial and heart function, thereby lessening the impact of diabetes on the heart.

We also found that as little as two weeks of a high-fat and high sucrose diet caused the heart to significantly increase the amount of fatty acid that it metabolizes and reduces the amount of glucose that is metabolized. This pattern is associated with a reduced ability of the heart to efficiently utilize oxygen to make energy for heart muscle contraction. This suggests that short-term changes in diet can have a profound effect on heart function. Our laboratory research efforts clearly show that rigorous research programs hold the promise of not only discovering causes of diabetic complications, but also for developing new insights into treatments for diabetes and its complications.

Diabetes complication research has dramatically increased in scope over the past few decades. Our lab has been actively engaged at the forefront of the effort to better understand cardiovascular complications. At the same time, as we advance our knowledge of mechanisms of cardiovascular complications associated with diabetes, we are also training the next generation of researchers. Research solves problems, informs the direction in which new therapeutic developments should occur and provides the human capital to continue new discoveries in the future.

Every dollar spent on diabetes research is an immense investment in our future—in healthcare dollars and, most importantly, in lives. Although there are groups of individuals who are genetically predisposed to have diabetes, all classes, age groups and genders can be affected and die from its complications. Diabetes can strike anyone. As the number of people with diabetes increases, the world will incur a great burden of disease and its devastating cardiovascular complications. We believe our efforts will help to lessen, or perhaps eliminate, this burden.

Dr. Abel and postdoctoral fellow Sandra Sena, PhD
The role of fat in obesity-related cardiovascular complications

It is well known that obesity predisposes individuals to insulin resistance, type 2 diabetes, and cardiovascular complications. The specific causes of obesity-related cardiovascular complications are unclear. However, with funding from the American Diabetes Association, we are getting closer to uncovering the answers we desire.

J. David Symons, PhD, of the University of Utah is examining cardiovascular complications such as hypertension (high blood pressure) and arterial dysfunction (inability of blood vessels to function appropriately) in mice. He is the recipient of a Basic Science Award. In his research entitled “The role of ceramide in obesity-related vascular dysfunction” Dr. Symons explains that persons with diabetes are predisposed to cardiovascular complications such as high blood pressure and poor vessel function. Obtaining information about these complications is key in the fight against diabetes.

Dr. Symons is specifically focusing on the contribution of the breakdown of fat during metabolism and how it relates to high blood pressure and blood vessel dysfunction. Using mice that consume a high fat diet, pharmacological and genetic methods are being used to eliminate the contribution from one product of fat metabolism called ceramide. As Dr. Symons explains, “This could be directed toward development of an intervention that might have similar effects in humans.”

Dr. Symons is testing the hypothesis that increased accumulation of ceramide in response to over nutrition (e.g., high-fat feeding) might contribute to cardiovascular complications by reducing the available amount of a chemical compound called nitric oxide. Nitric oxide is a vasodilator (widens and relaxes the blood vessels) and it is also produced by cells that line the inner surface of the blood vessels. There is a delicate balance between the production of nitric oxide and the destruction of this compound. If the destruction of nitric oxide (e.g., by ceramide) outweighs the production of this compound, the balance might be tipped toward developing cardiovascular complications.

Preliminary results have supported his hypothesis. For example, mice that consume a high fat diet and become obese develop cardiovascular complications. Interestingly, when mice consume a high fat diet and are treated with blockers of ceramide production, the cardiovascular complications do not develop. Similar results have been obtained when individual blood vessels are incubated directly with the saturated fatty acid palmitate (a fatty acid that is commonly consumed by humans). In these studies palmitate causes blood vessel dysfunction. Again, these effects can be markedly improved when the accumulation of ceramide is prevented.

Dr. Symons research now is focusing on exactly how ceramide might reduce nitric oxide bioavailability and promote cardiovascular complications. Dr. Symons comments, “An urgent need exists to define the factors that contribute to cardiovascular complications so that new therapeutic targets and interventions can be designed. I would not be able to continue this research without the generous funding from the American Diabetes Association. I am grateful to the Association for finding the research worthy and the donors for providing the financial support.”