Hypotheses Explaining the Mystery of Diabetic Cardiomyopathy Include Fatty Acids, Transcription Factors

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Factors such as fatty acids, sex differences, and little-known transcription factors may account for some of the mystery of why diabetes is toxic to the myocardium. The evidence for these factors and how they contribute to diabetic cardiomyopathy (DC) were reviewed in a symposium.

Changes in diet and exercise are insufficient to improve outcomes in patients with DC, according to Clay F. Semenkovich, MD, Washington University School of Medicine St. Louis, Missouri, USA. The Look AHEAD study in 5145 participants with type 2 diabetes (T2DM) showed that weight loss did not reduce cardiovascular (CV) events, and that a >8% reduction in weight in Year 1 was associated with only a 1.3% rate of diabetes remission. Further, near ideal glycemic control, statin therapy, and inhibition of the renin angiotensin system (RAS) do not prevent premature death from heart disease.

While it is known that lipids contribute to heart disease, the role of fatty acids from certain sources to prevent or limit the consequences of heart failure in diabetes is not widely appreciated.

Insulin regulates the enzyme fatty acid synthase to promote fatty acid synthesis, a process which normally occurs only in nutrient-rich cells, but which is inappropriately turned on in the failing heart. Turning on fatty acid synthase channels lipids to the production of phospholipids. This may be one link between diabetes and cardiomyopathy, and may suggest therapeutic possibilities, such as drugs that modify phospholipids and thereby reduce cardiomyopathy, Dr. Semenkovich suggested.

T2DM is a major risk factor for the development of cardiac dysfunction and heart failure, even if ischemic heart disease is excluded, according to Linda R. Peterson, MD, Washington University School of Medicine, St. Louis, Missouri, USA.

Both T2DM and obesity without T2DM are independent risk factors for the development of heart failure. Men and women, however, do not have the same risk of heart failure with either T2DM or obesity. Both obese and diabetic women have a greater risk of developing heart failure than men.

Substrate metabolism is needed for the generation of adenosine triphosphate (ATP) and cardiac function. Free fatty acids (FFA) are the primary energy source for the myocardium. However, excessive uptake and oxidation and/or storage of fats can cause myocardial dysfunction in animal models of T2DM. In humans with T2DM myocardial utilization of FFA is much higher in women, likely because they typically have a higher percentage of body fat and higher plasma FFA levels than men.

A number of studies now show that sex was the predominant predictor of myocardial fat metabolism. Plasma FFA levels, FFA uptake, and fat oxidation were higher in diabetic women than men, even after controlling for obesity and body mass index. Furthermore, when women move from being obese to having diabetes, although the total amount of FFA oxidized increases the percentage of FFA oxidized decreases. That is to say that the amount of FFA taken up overwhelms even the increased oxidation rate in the diabetic woman's heart.

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Whether these sex-related changes in myocardial metabolism cause part of the sex-related differences in heart failure rates in obese and diabetic humans is not yet clear. However, it is also interesting to note that the hearts of men and women with T2DM do not respond in the same way to the standard diabetic therapies. For example, the myocardium in women decreases its FFA utilization significantly in response to rosiglitazone, but the myocardium in men does not. In sum, sex has a major effect on myocardial metabolism, and response to therapy, and may play a role in the known sex-related differences in the development of diabetic cardiomyopathy.

The role of biomarkers, such as the Forkhead box-containing O family of transcription factors (FOXO), which play an important role in determining how insulin affects the heart, was reviewed by Joseph A. Hill, MD, PhD, Southwestern Medical Center, Dallas, Texas, USA.

FOXO1 and FOXO3 are highly expressed in the myocyte, and have been shown to control insulin signaling in the heart. Their persistent activation leads to insulin resistance and then diabetic cardiomyopathy, according to Dr. Hill. The FOXO family has been shown to control cell death and remodeling in the muscle and liver. Thus, it is possible that FOXO factors also control the life cycle of myocytes.

In addition, FOXO lies at the extremity of the insulin signaling cascade; when insulin binds to a cell, it causes the inactivation of FOX O actors, leading to glucose uptake. But if FOX O is overexpressed in cells, they become insulin-resistant, and the insulin cascade is interrupted.