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TRANSLATIONAL PERSPECTIVES

Potentiation of Insulin Signaling Contributes to Heart Failure in Type 2 Diabetes

A Hypothesis Supported by Both Mechanistic Studies and Clinical Trials

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SUMMARY

The heightened risk of heart failure in type 2 diabetes cannot be explained by the occurrence of clinically overt myocardial ischemic events or hyperglycemia. Experimentally, insulin exerts detrimental effects on the heart, vasculature, kidneys, and adipose tissue that can lead to heart failure. In both randomized clinical trials and observational studies, antihyperglycemic drugs that act through insulin signaling (i.e., sulfonylureas, thiazolidinediones, and incretins) increase the risk or worsen the clinical course of heart failure, whereas drugs that ameliorate hyperinsulinemia and do not signal through insulin (i.e., metformin and sodium-glucose cotransporter 2 inhibitors) reduce the risk of heart failure. (J Am Coll Cardiol Basic Trans Science 2018;3:415–9) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The primary aims of the treatment of patients with type 2 diabetes are control of hyperglycemia and reduction in the risk of macrovascular and microvascular events. Historically, the definition of macrovascular events has generally focused on the occurrence of occlusive or thrombotic events in atherosclerotic vessels (i.e., myocardial infarction, stroke, and major limb ischemia); however, heart failure is a common and serious complication of type 2 diabetes (1), and its occurrence cannot be explained by ischemic injury to the heart. Little is known about why heart failure is so common in patients with type 2 diabetes, even when cardiovascular risk factors are well-controlled (Supplemental Appendix A).

The most distinctive feature of type 2 diabetes is hyperinsulinemia. Insulin can exert important adverse effects on the heart, vasculature, kidneys, and adipose tissue, which can hasten the onset of heart failure or lead to worsening of its clinical course. Of interest, the phenotype of heart failure appears to differ in patients with types 1 and 2 diabetes, possibly because only the latter patients have sustained hyperinsulinemia. Furthermore, many antidiabetic drugs that work through the actions of insulin have been associated with an increased risk of heart failure and an increased mortality in patients with established symptoms (1). By contrast, antihyperglycemic drugs that do not depend on insulin signaling often reduce the risk of heart failure, and it

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is possible that their action to ameliorate hyperinsulinemia contributes to this benefit (Supplemental Appendix A).

EFFECT OF INSULIN ON THE HEART, VASCULATURE, KIDNEYS, AND ADIPOSE TISSUE

Insulin receptors are ubiquitously expressed and are abundant in the heart and blood vessels. Interaction of insulin with its receptors leads to activation of 2 intracellular pathways: the Akt/mTOR signaling cascade and the mitogen-activated protein kinase (MAPK)/extracellular-regulated kinase pathway. Experimentally, overexpression of Akt leads to pathological cardiac hypertrophy, and if sustained for long periods, to heart failure. A reduction of insulin or Akt signaling in murine models of cardiac hypertrophy prevents heart failure, suggesting that this mechanism contributes to adverse cardiac remodeling. At the same time, activation of the MAPK/extracellular-regulated kinase pathway depresses cardiac contractility and enhances matrix remodeling, even in the absence of hypertrophy; it may also lead to the release of proinflammatory cytokines, leading to fibrosis. Either pathway (acting alone or in concert) might provide a molecular basis for an effect of insulin to cause heart failure (Supplemental Appendix B).

Hyperinsulinemia may also have important effects on the structure and function of the vasculature. Although insulin signaling through the Akt pathway might be impaired in endothelial cells in states of insulin resistance, activation of MAPK signaling pathways remains active, resulting in the induction and potentiation of various endogenous vasoconstrictors. Additionally, insulin can contribute directly to vascular smooth muscle cell hyperplasia (Supplemental Appendix B).

Insulin exerts a powerful antinatriuretic action, which may have evolved to counter the natriuresis caused by hyperglycemia. The infusion of insulin increases sodium reabsorption in the proximal and distal tubules, promotes the actions of angiotensin II, and inhibits the effects of endogenous natriuretic peptides. Insulin can directly increase activity of numerous ion transport mechanisms in the renal tubules, including the epithelial sodium channel, sodium-phosphate cotransporter, sodium-hydrogen exchanger type 3, and sodium-potassium adenosine triphosphatase (Supplemental Appendix B).

Additionally, insulin promotes adipogenesis by facilitating the transition of mesenchymal cells into preadipocytes and by enhancing their differentiation into mature fat cells (Supplemental Appendix C). Such an action may be particularly important if it occurs in epicardial adipose tissue, which is characteristically hypertrophied in type 2 diabetes (2). The accumulation and dysfunction of epicardial adipose tissue causes the release of numerous proinflammatory adipocytokines, which can adversely affect the structure and function of the adjoining myocardium, with which it shares an unobstructed microcirculation. This inflammatory response may lead to microvascular rarefaction and cardiac fibrosis, both of which can impair ventricular distensibility. Insulin can also promote fibroblast proliferation in the myocardium and the secretion of collagen, further impairing the ability of the cardiac chambers to enlarge (Supplemental Appendix C). If the antinatriuretic action of insulin leads to plasma volume expansion, the net result is ventricular overfilling, which leads to the syndrome of heart failure with a preserved ejection fraction. This phenotype is particularly common in patients with type 2 diabetes. Insulin can therefore exert adverse effects on the heart, vasculature, kidneys, and adipose tissue, which (acting in concert) can lead to heart failure or accelerate the clinical course of the disease (**Figure 1**).

CONTRASTING EFFECTS OF TYPES 1 AND 2 DIABETES ON HEART FAILURE

If insulin exerts adverse biological and pathophysiological effects that lead to heart failure, then the incidence of heart failure might be expected to differ in patients with type 1 versus type 2 diabetes because only the latter characteristically have sustained hyperinsulinemia (Supplemental Appendix D). In the only prospective study in type 1 diabetes that measured ventricular function and biomarkers of heart failure, the incidence of heart failure over a 7-year follow-up period was low, unless patients developed overt hypertension or coronary artery disease (3). In contrast, the incidence of heart failure is increased 2- to 3-fold in type 2 diabetes, and this risk cannot be readily attributed to known cardiovascular risk factors.

Differences in the cardiac effects of types 1 and 2 diabetes have also been observed in animal models of the 2 diseases (Supplemental Appendix D). Rodent models of type 2 diabetes, including *db*/*db* mice, *ob*/*ob* mice, and Zucker diabetic fatty rats, exhibit notable degrees of ventricular hypertrophy and fibrosis, which is accompanied by mitochondrial dysfunction, oxidative stress, abnormalities of calcium handling, and activation of neurohormonal systems. Echocardiographic studies reveal both systolic and diastolic dysfunction. In contrast, animal