Optimal glycemic control improves outcomes of chronic heart failure

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Abstract

There is a high prevalence of heart failure in patients with diabetes mellitus due to hyperglycemia-induced metabolic disturbances and remodeling of myocardium, as well as increased incidence of ischemic cardiomyopathy. Patients with heart failure and concurrent diabetes have an increased mortality and hospital readmission than those without diabetes. Little is known about the impact of diabetes control on the clinical outcomes of heart failure. It is likely that optimal control of diabetes with insulin or other hypoglycemic agents restores myocardial metabolic imbalance and reduces mortality and hospital readmission in heart failure.

INTRODUCTION

Previous studies have suggested that the prevalence of heart failure is several times higher in diabetic patients than in age-matched control subjects ([1], [2]). Recent clinical studies have also demonstrated that diabetes mellitus has significant impact of on prognosis in patients with heart failure. Patients with diabetes and heart failure have a higher mortality and hospitalization rates than patients with heart failure but no diabetes ([3],[4],[5],[6],[7]). The increased risk for adverse cardiovascular outcomes seems to occur mainly in diabetic and heart failure patients who had developed ischemic cardiomyopathy ([4]). In contrast, in patients with nonischemic aetiology, diabetes was not a predictor for all-cause death or cardiovascular death, or even associated with a decrease in cardiovascular mortality ([4]).

Given the significant negative impact of diabetes on heart failure outcomes, the potential of glycemic control in improving the outcome of diabetic patients with heart failure has not been fully examined. It is likely that optimal glycemic control might be able to reduce mortality and hospitalization in heart failure patients with diabetes, and should be considered as part of a comprehensive management strategy in such patients.

PATHOPHYSIOLOGY OF HEART FAILURE IN DIABETICS

The mechanisms of diabetes in leading to heart failure are not entirely clear. Recent studies have suggested several specific cellular or metabolic pathways where diabetes may compromise myocardium leading to heart failure.

First, the coexistence of myocardial ischemia, hypertension, and a specific diabetic cardiomyopathy seems to independently and cooperatively contribute to biochemical, anatomic, and functional alterations in cardiac cells and tissues that impair cardiac function ([8]). Diabetic cardiomyopathy, characterized by myocellular hypertrophy and myocardial fibrosis, contributes to the high incidence and poor prognosis of heart failure. Diabetic cardiomyopathy has been found to be associated with depressed mechanical function, electrophysiological abnormalities, defects in subcellular organelles, and receptor downregulation because of chronically elevated catecholamine levels ([8]). Hypertension is a common complication of diabetes and is associated with further damage to the myocardial contraction and ventricular function through increased myocardial fibrosis and development of coronary artery disease or myocardial ischemia ([8]).

Diabetic heart failure patients may have a higher risk of coronary plaque rupture and thrombosis. Recurrent myocardial infarction is a major cause of death in patients with ischemic heart failure;in addition, non-fatal myocardial infarction may further deteriorate left ventricular function in patients with ischemic heart failure.

Second, autonomic dysfunction commonly seen in patients with diabetes may contribute the development of

cardiomyopathy and heart failure. Renin-angiotensin system and sympathetic nervous system are two important compensatory mechanisms to maintain a relatively stable hemodynamics in the early stage of ventricular dysfunction. Although activation of the adrenergic and renin-angiotensin systems is quite effective for short-term compensation, there are long-term adverse consequences of chronic activation of these systems that may override any initial benefit. The harmful effect of long-term activation of these systems include progressive loss of cardiac myocytes, cellular hypertrophy, depletion of high-energy phosphate reserves, and norepinephrine toxicitymay, all of which may lead to further decreases of ventricular function ([9]).

DIABETES AS A RISK PREDICTOR FOR HEART FAILURE

The prognostic importance of diabetes in patients with heart failure was demonstrated in the well-known Framingham publications ([3]). Retrospective analyses of the SOLVD trials have suggested that diabetic status may be useful as a prognostic indicator in HF patients ([10]). In this study, both all-cause mortality and cardiovascular mortality at a mean follow-up of 3 years were significantly higher in diabetic than in non-diabetic heart failure patients ([10]). Recent evidence suggests that the effect of diabetes mellitus on survival is more pertinent to heart failure of ischemic origin; diabetes mellitus is associated with an increased risk for all-cause mortality in patients with ischemic heart failure, but not in patients with non-ischemic heart failure ([11]). The effect of etiology was also recently studied in patients with advanced heart failure enrolled in the BEST trial which showed that diabetes conferred an increased risk for adverse cardiovascular events in patients with ischemic etiology ([13]). In contrast, in patients with nonischaemic etiology, diabetes was not a predictor for all-cause death or cardiovascular death ([12]). Diabetics with heart failure of nonischemic etiology may have opposite prognostic implications in heart failure with ischemic etiology. In a relatively large cohort of study, diabetes was actually associated with decreased cardiovascular mortality ([4]). The reasons for the reduced mortality in the non-ischemic heart failure are unknown and the results should be interpreted with caution.

SUMMARY

Although there are strong evidence for increased cardiovascular mortality in patients with heart failure and diabetes, there is little prospective study on the benefits of aggressive diabetes control in such patients. Patients with diabetes have an increased level of myocardial free fatty acids that have been shown to depress myocardial contractility and increase myocardial oxygen consumption ([13]). In a recent study that included 63% of cardiac surgery patients with and without diabetes, lowering glucose to normoglycaemia allowed a 32% reduction of mortality from multi-organ failure ([14]). In another study on patients with diabetes mellitus and acute myocardial infarction, standard treatment plus insulin-glucose infusion for at least 24 hours followed by multidose insulin treatment improved long term survival, and the effect seen at one year continues for at least 3.5 years, with an absolute reduction in mortality of 11% ([15]).

It is likely that optimal glycemic control with insulin or other hypoglycemic drugs plays an important role in improving the clinical outcomes of heart failure. Optimal glycemic control offers benefits in cardiac metabolism and performance in heart failure patients by decreasing myocardial free fatty acid oxidation and increasing glucose utilization, and may be particularly useful in heart failure patients with ischemic cardiomyopathy.

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