Editorial

Dysglycemia and Heart Failure Hospitalization

What Is the Link?

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Large epidemiological studies, including the Framingham Heart Study, the National Health and Nutrition Examination Survey, and the Cardiovascular Health Study, have shown that diabetes mellitus is an independent risk factor for the development of heart failure.\(^1\)\(^-\)\(^3\) Overall, the risk is approximately doubled, but the relative increase may be greater in younger compared with older individuals (and in younger women compared with younger men).\(^1\)\(^-\)\(^9\) In diabetic individuals, the risk of developing heart failure is greatest in those with an elevated body mass index, poor glycemic control (as indicated by hemoglobin A\(_1c\) level), nephropathy, retinopathy, and coronary heart disease.\(^1\)\(^-\)\(^9\)

In an investigation of 20,810 nondiabetic patients receiving care in Veterans Affairs medical centers, Nielson and Lange\(^11\) found that higher morning glucose was independently associated with a linear increase in risk of incident heart failure (clinic diagnosis or admission). Ingelsson and colleagues,\(^12\) in a study of 1187 Swedish men \(\geq70\) years of age, showed that 2-hour glucose during an oral glucose tolerance test (as well as fasting serum proinsulin concentration and clamp glucose disposal rate) was independently related to incident heart failure hospitalization.

These studies raise many questions. None describe the potential role of intercurrent events such as acute coronary syndromes (or even change in blood pressure) in explaining subsequent hospitalization for heart failure.\(^13\) Clearly, dysglycemia often is associated with a diffuse and aggressive form of coronary artery disease, which, in turn, could lead to myocardial injury and failure. Another potentially confounding issue is the known high prevalence of dysglycemia in patients with heart failure and even asymptomatic left ventricular systolic dysfunction (which was not an exclusion criterion in the present study).\(^14\) This issue raises the question of whether dysglycemia serves as a marker for preexisting (but unrecognized) ventricular dysfunction. Similarly, diabetes mellitus and dysglycemia are associated with worse symptoms and lesser functional capacity in patients with heart failure and left ventricular systolic dysfunction; therefore, dysglycemia may result in earlier presentation of patients.\(^14\) The role of the kidney also could be important because dysglycemia is associated with renal dysfunction. Whether serum creatinine concentration is an adequate measure of renal function (and therefore whether renal function has been adequately adjusted for) is open to debate. Concomitant therapies also could be important (eg, patients treated with a thiazide diuretic for hypertension might be at increased risk of both dysglycemia and heart failure).

Dysglycemia and heart failure may simply have common pathophysiological origins or drivers. For example, overactivity of the sympathetic nervous system has long been related to insulin resistance and is clearly important in heart failure.\(^15\)\(^,\)\(^16\) Similarly, that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers appear to prevent the development of heart failure and possibly diabetes mellitus suggests a role for the renin-angiotensin system in both conditions.\(^15\)\(^-\)\(^17\)

On the other hand, dysglycemia may, in some way, be directly implicated in the pathophysiology of developing heart failure (as opposed to acting as a marker for preexisting ventricular dysfunction or promoting an intercurrent event leading to myocardial injury). Why might this be? The first point to make is, of course, that glucose per se might not be the culprit. Hyperinsulinemia could be important, perhaps by causing myocardial hypertrophy.\(^15\)\(^,\)\(^16\) The formation of advanced glycosylation end products may cause collagen cross-linking and reduce ventricular distensibility and vascular compliance. Thus, it is a pity that none of the aforementioned studies described whether the cases of heart failure had a low or preserved ejection fraction. That information might have given a clue to the pathophysiological basis of the association between dysglycemia and heart failure, especially in view of the speculation that diabetes mellitus is associated with accelerated myocardial fibrosis, hypertrophy, and diastolic dysfunction.\(^15\)\(^,\)\(^16\)

Advanced glycosylation end products also have been proposed to cause modification of sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\) ATPase 2a. Hyperglycemia also may be...
associated with oxidative stress, altered intracellular signaling, decreased production of vascular endothelial growth factor, and altered gene expression. Similarly, autonomic neuropathy and microangiography are recognized complications of diabetes mellitus but may develop in early stages of dysglycemia. Another important consideration is myocardial metabolism, which may become more dependent on free fatty acids in dysglycemic states, resulting in uncoupling of oxidative phosphorylation and potentially reduced contractility.\textsuperscript{15,16}

The authors of the present report correctly point out that proof of the hypothesis that dysglycemia causes heart failure is a trial of blood glucose lowering. This notion is premature. As summarized above, the relationship between dysglycemia and heart failure remains an association without a clear mechanistic basis (which may not be direct). Of even greater and practical importance, the choice of blood glucose-lowering strategy would currently be problematic. Few would wish to use a thiazolidinedione for fear of precipitating heart failure.\textsuperscript{18} Metformin would have to be stopped after development of heart failure in view of its current (but probably unjustified) “black box” warning. Do we really want to start insulin in this population?

Held and colleagues\textsuperscript{18} have taken the field an important step forward and illustrated the importance of cardiovascular and diabetic physicians working together to better understand the relationship between dysglycemia and heart failure.

Disclosures

None.

References


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