GLP-1 Therapy
Beyond Glucose Control

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The number of diabetic patients is increasing at an alarming rate and, according to the World Health Organisation, is estimated to reach 300 million worldwide by the year 2025. Coronary heart disease is the leading cause of death in these patients. Diabetic patients are 2 to 3 times more likely to develop coronary heart disease, and they experience worse clinical outcomes after coronary artery angioplasty, cardiac bypass surgery, acute myocardial infarction, and the onset of cardiac failure. Clearly, new treatment strategies that are specifically directed to improving clinical outcomes in diabetic patients with coronary heart disease and in those patients who develop cardiac failure need to be developed.

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Emerging research studies suggest that newer antidiabetic therapies not only control glucose levels but also have an impact on cardiovascular disease. In this regard, glucagon-like peptide-1 (GLP-1), the synthetic analogue of which is already in clinical use as an antidiabetic therapy (exenatide), may exert beneficial cardiovascular effects independent of its glucose-lowering actions. The active form of GLP-1 is the amide GLP-1(7-36), which is secreted by entero-endocrine L cells of the ileum and colon in response to a meal. GLP-1(7-36) reduces postprandial hyperglycemia and induces weight loss by stimulating insulin secretion from β cells in the pancreas (its incretin action), inhibiting glucagon secretion from pancreatic α cells, inhibiting gastrointestinal secretion and motility, and causing satiety by acting on appetite-control centers in the brain (reviewed in reference 2). These GLP-1 effects are mediated by binding to the GLP-1 receptor, which is a G-coupled receptor linked to adenylate cyclase via a stimulatory G protein and is expressed in pancreatic islet cells and in the kidney, lung, brain, gastrointestinal tract, and heart. The half-life of GLP-1(7-36) in circulation is very brief (1 to 2 minutes), as it is rapidly degraded by the enzyme dipeptidyl peptidase-IV (DPP-IV) to the metabolite GLP-1(9-36), which does not act at the GLP-1 receptor. Importantly, as an antidiabetic agent, GLP-1 does not cause hypoglycemia, as both its stimulatory effect on insulin secretion and its inhibitory action on glucagon release are inhibited in the presence of plasma glucose levels at or below fasting levels.

Clearly, diabetic patients benefit from the cardiovascular risk reduction accrued from the glucose-lowering and weight-reducing effects associated with GLP-1 therapy. However, experimental studies have described non–glucose lowering effects on the cardiovascular system with GLP-1(7-36) treatment. These were initially observed in preconstricted pulmonary arteries, in which vasodilatation was induced by GLP-1(7-36) in an endothelium-dependent manner. Subsequent studies have reported that GLP-1(7-36) is capable of improving endothelial function in a hypertensive rat model as well as in diabetic patients with stable coronary heart disease. Several experimental rodent studies have observed an increase in both arterial blood pressure and heart rate in response to GLP-1(7-36) treatment, an effect that has been attributed to central regulation of the autonomic nervous system. Furthermore, mice lacking the GLP-1 receptor were reported to have lower heart rates, worse left ventricular (LV) diastolic function, greater LV wall thickening, and impaired LV contractile function, suggesting a potential endogenous cardiovascular role for GLP-1(7-36). However, this hemodynamic effect associated with GLP-1(7-36) treatment in rodent hearts was not reproduced in the porcine heart. Similarly, clinical studies of diabetic patients have reported no change in either arterial blood pressure or heart rate after a chronic subcutaneous infusion of GLP-1(7-36).

However, in the failing myocardium, several studies led by Shannon’s research group have reported that GLP-1(7-36) therapy confers beneficial effects on LV contractile function. In a canine model of pacing-induced dilated cardiomyopathy, 48-hour treatment with GLP-1 improved myocardial insulin sensitivity and glucose uptake, increased stroke volume and cardiac output, and decreased LV end-diastolic volume, heart rate, and systemic vascular resistance. Using a canine model of myocardial stunning, 24-hour therapy with GLP-1 improved regional contractile function. In a small proof-of-concept clinical study comprising 21 patients presenting with an ST-segment elevation myocardial infarction and impaired LV systolic function (LV ejection fraction <40%) who were undergoing primary percutaneous coronary intervention, a 72-hour GLP-1 infusion improved LV ejection fraction from 29% to 39% in both diabetic and nondiabetic patients. In 12 patients with chronic heart failure (New York Heart Association class III and IV), 5 weeks of chronic GLP-1 treatment increased LV ejection fraction from 21% to 27%, augmented maximum myocardial oxygen consumption, and improved the 6-minute walk test and quality of life in both diabetic and nondiabetic patients. In 10 patients undergoing cardiac bypass surgery, 48 hours of GLP-1 therapy (starting 12 hours before surgery) improved LV ejection fraction from 28% to 45%, increased left ventricular stroke work index from 24% to 56%, and improved 6-minute walk test and quality of life scores.
before surgery) reduced inotrope requirements and improved glycemic control, although it did not improve LV ejection fraction, in both diabetic and nondiabetic patients.\textsuperscript{15} The mechanism through which GLP-1 improved LV contractile function in these different settings is unclear, although it may in part be because of increased myocardial glucose uptake.

Findings from our laboratory suggest that GLP-1(7-36) therapy is capable of limiting acute myocardial ischemia-reperfusion injury, as evidenced by a reduction in myocardial infarct size in both the isolated and in situ rat heart when GLP-1(7-36), coadministered with a DPP-IV inhibitor, was given to the heart before a period of sustained ischemia followed by reperfusion.\textsuperscript{16} In addition, we have also observed, in an isolated rat heart model, that GLP-1(7-36) is protective against myocardial ischemia-reperfusion injury when given either as a preconditioning mimetic or at reperfusion.\textsuperscript{17} The mechanism underlying this cardioprotective effect is independent of any effect on glucose and has been linked to GLP-1 receptor activation and recruitment of intracellular signaling pathways involving Akt, Erk1/2, p70S6K, and AMPK and its metabolite GLP-1(9-36) may be capable of exerting some of the beneficial cardiovascular effects of GLP-1(7-36), the metabolite that is generated by DPP-IV, is also capable of increasing myocardial glucose uptake, improving LV contractile function in a canine model of pacing-induced dilated cardiomyopathy,\textsuperscript{19} improving posts ischemic myocardial injury and LV contractile function,\textsuperscript{20} and inducing vasorelaxation through a mechanism that involves nitric oxide and cGMP.\textsuperscript{20} The situation is further complicated by the recent report that some of the beneficial cardiovascular effects of GLP-1(7-36) have been shown to be present in mice lacking the GLP-1 receptor.\textsuperscript{20} These findings suggest that there may be a currently unidentified GLP-1 receptor or that GLP-1(7-36) and its metabolite GLP-1(9-36) may be capable of exerting non–receptor-dependent effects on the cardiovascular system.

In this issue of Circulation: Heart Failure, a new study by Shannon’s research group\textsuperscript{21} has demonstrated beneficial cardiovascular effects with chronic GLP-1(7-36) therapy (comprising 3 months of subcutaneous infusion) in a rat model of progressive, hypertensive-related heart failure, in terms of preserved LV systolic function, less cardiac apoptosis, increased myocardial glucose uptake, and most importantly, improved survival (from 44\% to 72\%). This is the first study to examine the effect of chronic GLP-1 therapy on survival in a clinically relevant heart failure experimental model, and the findings suggest that this therapeutic strategy may improve clinical outcomes in patients with cardiac failure. To ascertain whether the cardioprotective effects of GLP-1 are maintained with chronic therapy in this particular heart failure model, it would have been interesting to determine whether the myocardium was more resistant to myocardial infarction. In addition, whether this therapeutic strategy confers the same beneficial effects in the diabetic failing myocardium remains to be determined.

The use of GLP-1 as a clinical therapy, however, is hampered by the need to administer it as an infusion, because it is rapidly broken down in plasma by DPP-IV. Therefore, as a therapeutic antidiabetic strategy, synthetic analogues of GLP-1 (such as exenatide and liraglutide) that are resistant to the degradative actions of DPP-IV have been developed. In addition, pharmacological inhibitors of DPP-IV that are capable of augmenting endogenous levels of GLP-1, such as sitagliptin and vildagliptin, are in clinical use. Another innovative, experimental, alternative approach to chronic administration of GLP-1 is to use adenoviral gene therapy, an approach that has been demonstrated to successfully treat hyperglycemia in a diabetic mouse model for up to 2 months.\textsuperscript{22}

Whether the beneficial cardiovascular effects observed with GLP-1 can be reproduced by these newer antidiabetic therapies needs to be investigated. It is important to appreciate that these 2 pharmacological approaches may have differing cardiovascular effects, depending on the extent to which the drug therapy potentiates either endogenous levels of GLP-1(7-36) or its metabolite GLP-1(9-36).\textsuperscript{20} Initial studies suggest that the GLP-1 analogue exendin-4 is capable of reducing myocardial infarct size when administered toperfused rat hearts at the onset of myocardial reperfusion.\textsuperscript{23}

Therefore, the ability of the newer antidiabetic agents such as GLP-1 to confer cardioprotection, independent of their effect on glucose levels, allows for the possibility of developing an antidiabetic therapy that not only combats hyperglycemia in diabetic patients but is also able to improve cardiovascular outcomes in diabetic and nondiabetic patients. Interestingly, the results of initial clinical studies examining chronic GLP-1 therapy seem to suggest that both nondiabetic and diabetic patients may benefit from its salutary cardiovascular effects.\textsuperscript{13-15} Clearly, further experimental and clinical studies are needed to determine whether synthetic GLP-1 analogues and DPP-IV inhibitors are able to reproduce the beneficial effects of GLP-1 therapy in terms of protection from acute myocardial ischemia-reperfusion injury and the consequences of cardiac failure.

Disclosures

None.

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