

Pleiotropic Effects of GLP-1. Cardiovascular Evidence of Effectiveness

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ABSTRACT

Patients with diabetes are characterized by the development of cardiovascular complications: nephropathy, retinopathy, neuropathy, ischemia or hypertensive etc. Therefore, the cardiovascular involvement is the leading cause of death in patients with Diabetes Mellitus type 2 (DM2). Despite intensive treatment on classical factors of cardiovascular disease (blood pressure levels, LDL cholesterol, etc.), patients with diabetes have a high number of cardiovascular events and the onset and prognosis of these are related to glycemic control parameters, glycosylated hemoglobin (HbA1c). On the other hand, the question of the cardiovascular protective effect of some hypoglycemic treatments has been raised, asking what he has done to know more accurately about the safety and cardiovascular effects of the treatments we have today. The two most important incretin hormones are GIP (gastric inhibitory polypeptide) and GLP-1 (glucagon-like peptide-1). Treatment based on GLP-1 is a novel weapon in T2DM that achieves a reduction in HbA1c with other metabolic effects: weight loss and extra effect in dyslipidemia and blood pressure. In the last years other beneficial actions such a protector effect against myocardium ischemia and other actions in basals were reported. In this article we will try to explain the evidence of GLP-1 treatments and its cardiovascular effects.

Keywords: GLP-1; T2DM; Myocardium Ischemia

1. Introduction

The incidence of type 2 diabetes is a health problem now and with future prospects uncertain. It is estimated to reach 300 million diabetic patients in the coming years [1]. Patients with diabetes are characterized by the development of cardiovascular complications: nephropathy, retinopathy, neuropathy, ischemia or hypertensive etc. [2]. Therefore, the cardiovascular involvement is the leading cause of death in patients with Diabetes Mellitus type 2 [3]. Despite intensive treatment on classical factors of cardiovascular disease (blood pressure levels, LDL cholesterol, etc.), patients with diabetes have a high number of cardiovascular events and the onset and prognosis of these are related to glycemic control parameters, glycosylated hemoglobin (HbA1c) [4].

On the other hand, it has raised the question of the cardiovascular protective effect of some hypoglycemic

treatments, rosiglitazone, [5,6] asking what he has done to know more accurately about the safety and cardiovascular effects of the treatments we have today.

2. Incretins

The incretin effect is known as the amplification of the insulin response that occurs after oral ingestion of glucose in the administration of an equivalent amount intravenously. This effect is responsible for up to 60% of the increase in insulin secretion after ingesta [7].

Incretins are intestinal peptides original in response to intake. Among its effects include stimulation of insulin production, suppression of glucagon thereby reducing hepatic glucose production and inhibition of β -cell apoptosis [8]. Nauck *et al.* [9], showed in 1986 that the incretin effect was decreased in patients with type 2 diabetes because they decrease in the concentrations of GLP-1

(and GIP), after ingestion. Its efficacy is mediated by its action on GLP-1 receptor abundantly expressed in the gastrointestinal tract but may be present also in pancreatic tissue, lung and stomach, nervous system, heart, vascular smooth muscle cells and macrophages. For this reason, besides the already mentioned hypoglycemic effect, GLP-1 effects are attributed regulation about the appetite, decreased gastric emptying, increased peripheral insulin sensitivity, as well as neuro and cardioprotective effects [4,10]

Thus, treatments aimed at acquiring an incretin effect have been for many years an attractive therapeutic target that nowadays is part of our medical arsenal. Also we have drugs GLP-1 analogues resistant to inactivation of the enzyme DPP-4 (liraglutide), incretin mimetics resistant to DPP-4 (exenatide) and inhibitors of the enzyme DPP-4 (vildagliptin, sitagliptin, saxagliptin).

3. GLP-1 and Cardiovascular Risk Factors

Exenatide has shown a reduction of about 1% in HbA1c in patients without prior treatment or with sulfonylureas and metformin alone or in combination. It also adds a beneficial effect on fasting blood glucose and postprandial glucose [11-14], with a reduction in weight up to 5.3 kg in those studies for 3 years [15]. Similarly Liraglutide reduces HbA1c over 1% in patients with different combinations of antidiabetic orales [16-18] and even compared to glargine insulin [19] with a beneficial effect on weight. In those studies comparing the effect of liraglutide vs. exenatide, liraglutide shows a greater reduction in HbA1c (-1.12% vs. 0.79%, $P < 0.05$) with similar effect on weight loss (3 kg approximately) in 26 studies weeks [20].

Furthermore, liraglutide and exenatide have shown a reduction in cardiovascular risk factors including dyslipidemia and blood pressure. In a meta-analysis of 6 studies performed more than 2000 patients exenatide showed a reduction systolic (SBP) without changes in diastolic blood pressure (DBP). This effect could not be explained completely by weight loss [21]. Liraglutide has demonstrated in the 6 studies LEAD a reduction of 2.5 mmHg SBP. This effect has been demonstrated in the first 2 weeks before the weight loss [22]. Regarding the lipid profile exenatide has demonstrated a decrease in the concentration of triglycerides by 12%, 5% total cholesterol, LDL 6% and increased HDL cholesterol by 24% in studies conducted at 3 years [15].

In addition to these cardiovascular effects have been reported in animal studies and human *in vitro* different actions of analogues of GLP-1 on macrophages and monocytes by decreasing their accumulation in atherosclerotic plaques and reducing production of inflammatory mediators such as TNF- α or CD11b expression [23].

4. GLP-1 in the Cardiovascular System

Vascular function:

Different studies in healthy patients have been conducted to determine the effect of acute or chronic analogs of GLP-1 in the endothelium. First, the acute treatment has been shown to increase blood flow to endothelium-dependent vascular level in non diabetic patients [24] and in diabetics with stable coronary disease [25]. Moreover chronic treatment with GLP-1 analogs has shown improvement in endothelial function and vasoconstriction in rats diabetes induced with estreptozocine [26]. In addition, some studies suggest that this improvement in endothelial dysfunction provides vasodilation and improved blood flow to areas distal, common site for the development of complications associated with diabetes [4]. One of the potential mechanisms by which GLP-1 analogs affect the vascular tree is due to the reduction of the toxic effect of glucose on the endothelial cell. GLP-1 has been shown to decrease the deleterious effect of advanced glycation products (AGE) in the endothelium [27].

Cardiac function:

Most studies designed to determine the effect of GLP-1 on cardiovascular function have focused on models of ischemia and reperfusion. Studies *in vivo* and *in vitro* with cardiomyocytes in mice have shown that after a period of ischemia and subsequent reperfusion, the mice treated with GLP-1 analogs significantly reduce the size of the infarct zone post-ischemia improve cardiac contractility, systolic function and diastolic function [28]. Similar experiments have given similar results in canine models of dilated cardiomyopathy [29] and porks [30]. In humans, a small, non-randomized study in patients, most non-diabetics, who had undergone coronary revascularization after acute myocardial infarction and to which he had been given an infusion of GLP-1 analogs for 72 hours, an improvement in ejection fraction and better left ventricular myocardial contractility had been reported. In this sense Sokos *et al.* [31] selected 20 patients who underwent aortocoronary bypass and who infused GLP-1 analogues. Observed in the treated group that the use of vasoactive or inotropic drug was lower and there were fewer arrhythmias. In additional studies, infusion of GLP-1 analogs for 48 hours in patients non-diabetics and heart failure reduced fasting glucose levels and insulin levels increased compared to placebo associated with an increased heart rate and blood pressure but no impact hemodynamics.

The mechanism by which it acts is not clarified. It is thought that the myocardium after ischemia increases glucose uptake. This increase improves glucose oxidation and producing more ATP than from the free fatty acids. In addition to this increased supply of glucose to

myocardial ischemia occurs a minor ischemic damage. That has been regarded as a cardioprotective effect of the myocardium with consequent smaller necrosis [32] zone. What we do not know if this action is mediated by GLP-1 receptor exclusively or by an intermediate metabolites such GLP-1 (9 - 36), an antagonist receptor have also shown beneficial effect after ischemia [4].

5. Conclusion

Therapies based on incretins, GLP-1 have proven to be an effective treatment for glycemic control with very beneficial effects on weight, blood pressure and lipid profile. Moreover, although the results are preliminary, we observe a beneficial effect on associated complications of DM2. The modifications to the atherosclerotic plaques and improving endothelial dysfunction make us foresee a very beneficial effect on cardiovascular disease prevention. On the other hand, with the data in models of ischemic heart disease, and the cardioprotective effect of GLP-1, demonstrated in animal and human experiments, we do consider the possibility of a beneficial effect beyond the treatment of cardiovascular risk factors. However, the data in the treatment in diabetes and heart failure are not as conclusive. In these patients, we must not forget the side effects of current therapies against type 2 diabetes: the water retention of glitazons and insulin or the contraindicated indication of metformin in patients with renal failure. Although larger, prospective, randomized studies are needed in order to determine the safety of GLP-1 analogs in heart failure, we can not discard them when planning the best treatment for this kind of patients.

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