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GLP 1 and Macrovascular Complications

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Abstract

Type two diabetes remains to be one of the most challenging chronic diseases affecting 26 million people in the United States. Despite advances in the management of this illness, a large number of diabetics suffer from disease related complications. Heart disease and stroke account for a significant percentage of death in diabetics. Advancing treatment options for diabetics beyond glycemic control and Hba1c levels to prevent macrovascular complications should be the target of our management. GLP1, a member of the pro-glucagon incretin family, and GLP1 analogues seems to have beneficial effects on the macrovascular levels, in addition to their established effect on the glycemic control. This article reviews the potential effect of GLP1 family on the macrovascular complications including cardiovascular, cerebrovascular, and peripheral vascular diseases.

Keywords: GLP-1; T2DM; HbA1c; Incretins; Macrovascular; Cardiovascular; Cerebrovascular; Peripheral vascular diseases

Introduction

Despite all the advances in the medical realm, type 2 diabetes remains a chronic health care problem with significant public health burden secondary to its macrovascular (stroke/myocardial disease and ischemia/and peripheral vascular disease) as well as microvascular complications (neuropathy/retinopathy/nephropathy). It is estimated that almost 26 million Americans (8.3 % of the United States population) are suffering from diabetes mellitus, in addition to 79 million cases of prediabetes [1]. When compared to non DM adults, death rates seems to be 2-4 folds more in DM patients [2]. In fact, both stroke and heart disease account for 65% of deaths in the DM patients. Moreover, it is well established that diabetic patients have worse prognosis post-acute myocardial infarcts [3,4,5].

While targeting the glycemic control is the main focus of diabetes management and care, addressing other parameters to prevent macrovascular disease is of great importance. Randomized clinical trial data from studies including the United Kingdom Prospective Diabetes Study (UKPDS) [6], The Veterans Affairs Diabetes Trial (VADT) [7], Action in Diabetes and Vascular Disease (ADVANCE) [8] and The Diabetes Control and Complication trial (DCCT) [9] demonstrated the effect of strict glycemic control in reducing the microvascular complications of diabetes when compared to standard glycemic control. However, the impact of this intensive glycemic control is less clear and doesn't appear to affect the macrovascular complications [10]. Given these facts, the US Food and Drug Administration recommended that manufacturers of new antidiabetes drugs should provide evidence that their regimens don't increase the cardiovascular events [11]. Preferentially, antidiabetes drugs should have favorable effects on macrovascular outcomes, reducing the risks of myocardial infarctions, stroke and heart failure. Recently, a new class of drugs, the glucagonlike peptide, has emerged with promising macrovascular protective effects [12].

Glucagon like peptide 1 (GLP1), a member of pro-glucagon incretin family, is secreted by the L cell of the intestine postprandially. The majority of circulating GLP1 is GLP1 (7-36) which is rapidly metabolized by the enzyme dipeptidyl peptidase 4 into GLP1 (9-36). GLP1 has several proven biological actions in both diabetics and healthy individuals, mediated through a G-protein-coupled receptor (GLP1-R). This receptor is present abundantly as expected in the GI

tract, but surprisingly is also available in the heart, nervous system, endothelial cells, vascular smooth muscle cells, and macrophages [13].

GLP1 seems to (a) stimulate insulin secretion in a glucose dependent manner (b) reduce glucagon secretion (c) suppress appetite and food intake (d) and slow gastric emptying [14,15]. Currently, GLP1 analogues has been approved for the treatment of type two diabetes and are included in the 2009 recommendations of the American Association of Clinical Endocrinologists/American College of endocrinology (AACE/ACE) consensus panel for patients with HbA1c in the range of 7.6%-9% as a dual therapy with metformin [16]. Moreover, the 2009 American Diabetes Association ADA/European Association for the Study of Diabetes (EASD) consensus algorithm for initiating and adjusting antidiabetes medication include GLP1 agonists as part of tier 2 agents to be considered after patients are started on tier 1 therapies (lifestyle changes, metformin, followed by the addition of either sulfonylurea or basal insulin) [17].

The FDA approved GLP1 analogues include: 1) liraglutide for once daily injection; 2) exenatide twice daily injection and long- acting release exenatide recently approved by the FDA (January 2012).

Other drugs are still in phase 3 trials (Lixisendatide bid/ZP10 and Albiglutide) [18].

In view of the high prevalence of macrovascular complications in the diabetic population, and the absence of an antidiabetic agent capable of targeting these complications as well as the glycemic control, we will be discussing the macrovascular effects of GLP1 analogues, focusing on their potential beneficial influence on cardiovascular, cerebrovascular and peripheral vascular complications.

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GLP1 and Cardiovascular Disease

GLP1 and myocardial ischemia

Being a major complication and a direct cause of mortality in diabetic patients, myocardial ischemia seemed to be an encouraging topic to the researchers to look into, in order to reduce its impact and occurrence in diabetic patients. A variety of research studies have dwelled into the role of GLP1 on both the infarct size and pre ischemic conditioning. Interestingly, GLP1 administration seemed to have beneficial effects on both parameters.

Both *in vitro* and *in vivo* studies in rat models with myocardial ischemia have demonstrated the ability of GLP1 to reduce the infarct size. For example, Bose et al. demonstrated that GLP1 infusion in the presence of DPP-4 inhibitor significantly decreased the infarct size at the end of 2hr reperfusion injury following 30 min of ischemia in rat models [19]. Another study also proved the cardioprotective effect of exendin (GLP1 analogue) regarding infarct size in mice models and its ability *in vitro* to increase the survival of cardiomyocytes exposed to hypoxia [20]. Moreover, Ban et al. studied the myocardial contractility and coronary blood flow post ischemia in mouse perfused heart model infused with GLP1 and GLP1 (9-36) metabolite. Both myocardial contractility and coronary blood flow were improved post infusion [13].

GLP1 also improved myocardial contractility in post ischemic rat hearts [21], and dogs with pacing- induced dilated cardiomyopathy [22]. However, an early study looking at the effect of GLP1 infusions in non-diabetic porcine models with 60 min ischemia followed by 2hr reperfusion showed no effect on infarct size [23].

In addition to its cardioprotective effects on non-diabetic hearts, GLP1R agonists have also been shown to have beneficial effects on hearts of diabetic mice models. Pretreatment with liraglutide was able to reduce the infarct size and improve the cardiac function of both diabetic and non-diabetic rats post either myocardial infarction or ischemia /reperfusion injury [24]. However the cardioprotective effect of GLP1 demonstrated in animals models both *in vivo* and vitro needs further validation in the clinical setting especially with the promising results available.

GLP1 and left ventricular function

Left ventricular function is one of the major parameters affected post myocardial ischemia. An acute myocardial ischemia in surviving post MI diabetics is often translated into a decrease in the left ventricular function. Given this fact, the potential presence of a medication that improves the ventricular function post MIS and the quality of life in such patients is of great importance.

Recent data from animal studies and human clinical trials shows the effect of GLP1 in improving myocardial function, left ventricular (LV) function, cardiac output and increased quality of life.

In humans, 72 hour infusion of Glp1 was shown to improve LVEF, global and regional wall motion scores and decrease the hospital stay and mortality in human subjects with LV dysfunction and acute MI post angioplasty compared to control subjects [25]. Moreover, continuous GLP1 administration for 5 weeks in 12 subjects with New York Heart Association (NYHA) class 2-4 heart failure with or without diabetes revealed a significant improvement in LV function, functional status and quality of life [26]. Additionally, 60 hour GLP1 infusion in 20 subjects undergoing coronary artery bypass surgery resulted in improved glycemic control, decreased need for inotropic

support, vasoactive infusions and antiarrhythmic drugs [27]. Some other studies show conflicting outcomes. For example, Halbrik et al. demonstrated that a 48 hr course of GLP1 in non-diabetic patients with congestive heart failure (secondary to coronary artery disease), LVEF < 40%, and stable NYHA class 2 and 3 didn't improve significantly the cardiovascular function, although modestly increased both the heart rate and diastolic blood pressure [28].

Taken together, GLP1 seems to have a favorable outcome in patients with heart failure and diabetes that needs to be further proven in larger randomized controlled trials. There are two cardiovascular outcome trials with GLP 1 analogues that are ongoing. 9,000 subjects with type two diabetes are being followed for an average of 4.5 years to assess the effect of liraglutide on cardiovascular outcomes including MIs, cardiovascular death, and stroke in the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results-A long Term Evaluation (LEADER) trial. The results of this trial are expected to be out in 2016 [29]. Another trial, The Exenatide Study of Cardiovascular Event Lowering (EXSCEL), is exploring the impact of once daily long acting release exenatide injection in 9500 patients with type two diabetes on cardiovascular events. The results of this trial are anticipated to be available in 2017 [30].

GLP1 and cardiovascular risk factors

Diabetic patients suffer from multiple co-morbidities including obesity, dyslipidemia, high blood pressure and accelerated atherosclerosis all of which are independent risk factors for cardiovascular disease.

Interestingly, Glp1 and its agonists have been shown in a variety of studies to possess a positive impact on cardiovascular risk factors including blood pressure lowering effect, weight loss promotion and dyslipidemia/atherosclerosis reduction.

Blood pressure lowering effects of GLP1/GLP1R have been observed in type two diabetic humans. In a small double blind placebo controlled pilot study of normotensive type two diabetic individuals, exenatide lowered the systolic blood pressure with no effect on both the diastolic blood pressure and the heart rate [31]. Okerson et al. conducted a larger study with longer duration that also showed the ability of exenatide to reduce the systolic blood pressure as compared to placebo and insulin. The effect of exenatide in this study was more significant for hypertensive diabetic patients with systolic blood pressure readings above 150mm Hg [32].

Another randomized controlled trial in type two diabetic patients demonstrated that GLP1analogue liraglutide combined with metformin and/or rosiglitazone also reduced the systolic blood pressure when compared to placebo. Both 1.2 and 1.8 mg once daily doses of liraglutide were able to decrease the systolic blood pressure compared to placebo (decrease by 6.7mmHg and 5.6mm Hg verses 1.1 mmHg respectively). This study showed significant reduction of body weight in liraglutide treated subgroup, however it seems that the blood pressure lowering effect occurred before the weight loss [33].

Concerning body weight, randomized clinical trials looking at exenetide effect compared to insulin in 60 diabetic subjects on metformin therapy for a year showed significant reductions in body weight, waist circumference, and total body and trunkal fat (-6%,-5%,-11%-13% respectively) [34]. Another randomized open label clinical trial evaluated the administration of exenetide versus placebo in 217 diabetic patients on either metformin or sulfonylurea. The results showed decrease in body weight from baseline (-5.3 kg at 3 years), reduction in TG, total cholesterol, LDL concentration (12%, 5% and 6% at 3.5 years respectively), and a significant increase in HDL levels (24%) [35].

Recent data also support the ability of exenatide in reducing postprandial lipids and lipoproteins acutely independent of weight loss in subjects with glucose intolerance or recent onset diabetes [36]. Shwartz et al. demonstrated the ability of a single injection of exenatide prior to a high calorie fat enriched meal to decrease 8h increase in lipids, TG, and lipoproteins. Another recent retrospective study emphasized the effect of exenatide on lipids and weight loss. It reviewed 131 diabetic patients and revealed that treatment with exenatide for 1.5-3.5 years had maintained reductions in weight, systolic blood pressure, TG that reverted to baseline levels 6 months post exenatide cessation [37].

It is well known that macrophages, endothelial cells, and cardiomyocytes contain GLP1R. GLP1 seems to exhibit protective effects against atherosclerosis via interfering in the adhesion and inflammatory processes. Arakawa et al. showed that treatment of apoE (-/-) mice with exendin suppressed monocyte adhesion to the endothelium and reduced atherosclerogenesis. Additionally, *in vitro* treatment of mice with exendin -4 suppressed mRNA expression of TNF alpha, and other chemo attractant proteins. In humans, exendin -4 administrations to monocytes lead to a reduction in CD11b expression [38].

GLP1 and Cerebrovascular Disease

Other than cardiovascular diseases, cerebrovascular insults/strokes are one of the most feared macrovascular complications of diabetes.

A neuro protective role for GLP1 has been suggested in a number of animal model studies. GLP1R are present in the brains of both rodents [39] and humans [40]. Furthermore, GLP1R were found to be both expressed and functional in cultured embryonic primary neurons. This was clearly demonstrated by isolating GLP1 mRNA from these cells [cerebral cortical neurons/ventral mesencephalic neurons] and eliciting a rapid transient increase in intracellular cAMP levels post incubation with GLP1 10 nM [41].

GLP1 and stroke

Exendin 4 treatment reduced infarct size (by more than 50%) and improved functional outcome in a well characterized rodent model of stroke (middle cerebral artery occlusion). Parallel studies were conducted on both wild type and GLP1 knockout mice to study the mechanism of such effects. The neuroprotection of exendin 4 could be demonstrated in the wild type but not in the knockout mice, indicating a receptor mediated mechanism [41]. These data were further supported by Teramoto et al. who showed that intravenous exendin 4 treatment post 60 min focal cerebral ischemia significantly decreased infarct volume, improved functional deficit, reduced oxidative stress, inflammatory response, and cell death [42]. In both studies, various physiologic parameters were assessed including glucose, insulin, body temperature and cerebral blood flow. None of the parameters were changed when comparing exendin -4 treated models versus placebo, or pre and post exendin 4 infusion. The lack of any effect of exendin 4 on these parameters, in particular on the cerebral blood flow, implies a centrally mediated mechanism of the protective effect. It is worth noting that there are still no human clinical trials to study the effect of GLP1 as means of neuroprotection. Moreover, none of the animal models studied were diabetics, which open the room for further studies and investigations to be conducted using diabetic subjects.

GLP1 and Peripheral Vascular Disease

Concerning GLP1 and their effects on the peripheral vascular system, limited data are available. Most of the research is focused on both the cardiovascular and the cerebrovascular complications given their association with high mortality.

A number of research studies demonstrated a vasodilatory effect of GLP1.

Recently both GLP1 and its metabolite were found to have a glucose independent vasorelaxant effects on phenylephrine- preconstricted rat mesenteric arteries. Interestingly, this same experiment showed a preserved vasodilatory effect of GLP1 and its metabolite in the absence of a functional GLPR (GLPR-/-mice), suggesting a GLP1R independent pathway. It is also worth noting, that exendin 4 treatment had no vasodilatory effect in the phenylephrine preconstricted rat mesenteric arteries [43]. In support to GLP1 vasodilatory ability, Green et al. conducted a study on phenylephrine preconstricted rat thoracic aortic rings. In this study Green demonstrated that GLP1 and GLP1 metabolite (GLP19-36) had vasodilatory effects. However in this study, exendin-4(1-39), exendin (9-39), and nonpeptide GLP1 agonist were all able to cause the relaxation of the rings, although to a lesser degree compared to GLP1 [44].

Another study conducted on healthy non diabetic, nonsmokers, non-hypertensive subjects showed that GLP1 infusion increased forearm blood flow compared to baseline and augmented the response to acetylcholine [45].

Concerning the mechanism underlying the vaso relaxant properties of GLP1, little is understood. However, the mere fact that both GLP1 and its metabolite and not exendin exhibited a vasodilatory response in both wild type and GLP1R absent mice, suggests that the GLP1R activation is not the sole pathway involved in the vasorelaxant effects. In fact, endothelium dependent nitric oxide (NO)/c GMP mechanism has been proposed by some. In support of this hypothesis, Ban et al. showed that treatment of mouse mesenteric arteries with nitric oxide synthase inhibitor blocked the vasodilatory response to both GLP1 and GLP1 (9-36) [33]. However, conflicting data came from rat thoracic aorta were the GLP1 induced relaxation was similar in endothelium intact and denuded preparations as well as in the presence of NOS inhibitors [33]. In this study the authors suggested the involvement of cAMP/ATP-sensitive k⁺ channels pathway.

Conclusion

The failure of the traditional antidiabetic regimens to decrease the macrovascular complications of type two diabetes has been a great concern when dealing with such a chronic disease especially with the high mortality / morbidity and public health cost associated with these complications.

In this review GLP1 showed promising effects translated into reductions in cerebral and cardiac infarct size, improvement in LV, decrease of cardiovascular risk indicators, and vasodilation. However, most of the data provided comes from animal studies or small human trials, therefore additional larger clinical trials, such as the LEADER study and the EXCEL study, are needed to further support these observations.

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