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Impact of Increasing GLP-1 on Markers of Inflammation, Glucose Control and Cardiovascular Risk Factors in Patients With Type 2 Diabetes

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Abstract

There is a strong established relationship between diabetes and cardiovascular disease. Much of the latest research studies have identified a link between the inflammatory processes and the pathogenesis of both cardiovascular disease and diabetes. Specific inflammatory markers include: Interleukins 1,6,18; C-reactive protein, Fibrinogen, Tumor Necrosis Factor-α , PAI-I and cell adhesion molecules. As a result, there has been an emphasis on identifying therapeutic approaches that would improve both markers of inflammation and glucose control. The endocrine hormones known as incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are produced in the gastrointestinal tract following ingestion of a meal. In individuals with type 2 diabetes, endothelial dysfunction associated with premature atherosclerosis has been well documented. The purpose of this paper is to determine whether increasing levels of GLP-1 reduce markers of inflammation while improving both glucose control and cardiovascular risk factors. The review of literature explored the impact of increasing GLP-1, either though DPP-IV inhibitors or GLP-1 analogues, on various inflammatory markers in patients with type 2 diabetes. The studies reviewed provided ample support for the use of DPP-IV inhibitors to improve both glycemic control and cardiovascular risk factors. GLP-1 analogues also appear to have a similar impact, but with the added benefit of weight loss. In addition, patients with type 2 diabetes frequently have coagulation abnormalities leading to a prothrombotic state. Thus the reduction in fibrinogen, C-reactive protein and plasminogen activator inhibitor observed during the review of literature supports the potential for DPP-IV inhibitors and GLP-1 agonists to exhibits an antithrombotic effect. These findings are of clinical significance as these treatments may potentially slow the progression of premature cardiovascular disease as well as reduce thrombotic events in patients with type 2 diabetes.

Introduction

The relationship between diabetes and cardiovascular disease has been the focus of many empirical investigations. Across time, researchers have explored a link between inflammatory processes and the pathogenesis of both diabetes and cardiovascular disease. Consequently, there has been an emphasis on identifying therapeutic approaches that would improve both markers of inflammation and glucose control; thereby slowing the progression of premature cardiovascular disease in patients with type 2 diabetes. The purpose of this review is to examine the role of increased levels of GLP-1 in reducing markers of inflammation.

Statement of the Problem

Given the known relationship between diabetes, premature cardiovascular disease and the inflammatory involvement; it is important to explore inflammatory markers and therapies that may reduce their negative impact on endothelial function.

Research Question

In patients with type 2 diabetes, does increasing GLP reduce markers of inflammation, while improving both glucose control and cardiovascular risk factors.

Literature Review

- An article search of the following electronic medical databases was conducted; PubMed, The Cochran Library, DynaMed and MEDLINE. A combination of keywords and subject headings were used, with search terms including: type 2 diabetes, DPP-IV inhibitors, GLP-1 agonist, incretins, inflammation, cardiovascular disease.
- Full articles were retrieved for further review if the information given suggested that the study: included patients with type two diabetes mellitus, measured pre and post markers of inflammation, cardiovascular risk factors or changes in glucose following either a DPP-IV inhibitor or a GLP-1 agonist active intervention.
- Tremblay et al. 2014 conducted a double blinded, cross over study using Sitagliptin (Januvia) or placebo. Thirty men and six postmenopausal women, (who were not receiving HRT), with type 2 diabetes participated in the study. Mean age and BMI, 58.1 and 30.7, respectively. The treatment with 100mg of Sitagliptin significantly reduced the levels of CRP, IL-6 and IL-18 by -44.9% (P = 0.006), -24.7% (P = 0.04) and -7.3% (P = 0.004), respectively. Additional findings included a significant inverse correlation between changes in GLP-1 and changes in CRP levels (r = 0.41, P = 0.01) with Sitagliptin therapy vs placebo. In the fasting state, Sitagliptin led to significant reductions in plasma cholesterol (-5.1%, P = 0.001). apoB (-4.7%, P = 0.003), and LDL-C (-5.2%, P = 0.003) without affecting plasma levels of triglycerides, free fatty acids and HDL-C when compared to placebo.
- In a 12 week single center, randomized placebo controlled double blinded prospective study, Makdissi et al. 2012, enrolled 22 obese subjects with type 2 diabetes with hemoglobin A1c between 7.5% and 9%. None of the subjects had any micro/macrovascular complications of diabetes. Subjects were randomized to receive either Sitagliptin 100mg (N = 12; 6 male and 6 female) or placebo (N = 10). Results showed fasting GLP-1 concentrations increased 63% ± 20% (from 9.1 ± 2.8 to 15.8 ± 4.0) at 12 weeks. A significant reduction in plasma concentrations of CRP and IL-6 by 24 ± 7 and 24 ± 8%, respectively (P <0.05) in the Sitagliptin treated group. HgbA1c fell significantly from 7.6 ± 0.1 to 6.9 ± 0.3% (P < 0.01), serum triglycerides decreased from 209 ± 20 to 159±19mg/dl. There was no significant changes in BMI, blood pressure or cholesterol concentrations in either the treatment or placebo groups.
- Pettigrew, et al. assessed the effect of Liraglutide on biomarkers for cardiovascular risk in patients with type 2 diabetes. The researchers randomized 165 patients with type 2 diabetes to either a placebo or 0.65mg. 1.25mg or 1.9mg of Liraglutide for 14 weeks. Pre and post measurements of hsCRP, IL-6, TNF-α and plasminogen activator inhibitor (PAI-1) and B-type natriuretic peptide (BNP) were measured. Results showed a significant decrease between baseline levels of PAI-1 and BNP levels following higher dose treatment (1.25mg and 1.90mg) of Liraglutide,(-29%; P = 0.018 and -25%; P = 0.045, respectively. There was a non-significant, but dose dependent reduction in hsCRP; (0.65mg = -3%; P = 0.85; 1.25mg = -12%; P=0.46; 1.90mg = -20%; P = 0.22).

Discussion

- Based on the studies discussed, DPP-IV inhibitors have been shown to improve glycemic control and, based on the small trials, appear to have great potential to provide beneficial cardiovascular effects due to their positive impact on reducing inflammatory markers.
- GLP-1 agonists also appear to have similar benefits as DPP-IV inhibitors with the added benefit of weight loss. In addition, patients with type 2 diabetes frequently have coagulation abnormalities leading to a prothrombotic state. Thus the reduction in fibrinogen, C-reactive protein and plasminogen activator inhibitor observed during the review of literature supports the potential of DPP-IV inhibitors and GLP-1 agonists having an antithrombotic effect.
- A decrease in HgbA1c, inflammatory markers (e.g. CRP, TNF-α), Free Fatty Acids and Triglycerides were common themes presented during the review of literature looking specifically at the role of DPP-IV inhibitors and their impact on increasing GLP-1.
- DPP-IV inhibitors have been shown to be well tolerated, weight neutral and less expensive. They do, however have less of an impact on A1c as compared to the GLP-1 analogues.
- A common theme found with GLP-1 analogues, as seen with DPP-IV inhibitors, is the reduction in the inflammatory markers independent of changes in weight. Oxidative stress as measured by PGF2α, was found to also decrease with the addition of a GLP-1 analogue.
- Hypoglycemic events were essentially non-existent with DPP-IV inhibitors and GLP-1 analogues.

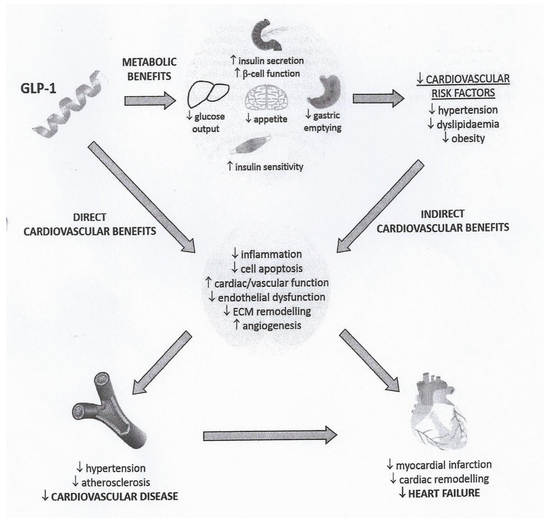

Figure 1. Adapted from "Selective targeting of glucagon-like peptide-1 signaling as a novel therapeutic approach for cardiovascular disease in diabetes", by M. Tate, A. Chong, E. Robinson, B. Green and D. Grieve, 2014, *British Journal of Pharmacology,* e172. Copyright 2014 by the British Pharmacological Society.

Applicability to Clinical Practice

- The findings of this research project are applicable to several areas of clinical practice. The literature supports the anti-inflammatory effect of both DPP-IV inhibitors and GLP-1. While these pharmacologic therapies have been on the market for over a decade, there utilization is not optimized.
- Given the minimal risk of hypoglycemia associated side effects with both DPP-IV inhibitors and GLP-1 analogs, as well as their impact on HgbA1c reduction, it seems most appropriate for there to be a shift in the prescribing habits of clinicians as they work with patients to help achieve improved glycemic control.
- Both of these classes of therapy have been shown to reduce markers of inflammation, which shows promise in reducing the progression of cardiovascular disease and possibly thrombotic events.
- Clinicians will be assisting patients with not only managing glucose with anti-diabetes medications, but also cardiovascular risk factors. Lifestyle modification, albeit challenging for patients to embrace and sustain, is part of the practice guidelines regardless of where the patient falls in the algorithm and should remain part of the treatment plan.
- Clinicians should be working with patients to enhance management of all comorbidities associated with diabetes, especially cardiovascular. It seems reasonable to select diabetes medications that will target both chronic diseases. There are oral medications on the market that have combined DPP-IV inhibitors with metformin.
- Clinicians need to be current and relevant in both medical and pharmacologic knowledge, which impacts their prescribing habits and quality of patient care.

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