Abstract: BACKGROUND: Type 2 diabetes is a chronic, progressive disease with a multi-faceted pathophysiology. Beyond the known defects of insulin resistance and beta-cell insufficiency, derangement of incretin hormones normally produced from the gut wall in response to food intake play an important role. In recent years, the 'incretin-based' therapies (IBTs) have been developed to address hyperglycemia through either mimicking the action of the endogenous incretin glucagon-like polypeptide (GLP-1) (GLP-1 receptor agonists) or by inhibiting the activity of the enzyme that degrades GLP-1 (the dipeptyl peptidase-4 inhibitors). OBJECTIVE: We reviewed available evidence on the glucose lowering and anti-atherogenic effects of IBT. RESULTS: In addition to their glucose-lowering and weight-neutral or weight-reducing actions, IBT decrease systolic blood pressure and improve fasting and postprandial lipid parameters by reducing total-cholesterol, low-density lipoprotein-cholesterol and triglycerides concentrations, and increasing high-density lipoprotein-cholesterol values. Reduced high-sensitivity C-reactive protein levels and improved endothelial dysfunction have been reported too. CONCLUSIONS: IBT have several beneficial effects on cardiovascular risk factors and, for this reason, it has been recently suggested to extend the use of these drugs in diabetic patients with cardiovascular complications. Yet, the long-term effects of IBT on subclinical or clinical atherosclerosis remain to be established by future studies.

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Glucose lowering and anti-atherogenic effects of incretin-based therapies: GLP-1 analogues and DPP-4-inhibitors

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Background: Type 2 diabetes is a chronic, progressive disease with a multifaceted pathophysiology. Beyond the known defects of insulin resistance and β-cell insufficiency, derangement of incretin hormones normally produced from the gut wall in response to food intake play an important role. In recent years, the ‘incretin-based’ therapies (IBTs) have been developed to address hyperglycemia through either mimicking the action of the endogenous incretin glucagon-like polypeptide (GLP-1) (GLP-1 receptor agonists) or by inhibiting the activity of the enzyme that degrades GLP-1 (the dipeptidyl peptidase-4 inhibitors).

Objective: We reviewed available evidence on the glucose lowering and anti-atherogenic effects of IBT.

Results: In addition to their glucose-lowering and weight-neutral or weight-reducing actions, IBT decrease systolic blood pressure and improve fasting and postprandial lipid parameters by reducing total-cholesterol, low-density lipoprotein-cholesterol and triglycerides concentrations, and increasing high-density lipoprotein-cholesterol values. Reduced high-sensitivity C-reactive protein levels and improved endothelial dysfunction have been reported too.

Conclusions: IBT have several beneficial effects on cardiovascular risk factors and, for this reason, it has been recently suggested to extend the use of these drugs in diabetic patients with cardiovascular complications. Yet, the long-term effects of IBT on subclinical or clinical atherosclerosis remain to be established by future studies.

Keywords: cardiovascular risk, diabetes, DPP-4 inhibitors, GLP-1 analogues


1. Introduction

Type 2 diabetes (T2D) is a chronic disease characterized by insulin resistance, a steady impairment in glucose-induced insulin secretion caused by a progressive decrease in β-cell function and inappropriately regulated glucagon secretion. These pathophysiologic defects result in persistent hyperglycemia and an increased risk of both microvascular and cardiovascular complications. Traditional treatments for T2D have used oral agents in a stepwise manner, followed by insulin therapy. Unfortunately, this approach does not address the progressive decline in β-cell function and is often associated with undesirable weight gain. In the past few years, new drugs that act by modulating the gut-based incretin system of hormones have been introduced for the management of hyperglycemia in T2D. These medications, collectively known as incretin-based therapies (IBTs), act by either mimicking the actions of glucagon-like polypeptide-1 (GLP-1) or by inhibiting its enzymatic
Glucose lowering and anti-atherogenic effects of incretin-based therapies: GLP-1 analogues and DPP-4-inhibitors

Table 1. Characteristics of the incretin hormones GLP-1 and GIP.

| GLP-1: secreted by ‘L’ cells in the ileum and colon | GIP: secreted by ‘K’ cells in the duodenum |
| GLP-1: secreted by ‘L’ cells in the ileum and colon |
| Suppression of glucose output from the liver by glucose-dependent inhibition of glucagons secretion (GLP-1 only) |
| Enhanced β-cell proliferation and survival in animal models and human islet cell lines |
| Retardation of gastric emptying leading to early satiety |
| Inactivation by dipeptidyl peptidase-4 enzyme and elimination by the kidneys |
| Central suppression of appetite (GLP-1 only) |
| Reduction of fasting glucose (GLP-1 only) |

GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1.

degradation, thus, prolonging its action. These novel agents offer the potential of reducing body weight or preventing weight gain while lowering glucose levels. Although promising, the durability of these effects and their long-term clinical benefits need to be further elucidated. The impact of incretin-based treatments on atherosclerotic risk factors (such as blood pressure and plasma lipids) is also under investigation. Substantial evidence demonstrates that the GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors produce modest reductions in systolic blood pressure and, in some cases, diastolic blood pressure. Reductions in the triglyceride level and significant improvements in total, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol have also been observed. These effects on cardiovascular risk factors are exciting potential beneficial features of IBT. The glucose-lowering and potential anti-atherogenic actions of these medications are the subject of this review article.

2. The ‘incretin’ concept

Incretins are hormones produced by the gastrointestinal tract in response to oral food ingestion. They help to maintain glucose homeostasis through their coordinated effects on islet α and β cells, thereby, inhibiting glucagon output and stimulating insulin secretion in a glucose-dependent manner [1]. GLP-1, the predominant incretin hormone, is produced by the L cells of the ileum, while glucose-dependent insulinotropic polypeptide (GIP) is produced by the K cells in the jejunum. In addition to their actions on endocrine pancreatic function, both GLP-1 and GIP appear to have local and CNS effects that slow gastric emptying and decrease appetite (Table 1). The ‘incretin effect’ is diminished or lost over time in people with T2D (Figure 1). Although GLP-1 has marked benefits in patients with T2D, native GLP-1 administration as a treatment strategy is severely limited by a short half-life in vivo due to inactivation by DPP-4 and the impracticality of continuous infusion. Thus, pharmacologic strategies have evolved to overcome these limitations, either directly by modifying native GLP-1 to make it resistant to the effects of DPP-4 or indirectly by inhibiting the action of DPP-4. Therefore, new treatments for T2D have been introduced recently that utilize the natural glucoregulatory effects of incretin hormones [2]. These incretin enhancers are pharmacologic agents that explore a physiologic approach to the management of T2D while limiting some of the undesirable side effects such as hypoglycemia and weight gain [3,4]. They lower hemoglobin A1c (A1c), body weight and postprandial glucose excursions. Animal studies have demonstrated improvements in β-cell function in vivo [5].

In April 2005, the FDA approved the first incretin mimetic, exenatide, a GLP-1 receptor analogue resistant to DPP-4 degradation, as adjunctive therapy for patients with T2D. Because the GLP-1 analogues (also known as ‘GLP-1 agonists’ or ‘mimetics’), require injection, considerable effort has been devoted to creating an oral agent targeting the incretin pathway. Inhibition of DPP-4 extends the half-life of native incretins, thereby, prolonging their effects. In October 2006, the FDA approved the first oral incretin enhancer, sitagliptin, a selective DPP-4-inhibitor, for use as monotherapy or in combination with metformin or thiazolidinedione. Additional incretin-based agents are also in late-stage development.

Exenatide mimics the actions of endogenous GLP-1 when given subcutaneously by injection, while sitagliptin and vildagliptin are agents that inhibit the enzyme DPP-4 responsible for degradation of GLP-1 and other incretins. IBT is used adjunctively in patients with T2D who fail to achieve glucose targets with oral agents. Sitagliptin and vildagliptin can also be used as monotherapy in patients T2D uncontrolled by diet. The latter medication has been approved in the EU but not in all other countries, such as the US. Once-weekly exenatide and once-daily liraglutide are other mimetics in development. Recent evidence appears to suggest that the salutary effects of IBT extend beyond glucose metabolism; thus, a stabilization of body weight and beneficial actions on lipids and blood pressure may exert a combined anti-atherogenic profile. These and other potential actions are summarized in Table 2 and discussed in the following sections.

3. Effects on glucose metabolism

A wealth of data has been accumulated on the use of incretin mimetics and DPP-4 inhibitors in the treatment of T2D. Their actions predominantly target postprandial hypoglycemia. A critical review of Phase III clinical trials of exenatide, sitagliptin and vildagliptin [6] showed that the use of exenatide was associated with reduction in A1c levels of ~0.8% compared with baseline, while sitagliptin or vildagliptin lowered average A1c by 0.7%. Treatment-related hypoglycemia was generally mild, occurring mainly in combination with sulfonylureas (SUs). Exenatide treatment leads to a weight loss of around 2 kg at 30 weeks, whereas sitagliptin and vildagliptin...
have neutral effect on weight. About 5 – 10% of patients have adverse effects of abdominal fullness, nausea and vomiting. Dose-dependent nausea dissipates over time and is attenuated by slow titration during initiation of therapy. Sitagliptin and vildagliptin are generally well tolerated. In short, exenatide, sitagliptin and vildagliptin are useful as add-on agents for T2D that is suboptimally controlled with oral agents, particularly when there is concern about weight gain and hypoglycemia, or when postprandial hyperglycemia is predominant.

The higher the initial A1c, the more pronounced is the glucose-lowering effect of IBT. In twice-daily doses of 5 or 10 μg for 30 weeks, exenatide lowered the A1c by 1.7% in the group with a baseline A1c of 9.0% or greater, compared with 0.7% for those with a baseline A1c < 9% [7]. Interestingly, the difference was sustained with reductions of 2.0 and 0.8%, respectively, at 82 weeks. The addition of liraglutide to metformin, glimepiride, or both, for 26 weeks resulted in a greater glucose reduction with increasing A1c [8]. Patients in the upper quartile (mean baseline A1c 9.5 – 9.8%) experienced a reduction in the A1c of 1.3 – 1.8% compared with 0.5 – 0.9% for those in the lowest quartile (mean baseline A1c 7.2 – 7.3%). The challenges and feasibilities of replacing SU with IBT in patients with T2D have been addressed as well [9]. SUs can cause weight gain and increase the risk of hypoglycemia. They are thought to be associated with accelerated β-cell apoptosis, suggesting that they may actually promote the progressive decrease in β-cell mass and the need for insulin replacement. In contrast, the β-cell-preserving properties of IBT potentiate glucose-stimulated insulin secretion in T2D. The insulinotropic effects of IBT are glucose-dependent, minimizing the risk of hypoglycemia.
Administration of insulin in T2D can roughly mimic physiologic insulin secretion when used in a basal-bolus fashion. However, it does not address the underlying pathophysiology, and hypoglycemia is a potential barrier to treatment adherence and glycemic control. Weight gain can exacerbate hyperglycemia or insulin resistance. The potential of IBT for limiting weight gain while controlling glucose is in contrast to insulin [10]. In a 52-week comparison study, the addition of exenatide lowered fasting glucose and A1c (mean, -1.04%) similar to twice daily biphasic aspart insulin when added to a stable regimen of metformin/SU [11] while achieving a greater reduction in postprandial glucose and a weight loss of 5.4 kg. It follows that when oral agents have failed to maintain adequate glycemic control, IBT may be particularly well suited to the treatment of T2D patients who are overweight or obese with primarily post-meal glucose peaks. Exenatide therapy has been proposed as an alternative to insulin in patients with treatment failure with either metformin monotherapy or metformin–SU combination [10]. The exact place of IBT plus available oral antidiabetic agent treatment remains an area of ongoing study [12,13].

Liraglutide is a new GLP-1 agonist that shares considerable amino-acid homology with human GLP-1. Structural modifications, primarily the addition of a palmitate side chain, allow for greater self-association, albumin-binding to albumin, prolonged absorption and resistance to inactivation by the enzyme DPP-4. A 26-week, double-blind trial demonstrated the noninferiority of liraglutide compared to glimepiride in a cohort of overweight patients with T2D inadequately controlled with metformin monotherapy [14]. Other studies have demonstrated the beneficial effects of liraglutide on weight and body composition [15,16].

The family of oral DPP-4 inhibitors has actions on postprandial as well as fasting glucose levels. Sitagliptin is approved as monotherapy or as adjunct to metformin and SUs in the treatment of T2D, lowering A1c by a mean of -0.74% compared with placebo in a 24-week monotherapy trial without causing significant nausea or vomiting [17]. A similar but more modest effect from baseline was observed with the addition of sitagliptin to pioglitazone over a 24-week period [18]. Vildaglaptin has also shown efficacy as monotherapy in clinical studies [19,20]. In drug-naive patients, vildaglaptin 50 mg twice daily decreased the A1c by 1.3%, similar to rosiglitazone 8 mg daily. In patients with a baseline mean A1C of 10%, the reductions were 1.8 and 1.9%, respectively [21]. Alogliptin, still in development, has yielded similar results in patients who were inadequately controlled with lifestyle changes [22].

A recent meta-analysis of randomized controlled trials [13] showed that IBT with GLP-1 analogues or DPP-4 inhibitors in adults with T2D is effective in improving glycemia, with greater reductions in postprandial glycemia and favorable (GLP-1 analogues) or neutral (DPP-4 inhibitors) effects on weight. Regarding adverse events, glucagon-like peptide 1 analogues were associated with gastrointestinal adverse effects, while DPP-4 inhibitors had a slightly increased risk of infection (nasopharyngitis and urinary tract infection) and headache. Further, in the few available trials, incretin-based medications were found to be not inferior compared with non–incretin-based pharmacologic therapies, including insulin glargine or biphasic aspart, glimepiride, metformin, glipizide or thiazolidinediones, with the exception of metformin being superior to vildaglaptin [13]. Additional trials comparing IBTs with existing therapies are also ongoing.

4. Effects on body weight

Infusions of GLP-1 reduce gastric emptying, increase satiety and mitigate hunger in clinical studies in both healthy volunteers and patients with T2D [23]. IBT has glucose-lowering actions that are associated with lack of weight gain and even weight loss. GLP-1 agonists have the potential to induce significant weight reduction concurrently with improved glycemic control, while DPP-4 inhibitors exhibit a weight-neutral profile [13]. The weight is lost from visceral fat, is mediated by gastrointestinal and CNS effects, and appears to be durable as long as therapy is continued. The actual amount of weight change, however, is variable; some individuals lose impressive amounts of weight, while others lose little or none at all. Although nausea and vomiting can occur in a subset of patients with GLP-1 agonist therapy, the weight loss is not thought to be directly attributable to these side effects. No difference in the degrees of weight loss has been observed in patients who experience gastrointestinal symptoms compared to those who do not. Some of the weight-reducing properties of IBT have been alluded to in the preceding section.

A succession of three studies evaluated the addition of exenatide 10 µg twice daily to SU, metformin or a combination of SU–metformin therapy. Weight loss ranged from a mean -1.6 to -2.8 kg over a 30-week period, and A1c levels were lowered from a mean -0.78 to -0.86% [24-26]. The weight loss with exenatide was gradual, dose-dependent and without an apparent plateau. Similar results have accrued from combination studies of exenatide to thiazolidinediones [27].

Extension studies have suggested continued weight loss in a subset of these patients. Interestingly, trials with a longer-acting preparation of exenatide (exenatide LAR) administered once weekly have demonstrated a different dose response for the glucose-lowering properties compared with the effect on body weight [28]. It appears that higher doses are required to obtain a robust and sustained reduction in weight. By 15 weeks of therapy, there was a 3.8-kg reduction in body weight in subjects treated with the highest dose.

The LEAD (Liraglutide Effect and Action in Diabetes) program represents a large series of studies undertaken in ~ 4200 patients to characterize the effect of liraglutide over the spectrum of T2D. Studies were performed with liraglutide as monotherapy, in combination with metformin, in combination with an SU, in combination with metformin and a thiazolidinedione, and in combination with metformin plus an SU [14,29,30]. A1c reductions were seen in each of these
5. Effects on blood pressure

Beyond the positive effects on glucose metabolism and body weight, the incretin enhancers seem to have beneficial effects on blood pressure and blood lipids that may contribute to reduced cardiovascular risk [33]. In general, modest reductions in blood pressure are observed with both GLP-1 receptor agonists and DPP-4 inhibitors. Although modest, such reductions may be of significant clinical significance in patients with T2D. Note that the National High Blood Pressure Education Program Coordinating Committee in the latest report on prevention, detection, evaluation and treatment of high blood pressure has stated that each increment of 20/10 mmHg above 115/75 mmHg doubles the risk of cardiovascular disease [34].

In a retrospective study, therapy with exenatide (5 μg twice daily for 26 weeks) in 38 obese patients not controlled with oral hypoglycemic agents and insulin led to a reduction in the systolic blood pressure (-9.2 mmHg, p = 0.02) [35]. Similar findings were obtained by another study that examined the long-term effects of exenatide (5 – 10 μg twice daily for 82 weeks) in overweight metformin-treated individuals; the reduction was found in both diastolic and systolic blood pressure (-4.1 and -6.3 mmHg, respectively, p < 0.05 for both) [36]. Other studies have investigated the effects of liraglutide on blood pressure. In a double-blind placebo-controlled study, liraglutide as monotherapy at different doses in 163 diabetic subjects for 14 weeks was able to significantly improve systolic blood pressure (up to 7.9 mmHg with the maximum dose of 1.9 mg daily); in addition, in relation to placebo, the mean diastolic blood pressure decreased significantly by 2 – 3 mmHg with all liraglutide doses [36]. The LEAD studies have further shown the beneficial effects of 26 weeks of therapy with liraglutide on blood pressure levels [37]. It should be also noted that, in general, the reductions in blood pressure seen with exenatide and liraglutide administration were not due to weight loss. Finally, sitagliptin significantly reduced blood pressure in a pilot study of 19 non-diabetic subjects with mild to moderate hypertension (9 on monotherapy and 10 on combination antihypertensive therapy), randomized to sitagliptin 50 or 100 mg or placebo twice daily for 5 days [38].

6. Effects on lipid profile

Several studies have investigated the impact of therapy of incretin enhancers on the lipid profile in patients with T2DM. Regarding DPP-4 inhibitors, sitagliptin has been found beneficial as both monotherapy and as combination therapy. Administered at doses of 5, 12.5, 25 or 50 mg twice daily for 12 weeks in subjects who were either drug-naive or on oral monotherapy (except a thiazolidinedione) [39], sitagliptin at doses greater than 5 mg reduced triglyceride levels by 9 – 14% and increased HDL-cholesterol concentrations by 4% compared to placebo (p < 0.05 for both).

Other authors have studied the effects of sitagliptin on plasma lipids in combination with metformin, pioglitazone, glimepiride and glipizide. When added to pre-existing metformin therapy (< 1500 mg/day), sitagliptin at doses of 100 mg/day for 24 weeks resulted in a small but significant decrease in levels of total cholesterol, triglycerides and non-HDL-cholesterol, and a small but significant increase in HDL-cholesterol concentration compared with the metformin arm (Table 3) [40]. The study was continued for an additional 80 weeks and results of an interim analysis at 54 weeks suggest a sustained reduction in triglycerides and HDL-cholesterol levels with sitagliptin use [41]. In another study, sitagliptin added to on-going pioglitazone therapy (30 or 45 mg/day) at doses of 100 mg/day for 24 weeks led to a significant decrease in levels of plasma triglycerides, while no significant differences were noted in the other lipid parameters (Table 3) [18]. Finally, in an active controlled study evaluating sitagliptin 100 mg versus glipizide 5 mg day added to metformin for 52 weeks, the former resulted in a greater increase in HDL-cholesterol concentrations (3.7 versus 1.2%) [42].

Vildagliptin also improved plasma lipid parameters in patients with metformin-resistant T2D. Patients were randomized to vildagliptin (50 mg twice daily) or pioglitazone (30 mg daily) for 24 weeks [43]. Compared to pioglitazone, vildagliptin reduced total and LDL-cholesterol by 7 and 10%, respectively (p < 0.001 for both); by contrast, triglycerides reduced more and HDL-cholesterol increased more after pioglitazone than vildagliptin (10 versus 1%, p = 0.004 and 15 versus 1%, p < 0.001, respectively). Similar results have been observed when compared to rosiglitazone, although the reduction in triglyceride concentrations with vildagliptin was higher (14%) than in the comparison with pioglitazone [21].

Regarding the GLP-1 receptor agonists, exenatide (5 μg twice daily, for a mean of 26 weeks) led to a reduction in total cholesterol of 8.5% (p = 0.03) and in triglycerides of 26% (p = 0.01) when added in obese patients with T2D not controlled with oral hypoglycemic agents and insulin [35]; notably, in this retrospective study, no changes in plasma
back to early observations that ingested glucose results in a considerable increase in insulin and glucagon secretion, particularly during the postprandial period, leading to hyperglycemia.

The incretin concept, as it is currently understood, dates back to early observations that ingested glucose results in a considerably larger and more sustained insulin response than glucose administered intravenously. Impairments in the incretin response in patients with T2D may contribute to dysregulation of insulin and glucagon secretions, particularly during the postprandial period, thus, leading to hyperglycemia. The recent introduction in the market of the new antidiabetic drugs modulating the incretin system, such as the GLP-1 receptor agonists and the DPP-4 inhibitors, may open new horizons in the management of T2D.

In addition to their glucose-lowering and weight-neutral or weight-reducing actions, substantial evidence demonstrates that the GLP-1 receptor agonists and DPP-4 inhibitors produce decreases in systolic blood pressure and, in some cases, diastolic blood pressure. Furthermore, IBT has been shown to improve fasting and postprandial lipid parameters by reducing total cholesterol, LDL-cholesterol and triglycerides concentrations, and increasing HDL-cholesterol values. Improved endothelial dysfunction in T2D patients with established coronary heart disease have been reported with GLP-1 [49] and reduced high-sensitivity C-reactive protein levels with exenatide administration was found in subjects with T2D [50]. Due to these beneficial actions on cardiovascular risk factors, it has been recently suggested using these drugs in diabetic patients with cardiovascular complications (as reviewed in [51]). Yet, the long-term effects of therapies with GLP-1 receptor agonists and DPP-4 inhibitors on subclinical (e.g., increased carotid intima-media thickness) or clinical (e.g., cardiovascular morbidity and mortality) atherosclerosis remain to be established by future studies.

8. Expert opinion

The recent introduction in the market of the new antidiabetic drugs modulating the incretin system has opened new horizons in the management of T2D. The incretin concept dates back to early observations that ingested glucose results in a considerably larger and more sustained insulin response than glucose administered intravenously. Two incretins have been identified within the gastrointestinal tract with the property of stimulating insulin release: GIP and GLP-1. Impairments in the incretin response may contribute to dysregulation of insulin and glucagon secretion, particularly during the postprandial period, leading to hyperglycemia.

Although GLP-1 given experimentally has marked benefits for postprandial lipemia (as reviewed in [45]), in a pilot study [46], treatment with GLP-1 was associated, postprandially, with reduced VLDL triglycerides, while LDL- and HDL-cholesterol concentrations were unchanged; notably, GLP-1 increased LDL particle diameter as compared to the control group. Similarly, postprandial triglycerides were reduced in another study investigating the effects of acute GLP-1 administration in healthy volunteers [47]. Matikainen et al. [48] investigated in a randomized, double-blind, placebo-controlled study the effect of vildagliptin (50 mg twice daily for 4 weeks) on postprandial lipemia in T2D; vildagliptin reduced postprandial levels of total triglycerides and those contained in triglyceride-rich lipoproteins.

7. Conclusion

The incretin concept, as it is currently understood, dates back to early observations that ingested glucose results in a considerably larger and more sustained insulin response than glucose administered intravenously. Impairments in the incretin response in patients with T2D may contribute to dysregulation of insulin and glucagon secretions, particularly during the postprandial period, thus, leading to hyperglycemia. The recent introduction in the market of the new antidiabetic drugs modulating the incretin system, such as the GLP-1 receptor agonists and the DPP-4 inhibitors, may open new horizons in the management of T2D.

In addition to their glucose-lowering and weight-neutral or weight-reducing actions, substantial evidence demonstrates that the GLP-1 receptor agonists and DPP-4 inhibitors produce decreases in systolic blood pressure and, in some cases, diastolic blood pressure. Furthermore, IBT has been shown to improve fasting and postprandial lipid parameters by reducing total cholesterol, LDL-cholesterol and triglycerides concentrations, and increasing HDL-cholesterol values. Improved endothelial dysfunction in T2D patients with established coronary heart disease have been reported with GLP-1 [49] and reduced high-sensitivity C-reactive protein levels with exenatide administration was found in subjects with T2D [50]. Due to these beneficial actions on cardiovascular risk factors, it has been recently suggested using these drugs in diabetic patients with cardiovascular complications (as reviewed in [51]). Yet, the long-term effects of therapies with GLP-1 receptor agonists and DPP-4 inhibitors on subclinical (e.g., increased carotid intima-media thickness) or clinical (e.g., cardiovascular morbidity and mortality) atherosclerosis remain to be established by future studies.

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reductions in postprandial glycemia and favorable (GLP-1 analogues) or neutral (DPP-4 inhibitors) effects on weight. Regarding adverse events, glucagon-like peptide 1 analogues were associated with gastrointestinal adverse effects, while DPP-4 inhibitors had a slightly increased risk of infection (nasopharyngitis and urinary tract infection) and headache. Further, in the few available trials, incretin-based medications were found to be not inferior compared with non-incretin-based pharmacologic therapies, including insulin glargine or biphasic aspart, glimepiride, metformin, glipizide or thiazolidinediones, with the exception of metformin being superior to vildagliptin. Additional trials comparing IBTs with existing therapies are also ongoing.

The appealing aspect of these agents lies in their weight-neutral or even weight-reducing effects concurrent with their glucose-lowering actions. Preliminary data suggest that IBTs may preserve β-cell function in the long-term, thus, promising to be disease-modifying drugs. Using these agents early in the diabetic process may indeed be effective in preventing the disease or retarding its progression. The GLP-1 receptor agonists could be particularly beneficial in overweight or obese patients who have cardiovascular risk factors. In particular, there is promising evidence that IBTs have salutary effects on blood pressure and lipid profile. Through beneficial actions on the risk factors that often cluster in individuals with diabetes (obesity, hyperglycemia, hypertension and dyslipidemias), incretin-based treatments may potentially reduce cardiovascular morbidity and mortality from this devastating disease. This needs to be tested by future prospective studies and will probably become one of the ‘hot topics’ in diabetes and cardiovascular prevention in the next few years.

**Declaration of interest**

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

**Bibliography**

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

**An interesting article showing the effects of sitagliptin (in combination with pioglitazone) on plasma lipids in patients with T2D.**


32. Colagiuri S, Friad A, Zdravkovic M, et al. Liraglutide, a human GLP-1 analogue, reduces systolic blood pressure in subjects with type 2 diabetes. Program and abstracts of the European Association for the Study of Diabetes (EASD) 44th Annual Meeting; September 7-11, 2008; Rome, Italy; abstract 899


• A recent interesting article reviewing the role of incretins in cardiovascular control.


•• An interesting article showing the effects of sitagliptin (in combination with metformin) on plasma lipids in patients with T2D.

41. Karasik A, Wu M, Williams-Herman D, Meininger G. Sitagliptin added to ongoing metformin therapy provides sustained glycemic control over 54 weeks, with a low incidence of hypoglycemia and with weight loss. Diabetes 2007;56(Suppl 1):A139


44. Blonde L, Rosenstock J, Sesti G, et al. Liraglutide: superior glycemia control vs exenatide when added to metformin and/or SU in type 2 diabetes. Paper presented at: Canadian Diabetes Association/Canadian Society of Endocrinology and Metabolism Annual Meeting; October 15-18, 2008; Montreal, Quebec, Canada


• A comprehensive review on the effects on postprandial lipid metabolism of current agents used for the management of T2D.


• A recent review on the future challenges for incretin-based therapies.

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