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REVIEW

Uncertainties around incretin-based therapies: A literature review

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Abstract *Background:* Diabetes mellitus is a chronic debilitating and non-communicable disease. It has several long-term outcomes that are associated with various end organ damage, mainly the heart, blood vessels, eyes, nerves, and kidneys. There are different modalities of treatment of diabetes. The recent incretin-based therapies provided an innovative class of drugs including GLP-1 receptor agonists and DPP-4 inhibitors. This review aims to summarize the available evidence of their effectiveness. *Method:* This is a narrative review. Several databases were searched. Search terms used were MeSH and keywords with different combinations of Boolean operators according to the database but were comparable. Studies included were: randomized controlled trials, cohort and case-controlled studies, health technology report, meta-analysis, and systematic reviews. Results were analysed and reported in a narrative style with emphasis on the effectiveness and adverse effects of various types of incretin based therapies. *Results:* 17 articles were retrieved as they fulfilled the inclusion criteria. They were heterogeneous in terms of interventions, participants, settings and outcomes. Studies varied in their quality and/or reporting of their findings conducted in several settings. There are two types of incretin: Glucose dependent Insulinotropic Peptide (GIP) and Glucagon-like Peptide 1 (GLP-1). There is no question that incretin-based glucose-lowering medications have demonstrated to be effective glucose-lowering drugs. They proved an evidence-based efficacy profile and appear to do so with significant effects to stimulate weight loss with minimal hypoglycaemia. However, there are few side effects that should not be overlooked when deciding to use such therapies. *Conclusion:* The findings of our review presented here, do not prove that these agents are unsafe, but it does suggest that the burden of evidence now rests with those who hope to persuade us of their safety. Continuous clinical monitoring and more research are essential to clarify the actions of GLP-1R agonists and DPP-4 on the normal and diabetic exocrine pancreas.
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Contents

1. Introduction

Diabetes mellitus is a chronic debilitating and non-communicable disease characterized by chronic hyperglycaemia and resulting from a defect in insulin secretion, insulin action, or both (Alberti and Zimmet, 1998; American Diabetes Association, 2011). It has several long-term outcomes that are associated with various end organ damage, mainly the heart, blood vessels, eyes, nerves, and kidneys (ADA, 2010). Furthermore, diabetes estimated to cost the government of Saudi Arabia about $1.87 billion annually (Almalki et al., 2011).

The number of people with diabetes in 2012 has been estimated to be 381.8 million worldwide with an anticipated increase of 55% to 591.9 million by 2035 (Guariguata et al., 2014). In Saudi Arabia, the estimated prevalence of diabetes in 2011 is 16.2% and estimated to be 20.8% in 2030 (Whiting et al., 2011). There remain large variations in the burden of diabetes across countries and income groups.

Although the number of patients with diabetes that successfully achieve target levels of A1C is gradually improving, a considerable number of subjects continue to fall short of satisfactory treatment goals, leaving them at high risk for the development of diabetes-associated complications (Hoerger et al., 2008). Suggested initial therapy generally includes lifestyle management and patient education joined with metformin therapy. Although metformin is widely accepted as the preferred medication for the initial treatment of type 2 diabetes (T2DM), there is still a considerable uncertainty and lack of consensus regarding the choice of additional agents that need to be added to metformin to optimize glycaemic control (Drucker et al., 2010). Other oral hypoglycaemic agents included also Sulphonylureas such as glipizide, glimepiride, and glyburide that induce the increased secretion of insulin. Moreover, insulin, as injection, might be introduced in the early stage of diabetes, depending on the number of risk factors the patients may have and the progression/deterioration of the diabetic stage.

Various drawbacks are associated with the previously discussed available medications. Amongst the concerns attributed to the available anti-diabetic medications are that they do not stop the progressive loss of β cell function, hence, ultimately they decreased their efficacy and necessitating the need for exogenous insulin injections (Amori et al., 2007). Most of the available therapies except metformin are associated with weight gain and this is disappointing since we know the strong relationship between obesity and type 2 diabetes (Verspohl, 2009). Studies in Canada show that nearly half of all patients with T2DM and who are under medication do not attain the recommended HbA1c levels of ⩽7% (Canadian Diabetes Association, 2008).

Recent developments in the treatment of diabetes have provided additional options for the control of diabetes mellitus. Incretin-based therapies are one of the breakthroughs that stimulate insulin secretion and reduce glucagon secretion, resulting in reduction of hepatic glucose production (Perfetti et al., 2000; Tourrel et al., 2001; Hui et al., 2003). There are two classes of drugs based on the incretin system: GLP-1 receptor agonist, such as exenatide and liraglutide and DPP-4 inhibitors that delay endogenous degradation of GLP-1 inhibiting DPP-4 (Triplitt et al., 2007). There are world-wide uncertainties and controversies regarding the use of such therapies. Therefore, the aim of the review is to summarize an updated evidence of the effectiveness and safety of incretin-based agents.

2. Review question

What is the effectiveness of Incetine-based medications and their side effects in patients with T2DM?

3. Method

This is a narrative review of the evidence from the literature in order to answer the above-mentioned question.

We searched five databases including the following: the Cochrane library, MEDLINE, EMBASE, TRIP, and Science direct. We also searched databases of ongoing trials (clinicalTrials.gov/ and controlled-trials.com). Furthermore, we looked for other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, (systematic) reviews, meta-analyses and health technology assessment reports.

Search terms used were MeSH and keywords with different combinations of Boolean operators according to the database but were comparable (see Appendix A for search terms). Outcomes measures included: glycaemic control (HA1c), body mass index (BMI), lipids profiles, medications adherence, quality of life, mental health outcomes, utilization of health services, adverse effects, and economic outcomes. Search was

conducted on April 2013 and updated on February 2015. We decided not to have a time limit to the search in order to follow the history of development of incretin. Studies included were: randomized controlled trials, cohort and case-controlled studies, health technology report, meta-analysis, and systematic reviews. In addition, books and general reviews were retrieved also providing the history of incretin and their development. Results were analysed and reported in a narrative style with emphasis on the effectiveness and adverse effects of various types of incretin-based therapies.

4. Results

Search revealed 67 hits. Of these, 57 studies were excluded and 17 articles were retrieved as they fulfilled the inclusion criteria. They were heterogeneous in terms of interventions, participants, settings and outcomes. Studies varied in their quality and/or reporting of their findings conducted in several settings including the following: primary and secondary care. They also differed in the methods and instruments used to assess the effectiveness of different types of incretin in controlling T2DM. Majority of the studies were conducted in Western countries. All the studies discussed the development and/or compared the effectiveness of incretin-based drugs with other hypoglycaemic agents. In all the studies, follow-up of patients ranged from 8 weeks to 12 months.

This review revealed that there are two types of incretin: Glucose-dependent Insulinotropic Peptide (GIP) and Glucagon-like Peptide 1 (GLP-1). GIP was the first incretin to be defined and capable of inhibiting gastrointestinal motility and the secretion of gastric acid in animals (Brown et al., 1974). GIP is synthesized by the K cells of the proximal ends of the jejunum and duodenum in response to high levels of fat and glucose after intake of food. GIP is easily degraded by dipeptidyl peptidase 4 (DPP4), which occurs quickly after its release (Deacon et al., 2000a,b). GIP has its own receptors (glycoproteins) and acts by exerting insulin-tropic effect that is primarily induced by glucose (Ross and Dupre, 1978). Additionally, GIP takes part in the metabolism of fat in cells of the adipose tissue. There are numerous extra-pancreatic effects of GIP such as in the gastrointestinal tract, very high levels of GIP are required to inhibit the secretion of gastric acid and gastrointestinal motility in humans (Nauck et al., 1992).

Amongst the molecules that can assign to GLP-1 Receptors (GLP-1R) and activate it is Exendin-4 (Ex-4), formerly known as the investigational agent AC2993 and currently as Exenatide (a synthetic version of Ex-4) (Göke et al., 1993). The expression of GLP-1R is detected in the heart, gastrointestinal tract, nervous system, lung, pituitary glands, skin, C cells of thyroid, β cells of the pancreas and in the pancreatic duct (Kim and Egan, 2008). Binding of GIP, GIP-1 and their receptors leads to the stimulation of glucose-dependent production of insulin from the β cells (Lonart et al., 2003). Furthermore, it has been found that in the brain, GLP-1 is thought to have a role in the regulation of body weight, food intake, and appetite (Kim and Egan, 2008).

GLP-1 has numerous extra-pancreatic effects. For example, in the cardiovascular system, GLP-1 has been observed in vascular smooth muscle cells, endothelial cells, and cardiac myocytes (Ban et al., 2008). They maintained cardiac contractility and modulation of the resting heart rate and blood pressure by neuroendocrine and autonomic control through vagal innervation (Yamamoto et al., 2002). Moreover, GLP-1 has cardioprotective effects, which assist to protect against heart failure or ischaemic destruction by increasing myocardial glucose uptake via increasing production of nitric oxide (Nikolaidis et al., 2005).

In patients with T2DM, GIP with GLP-1 was found to be responsible for more than 80% of the incretin effect that follows after eating of any meal (Freeman, 2009a,b). However, this effect could be diminished and the receptors desensitized overtime. Researchers suggested that this was caused by free fatty acids and chronic hyperglycaemia (Zhou et al., 2007; Kim and Egan, 2008). Subsequently, wide-ranging research has been advanced to expand GLP-1 action for longer period and hence normalization of plasma glucose in type 2 patients (Knop et al., 2009; Kaur et al., 2014). This resulted in the development of GLP-1 receptor agonists or DPP-4 enzyme inhibitors.

4.1. GLP-1 receptors agonists

These agonists are analogues of GLP-1 and they attach to GLP-1 receptors and stimulate them thereby causing improved production of insulin, inhibition of glucagon production, and slow gastric emptying (Ross and Ekoe, 2010). For example; Exenatide is a synthetic form of exendin-4 (Ex-4) that is isolated from saliva of the Gila monster (Freeman, 2009a,b). Exenatide was introduced in Europe in May 2007. Exenatide attaches to GLP-1R with larger affinity than GLP-1 and its strength in reducing the level of blood glucose is 5000 times higher than that of native GLP-1 (Parkes et al., 2001). It is administered subcutaneously twice daily either as monotherapy or in combination with a thiazolidinedione, sulfonylurea, or metformin (Freeman, 2009a,b). Liraglutide (Victoza) is another GLP-1 agonist, which is currently used widely. Injection of the liraglutide is subcutaneous and it takes between 10 and 14 h to achieve the peak plasma concentration (Agersø et al., 2002).

Recently, Exenatide long acting release (LAR) has been developed, which is the long-acting form of exenatide that is given once weekly (Knop et al., 2009). The efficacy of exenatide LAR was investigated by Kim and colleagues (Kim et al., 2007) and they found that it causes a 1.4–1.7% reduction in HbA1c levels. Compared to placebo, it reduces the average level of glucose in the blood by 39.6 mg/dl and 45 mg/dl when used at a dose of 0.8 mg and 2.0 mg respectively. Authors highlighted that for the patients under the 0.8 mg and 2.0 mg doses of exenatide LAR, 36% and 86% respectively, they were shown to achieve HbA1c levels equal to or less than 7%. Furthermore, the efficacy of exenatide LAR was compared to that of exenatide and it was found that over time, exenatide LAR is more effective than exenatide in lowering the level of HbA1c (Blevins et al., 2011).

The Liraglutide Effect and Action in Diabetes (LEAD) studies were also conducted examining the efficacy and safety of the drug using diverse treatment regimens. There were 6 studies comparing different regimen (Buse et al., 2009; Garber et al., 2009; Marre et al., 2009; Nauck et al., 2009; Riche et al., 2009; Zinman et al., 2009). In all these trials, researchers found that when liraglutide is used singly and/or

in combination with other hypoglycaemic medications (glime-piride, metformin, rosiglitazone, insulin glargine) to treat T2DM, there was a dose-dependent reduction in HbA1c levels and that liraglutide is more effective in lowering the glycaemia burden and body weight than the comparative existing drugs. However, the main adverse events were nausea and vomiting, which observed as a dose-independent effect and fades 4 weeks after the onset of treatment.

4.2. Dipeptidyl peptidase 4 (DPP4) inhibitors

DPP4 inhibitors exert their effect by inhibiting the dipeptidyl peptidase 4 enzyme (DPP4), which is responsible for degrading GLP-1 and GIP. This will improve their availability and hence reduced levels of blood glucose due to the insulinotropic effect of GLP-1 (Ross and Ekoe, 2010). Currently, sitagliptin, vildagliptin, saxagliptin, and linagliptin are available as DPP-4 inhibitors. They differ in their bioavailability, half-life, peak plasma level, and excretion method (Renal or hepatic). For example; Vildagliptin is the only one that is established to be effective and well tolerated in type 2 diabetic patients aged ⩾65 years, compared to other DPP-4 inhibitors, when given as monotherapy or in combination (Pratley et al., 2007; Schweizer et al., 2009, 2011). Treating diabetes mellitus in older population is uniquely challenging. This is due to the risk of hypoglycaemia associated with using oral anti-diabetic medications or insulin and the risk of marked unawareness of hypoglycaemia in such population (Chelliah and Burge, 2004; Bremer et al., 2009). Vildagliptin is a highly selective DPP-4 inhibitor and a promising add-on partner to metformin (Bosi et al., 2009). This is particularly true in the elderly patients with some renal impairment. However; Sitagliptin, for example, needs to be excreted via the kidney (compared to Vildagliptin that is excreted via the liver) and might not be suitable for diabetic patients with some impairment of the renal function (Kim and Egan, 2008). The advantage of Sitagliptin is its long half-life and therefore, can be used as once daily, while Vildagliptin should be used on twice daily basis.

DPP4 inhibitors have several drug interactions. For example; the anticoagulant action of warfarin is increased by exenatide. Additionally, monoamine oxidase inhibitors may enhance the hypoglycaemic effect of incretins, beta-blockers may mask the hypoglycaemic effect of the drugs when given together, and Sitagliptin has been shown to enhance the plasma levels of digoxin (Andukuri et al., 2009; Brown et al., 2009). Corticosteroids, diuretics, and diazoxide may impede the antidiabetic effects of the incretin-based drugs. Oestrogens and progestogens may impede the hypoglycaemic activity of the drugs while testosterone may enhance the hypoglycaemic activity (Scheen, 2010).

In a Cochrane systematic review conducted in 2008, authors found that DPP-4 inhibitors have some theoretical benefits over existing therapies with oral antidiabetic medications. Researchers found that DPP4 inhibitors lower HbA1c levels in a manner that is similar to that of thiazolidinediones, sulfonylureas, and metformin (Richter et al., 2008). Therefore, they suggested that DPP-4 inhibitors should presently be limited to individual patients. Long-term data particularly on cardiovascular outcomes and safety are urgently needed before the widespread use of these new drugs. However, in 2012,

another systematic review was published as more trials have been conducted since the inception of DPP-4 inhibitors and showed that a large body of data supports the long-term safety of gliptin treatment and refutes an increased risk of infections including naso-pharyngitis and urinary tract infections (Goossen and Gräber, 2012). Moreover, several case reports of pancreatitis with DPP-4 inhibitor treatment have led to the inclusion of a warning report on all product labels, and urged an assessment of the pancreatitis risk established on observational pharmacy claims (Garg et al., 2010; Raschi et al., 2013) and pooled patient data (Engel et al., 2010). These post hoc analyses do not support a significantly elevated risk of increasing pancreatitis with gliptin treatment over the near threefold standard risk that patients with diabetes have over healthy controls (Gooßen and Gräber, 2012).

5. Discussion

This review showed that incretin-based treatment has several advantages. There is no question that incretin-based glucose-lowering medications have demonstrated to be effective glucose-lowering drugs. GLP-1 receptor agonists prove an evidence-based efficacy profile and appear to do so with significant effects to stimulate weight loss with minimal hypoglycaemia. However, there are few side effects that should not be overlooked when deciding to use such therapies.

Type 2 diabetes is a complex disease characterized by resistance of the insulin action and eventually a decrease in insulin secretion. Current therapeutic options for type 2 diabetes such as sulphonylureas, metformin, thiazolidinedione and α-glucosidase inhibitors are often failed to reach the recommended targets for glycaemic control. Effectiveness of these medications usually declines as the disease progresses because of deterioration of β cell function. Moreover, use of the available therapies is usually restricted due to inconvenient side effects such as hypoglycaemia and weight gain. Incretin based treatments have been developed after understanding of the incretin physiology and their role in type 2 diabetes. They targeted multiple features of pathophysiology of type 2 diabetes including progressive deterioration of β cell function as well as high plasma glucagon level. However; there are some adverse events that should be considered when treating T2DM patients. Additionally, Incretin therapies are expensive.

Our review found to be consistent with recent systematic reviews (only structured abstracts). For example, in a recent systematic review, researchers found that Liraglutide and exenatide once weekly resulted in greater improvement in haemoglobin A1C and fasting plasma glucose than other incretin based therapies. In comparison with exenatide twice daily, they resulted in less effect on post-prandial glucose, comparable reduction in body weight and produced a good adverse event profile (CRD, 2015a,b). Another recent systematic review also ensured that Incretin-based treatments were effective in glycaemic control and presented other advantages (e.g., weight loss with exenatide and liraglutide), which may have an important influence on patient adherence to medication (CRD, 2015a,b). The authors concluded that incretin-based treatments were effective in glycaemic control in patients with T2DM; they also presented other advantages (like weight loss with exenatide and liraglutide).

Furthermore, in a systematic review conducted on 2014, reviewers found that DPP-4 inhibitors were not associated with a significant reduction in cardiovascular death, myocardial infarction, or stroke in patients with type 2 diabetes mellitus or impaired glucose intolerance (Morey-Vargas and Montori, 2014). Moreover, a recent Cochrane meta-analysis (structured abstract only) revealed that DPP4is and control treatments did not differ for pancreatitis, sever adverse effects (SAEs), pancreatic cancer, or total treatment-emergent SAEs (Morey-Vargas and Montori, 2014). The variations in the reporting of side effects could be explained by the fact that the number and duration of trials were insufficient to draw definitive conclusions on the adverse events of dipeptidyl peptidase-4 inhibitors. Other studies however suggest that incretin-based therapies do not increase one's risk of pancreatitis beyond the expected risk in people with T2DM (Olansky, 2010).

In the above summarized reviews, the majority of the studies addressed a clear research question, supported by suitable inclusion criteria. A range of appropriate sources were also searched to identify studies and attempts were made to find unpublished studies, however; only English language studies were included so publication bias could not be ruled out. Appropriate methods were also used to select studies, make quality assessments and summarize data, which reduced the chance of reviewer error and bias. The included studies were not generally of good quality and most were open label, so the reliability of the findings was not sufficient. Additionally, biased documentation of cases and residual confounding in the observational studies, and cautious selection of participants into the trials and potential for incomplete or biased reporting of their results, may explain these differences in their outcomes. Therefore, these studies cannot fully resolve the issue of valid occurrence of such adverse effects. In addition, low event rates and short trial might preclude adequate assessment of the risk for these side effects. These uncertainties muddle the decision to use DPP4-inhibitors. Patients and clinicians need to consider the benefits that these agents offer (e.g. modest anti-hyperglycaemic effects) and the availability of existing choices. Hence, it seems wise to avoid DPP4 inhibitors in patients with risk factors for (alcohol abuse, gallbladder stones) or a history of acute pancreatitis.

6. Implications

This review has several implications for practice and research. When incretin-based therapies invented, several studies suggested that they may expose patients with T2DM to some adverse events. However; more recent clinical studies and systematic reviews repudiate such prior publications that have indicated such adverse side effects. This review could be used as a basis for generating the hypotheses for adequately powered randomized clinical trials (RCTs) to rigorously and conclusively validate or refute the alarming signals from the use of incretin therapies noted in previous reviews.

The findings of our review presented here, do not prove that these agents are unsafe, but it do suggest that the burden of evidence now rests with those who hope to persuade us of their safety. Continuous clinical monitoring and more research are essential to clarify the actions of GLP-1R agonists and DPP-4 on the normal and diabetic exocrine pancreas.

Furthermore, enduring scrutiny and further studies are necessary to clarify the potential implication of reports of pancreatic injury, including pancreatitis and metaplasia, and rodent medullary thyroid cancer for human beings treated with Incretin-based agents. Moreover, at the individual patient level, clinicians need to base their decision to use incretin-based agents based on the available best evidence and patients' choice provided that they are well-informed of the benefits and risks of such medications.

Appendix A. search terms

Incretin$
GLP-1 receptor agonist$
DPP-4 inhibitor$
diabetes
glycaemic control
HA1c
body mass index
BMI
lipids profiles
medications adherence
quality of life
adverse effects
economic outcomes

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