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Therapeutic benefits of incretin hormones beyond glycemic control from a primary care perspective: A Narrative Review

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Abstract
The parallel rise in the prevalence of obesity and T2DM is a global health challenge. One of the pathogenesis involved in development and progression of type-2 diabetes mellitus is beta cell dysfunction. Until now, diabetes treatments could not restore the reduced function of pancreatic β cell, necessitating the need for advanced treatment options. This led to discovery of incretin hormones in the small intestine, which stimulates insulin secretion in response to glucose. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are two such incretin hormones, secreted by the small intestine in response to food ingestion. Important physiological effects of GLP-1 include enhancement of the insulinotropic response of beta cells to intake of nutrients, reduced gastrointestinal secretion and motility, as well as induction of satiety and ensuing reduction of food intake.
Recent evidence suggests that in addition to its established glucose-lowering actions, GLP-1 RAs may also exert several beneficial actions extending beyond glycemic control. The recent finding that GIP/GLP-1 receptor co-agonists like tirzepatide have superior efficacy compared to selective GLP-1 receptor agonists with respect to glycaemic control as well as body weight has renewed interest in GIP, which previously was thought to lack therapeutic potential.
This is a narrative review examining some of the 'beyond-glycemic" benefits of incretin hormones, focusing predominantly on GLP-1 RAs including blood pressure lowering, improvements in the lipid profile, improvements in myocardial and endothelial function. We explore how those effects may help reduce the cardiovascular burden in patients with diabetes. The aim is to encourage use of GLP-1 RA early in patients with established CVD risk factors to prevent CVD related complications and mortality.
Keywords: *glucagon-like peptide-1 receptor agonist, cardiovascular diseases, major adverse cardiovascular events, type 2 diabetes mellitus, obesity, GIP receptor.*

Introduction

The global prevalence of diabetes mellitus is increasing at an exponential rate and diabetes patients are well known to have an increased risk of both macro and micro vascular complications such as retinopathy, nephropathy, neuropathy as well as atherosclerotic disease. Hyperglycemia results from a combination of insulin resistance in the early phase of the disease process and relative insulin deficiency. Chronic hyperglycemia then

leads to glucose toxicity, which in turn leads to pancreatic beta cell dysfunction and exacerbates insulin deficiency in the late phase. The ultimate result of this is a viscous cycle of hyperglycemia leading to a worsening metabolic state. One of the barriers for achieving good glycaemic control is insulin resistance secondary to obesity which is a key feature in pathogenesis of T2DM[(1)].

Diabetes and obesity are two chronic health conditions leading to substantial morbidity and high mortality worldwide, especially in developed countries. They are considered the twin epidemics of the 21st century[(2)]. Neither disorder is a simple problem; rather, both are complex health issues combining genetic, epigenetic, and lifestyle factors, including socioeconomic and environmental impacts[(3)].

Incretins', also known as 'Incretin hormones', were first discovered in the early 1970s. The most important incretins include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 has a pivotal role in metabolic processes and was discovered in 1981 when it was isolated from the pancreatic islet of anglerfish. Further research identified GLP-1 in L cells of mammalian gut mucosa and later, it was proved that GLP-1 enhances insulin secretion in response to nutrient ingestion[(4)]. GLP-1 exerts physiological effects by binding to the GLP-1 receptor (GLP-1R) on target cells. The activation of GLP-1R triggers a complex intracellular signaling cascade, which at the end activates protein kinase A (PKA) pathway via production of cyclic adenosine monophosphate (cAMP). GLP-1R are found, not only in the pancreas, but in lungs, kidney, central nervous system, stomach, cardiomyocytes, and vascular endothelial cells[(5)]. Therefore, the biological effects of GLP-1 are manifold owing to its wide distribution. (*figure 1*)

The discovery and characterization of the GLPs spans over 3 decades and highlights how molecular biology, and traditional analyses of hormone action provides a firm scientific foundation for the development of multiple novel therapeutics for the treatment of not only diabetes but also obesity, and potentially other disorders.

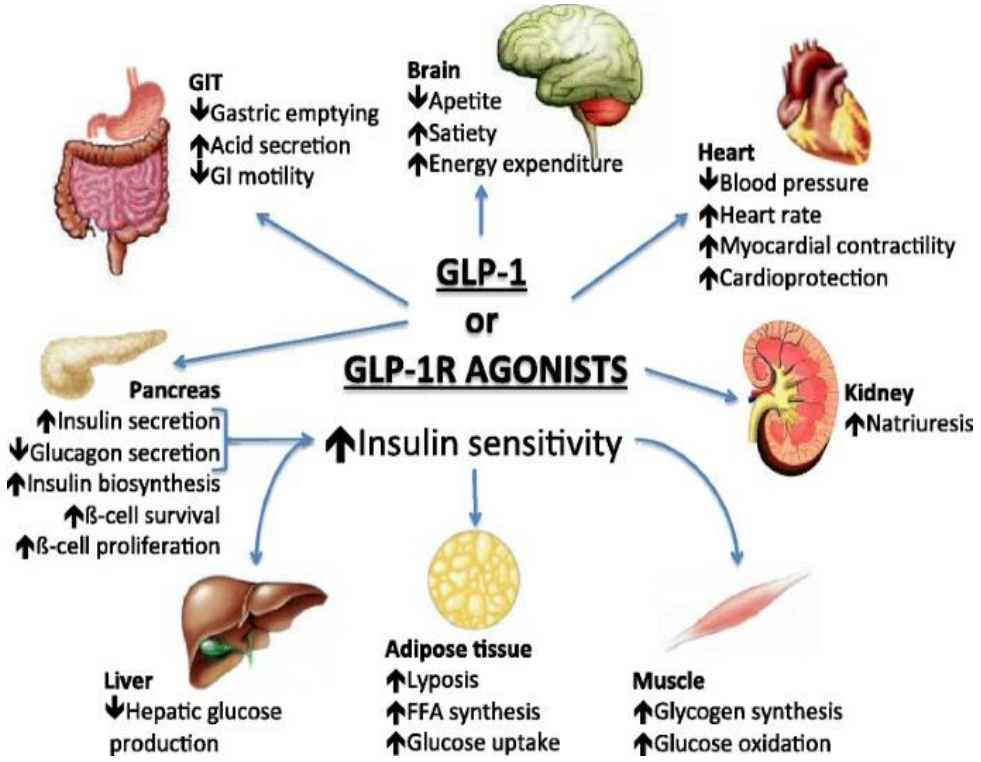

Figure 1 Physiological effects of Glucagon-like Peptide-1 receptor Agonists. GLP-1 RAs exerts various biological actions on several target organs.

Effects on glycemic control

It is well known that type 2 diabetes is a progressive disease. The UK Prospective Diabetes Study [UKPDS]- one of the largest studies conducted in patients with diabetes, showed glycemic control deteriorated over time in both the active treatment group and the control group independent of the antihyperglycemic agent used. Furthermore, the UKPDS data showed cell function had already declined by about 50% at the time of diagnosis in patients with type 2 diabetes[6]. A major defect underlying this decline in cell function is increased cell apoptosis, while new islet formation and cell replication are normal. Thus, therapeutic agents like the incretin hormones, which in animal and in vitro studies have been shown to inhibit apoptosis and increase cell proliferation, constitute advance in therapeutic strategies in management of diabetes[7].

The incretin effect describes the phenomenon that oral glucose, absorbed from the gut, leads to the stimulated secretion of both GIP and GLP-1, which in turn provides a stimulus to ß-cells in the islets of Langerhans to augment their insulin secretory responses. Therefore, the core effect of GLP-1 RAs in T2D is good glycaemic control, which is achieved through effects on GLP-1 receptors in the pancreas, essentially stimulating insulin release from pancreatic islet β-cells in a glucose-dependent manner and suppressing glucagon secretion from pancreatic islet alpha (α)-cells, which contributes to the reduction in blood glucose levels in people with hyperglycaemia[8]. This 'insulinotropic' action is highly dependent on plasma glucose concentrations. Therefore, high concentrations of GIP and GLP-1 do not cause hypoglycaemia[9]. GLP-1 inhibits glucagon secretion during hyperglycemia, but not when glucose levels return to euglycemia or during hypoglycemia. As a result, GLP-1 receptor (GLP-1R) agonists (GLP-1RA) reduce hyperglycemia with little risk of hypoglycemic episodes[9,10].

Effects on obesity

There is increasing evidence that obesity dysregulate many overlapping signaling pathways, including inflammation and oxidative stress and that obesity accelerates the onset of aging-related diseases. Obesity is related to an increased risk of other serious conditions and diseases such as diabetes, hypertension, cardiovascular disease, cancer, asthma, hypercholesterolemia. In support of this, obese patients have decreased lifespans and poorer clinical outcomes compared to their lean counterparts[11].

The mechanism of action of GLP-1RA to promote weight loss mainly includes the reduction of fat deposition through regulation of adipose tissue (lipolysis, fatty acid oxidation, and adipocyte differentiation) and the reduction of food intake through the central and peripheral nervous system. Adipose tissue mass control has been attributed, in part, to the effects of GLP1RA on the sympathetic nervous system (SNS) and appetite suppression[12]. The GLP-1RAs-associated weight loss is thought to be achieved through a variety of mechanisms, including the delayed gastric emptying, increased satiety, increased resting energy expenditure, as well as the direct influence of the appetite center of the brain[12].

Semaglutide and liraglutide are the two GLP1RAs that have been FDA-approved to treat obesity[12]. In the SCALE Diabetes trial, 6% weight loss was achieved over 52 weeks in people with T2D treated with 3 mg liraglutide once daily, with 25.2% of the trial subjects experiencing >10% weight loss[13]. In the STEP trial, administration of 2.4 mg of Semaglutide once weekly plus lifestyle intervention was associated with sustained, clinically relevant reduction in body weight of to -14.9% at 68 weeks compared with −2.4% with placebo[14].

A new drug, Tirzepatide, is the first peptide dual agonist for T2DM, which targets both glucagon-like peptide 1(GLP-1) and gastric inhibitory polypeptide (GIP) receptors. Due to its unique dual activity property, it is also referred to as

'twincretin'. The GIPR-GLP1R co-agonist produced superior reductions in HbA1c and body weight, relative to that achieved with 1 mg once weekly of Semaglutide in people with T2DM, prompting ongoing development of Tirzepatide as a weight loss agent for people with overweight or obesity[15].

Effects on cardiac and renal outcomes

Cardiovascular disease (CVD) is the leading cause of mortality in the UK, accounting for premature death in up to 40% of the population, and patients with diabetes are characterized by a significantly elevated risk compared to normoglycaemic individuals. Indeed, the Framingham Heart Study found that heart failure was twice as common in diabetic men, and five times as common in diabetic women aged 45–74 compared to the normal population, and this association was even stronger in younger patients[16]. Patients with T2 diabetes are considered for CVD secondary prevention because their risk level is similar to that reported in nondiabetic patients who have already suffered a MI[17].

A major goal and unmet need of T2D therapy is the prevention of macrovascular disease, and recent clinical trial results from SGLT2 highlight the potential for anti-diabetic therapy to reduce the burden of CV disease[18].

GLP-1 receptor agonists have demonstrated unique properties beyond glucose regulation. By mimicking the effects of endogenous GLP-1, they stimulate GLP-1 receptors, including those in cardiomyocytes and blood vessels. GLP-1-R agonists are thought to exert a cardioprotective effect by a few mechanisms, among which are the reduction in macrophage adhesion to the endothelium. This effect may lead to the reduction in atherosclerotic plaque formation[19].

Results of cardiovascular outcome studies showed that in addition to the cardiovascular safety of GLP-1 receptor agonists, some drugs in the class can have influence on major adverse cardiovascular event (MACE) reduction compared to placebo[20]. The primary and secondary outcome endpoints of MACE and nonfatal stroke demonstrated significant reductions in the dulaglutide-treated REWIND trial and the subcutaneous semaglutide-treated SUSTAIN-6 study[21,22].

A systematic review and meta-analysis in 2021 included data from eight large-scale cardiovascular outcome trials, pooling data for lixisenatide, liraglutide, injectable semaglutide, exenatide, albiglutide, dulaglutide, oral semaglutide, and efpeglenatide, studying of the effect of GLP-1 receptor agonists on cardiovascular and kidney outcomes in patients with type 2 diabetes. The results show that treatment with GLP-1 receptor agonists reduced the risk of MACE and its individual components; all-cause mortality; hospital admission for heart failure; and a composite kidney outcome of development of new-onset macroalbuminuria, decline in estimated glomerular filtration rate (eGFR) or increase in creatinine, kidney replacement therapy, or death attributable to kidney causes[23].

Tirzepatide's dual agonism of GLP1 and GIP receptors has also provided encouraging cardiovascular benefits beyond glycemic control, offering a potential new therapeutic option for treating cardiovascular diseases and heart failure[24]. Ongoing research, such as the SUMMIT trial, is presently assessing the safety and efficacy of tirzepatide in HF patients with preserved ejection fraction (HFpEF) and whether it can demonstrate superior cardiovascular safety and benefits compared to the currently approved GLP-1RA dulaglutide[25].

The FIGHT trial specifically evaluated the GLP-1RAs, liraglutide, in patients with HF with reduced ejection fraction (HFrEF). The trial did not show a significant advantage in reducing cardiovascular events or hospitalizations. However, it provided insights into liraglutide's safety and tolerability in this patient population [26]. Data from two large, well-powered clinical

trials, SURPASS-CVOT and SURMOUNT-MMO will provide robust evidence on the cardiovascular and metabolic benefits of tirzepatide, potentially expanding the treatment options for adults with T2DM, obesity, and related CVD complications[27].

To date, the only other class of type 2 diabetes therapy with an indication for reducing CV risk is the sodium–glucose cotransporter 2 (SGLT2) inhibitor class. SGLT2 inhibitors have exhibited better effects regarding a reduced incidence of HF, whereas GLP-1-R agonists have shown a reduced risk of CV events, particularly stroke[28]. As it stands different GLP-1-R agonists and SGLT2 inhibitors exert different effects on cardiorenal outcomes. Therefore, in terms of clinical practice and treatment management, an individualized approach should be considered.

Effects on MASLD

GLP-RAs have demonstrated not only effective weight loss and improved glycemic control, but also reduction of fat in the liver. This is a key step for preventing the progression of metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease. To date, the only treatment proved to be effective in MASLD is a weight loss of ≥7–10%, able to significantly improve the histological grade of fibrosis and steatosis, in addition to hepatic cytolysis[29].

Several studies found that GLP-1RAs might have direct effects on adipogenesis, lipotoxicity, fatty acid oxidation, cytokines related to hepatitis and fibrosis, and intestinal microbiota. Therefore, GLP-1RAs are of great significance in the treatment of MASLD[30].

The safety and efficacy of Liraglutide 1.8 mg daily were studied in people with overweight and metabolic dysfunction steatosis(MASH), previously known as Non alcoholic steatohepatitis over 48 weeks period[31]. Of the 52 volunteers enrolled in the trial, 39% of liraglutide-treated subjects demonstrated resolution of MASH vs. 9% randomized to placebo. Progression to fibrosis was also observed in fewer subjects randomized to Liraglutide[31].

The efficacy of semaglutide vs. placebo was evaluated in a large, 72-week double-blind phase 2 trial in individuals with Metabolic dysfunction steatohepatitis (MASH). Among volunteers treated with the highest dose of once-daily semaglutide, NASH resolution was detected in 59% of people vs. 17% in the placebo arm[32].

In the SURPASS 3 trial, a 52-week, multi-center, randomized, phase 3 open-label trial evaluated the efficacy and safety of Tirzepatide compared to titrated insulin Degludec in adults with type 2 diabetes. Participants taking Tirzepatide 15 mg experienced 47.11% relative reduction in liver fat content compared to 11.17% for insulin Degludec[33].

In a new SYNERGY-NASH phase 2 trial involving participants with MASH and moderate or severe fibrosis, treatment with tirzepatide for 52 weeks was more effective than placebo with respect to resolution of MASH without worsening of fibrosis[34]. Larger and longer trials are required to further assess the efficacy and safety of tirzepatide for the treatment of MASH**.**

Effects on blood pressure and lipids

When combined with other risk factors, such as dyslipidemia and diabetes, the impact of hypertension on cardiovascular risk becomes more pronounced. Therefore, effective hypertension control yields a significant cardiovascular protective effect. A reduction in blood pressure of at least 5 mmHg, if sustained, results in a 10% reduction in the risk of cardiovascular events and a 5% decrease in cardiovascular mortality over an average of 4 years[35].

The reduction in blood pressure by GLP-1 RAs is thought to be due to multiple mechanisms, such as increased urine excretion and natriuresis, activation of adrenergic receptors, activation of neural pathways leading to reduced sympathetic nervous system activity, heightened insulin

production resulting in vasodilation, direct vasodilatory action by stimulating GLP-1 receptors in blood vessels, and weight loss[36,37].
GLP-1 RA have also been shown to modestly reduce total cholesterol, LDL cholesterol, and triglycerides, suggesting a positive impact of GLP-1 RAs on atherosclerosis, leading to reduction of cardiovascular events[38]. The effects of GLP-1 RAs on lipids may also appear to be attributed to a definite correlation between decrease in body weight and improvements in the lipid profile[38]. Overall, the beneficial effects of GLP-1 RA on cardiovascular outcomes in high-risk patients with T2D are most likely explained by a combination of metabolic, vascular, antithrombotic and anti-inflammatory effects.

Effects on neurodegenerative disorders

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease, involving neurotoxic amyloid β peptides deposition along with neurofibrillary tangle formation as a key pathological hallmark of the disease. Recent evidence suggests that inflammation may be a third important component which, once initiated in response to neurodegeneration or dysfunction, may actively contribute to disease progression and chronicity[39]. Interestingly, increased inflammation and neurodegenerative disease risk have been associated with type 2 diabetes mellitus (T2DM) and insulin resistance (IR), suggesting that treatments that mitigate T2DM pathology may be successful in treating neuroinflammatory and neurodegenerative pathology as well[40]. Preclinical studies have so far demonstrated suppression of neuroinflammation by GLP-RAs and exenatide, given either twice daily or once weekly, improved disease activity scores in people with Parkinson's disease[40].
The therapeutic potential of oral semeglutide is further being explored in clinical trials, in populations with and without co-existing vascular disease[53].
Successful outcomes from these trials could lead to new, effective treatment options for millions of individuals affected by Alzheimer's and Parkinson's Disease, ultimately improving their quality of life and improve disease management.

Side effects/safety of GLP-1 RAs

Gastrointestinal complaints are the most common side effects seen with GLP-1 RA, including nausea (25%–60%), vomiting (5%–15%), and diarrhea (However, these are often transient and rarely leads to therapy discontinuation[49]. Side effects of tirzepatide are comparable to GLP-1 agonists, as it is a dual GIP/GLP-1 agonist. The risk of hypoglycemia with GLP-1 RA is minimal unless these drugs are used in combination with agents that cause hypoglycemia, such as insulin or sulfonylureas, which should be stopped, or their doses reduced when starting these patients on a GLP-1 RAs[42]. A systematic review revealed an association between GLP-1 RAs and an increased risk of gallbladder or biliary disorders. This correlation was particularly notable in cases involving higher dosage and prolonged usage[43].
In the last year, the European Medicines Agency (EMA), Food and Drug Administration (FDA) and the Medicines and Healthcare Products Regulatory Agency in the United Kingdom (MHRA) began investigations into whether glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are causally related to suicidality, prompted by reports of 2 cases of self-injury and suicidal thoughts associated with semaglutide and liraglutide in Iceland[44].
Although plausible mechanisms exist to explain how GLP-1RAs might increase suicidality, plausible mechanisms also exist to support anti-depressant effects[45]. The current evidence for an association between GLP-1RAs and suicidality is limited, based essentially on case reports and pharmacovigilance surveillance systems. Large trials have been unable to detect a direct causal relationship, leading to conclusion from the health regulatory agencies that there was

disproportionate reporting of suicidal behavior, suicide attempts, and completed suicide. After taking into consideration confounders, no causal link between GLP-1 RAs and suicidality exists[46]. Yet suicidality concerns should not be dismissed as patients with chronic disease and obesity are likely to have co-existing mental health conditions.

Contraindications

GLP-1 RA are contraindicated in pregnancy and breastfeeding, contraception is recommended in women of childbearing age. Patients with severe gastrointestinal diseases such as gastroparesis and inflammatory bowel disease should avoid GLP-1 RA because of their effect of slowed gastric emptying and potential exacerbation of gastrointestinal symptoms. A causal relationship between GLP-1 analogs and pancreatitis or pancreatic cancer is still unknown. The most recent evidence suggests that the risk is lower than previously thought[47]. Nonetheless, GLP-1 agonists should not be prescribed in patients with a history of pancreatitis and should be discontinued in those who develop pancreatitis during treatment.

A recent large Scandinavian cohort study using nationwide data from Sweden, Denmark, and Norway investigating the risk of thyroid cancer among patients treated with GLP1 RAs showed there is no substantially increased risk of thyroid cancer, although small risk increases cannot be excluded[48]. The FDA still advices that GLP-1 RAs are not recommended in patients with a personal or family history of multiple endocrine neoplasia 2A, multiple endocrine neoplasia 2B, or medullary thyroid cancer.

Where do GLP-1RAs sit in the treatment paradigm?

A paradigm shift has occurred recently in terms of T2DM management. GLP1RAs have significantly advanced the management of T2DM, kidney health, and Cardiovascular health, supported by robust findings from Cardiovascular outcome trials. GLP-1 RAs' major advantage of over conventional anti-diabetic therapies, such as sulphonylureas and insulin is that its insulinotropic actions are dependent on ambient glucose concentrations, thus mitigating the risks of hypoglycaemia.

The American Diabetes Association and the European Association for the Study of Diabetes (EASD) have released the latest "standards of care in Diabetes" following a systematic examination of publications since 2018 which has informed its new recommendations[50]. With regards to medication management, for patients with clinical cardiovascular disease, a sodium–glucose cotransporter-2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended[50]. The main goal in high CV risk patients should be the reduction in cardiorenal risk, which can be achieved using either SGLT2 inhibitors or GLP-1-R agonists. The choice of the exact drug is made depending on the comorbidities. SGLT2 inhibitors are preferred to GLP-1-R agonists in patients with documented HF or CKD and should constitute the first-line treatment. Treatment should be in parallel to adequate primary disease medication. In subjects with ASCVD or high CV risk, the EASD guidelines do not prioritize SGLT2 inhibitors over GLP-1-R agonists; therefore, they can be used interchangeably[51].

Dual Peptides like Tirzepatine have also evolved from promising antihyperglycemic agents to becoming crucial cardiometabolic therapies with significant CV benefit. Thus, tirzepatide could be a breakthrough in the treatment of T2 diabetes. As such, further research in synthetic peptide therapeutics has gained increasing momentum.

Conclusion

Primary care providers are usually faced with the challenge of not only managing diabetes itself, but also preventing hypoglycemia and weight gain associated with intensive disease management and

reducing cardiovascular risk. Diabetes care has evolved over the last two decades, shifting from a glucose-centric approach to multifactorial intervention with the aim of minimizing CV morbidity and mortality.

Both diabetes and cardiology guidelines and professional societies have responded to this paradigm shift by including strong recommendations to use SGLT2i and/or GLP-1 RA, with evidence-based benefits to reduce cardiovascular risk in high-risk individuals with type 2 diabetes, independent of the need for additional glucose control[52].

Both SGLT2 and GLP-1 RAs are now recommended as first-line therapy independently of background glucose-lowering agents, current human glycated hemoglobin (HbA1c) level or HbA1c targeted level in patients with T2DM and established or subclinical atherosclerotic cardiovascular disease (ASCVD) or CKD with the caveat that, in the latter, SGLT2 inhibitors ought to be preferred[51].

The importance and benefits of combining lifestyle interventions such as diet and exercise, together with GLP1-RAs, should not be neglected in clinical practice.

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