REVIEW ARTICLE

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Potential of Semaglutide in the treatment of Type 2 Diabetes Mellitus: An Overview

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ABSTRACT

Type II DM is one of the most challenging and escalating health problems that currently reached epidemic proportions in all countries of the world with a large increase in obesity. The global prevalence of type 2 diabetes in 2010 was 6.4% and it will increase to 7.7% by 2030 including adults. Weight gain is the major side effect associated with all hypoglycaemic drugs. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are the only medication class involved with body weight reduction, according to the guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Currently, there are six GLP-1 receptor agonists are approved for treatment of Type II DM. The present article summarizes recent developments and discusses the safety and tolerability of semaglutide in the treatment of Type II DM including pharmacological properties. Semaglutide is a mono-acylated peptide and structurally similar to liraglutide with fatty acid side chain. In clinical studies, significant dose dependent reductions in HbA1c were found at higher doses (≥0.8 mg) of semaglutide once weekly administration. In June 2013, the phase III clinical-trial programme called SUSTAIN was initiated in which semaglutide will be compared head-to-head with exenatide once-weekly (NCT01885208).

Keywords: - Semaglutide, Type 2 Diabetes Mellitus, Glucagon, hypoglycaemic.

INTRODUCTION

Diabetes mellitus is a result of complex metabolic dysfunction. It is characterized by most commonly hyperglycaemia due to impaired insulin secretion and resistance to insulin action and hyperlipaemia, glycosuria, polydipsia, and sometimes ketonaemia are the other factors closely related to diabetes mellitus [1]. This chronic metabolic disorder affects the body's ability to produce insulin and cause long term damage and failure of various organs [2]. Diabetes can be broadly classified as Type I or Insulin-dependent diabetes mellitus (IDDM)

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and Type II or Non-insulin dependent diabetes mellitus (NIDDM). Type I diabetes, also known as juvenile-onset diabetes mellitus and mostly occurs in adults. Type II DM mostly developed after the age of 40 years [3]. Type II DM is associated with a reduced gene expression of HK2 (Hexokinase 2) in muscle and obesity. At present, obesity is the most serious factor for Type II DM. Type II DM has currently reached epidemic proportions in all countries of the world with a large increase in obesity [1]. In 2010, it was estimated that almost 285 million people worldwide affected with Type II DM, and this is predicted that in 2030 there will be 439 million people affected from Type II DM. The global prevalence of type 2 diabetes in 2010 was 6.4% and it will increase to 7.7% by 2030 including adults [5]. It is estimated that the Type II diabetic prevalence in the United States will increase to 44 million from 2010 to 2034 [6]. In developing countries, the diabetic mortality rate is higher than 80% [7]. The Type II DM patients are increasing due to population growth, irregular lifestyle, overweight and urbanization [8]. After time Type II DM results in various complications such as Cardiovascular disease (coronary artery disease and stroke), Kidney disease (diabetic nephropathy), Nerve disease (diabetic neuropathy), and Eye disease (diabetic retinopathy) [9]. Although there are many therapeutic agents are developed against Type II DM but an ordinary disorder of the past has turned into a modern day prevalent over a whole world [4].

The objectives of the treatment of Type II DM include:

1) Enhancement of insulin secretion from pancreas.
2) Reduction of the glucose absorption from GIT.
3) Reduction of insulin requirement in organs.

The target of hypoglycaemic drugs is to regulate glucose homeostasis to prevent the development of complications. All hypoglycaemic agents, that have traditionally been available for the treatment of Type II DM, have been reported weight gain as a major side effect [13]. Even in properly selected patients, sulfonylureas may fail from the beginning due to continuing insulin resistance. Another disadvantage of available sulfonylureas is they have little or no effect in reducing the mealtime increase in glycaemia [14]. Combined use of a sulphonylurea and a biguanide produce GIT complications, severe trauma or stress. Despite their limitations, oral hypoglycaemics are suitable therapy, but obesity is major complications associated with these agents.

Table 1.1 Hypoglycaemic agents for glycemic control in type 2 diabetes mellitus

Medication Class	Mechanism of action	Drawbacks
Sulfonylurea (Glipizide)	Stimulate insulin release from pancreatic islets of β-cells and inhibit the ATP sensitive K^+ channels	Hypoglycaemia, Weight gain [10]
Biguanides (Metformin)	Suppress gluconeogenesis and retard intestinal absorption of glucose	GIT problems, lactic acidosis [11]
Thiazolidinediones	Activate PPARγ in muscle cells and reduce the insulin resistance by stimulation of GLUT4 expression	Plasma volume expansion, Weight gain [11]
Alpha glucosidase inhibitor	Retard the intestinal absorption of glucose	Flatulence, bloating [12]

In all available agents, biguanides and alpha-glucosidase inhibitors having weight neutral effect, but thiazolidinediones and sulfonylurea's produces a weight gain side effect [1].

Incretin peptide hormone therapy (GLP-1 RAs) is the effective treatment approach to overcome this problem [13]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are the only medication class involved with body weight reduction, according to the guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [15].

There are various polypeptide hormones have been identified that are secreted from intestinal cells and play a vital role in carbohydrate metabolism. Among these is the incretin hormone which is known as the backbone of peptide therapeutics. There are two incretin hormones were identified, respectively: glucose dependent insulinotropic peptide (GIP) and Glucagon-like peptide-1(GLP-1).

GLP-1 is a polypeptide incretin hormone and composed of 30 amino acids [16-17]. GLP-1 is produced from enteroendocrine L cells located in the distal intestine after eating meals, and produces their actions by binding to specific receptors [18-19]. GLP-1 is synthesized from pre- proglucagon gene and considered as the specific proteolytic product which potentiates the insulin secretion. GLP-1 secretion occurs rapidly after the meal ingestion in two phases. First phase consists of direct contact of meal with enteroendocrine L cells followed by second phase [16, 20]. GLP-1 acts through GLP-1 receptors that are specific G-protein coupled receptors, in the portal vein trigger

vagal afferents, generate efferent signals stimulating pancreatic insulin secretion and block glucagon secretion; this is mediated by neuronal pathways within the brain [21]. GLP-1 receptors (GLP-1R) are found in the ß-cells of pancreas, heart, blood vessels, gastrointestinal tract (GIT), kidney, lung, central and peripheral nervous system [18].

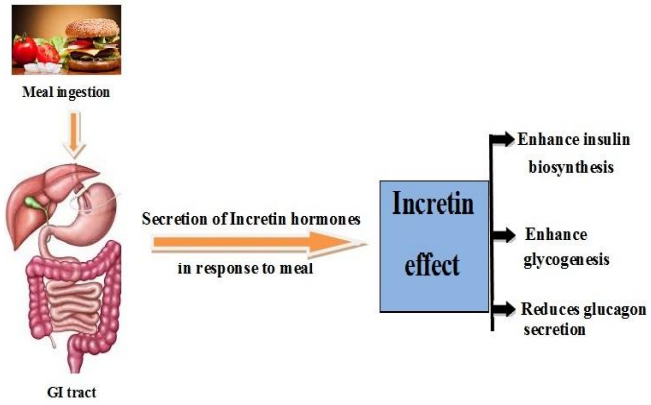

Figure 1- Incretin hormones (GLP-1 and GIP) are released from small intestine after meal ingestion and produce incretin action. This increase insulin secretion and decrease glucagon secretion. The glycogen formation also enhanced.

GLP-1 or receptor agonists have widespread pharmacological effects. They maintain glucose homeostasis, and functional status of adipose tissues and muscles. The effects of the GLP-1 or receptor agonist are depicted in table 1.2. GLP-1 or receptor agonists are capable of enhancing the glycogenesis followed by enhancing the insulin secretion. These are tending to produce a fall in blood pressure and have cardio protective action on the heart. GLP-1 or receptor agonists also increase the excretion of sodium and decrease H^+ excretion [18].

The most common adverse effects of GLP-1 RAs are gastrointestinal disorders (nausea, vomiting and diarrhoea) which are mostly transient and can be minimized by gradual adjusting of the dose [1]. Beyond the gastrointestinal side effects, pancreatic cancer and acute pancreatitis are also observed in recent findings, so the discussion is ongoing on these findings [9].

Table 1.2 Pharmacological actions of GLP-1 or GLP-1 receptor agonist

Organ	Pharmacological action
Pancreas	Enhance insulin secretion, increase Beta cell survival and proliferation, reduces glucagon secretion [22]
Liver	reduces hepatic glucose production
Adipose tissue	increase lyposis, enhance glucose uptake and storage [18]
Stomach	decrease gastric emptying and increase acid secretion [23]
Heart	increase heart rate and cardio protection, enhance myocardial contractility, decrease in blood pressure [20]
Brain	decrease apetite, increase energy consumption,enhance neuroprotection [15]
Muscle	increase natriuresis [9]

The weight reduction is the major advantage of GLP-1 RAs. Recent studies have found to be the optimum dose of exenatide and dulaglutide reduces the weight [15].

GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4) [19] which break off the two N-terminal amino acids and to make the hormone inactive with regard to the insulinotropic effect [9]. Structure activity describes that the C- terminal part of the GLP-1 peptides provide an essential component of receptor binding and N- terminal part is essential for receptor activation [21]. Due to inactivation by DPP-4 enzyme, they have a shorter plasma half life approximately 2 minutes. GLP-1 mainly excreted out through the kidney by glomerular filtration as well as tubular secretion [20]. Elimination rate is decreased in obese patients as compared to normal individuals. Due to shorter plasma half life and instant elimination, native GLP-1 is not suitable for clinical use [Asger Lund et al. (2013)]. To circumvent this problem, either DPP-4 enzyme inhibitors are used or to make DPP-4 resistant GLP-1 agonists [19].

Currently, there are six GLP-1 receptor agonists are approved for treatment of Type II DM. Exenatide is a synthetic version of exendin-4 and available in the market under the trade name Byetta® (Bristol Myers Squibb–AstraZeneca). Exenatide has a shorter duration of action and available for twice-daily subcutaneous administration [9]. Exendin-4 is a 39 amino acid peptide extracted from the venom of the Heloderma suspectum lizard that have 53% amino acid sequence identity with native GLP-1 and is a potent GLP-1 receptor agonist [20]. This amino acid sequence identity with native GLP-1 is high in liraglutide, about 97% [19]. Liraglutide was approved in 2009 and available in the market under the trade name (Victoza®) [1]. After dosing once daily by the subcutaneous route, the plasma half life of liraglutide is longer (12-13 hours) due to a fatty acid side chain, which enhances the noncovalent binding of liraglutide to plasma protein, this diminished the GLP-1 release from plasma protein, thus prolonging the duration of action [24]. In available GLP-1 RAs, liraglutide is most effective drug in Type II DM associated obesity [1].

Table 1.3 Classification of GLP-1 receptor agonist

Duration of action	GLP-1 receptor agonist	Administration route
Short- acting	Exenatide (Byetta®) Lixisenatide (Lyxumia®)	subcutaneous subcutaneous
Intermediate acting	Liraglutide (Victoza®)	subcutaneous [24]
Long acting	Albiglutide (Tanzeum®, Eperzan®) Dulaglutide (Trulicity™) Exenatide (Bydureon®) Semaglutide	subcutaneous [25] subcutaneous subcutaneous subcutaneous [26]

Lixisenatide is another available GLP-1 RAs which is marketed under the trade name Lyxumia® [24]. Lixisenatide has strong binding affinity to GLP-1 receptor [27] and consists of 44 amino acids and structure homologous of exendin-4 with 6- lysine units at C-terminals [9]. The terminal plasma half life of lixisenatide is 3 hours [1] and has a shorter duration of action, thus possibly used as a treatment option [23]. Lixisenatide in dosing once-daily by subcutaneous route shows significant improvements in antidiabetic therapy (HbA1c reduction between 0.7 and 0.8%).

Albiglutide is a GLP-1 receptor agonist developed by fusion of GLP-1 analogs coupled to albumin [9] and degradation is prevented by amino acid substitution at the DPP-4-sensitive hydrolysis site [26]. Albiglutide (Tanzeum) is approved GLP-1 receptor agonist sponsored by GlaxoSmithKline [25]. When compared with other GLP-1 receptor agonist, lower rates of gastrointestinal side effects are found in albiglutide [28]. But albiglutide is not recommended for Type II DM patients who have a history of medullary thyroid carcinoma (MTC) or have multiple endocrine neoplasia syndrome type 2 [29]. Furthermore, the plasma half life of albiglutide is 6 to 8 days in humans [1] and has a longer duration of action. Albiglutide in dosing once-weekly by subcutaneous route shows significant reduction in HbA1c (0.8%) [30]. Albiglutide is indicated as monotherapy or combination therapy with metformin, sitagliptin, pioglitazone and glimepiride [9]. Recently, other approved GLP-1 receptor agonist is dulaglutide in which GLP-1 analogs coupled with the Fc fragment of IgG and have a longer duration of action [24]. The FDA approved dulaglutide for the treatment of Type II DM in the United States in September 2014 [15]. The dulaglutide molecule consists of two identical GLP-1 moieties that are covalently fused to an immunoglobulin chain by a small peptide linker [31]. The plasma half life of dulaglutide has been reported 4 days in humans [9]. Clinical trials suggest that dulaglutide in dosing once-weekly by subcutaneous route shows dose dependent effect in HbA1c reduction (1.52%) as compared with placebo [32]. As observed for dulaglutide the effects on heart rate and blood pressure were moderate [15]. Gastrointestinal adverse effects (nausea, vomiting and diarrhoea) are seen with dulaglutide administration [31] but a recent study report finds no sign of antibody formation against dulaglutide [32]. Over the past few decades, there has been considerable interest in developing GLP-1 receptor agonist as an effective approach for obesity related Type II DM disorder.

Table 1.4 Overview of GLP-1 receptor agonists in clinical trials

[GLP-1 RAs	Sponsor	Dosing	Coupled moiety	Present status	Indication
Exenatide	Eli Lilly/Amylin Pharmaceuticals	Twice-daily	39 aa peptide	Approved in 2005	Type II DM, (Byetta®), Obesity
Liraglutide	Novo Nordisk	Once-daily	Peptide linked to fatty acid side chain	Approved in 2009	Type II DM, (Victoza®), Obesity
Exenatide	Eli Lilly/Amylin Pharmaceuticals	Once-weekly	39 aa peptide	Approved in 2012	Type II DM, (Bydureon®), Obesity
Lixisenatide	Zealand Pharma A/S/Sanofi-Aventis	Once-daily	44 aa peptide	Approved in 2013	Type II DM, (Lyxumia®), Obesity, CV
Albiglutide	GlaxoSmithKline	Once-weekly	Serum albumin fused with GLP-1	Approved in 2014	Type II DM, (Tanzeum®, Eperzan®) obesity
Dulaglutide	Eli Lilly Pharmaceuticals	Once-weekly	Immunoglobulin side chain	Approved in 2014	Type II DM, (Trulicity™), Obesity, CV
Semaglutide	Novo Nordisk	Once-weekly	Fatty acid side chain	Phase III	Type II DM
CVX096	Pfizer	S.C.	Antibody	Phase I	Type II DM
ZYOG1	Zydus-Cadila Group	Oral	aa peptide	Phase I	Type II DM
ZP2929	Zealand Pharma	Once-daily	aa peptide	Phase I	Type II DM

Abbreviations: aa: amino acid; CV: cardiovascular effects; s.c: subcutaneous

There are many GLP-1 agonists are approved in the US and EU that are globally marketed under different brand names.

The present article summarizes recent developments and discusses the safety and tolerability of Semaglutide in the treatment of Type II DM including pharmacological properties.

Semaglutide is a novel, long acting glucagon-like peptide 1(GLP-1) receptor analogue being developed by Novo Nordisk (Copenhagen, Denmark) for the treatment of type II Diabetes mellitus. Novo Nordisk is also developing an oral formulation of semaglutide [35].

Semaglutide consists of 37 amino acid linked with fatty acid side chain for once weekly administration [34]. In phase II clinical studies, therapeutic efficacy and safety of semaglutide was studied that found mostly similar to liraglutide [36]. An oral formulation of semaglutide (OG217SC) has successfully investigated under the phase II trial. In this phase II trial, therapeutic efficacy, safety and the dose range of oral semaglutide once daily was compared with oral placebo or semaglutide injection once weekly and found positive results for phase II trials with oral semaglutide [37]. Semaglutide once weekly is under phase III development in many countries worldwide. In December 2014, Novo Nordisk started a global phase IIIa program on semaglutide [38].

Table 1.5 Features and properties of semaglutide

Alternative names	NN9535; OG217SC; NNC 01130217
Sponsoring company	Novo Nordisk
Coupled moiety	Fatty acid chain
Molecular Formula	$C_{187}H_{291}N_{45}O_{59}$
Molecular Weight	4113.57754 g/mol
Mechanism of action	Glucagon-like peptide-1 receptor agonist
Route of administration	Subcutaneous injection, oral administration
Pharmacodynamics	Binds with Glucagon-like peptide-1 receptor and increase intracellular cAMP in beta cells, thus produce insulinotropic effect under dose dependent manner
Dose	Once weekly
Adverse events	Nausea, vomiting, dyspepsia, headache and decreased appetite
WHO ATC code	A10BX

2 Scientific Summary

2.1 Pharmacodynamic Properties

Semaglutide is a mono-acylated peptide and structurally similar to liraglutide [23] with three further modifications. These modifications build semaglutide for therapeutic use. First modification is amino acid substitution at position 8 (alanine to alpha-aminoisobutyric acid, a synthetic amino acid), second substitution at position 34 (lysine to arginine), and acylation with a stearic diacid includes larger spacer [23, 39]. Further, the fatty di-acid side chain has been conjugated towards a N6-[N-(17-carboxy-1-oxoheptadecyl-L-c-glutamyl [2-(2-aminoethoxy) ethoxy] acetyl [2-(2-aminoethoxy)ethoxy]acetyl] residue (Figure 2). This fatty acid conjugation provides long duration of action by convenient binding to albumin, thus decreasing their renal clearance [1]. The amino acid substitution at position 8 makes semaglutide, DPP-4 resistant and prevents degradation. Semaglutide is a structural homolog to native GLP-1 with 94% sequence identity [39].

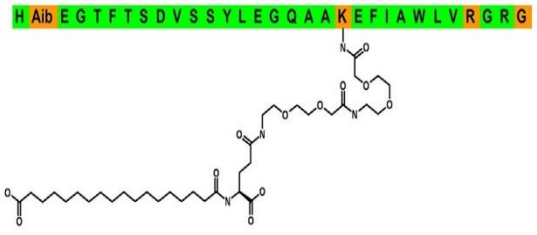

Figure 2- Structure of Semaglutide

Semaglutide is an incretin mimetic that binds with glucagon like peptide-1 receptor and produce their insulinotropic effect under dose dependent manner [18]. Semaglutide also reduces glucagon release and delays gastric emptying [1].

In clinical studies, significant dose dependent reductions in HbA1c were found at higher doses (≥0.8 mg) of semaglutide once weekly administration. Semaglutide with 0.8 mg and 1.6 mg doses subcutaneously found more effective as compared to liraglutide (1.2 mg and 1.8 mg subcutaneously) [9]. The study showed that one subject (1.6 mg highest dose) of semaglutide developed low-titer non-neutralizing antibodies against semaglutide which did not produce any effect with native GLP-1. Severe hypersensitivity reactions were not reported in clinical studies [40].

2.2 Pharmacokinetic Properties

Semaglutide is well absorbed into systemic circulation after subcutaneous injection and after entering into the bloodstream; it is widely bound to serum albumin. The plasma half-life in human is 160 h. Fatty acid side chain conjugation facilitates the serum albumin binding that provides prolonged action by reducing renal clearance and increase DPP-4 stability [1].

2.3 Therapeutic Trials

The tolerability, safety and efficacy of semaglutide in patients with Type II DM were evaluated in a phase II therapeutic trial. In a 12 week phase II study, semaglutide was evaluated at 5 different doses (0.1, 0.2, 0.4, 0.8, 1.6 mg) once-weekly and comparing to placebo. Semaglutide ≥0.2 mg dose decreased HbA1c from baseline up to 1.7% as compared to placebo (0.5% reduction) and for doses ≥0.8 mg also decreased body weight by up to 4.8 kg as compared to placebo (1.2 kg reduction) [1]. The study comparing semaglutide to liraglutide showed significant HbA1c reductions under dose-dependent manner with higher doses (≥0.8 mg) which is more effective than liraglutide (both 1.2 and 1.8 mg).

2.4 Adverse reactions

In the clinical study, all adverse events were considered mild-to-moderate, the most common being nausea, dyspepsia, vomiting, headache and decreased appetite. Withdrawals due to gastrointestinal side effects with semaglutide ranged from 14 to 28% with higher doses of semaglutide (≥0.8 mg) vs. 10% for liraglutide (1.2 mg).

2.5 Ongoing Clinical trials

In June 2013, the phase III clinical-trial programme called SUSTAIN was initiated in which semaglutide will be compared head-to-head with exenatide once-weekly (NCT01885208) [9].

3 Current Status

GLP-1 agonists have many therapeutic advantages over other available treatment options, including potential weight reduction.

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