Chapter 9

Impact of New Oral Glp-1 Drugs on Diabetes Treatment

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Abstract

Type 2 diabetes mellitus is a chronic metabolic disorder recognized by insulin resistance and progressive β-cell impairment, leading to prolonged hyperglycemia and increased risk of cardiovascular and metabolic complications, the incretin system mainly, GLP-1 and GIP which plays an important role in regulating postprandial blood glucose levels.GLP-1RAs are therapeutically effective antidiabetic agents that improve glucose-dependent insulin secretion, suppress release of glucagon, delays gastric emptying and promotes satiety, thereby improve glycemic control and assisting weight reduction. Traditionally, these therapies are available only in injectable form, which sometimes affect patient treatment compliance. The development of oral GLP-1 receptor agonists, such as oral semaglutide, represents a major advancement in diabetes treatment. This formulation uses the absorption enhancer that is (sodium N-(8-[2-hydroxybenzoyl] amino) caprylate) to improve absorption in GIT. Advancing oral GLP-1 receptor agonists on small molecules are being studied and may make treatment of diabetes easier, more effective

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and help patients take their medicines regularly.

Keywords: GLP-1 Receptor Agonists, Oral semaglutide, Incretin system, Glycemic control, Antidiabetic Therapy.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a very common long term metabolic disorder and it is identified by decreased insulin sensitivity and gradually worsening beta cell dysfunction. It is closely associated with increased disease burden, elevated mortality rates and adverse clinical outcomes. If unmanaged, persistent hyperglycemia can lead to hyperlipidemia, oxidative stress, meta inflammation and endothelial dysfunction, all of these promotes atherogenesis and lipid formation inside arterial walls [1]. It can be controlled by glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) and it is a super useful medicine to control obesity. Its role is to enhance insulin secretion, reduces the glucagon level and slows gastric emptying and also supports weight loss. It not only control diabetes but also controls risk of heart disease.GLP-1&GIP hormones controls the post meal blood sugar level, reduces appetite and maintain energy balance. Traditional Injectable medicine is difficult for patients to follow so oral semaglutide has been developed and shows the same benefits with higher rate of medication adherence [2,3].

2. Physiology of Glp-1 and Incretin System

The incretin system means involving food-responsive hormones that are released after the intake of food, which helps to maintain the body's blood glucose level. This process involves stimulation of insulin release from the pancreas and in some cases, it releases glucagon secretion. The excellent and beautiful incretin system contains various elements of biology, such as GLP-1 and glucose-

dependent insulinotropic polypeptide (GIP), as well as the principles, for instance, post-meal glucose control and energy balance [3-5]. The incretin system uses GLP-1 hormone for delayed gastric emptying and decreases small intestine motility; therefore, it slows absorption of nutrients and controls the post meal glucose spike. The system utilizes GLP-1 and reduces the risk of lipid metabolism, antiinflammation and cardiac protection. However, the gastrointestinal tract contains slightly rougher side effects such as nausea, vomiting, and early fullness [5]. Numerous beneficial effects shapes metabolism process where GLP-1 acts on the brain and GIP acts on insulin secretion in a glucose dependent manner [4].

An major idea related to the incretin system is “incretin effect” which shows the larger insulin response which is seen after oral glucose administration compared to intravenous for instance similar blood glucose levels[3].This mainly occurs due to the release of incretin hormones only when the glucose is consumed orally[3-4].the communication between the intestine and pancreas that maintains secretion of insulin is known as “enteroinsular axis”(entero-instestine,insular-pancreas)which plays an crucial in glucose homeostasis[4-5].

A proper understanding of GLP-1 biology has result in development of modern therapeutic agents such as GLP-1receptor agonists (Eg; semaglutide) and dual agonists (Eg; Tirzepatide). Therefore, in patients with type 2 diabetes and obesity these agents can help to manage body weight, lowers blood glucose levels and even improves cardiovascular health [3-5].

3. Mechanism of Action of Oral Glp-1

Oral GLP-1 receptor agonists act by copying the effect of body’s

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natural glucagon like peptide-1(GLP-1).The GLP-1hormone is secreted by intestinal L-cells due to nutrient intake that leads to control glucose in blood and appetite[4].Drug is taken by oral route and it is absorbed from the stomach/intestine into the bloodstream that reaches GLP-1 receptor which is a G-protein-coupled receptor acts on pancreatic β-cells, pancreatic α-cells and brain to glucose and appetite control[3,4].GLP-1 agonist binds to GLP-1(GLP-1R) on pancreatic cells which activates intracellular signaling pathway thereby increasing in cAMP (cyclic adenosine monophosphate) and activation of protein Kinase A (PKA) and Epac2 which produces glucose-dependent insulin secretion. In response to high glucose in blood, insulin is released and which helps to reduce hyperglycemia as well as lower the risk of hypoglycemia compared to some other drugs [3,4,5]. Activation of GLP-1R takes place in pancreatic α-cells which result in suppression of glucagon secretion [3,4].

Generally, glucagon increases blood glucose by stimulating hepatic glucose production in the liver. When GLP-1 based drugs reduces glucagon release, less glucose is produced in liver, which supports to lower blood glucose levels and promotes overall glycemic control[3,4].In gastric emptying section GLP-1 agonist delays gastric emptying and slows nutrient delivery to bloodstream which increases postprandial glucose it takes place through nerve-mediated pathway and direct muscular effects in the gastrointestinal tract[3,4].The effect in central nervous system is by activation of GLP-1R in hypothalamus and other brain regions triggers satiety and as well as suppresses appetite, reduced intake of food and decreased body mass with therapeutic benefit[3,4].

The first clinically approved oral GLP-1 drug was oral semaglutide which was developed by combining peptide with permeation

enhancer, the enhancer used is (sodium N-(8-[2-hydroxybenzoyl]amino)caprylate) it stimulates absorption of drug through stomach lining, tackling the challenge that peptides are usually degraded in the GIT,this allows the drug reach systemic circulation effectively and the dosing with once-daily oral administration is clinically beneficial[3].Oral semaglutide has same mechanism as injectable GLP-1 analogs, it acts via the GLP-1 receptor activation, promotes insulin secretion and glucose control whereas it requires special administration condition such as fasting and delay before eating to improve absorption of drug and to increase effectiveness[3,5].

Table 1: Incretin hormones and their role

Hormones	Source	Main Role
GLP-1	Intestinal L-cells	It stimulates insulin secretion
GIP	Intestinal K-cells	Enhances insulin release after meals

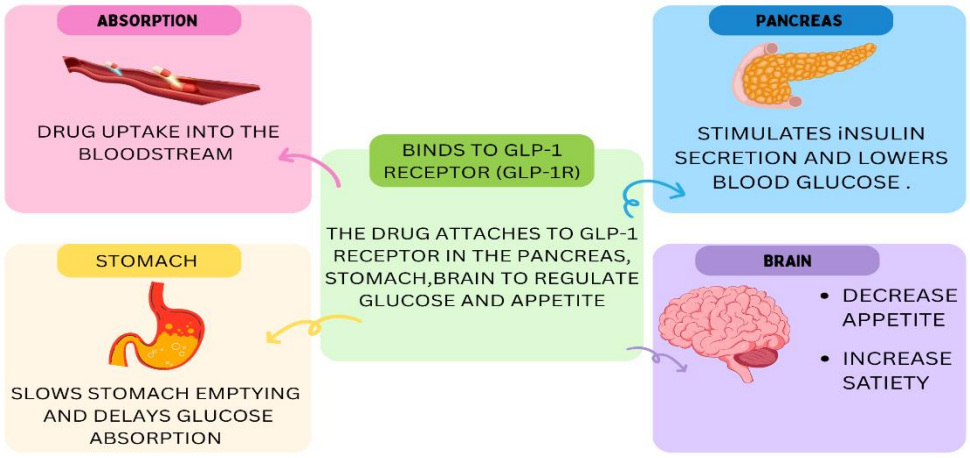

Figure 1: Mechanism of action of Oral GLP-1 Receptor Agonist

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4. Development and Pharmaceutical Challenges of Oral Glp-1 Drugs

GLP-1 is a peptide hormone which controls the blood glucose level and its action is to increase insulin and decrease glucagon and its slow gastric emptying and increase postprandial fullness [6,7]. The peptide drugs are difficult to give orally because of its stability issues like its degraded by stomach acid and digestive enzymes. In addition, their large molecules have poor intestinal permeability which lower the absorption.so this is why GLP-1 therapy was previously available only as injections form [6,7].

To overcome this absorption enhancers is used to improve oral delivery. The main enhancers used is SNAC (sodium-(8-[2-hydroxybenzoyl] amino) caprylate), the role is to protect peptide from enzymatic degradation and temporarily increases intestinal permeability [7,6]. This is possible to develop a oral semaglutide [7,6]. This was the first approved oral GLP-1 receptor agonist. In pharmacokinetics studies they observed SNAC which helps increase drug absorption and absorption is better in bloodstream, maintain plasma concentration and it is effective after oral administration. [7,9]. The several pharmaceutical challenges are faced in oral GLP-1 drug delivery other than degradation and poor absorption it also includes difficulty in maintaining peptide stability in acidic gastric environment, prevent the drug from digestive enzymes, and overcoming epithelial barrier and mucus barrier in GI all these factors limit the drug entry and which leads to limited oral bioavailability [6,8].

To overcome these issues, researchers have introduced additional pharmaceutical challenges such as PH modulation to reduce acidity

in stomach, modification of peptide backbone to improve stability, to enhance intestinal transport by mucus penetrating delivery systems and protective polymers and hydrogels are used to shield peptide from enzymes[6,8].Even with these development still some limitations are present namely poor absorption in the gut based on GI condition, low oral bioavailability, and is still very challenging to convert lab research to treat patients for good result[6,8,9].

5. Current and Emerging Glp-1 Therapies

Currently, oral glucagon-like peptide-1 receptor agonists (GLP-1 RAs) shows major development in the treatment of type 2 diabetes mellitus, offering user friendly administration compared to traditional injectable forms. Among these, oral semaglutide (Rybelsus®) is the only clinically approved available for clinical use by FDA[10].oral semaglutide is a peptide based agonist designed with absorption enhancer SNAC to improve gastrointestinal uptake and it is consumed once daily at doses of 3mg,7mg,or14mg[10].For optical bioavailability, the tablet need to be taken with water on empty stomach, must avoid food or other oral liquids for at least 30minutes after ingestion[10].In addition to peptide-based therapy, many oral non-peptide small-molecule GLP-1 RAs currently under formulation, includes danuglipron, lotiglipron, orforglipron(LY3502970)[12].these small molecules aims to mimic the therapeutic effects of GLP-1 agonists, but are easier to take and has fewer rules to consume. In clinical studies orforglipron has shown promising results, helps to lower blood sugar (HbA1c) and body mass in adults with type 2 diabetes [12]. These drugs are not yet approved for regular use, but they are the next type oral GLP-1 therapies and may have may have advantages in contrast to current peptide-based therapies [10,12].

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Table 2: Current GLP-1 receptor agonists for type 2 diabetes

Drug	Type	Route	Status
Semaglutide	GLP-1 agonist	Oral	FDA approved
Semaglutide	GLP-1 agonist	Injection	FDA approved
Liraglutide	GLP-1 agonist	Injection	FDA Approved

Figure 2: Representation of oral and injectable GLP-1 receptor agonist formulations used in the treatment of type 2 diabetes

6. Safety Profile Adverse Effects

These drugs are generally considered safe for adults patients , but few people may experience stomach-related side effects such as vomiting, nausea, or diarrhea[14,17].In elderly patients, the drugs show similar effectiveness and considered safe, but close clinical monitoring is recommended because they may have multiple medical conditions or may have increased sensitivity to drugs[13].In pediatric patients, these drugs shows good tolerability though limited information is available on long term safety so close clinical monitoring is advised[17].

7. Comparison with Injectable Glp-1 Ras

semaglutide is present in both oral and injectable forms; it differs from other GLP-1receptor agonists because it is available in injectable form and allowing physicians to choose suitable therapeutic approach depending on patients' needs and clinical factors [19]. Both oral and injectable form contribute a better control in people with type 2 diabetes mellitus. Whereas injectable form may produce slightly higher reductions in HbA1c, but oral formulations still provide clinically. Compared with any other antidiabetic agent's injectable semaglutide has shown greater result in weight loss whereas oral form also helps but in weight loss [19]. Both oral and injectable forms have a low risk of causing hypoglycemia, especially when they are not used together with insulin or sulfonylureas[20].In once a week injectable semaglutide is given which improves patient adherence and helps patients to continue the treatment compared with medicine that need to be consumed daily[19].Also tablet form of semaglutide offers a needle-free alternative, improve patient preference and supports earlier treatment initiation in T2DM management [20].these both form of semaglutide shows the same mechanism of action and therapeutic effects which includes glycemic control and weight reduction. The only difference is route of administration and dosing frequency, where injectable semaglutide offers less frequent dosing and sometimes slightly greater efficacy while oral semaglutide allows a non-injectable option in glycemic and weight outcomes [19,20].

8. Future Perspective

Future studies will evaluate cost-effectiveness and accessibility and help to reduce healthcare burden of diabetes[18].They may reduce the risk of cardiovascular problems and improve overall metabolic

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health, which can help long term diabetes treatment[15,10].In addition more easiest forms of medicines may help patients follow their treatment more ,without difficulty and simpler process of taking medicines may allow doctors to begin treatment at earlier stage[16,19].

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