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Possible role of Liraglutide on Pancreatic cells and Insulin Resistance

Hamss Muhammad Elsayed Ateia, Samah Mohamed Ahmed Ahmed, Shaimaa Ali Abdelrahman, Samar Mohamed Reda

Histology and Cell Biology Department, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author: Hamss Muhammad Elsayed Ateia

Email: hams.m021@medicine.zu.edu.eg, Hamssm3@gmail.com

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Abstract: The development of the pancreas is similar to that of other glands, where the duct appears firstly then cells implant around it creating gland lobules. The duodenal endodermal epithelium gives rise to both endocrine and exocrine parts of the pancreas. The germs of the glandule grow from the duodenum in the form of two buds, ventral and dorsal, during 2nd and 3rd weeks of pregnancy, when the embryonic length is about 3–4 mm. One of the most common serious problems facing the world nowadays is high fat diet (HFD)dependence and consequently obesity. Obesity is defined as excess fat accumulation in the body whether regional and/ or global. Weight gain and body fat accumulation tendency may have a genetic basis, however it is mainly because of environmental and lifestyle factors that depend on high-caloric intake and high fat fast food diet with a sedentary lifestyle. Insulin resistance is believed to be the main pathophysiological basis of T2DM and NAFLD that promotes the accumulation of fat in hepatocytes by promoting lipolysis and hyperinsulinemia. Recent studies have shown that Liraglutide can improve hepatic steatosis in a weight loss-independent manner that involves amelioration of insulin signaling pathways. On the other hand, it was reported that liraglutide exerts beneficial effects in NAFLD, with the underlying mechanisms potentially involving body weight reduction, improved blood glucose regulation, decreased lipid synthesis, autophagy induction, and free fatty acid β-oxidation

Keywords: *Liraglutide, Pancreatic cells*

Introduction

The development of the pancreas is similar to that of other glands, where the duct appears firstly then cells implant around it creating gland lobules. The duodenal endodermal epithelium gives rise to both endocrine and exocrine parts of the pancreas. The germs of the glandule grow from the duodenum in the form of two buds, ventral and dorsal, during 2nd and 3rd weeks of pregnancy, when the embryonic length is about 3–4 mm [1].

There are two separate ventral buds: right and left .The right ventral bud, located between the duodenum and the common bile duct bud, continue its growth, while the left ventral does not develop and disappears gradually. The dorsal bud is larger and located higher than the above-mentioned ventral buds. It develops towards the spine and settles between laminas of the dorsal mesentery of the duodenum and the stomach. This finally creates creating the superior part of the head, whole body and tail of the pancreas [2].

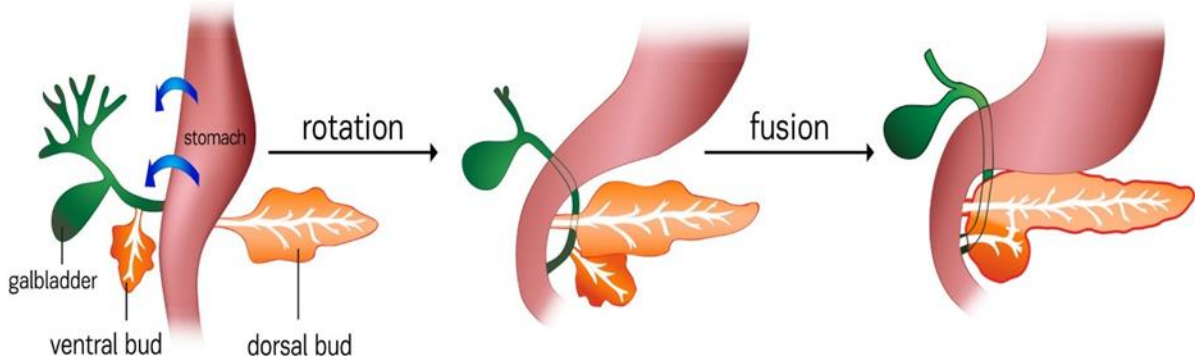

Diagram showing development and rotation of pancreas during embryogenesis [3]

During embryogenesis, the stomach and the duodenal rotation shifts the ventral bud to dorsally, and from the right to the left side of the embryo. Eventually, the ventral bud lies below and behind the dorsal bud creating the inferior part of the head, and the pancreatic uncinate process. In the beginning, each bud has its own independent duct that fuse tightly later in the 7th week of gestation. Part of the dorsal bud duct in the duodenal segment atrophies, while the remaining part fuses with the duct of the ventral bud, forming the pancreatic duct which communicates with the duodenum via the major duodenal papilla. [3]

The normal pancreas of an adult human is of an average volume of72 cm3, measuring 12–20 cm in length, 3–5 cm in height, and 1–3 cm in width. The pancreas has a hook elongated appearance. Macroscopically, it is divided into the head, neck, body, and tail. The pancreas is a retroperitoneal organ located on the posterior wall of the abdominal cavity. The head of the pancreas is surrounded by the duodenum, followed by the neck that lies near the superior mesenteric vessels. Then the body is behind the posterior wall of the stomach, and finally the tail reaching the hilum of the spleen [4].

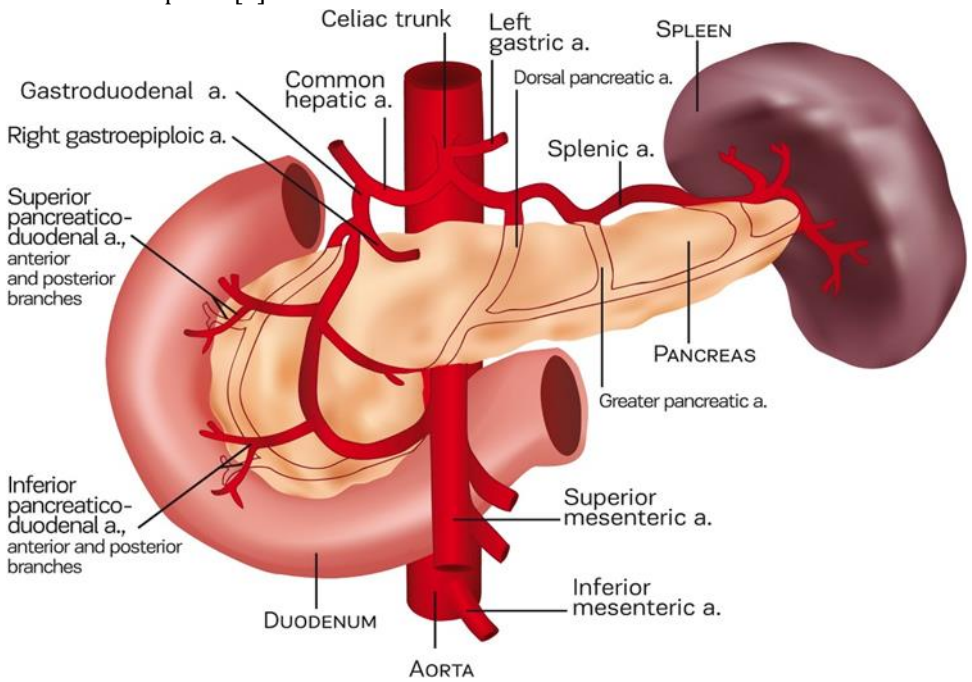

Diagram showing gross anatomy of the pancreas [3].

In contrast to most human body glands, the pancreas is not surrounded by a distinct fibrous capsule. The pancreatic duct's origin is in the tail of the gland, passing across the entire organ. it unites with the common bile duct forming the hepatopancreatic ampulla (ampulla of Vater) on the major duodenal papilla. An accessory

pancreatic duct (duct of Santorini) may be found in 41–52.5% of the population. It drains either to the duodenum through the minor duodenal papilla, or to the pancreatic duct in 30% of cases [3].

Histologically, the pancreas is a complex gland composed of both endocrine and exocrine parts. The exocrine portion of the pancreas is a compound tubuloacinar gland where the cells that form acini are arranged around a central lumen. The aggregation of these acini forms the pancreatic lobules which are separated by vascular connective tissue. Each acinar cell is pyramidal in shape with its base lying on the basal lamina separating the acinar cells from the connective tissue compartment. The round nucleus of the cell is basally located and is surrounded by basophilic cytoplasm. The apex of the cell, facing the lumen of the acinus, is filled with proenzyme-containing secretory granules (zymogen granules) [5].

The Golgi region, located between the nucleus and the zymogen granules, varies in size in inverse relation to the zymogen granule concentration. The basal cell membranes of acinar cells have receptors for the hormone cholecystokinin (CCK), and the neurotransmitter acetylcholine. Electron micrographs of acinar cells display an abundance of basally located RER, a rich supply of polysomes, and numerous mitochondria exhibiting matrix granules. The Golgi apparatus is well developed but fluctuates in size, being smaller when the zymogen granules are numerous and larger after the granules release their contents [6].

The zymogen granules may release their contents individually, or several secretory vesicles may fuse with each other, forming a channel to the lumen of the acinus from the apical cytoplasm. The acini are connected through the intercalated ducts to the intralobular ducts, that drain into the interlobular ducts. The proximal part of this duct system is lined with simple squamous epithelium, the distal part is lined with simple cuboidal epithelium. The larger interlobular ducts and the main ducts are lined with columnar epithelium and contain mucous-producing cells [7].

The endocrine pancreas is composed of highly vascular spherical aggregates of about 3000 cells each, known as islets of Langerhans. There are approximately 1 to 2 million islets that are distributed throughout the human pancreas mainly in the body and the tail forming the pancreatic endocrine portion. Each islet is about 300 μm in diameter and is surrounded by reticular fibers, which also enter the substance of the islet to encircle the supplying capillaries network [8].

Five types of cells compose the parenchyma of each islet of Langerhans: beta (β) cells, alpha (α) cells, delta (δ) cells (D and D1 cells), PP cells, and G cells. These cells cannot be differentiated from one another by routine histological examination, but immunocytochemical procedures allow them to be recognized. Electron micrographs also display the features that distinguish the various cells, especially the size and electron density of their granules. Otherwise, the cells do not exhibit any unusual morphological features but resemble cells that specialize in protein synthesis [9].

β-cells form the bulk of the pancreatic endocrine cell mass. A relative β-cell mass was found between 50 and 80% of the pancreatic islet. β- cell appears spherical to ellipsoidal and contains fewer aggregations of secretory granules than the alpha cells. The plasma membranes of adjacent beta cells are smooth in outline and closely apposed with a narrow intervening intercellular space. Insulin, secreted by β- cell, is stored in cytoplasmic secretory granules. They have a characteristic morphology with an electrondense core and a clear peripheral mantle. A β-cell is estimated to contain 9–13.000 secretory granules. β-cells in the human pancreas may show marked variation in granulation, cell size, and size of the nuclei [10].

The α-cells resemble somewhat the β-cells in shape, size, and nuclear outline. They are clustered into small groups of cells with restricted cytoplasmic reticulum, unattached ribosomes, mitochondria, and Golgi apparatus with lesser proportion than in β-cell. α-cells secrete glucagon that is stored in secretory granules with typical morphology; an electrondense core and a grayish peripheral mantle. The number of α-cells is estimated at 15–20% of the islet cell mass. the relative volume taken up by α-cells can vary significantly between islets with some islets containing up to 65% of α-cells [11].

The D (or δ) cells that release somatostatin form 5–10% of islet volume. Although all islet cells have neuron-like characteristics, the D-cells resemble small neurons most. They often form long slender processes with a

secretory-granule rich knob-like. furthermore, they end near a capillary suggesting focal and possibly paracrine secretion. The PP cell that secretes the least well studied of the islet hormones, PP hormone. This peptide hormone has been found immunocytochemically in two distinct cell types: PP immunoreactive cells, with round to angular secretory granules. The other type of cells was with small granules, formerly called D1 cells. The latest cell type is the Epsilon or Ghrelin cell. Adult islets contain less than 1% epsilon cells [12].

From the physiological point of view, the acinar cells of the exocrine pancreas synthesize, store, and release a large number of enzymes with a bicarbonate-rich buffer solution: pancreatic amylase, pancreatic lipase, pancreatic cholesterol esterase, ribonuclease (RNase), deoxyribonuclease (DNase), elastase, as well as the proenzymes trypsinogen, chymotrypsinogen, procarboxypolypeptidase. Pancreatic amylase and lipase break down carbohydrates and glycogen into disaccharides and fats into fatty acids and monoglycerides respectively [13].

In addition, pancreatic cholesterol esterase breaks down cholesterol esters into cholesterol and fatty acids. DNase and RNase break down DNA and RNA, respectively. Elastase breaks down the major component of elastic fibers, namely elastin. Furthermore, the proenzymes become converted in the duodenum into the active forms; trypsin, chymotrypsin, and carboxypolypeptidase. Trypsin and chymotrypsin break down proteins into short peptides, while Carboxypolypeptidase digests small peptides to form dipeptides and amino acids [14].

Release of the pancreatic enzymes is regulated by the hormone cholecystokinin (CCK) of the small intestine and acetylcholine of the parasympathetic nerve fibers. The centroacinar cells and intercalated ducts produce a serous, bicarbonate-rich alkaline fluid, which neutralizes and buffers the acid chyme that enters the duodenum from the stomach pylorus. This fluid is enzyme poor, and its release is regulated by secretin hormone and acetylcholine. Thus, the enzyme-rich and enzyme-poor secretions are regulated separately, and consequently released at different times or concomitantly [15].

In the endocrine pancreas, the cells of the islets of Langerhans produce insulin, ghrelin, amylin, glucagon, somatostatin, gastrin, and pancreatic polypeptide. The mainly produced two hormones are insulin and glucagon which have blood glucose regulatory functions. Insulin production begins in β cells of islets of Langerhans. Insulin is released in response to increased blood glucose levels. The released insulin binds to cell-surface insulin receptors on many cells, especially skeletal muscle, liver, and adipose cells thus decreasing blood glucose levels. Insulin release is induced by elevated blood levels of glucose, free fatty acids, amino acids as well as cortisol, growth hormone, gastric inhibitory peptide, secretin, CCK, and gastrin [7].

Glucagon, a peptide hormone is produced by α cells. Glucagon acts mainly on hepatocytes, causing these cells to activate a cascade of enzymes that eventually leads to the activation of glycogenolytic enzymes, as well as its action on fat cell lipases activating hepatic gluconeogenesis enzymes that is finally leads to glucose production, which is released into the bloodstream, increasing blood glucose levels [16].

Somatostatin hormone inhibits the release of hormones by α cells and β cells, reduces the motility of the alimentary tract and gallbladder. It also supresses the release of pancreatic enzymes and gastric hydrochloric acid (HCl) production. Vasoactive intestinal peptide (VIP) induces glycogenolysis and hyperglycaemia. It regulates intestinal motility and the tone of smooth muscles of the alimentary tract wall. Besides, VIP controls the secretion of ions and water by intestinal epithelial cells [17].

Another hormone which is Gastrin, secreted from G-cells, stimulates gastric HCl release, gastric motility and emptying, and cell division rate in gastric regenerative cells. The pancreatic polypeptide, which is secreted from PP-cells, inhibits the release of the pancreatic enzymes, gastric HCL and the bile from the gallbladder, however, stimulates the release of enzymes by the gastric chief cells. Ghrelin that is secreted from Ɛ-cells induces the sensation of hunger and modulates relaxation of the smooth muscle fibers of the gastrointestinal tract. Lastly, the Amylin hormone that is co-secreted with insulin by β- cells, inhibits stomach emptying. It has been suggested that amylin also inhibits the release of glucagon [18].

One of the most common serious problems facing the world nowadays is high fat diet (HFD)dependence and consequently obesity. Obesity is defined as excess fat accumulation in the body whether regional and/ or global.

Weight gain and body fat accumulation tendency may have a genetic basis, however it is mainly because of environmental and lifestyle factors that depend on high-caloric intake and high fat fast food diet with a sedentary lifestyle [19].

The HFD-dependence has a huge role in increasing nowadays prevalent chronic diseases, such as cardiovascular diseases, diabetes, and cancer. Moreover, HFD intake and obesity are associated with disturbed metabolism of nutrients, leading to excessive accumulation of fat in different body organs. One of the most affected organs by this fat disposition is the liver, leading to its damage and the occurrence of non-alcoholic fatty liver disease (NAFLD). It was indicated that NAFLD is accompanied by lipotoxicity leading to apoptosis and necrosis of hepatocytes up to liver necrosis in extreme cases, as well as intensification of oxidative stress and inflammation [20, 21].

Obesity also has a negative influence on many risk factors associated with cardiovascular disease (CVD), such as dyslipidaemia, atherosclerosis, increased blood pressure. Consequently, individuals who are obese are more prone to develop manifestations of CVD, particularly coronary heart disease , atrial fibrillation, heart failure, angina, myocardial infarction, and sudden cardiac death [22].

Furthermore, increased body weight and obesity lead to significant co-morbidity and even premature death. For example, metabolic syndrome describes a group of obesity associated dysmetabolic conditions that are mainly correlated with hyperinsulinemia and insulin resistance. It is notable that obesity severely emphasizes the complications of both hyperglycaemia and associated hyperinsulinemia; where the obesity related insulin resistance leads to an inability to utilise insulin and therefore hyperglycaemia. This prolonged hyperglycaemia involves a pancreatic response in the form of increased insulin secretion. These health risks increase significantly with increasing body mass index (BMI) and the degree of obesity [23].

Obesity, being a risk factor for cancer, the combined effects of high BMI and diabetes were considered responsible for 5-7% of all cancers in 2012. In men, strong evidence now exists showing association between obesity and colon, oesophageal, pancreatic, prostatic and kidney cancer. There is also an increased risk in women for endometrial, ovarian, colon, oesophageal, gallbladder, kidney, and pancreatic cancers that is related to excess body weight. It is also a risk factor for post-menopausal breast cancer. Furthermore, cancer mortality significantly increases by the effect of obesity and excess body weight, as shown in large population-based studies. [24, 25]

The HFD and obesity related hyperinsulinaemia and insulin resistance are major risk factors to a public health concern due to its high prevalence & the several comorbidities, which is T2DM. It is widely accepted that is the most important predictor of T2DM is excessive fat accumulation in the abdominal area. Indeed, the obesity and excessive weight gain related T2DM is estimated to represent 60 to 90% of T2DM incidence. Moreover, after T2DM onset, obesity also contributes to increasing morbidity and mortality rates. The worldwide prevalence of overweight and obesity is expected to reach 57.8% by 2030. Consequently, the global prevalence of T2DM has been expected to double between 2000 (2.2%) and 2030 (4.4%) [26].

Glucagon-like peptide-1 (GLP-1) is a peptide hormone and member of the incretin family with a glucoregulatory action. It is synthesized and secreted by enteroendocrine L-cells, that are distributed along a large portion of the GI tract, and to a lesser extent by neurons of the nucleus tractus solitarius (NTS) of the brainstem. GLP-1 is stored in secretory granules of L-cells until its secretion is triggered, and then uses endocrine and neuronal routes to perform its functions in the pancreas and CNS [27].

Postprandial GLP-1 secretion is influenced by both neuroendocrine and nutritional factors with a two-phase release profile. The initial secretory phase is 10 to 15 minutes after food intake, while the second one is 30 to 60 minutes postprandially. When secreted, GLP-1 induces vagal afferent neural fibres stimulation, along with diffusion into nearby capillaries, reaching the systemic circulation through the portal vein [28].

In the bloodstream, GLP-1 is highly susceptible to the catalytic activity of the enzyme dipeptidyl-peptidase IV (DPP-IV) followed by further catalytic activities in the liver. As a result, GLP-1's half-life is very short – about 1

to 2 minutes, thus, about 10-15% only of the newly secreted GLP-1 reaches the systemic circulation in its active forms [29].

Glucagon-like peptide-1 has a stimulatory effect on insulin synthesis, beta cell proliferation, insulin sensitivity, while inhibiting hepatic glucose production, beta cell apoptosis and acts on pancreatic alpha cells to reduce glucagon secretion. One of the most important effects of GLP-1 is its ability to stimulate carbohydrate consumption-related insulin secretion. In pancreatic β-cells, GLP-1 activates intracellular pathways that increase intracellular calcium concentrations leading to insulin exocytosis from secretory granules [29].

The GLP-1 seems to be responsible for nearly half of the total postprandial insulin secretion. This process, known as "incretin effect", is defined as the differential augmentation in insulin secretion observed after oral glucose intake, compared to intravenous glucose administration resulting in the same blood glucose concentrations. GLP-1 is partly fulfilling its actions in pancreatic βcells through an endocrine pathway by directly interacting with its receptors (GLP-1Rs). The glucose lowering effects of GLP-1 are also due to its strong inhibition of glucagon secretion by direct interaction with its receptors on pancreatic α-cells. [23].

In addition to its pancreatic action, GLP-1 plays a role in both homeostatic and non-homeostatic food intake regulations, that occur in specific CNS areas. Homeostatic regulation of food intake, related to short- and long-term energy status, takes place mainly in the hypothalamus and nucleus of tractus solitareus(NTS). GLP-1 is an important satiation signal that decreases food intake through its effects on the hypothalamus and brainstem [30].

It acts on the GLP-1Rs that are widely expressed in the vagal afferents, the Arcuate nucleus (ARC) of the hypothalamus, the striatum, the NTS of the brainstem and the substantia nigra, among other areas of the brain. A small quantity of GLP-1 appears to diffuse through the blood-brain barrier and directly bind to its receptors. However, due to its short half-life, endogenous GLP-1 is most likely to act on the CNS by indirect stimulation of the NTS and ARC neurons via the activation of vagal afferent neurons [31].

On the other hand, it also has a non-homeostatic food intake regulatory effect; as GLP-1 also has an effect on palatability, food motivation, hunger-driven feeding, the pleasant effect of high fat and high sugar foods mediated through mesolimbic and hypothalamic GLP-1Rs. Moreover, GLP-1 slows gastric emptying and therefore nutrient absorption. GLP1 is also believed to be cardioprotective and neuroprotective [32].

GLP-1 exerts several beneficial effects on β-cell dysfunction and impaired insulin secretion which are the main causes of chronic hyperglycaemia in T2DM patients, so it acts to improve diabetes mellitus (DM). First, GLP-1 promotes the expression of glucose transporter 2, that has a key role in glucose movement across the cell membrane, in pancreatic β-cell, along with GLP-1 induced insulin secretion and repressed glucagon secretion. In addition, GLP-1 decreases the secretion of proinflammatory cytokines, such as tumour necrosis factor α (TNFα), interleukin β (IL-β), and inducible nitric oxide synthase (iNOS). Therefore, GLP-1 restores pancreatic β-cell masses and insulin sensitivity [33].

It is generally well accepted that obesity and T2DM associated metabolic changes induce a decline in the secretion of GLP-1 from L-cells postprandially. Overtime, this change in GLP-1's secretion can lead to extra weight gain and T2DM deterioration [34].

Due to the previously mentioned data about GLP-1, targeting GLP-1Rs' activation with GLP-1 analogues and increasing GLP-1 half-life in the bloodstream became a scope of research for the management of obesity and T2DM. This led to the development of pharmacologic agents, named GLP-1Rs agonists (GLP1Ra). In fact, GLP1Ra resemble supraphysiological blood concentrations of GLP-1 and have a far longer half-life, varying between 1.5 hours and 5 days depending on the agent [35].

GLP-1Ra are considered effective drugs for the treatment of T2DM compared to other commonly used antihyperglycemic drugs such as sulfonylureas and thiazolidinedione. Pharmaceutical agents targeting GLP-1's action are associated with lower risks of hypoglycaemia, and have the advantage of promoting weight loss as well as potentially preventing, or at least delaying the progressive decrease in pancreatic β-cell function which generally requires increasing drug dosage [36].

Similar to endogenous GLP-1, GLP-1Ra primarily potentiate glucose-induced insulin secretion. In addition, GLP-1Ra reduce food intake, and stimulate energy expenditure, all additional beneficial outcomes in the context of obesity/insulin-resistance. A clinical study revealed that (GLP-1Ra) partially restored the first-phase insulin secretion in subjects with established T2DM [33].

Improving insulin sensitivity and β-cell function, six-week courses of GLP-1Ra significantly decreased the concentrations of plasma glucose in patients with T2DM. Interestingly, in vitro studies suggested that GLP-1Ra act directly on hepatocytes to limit endoplasmic reticulum stress. Furtherly, it activates AMP-activated protein kinase, supress lipogenesis or interact with the insulin signaling pathways [37].

Liraglutide is the first long-acting GLP-1 Ra based on the human GLP-1 sequence. Liraglutide has 97% amino acid homology to human GLP-1 that is designed with two structural modifications in the form of an amino acid substitution and attachment of a C16 acyl fatty acid chain to lysine 26 of the GLP-1 molecule which is a linker residue [38].

The latter modification increases Liraglutide's plasma half-life from 2 minutes to 13 hours by promoting binding to albumin in plasma and interstitial fluid. Only a small percentage (about 1–2%) of liraglutide circulates in a free (non-albumin-bound) form, ready to diffuse into tissues and bind receptors. The albumin-bound bulk forms a reservoir promoting prolonged action as it reduces renal excretion and stabilises it against metabolic degradation by peptidases [39].

Liraglutide was primarily used to treat T2DM, with respect to glycaemic control, It was proven to be effective in reducing haemoglobin A1c and alleviating Insulin resistance (IR). Abnormalities in the insulin signaling pathway play a key role in the occurrence and development of IR. Insulin receptor substrates (IRSs) are important cytoplasmic adaptor proteins in insulin signaling and play an important role in IR. The IRS family comprises several members, including IRS-1, IRS-2, IRS-3, IRS-4, IRS-5 and IRS-6 [40].

Among the IRS family, IRS-2 in liver specifically regulates insulin signaling and integrates insulin receptor (InsR) and insulin-like growth factor-1 receptor (IGF1R) signaling, which mediates the anabolic effects of insulin through the PI3 kinase (PI3K)-Akt cascade. Furthermore, mice lacking IRS-2 has shown a defective insulin-stimulated signaling pathway. Recent studies have shown that Liraglutide essentially restores brain insulin sensitivity through insulin signaling pathway [41].

Insulin resistance is believed to be the main pathophysiological basis of T2DM and NAFLD that promotes the accumulation of fat in hepatocytes by promoting lipolysis and hyperinsulinemia. Recent studies have shown that Liraglutide can improve hepatic steatosis in a weight loss-independent manner that involves amelioration of insulin signaling pathways. On the other hand, it was reported that liraglutide exerts beneficial effects in NAFLD, with the underlying mechanisms potentially involving body weight reduction, improved blood glucose regulation, decreased lipid synthesis, autophagy induction, and free fatty acid β-oxidation [42, 43].

Dyslipidaemia is an important and common comorbidity in patients with T2DM due to the presence of insulin resistance and metabolic disorder. The lipid profile of a T2DM patient typically includes a decrease in HDL cholesterol (HDL-C) and an increase in LDL cholesterol (LDL-C), total cholesterol, and triglycerides. The conjugation of dyslipidaemia with poor glycaemic control has a significant role in the development of atherosclerosis [44].

Another beneficial effect for liraglutide is its role in improving arterial hypertension (HT) which is a very common complication in T2DM patients. Clinical trial data so far concluded that treatment with GLP-1 analogues reduced blood pressure values. In fact, effects occur early,two weeks after the start of treatment,concluding that it is a weight loss- independent decrease and that other mechanisms may be involved. One possible mechanism could be direct activation of the GLP-1R in arteries and the renal system, including an improvement in endothelial function, as well as a vasodilator and natriuretic effect by inhibition of the renin angiotensin activating system (RAAS) [45].

Other mechanisms could be independent of GLP-1R, as the activation of nitric oxide by cyclic GMP. Endothelial dysfunction is a pathological process that links diabetic macro- and microvascular disease.Liraglutide

attenuates induction of plasminogen activator inhibitor type-1 (PAI-1) and vascular adhesion molecule (VAM) expression in human vascular endothelial cells (hVECs) in vitro. Consequently, it may be protective from endothelial dysfunction, which the early vascular abnormality in diabetic patients [46].

Liraglutide has been well-detailed in the (LEAD) study program of randomized controlled trials, which explored the efficacy and safety of subcutaneous injections of Liraglutide as monotherapy, or in combination with other oral antidiabetic agents. Being specifically focused on glycaemic targets, however a significant dose-dependent weight loss was observed in the LEAD trials first, and subsequently confirmed at the higher dose in the Satiety and Clinical Adiposity: Liraglutide Evidence (SCALE) program [47].

Liraglutide has been licensed internationally, as a diet restriction and increased exercise adjunct in patients with obesity with a BMI over 30 kg/m ^{2}, or 27 kg/m ^{2} - 30 kg/m ^{2} in combination with complications (e.g. prediabetes, T2DM, hypertension, dyslipidaemia), after the SCALE studies demonstrated clear evidence that Liraglutide treatment resulted in 6-7% weight loss. Liraglutide is licensed as Saxenda with a higher effective dose for weight management compared to Victoza licensed for T2DM [48].

In the SCALE-Diabetes study, 846 diabetic patients with overweight received in a random manner subcutaneous Liraglutide 1.8mg daily, 3.0mg daily or a placebo over a 56 week period, results came with >5% weight loss achieved in 54.3% in the 3.0mg group, 40.4% in the 1.8mg group and 21.4% in placebo group. The SCALE-Obesity randomised trial also demonstrated an obvious weight loss in the liraglutide treated group in comparison with the placebo group [49].

Although the SCALE-Obesity trial demonstrated an additional improvement in glycaemia, other cardiac and metabolic risk factors, as well as quality of life; it also demonstrated more severe adverse events in the Liraglutide treated group. The most commonly seen side effects were gastrointestinal, including nausea, diarrhoea, constipation, vomiting, dyspepsia, abdominal pain and reduced appetite, as well as upper respiratory tract infection, headache, fatigue,and dizziness [50].

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