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Incretin System in the Pathogenesis of Type 2 Diabetes and the Role of Incretin Based Therapies in the Management of Type 2 Diabetes

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1. Introduction

Discovery of incretin hormones and their role on glucose metabolism and pathogenesis of type 2 diabetes mellitus (T2 DM) are current interests of diabetology. Incretin hormones are secreted from intestinal endocrine cells in response to food ingestion and potentiate pancreatic insulin secretion when compared with iv glucose administration. Since malfunction of incretin hormones has been found to have role in T2 DM pathogenesis, incretin based therapies have been developed. Incretin effect, incretin hormones, functions, their role in pathogenesis of T2 DM and management of T2 DM with incretin-based drugs are discussed in this chapter.

2. Incretin effect, incretin hormones, secretion and functions

2.1. The incretin effect

Pancreas secrete insulin in response to the food content in the gastrointestinal lumen. Endocrine pancreas senses food ingestion via incretin hormones, nerve inputs and substrates to secrete insulin. This chain of secretion which starts with food ingestion and result with insulin secretion by endocrine pancreas is called enteroinsular axis [1, 2]. The first definition of incretin effect depend on the fact that, much more insulin secretion is induced by oral glucose than with iv glucose administration. So two-to three fold augmented insulin response to oral glucose compared with iv glucose is known as the incretin effect [3].

A duodenal extract has been found to reduce glucosuria first in early 20th century before the discovery of this phenomenon. The elements of the incretin effect were recognised much more

before their insulintropic effects. Glucagon like insulintropic peptide (GIP) is the first, which was discovered in 1973 by its inhibitory effect on gastric acid secretion and insulintropic effect was defined later. This discovery was followed by the definition of another intestinal peptide called glucagon like peptide 1 (GLP-1) ten years later. Discovery of incretin system, and its pathogenetic role in T2 DM caused an important evolution in pathogenesis and management of diabetes. This discovery pointed the role of gastrointestinal system and derived peptides on insulin secretion and glucose metabolism, which has not been taken into account for a very long time.

Postprandial rate of insulin secretion is assumed to be solely affected by the stimulatory effect of incretin hormones, and the role of gastrointestinal motility seems not to be accounted. Passage rate of the ingested foods through the gastrointestinal tract directly affects the secretion rate, secretion amount and the type of incretin hormone [4-6]. These mentioned gastrointestinal motility dependent events play an important role on postprandial glucose homeostasis. Effect of gastrointestinal motor function on glucose metabolism, pathogenesis of diabetes and glycemic regulation still need to be further evaluated.

2.2. Incretin hormones

There are two incretin hormones known to function on postprandial insulin secretion, which called GIP and GLP-1. Their malfunction and malsecretion have been shown to have role in the pathogenesis of T2 DM.

GIP is a large peptide hormone which is processed from a larger prohormone. Expression of GIP is widely distributed in the body, but the functions are not well understood at these locations. GIP is secreted from enteroendocrine, so called K cells, which predominantly located in the proximal duodenal mucosa but may be seen anywhere in the entire intestinal mucosa [7].

The other incretin hormone GLP-1 is derived from proglucagon peptide. Proglucagon gene is dominantly expressed in pancreatic alpha cells, brain stem and distal intestinal mucosal endocrine, so called L cells [8]. Posttranslational processing of proglucagon peptide differ between pancreatic alpha, brain and intestinal cells, resulting with different endproducts [9-10]. Proglucagon peptide contains two proglucagon peptides named glicentin and major proglucagon fragment. Pancreas contains these two proglucagon peptides in one molecule and secrete glucagon along with major proglucagon fragment. Pancreas processes glicentin to glicentin related pancreatic polypeptide (GRPP), glucagon, and intervening peptide 1 (IP-1), while major proglucagon fragment is not further processed in pancreas. Intestinal L cells secrete these two glucagon like peptide separately. Unlike alpha cells, intestinal cells have the ability to process major proglucagon fragment to GLP-1, GLP-2 and IP-2. Glicentin is not cleaved or partly cleaved into GRPP and oxyntomodulin in the intestinal cells [Figure 1].

Mechanism of organ specific posttranslational proglucagon processing is not fully determined. Several factors have been defined to have role in organ specific processing. Transcription factor named pax6 and the other novel regulator is β -catenin, which is the major effector in Wnt signalisation system are among these regulators. T cell factor 4 (TCF-4 or known as TCF7L2) has been discovered to mediate the Wnt pathway, and shown to induce proglucagon gene

Figure 1. Post-translational processing of proglucagon peptide in pancreas, intestine and brain (GRPP: Glicentin related polypeptide, IP-1: intervening peptide 1).

expression to produce GLP-1 in the intestinal endocrine cells, but not in alpha cells [11, 12]. Later a TCF-4 gene polymorphism has been found to be involved in susceptibility to T2 DM. This is an important evidence which proved a link between disrupted incretin effect and development of T2 DM.

Active forms of GLP-1 are GLP-1 (7-36) and GLP-1 (7-37). Lower than %25 of total amount of active form secretion leaves intestine, then 40-50% of this degraded in the liver. In conclusion a very low amount of active GLP-1 reaches into the systemic circulation [13, 14]. GLP-1 (7-36) is cleaved by dipeptidylpeptidase 4 (DPP-4) to GLP-1 (9-36). This enzyme is highly expressed in the brush border of the enterocytes and also in the endothelial cells of the enteric vasculature [15]. Inactive GLP-1 (9-36) and active GLP-1 (7-36) are also degraded by neutral endopeptidase 24.11 (NEP 24,11) to form another inactive form named GLP-1 (28-36) [16]. Although GLP-1 (9-36) and GLP-1 (28-36) are known as inactive forms, it has been shown that they may be as beneficial as their active counterparts on glucose metabolism [17, 18]. Active GLP-1 and its metabolites are cleared from kidneys [19].

Both incretin hormones has been shown to be important in food induced insulin secretion but their potency and molar secretion amounts differ. GIP is secreted into the circulation 10-fold higher amount than GLP-1, but the potency of GLP-1 exceeds GIP [20].

2.3. Incretin hormone secretion and regulation of secretion

Both incretin hormones are secreted from gastrointestinal endocrine cells response to food ingestion. Although it is very low in amount, incretins are also has been shown to secreted during fasting [21]. Proximal intestinal cells secrete GIP, while GLP-1 is secreted from distal ileal and colonic L cells. It is the amount of ingested foods and the gastric emptying rate which effect the type of incretin hormone secreted [22, 23]. For example small amounts of food and a rapid gastric emptying induce GIP secretion, while slow gastric emptying and large complex food portions induce GLP-1 secretion. The exact mechanism of how food components induce the selective secretion of incretin hormones are still not clear. Elements of glucose transport system, such as sodium glucose transporter 1 (SGLT-1) and G protein coupled long chain fatty acid receptors on L cells has been shown to mediate the pathways which induce enteric endocrine cells to secrete incretin hormones in a selective manner [24, 25]. In conclusion incretin hormone levels are very low during fasting state, they are secreted in response to ingested glucose and lipids. Food ingestion is the trigger which starts enteroinsular axis result with insulin secretion from pancreatic β -cells. Although neuronal pathways modulate insulin secretion, neuronal pathways do not have role in the induction of enteroinsular axis, since GLP-1 does not increase during cephalic phase of insulin secretion [26].

2.4. Functions of incretin hormones

The incretin GIP shows its actions via a G protein coupled membrane receptor which belongs to the secretin-glucagon receptor family [27, 28]. The other incretin GLP-1 also shows its effects on target cells via a G protein coupled GLP-1 receptor (GLP-1R), which is widely expressed in the body unlike limited secretion sites of GLP-1 [29]. Only one type GLP-1R has been defined in the body, and the organ spesific effects of GLP-1 is believed to be determined by the difference in the glycosilation of the receptor. Wide distribution of the receptor such as endocrine pancreas, brain, heart, gastrointestinal system and kidney, is responsible for the extrapancreatic and extraintestinal effects of the peptide.

Because GIP has been reported to be nearly not affected in diabetic patients, and there is a clear evidence of diminished GLP-1 secretion in T2 DM, this chapter will mention GLP-1 as a representative of incretine hormones [30, 31].

1. Effects of GLP-1 on β -cells:

It has been shown that GLP-1 has insulinomimetic, insulinotropic and insulinotrophic effects, which mean insulin-like, insulin secretory and regenerative and proliferative effects respectively.

Insulin-like effect of GLP-1 has been shown in several studies, in which GLP-1 inhibited hepatic glucose output [32, 33]. The mechanisms of inhibition of hepatic glucose output and involving receptors need to be clarified, since hepatocytes do not express GLP-1R.

Insulin secretion is potentiated by GLP-1 only in the presence of glucose. This effect starts with the interaction between the GLP-1 and its G protein coupled membrane receptor. GLP-1 induces insulin secretion only in the presence of glucose in the β -cell [34]. GLP-1

and glucose both increase intracellular cAMP levels synergistically, then cAMP induces protein kinase A (PKA) and cAMP regulated guanine nucleotide exchange factor II (cAMP-GEF II), also known as Epac2. These two system induce β -cells to secrete insulin by several mechanisms. Closure of ATP sensitive potassium channel and activation of calcium channels both cause depolarisation of β -cell, and then insulin secretion occurs. Both calcium derived from intracellular stores and extracellular space contribute in increase in intracellular calcium levels. Increase in intracellular calcium further stimulate insulin secretion via granule exocytosis. The latter calcium dependent insulin secretion may contribute to >70 % of overall GLP-1 induced insulin secretion. Induction of insulin secretion is not the only effect of GLP-1 on β -cells. Insulin gene promoter region which is mediated with PKA and possibly mitogen activated protein (MAP) kinase pathway are also modulated by GLP-1 [35]. Pancreatic duodenal homeobox-1 (PDX-1), which is a key regulator of developing pancreas, and essential for β -cell growth and insulin gene transcription in adulthood, has been shown to be regulated by GLP-1 [36]. Intracellular glucose concentration depends on the function of glucose transporter system, predominantly GLUT-2, and β -cells sense the presence of high glucose levels by the action of the enzyme glucokinase. These two effectors modulate insulin secretion and GLP-1 upregulates the transcription of glucose transporter and glucokinase genes [37].

Research on carcinogenesis and embryogenesis revealed an important intracellular signaling pathway named wnt. Insulinotropic, pancreatic and extrapancreatic insulinomimetic effects of GLP-1 and possibly its metabolites, has shown to be mediated by the activation of wnt pathway. Role of GLP-1 metabolites and GLP-1R in the induction of wnt pathway are not clear [38]. The pathway starts with a wnt ligand and LRP5/6-frizzled receptor complex interaction. The cytosolic effector of pathway is β -catenin (β -cat) and is tightly regulated by a phosphorylation-destruction complex. This complex is formed by glycogen synthase kinase 3 β (GSK-3 β), casein kinase 1 (CK-1), axin/conductin, adenomatosis poliposis coli (APC), and phosphorylated extracellular signal-regulated kinase (pERK) [Figure 2]. When the receptor complex is stimulated by a wnt ligand, phosphorylation complex which stimulate the degradation of β -cat by phosphorylation is disrupted. So β -cat escapes from phosphorylation and remains free. Free β -cat then enter to the nucleus and make complex with nuclear coactivator transcription factor named TCF-7. This β -cat-TCF-7 complex induce the target gene expression. Effector β -cat is degraded due to phosphorylation when the receptor is not stimulated. TCF-7 remain free when β -cat does not reach into the nucleus and free TCF-7 regulates the repression of target genes. The most attractive function of GLP-1 is its insulinotropic effect, which means a regenerative effect on β -cells and progenitor cells of pancreas [39]. Regeneration of β -cells is maintained by stimulation of β -cell proliferation and differentiation of ductal epithelial progenitor cells into β -cells by GLP-1 [40-44]. GLP-1 increases free β -cat in β -cells, which then induce wnt pathway to show its insulinotropic effects and decreasing glucotoxicity on β -cells. Anti-apoptotic effect of GLP-1 on β -cells has been currently defined and may be a promising cure for diabetes [45]. Oxidative stress, which play role in β -cell death is another possible target of GLP-1. Thioredoxin (TRX), the thiol oxidoreductase is an important

intracellular anti-oxidant. The function of TRX is downregulated by a binding protein, called TRX binding protein-2 (TBP-2). This binding protein has been shown to induce β -cell apoptosis, by increasing intracellular oxidative stress. Intracellular levels of TBP-2 closely correlate with blood glucose level [46, 47]. Several studies have found that GLP-1 decreases TBP-2 levels, which in turn increases intracellular TRX and decreases oxidative stress, and further β -cell damage [47, 48].

Figure 2. The wnt pathway and the role of GLP-1 on wnt pathway (APC:adenomatosis polyposis coli, CK-1: casein kinase 1, pERK: phosphorylated extracellular signal-regulated kinase, GSK-3β: glycogen synthase kinase 3β, β -cat:beta catenin, TCF-7: T cell like factor 7) (A and B: Inactive wnt pathway, C: Activation of wnt pathway by a wnt ligand, D: Activation of wnt pathway by GLP-1).

2. Effects of GLP-1 on alpha cells:

Glucagon plays an important role in pathogenesis of T2 DM. Glucagon hypersecretion has been shown during both fasting and postprandial states in patients with diabetes [49]. GLP-1 decrease glucagon secretion. The exact mechanism of this inhibition is not yet elucidated, but the most possible mechanism is the induction of pancreatic somatostatin secretion, which inhibit the glucagon secretion by paracrine manner [50, 51].

3. Effects of GLP-1 on gastrointestinal system:

Gastrointestinal system has a central role in nutrient metabolism with its absorption and endocrine functions. GLP-1 inhibits gastrointestinal system motility, gastrin induced gastric acid and exocrine pancreatic secretions, which lead to a physiological malabsorption state [52, 53]. This malabsorptive state contributes to alleviation of postprandial glucose excursions in diabetic patients.

4. Effects of GLP-1 on central nervous system and satiety:

Low levels of GLP-1 in the systemic circulation may not reach to the central nervous system, but it has been shown that GLP-1 mediated vagal stimulation may play role in decreased gastrointestinal motility. The effect of GLP-1 on vagal afferent sensorial neurons may be a local effect, which in turn these afferent neurons transmit the inputs to solitary tract nucleus, then inhibit the gastrointestinal motility [54, 55]. GLP-1 decreases food intake by inducing satiety. Hypothalamic satiety centers, predominantly arcuate nucleus has been shown to express GLP-1 receptors. But the exact mechanism of how peripheral GLP-1 stimulate these central receptors is not yet elucidated.

5. Pleiotropic effects of GLP-1

Nontraditional (pleiotropic) effects of GLP-1 and its metabolites is an evolving area of research. Wide expression of GLP-1R mediate the widespread action of the peptide. Insulin like effects of GLP-1 has been shown in heart and vasculature. Since cardiovascular diseases are the major contributor of mortality and morbidity in patients with T2 DM, scientific concerns about cardiovascular effects of GLP-1 and based therapies are growing. Preclinical and clinical studies revealed several cardioprotective effects of GLP-1. There are two possible mechanism of action of GLP-1 on cardiovascular system, one via GLP-1R, and the other one is receptor-independent [56]. Preliminary clinical studies show that GLP-1 decreases post-ischemic left ventricular dysfunction in patients with coronary heart disease [57, 58].

Invitro studies revealed that GLP-1 improves endothelial dysfunction via decreasing TNF- α , PAI-1 and cellular adhesion molecules [59]. But these observations need to be suggested by clinical studies.

A study with an insulin resistant patient population showed that GLP-1 increases renal sodium and fluid excretion, which is oppose to the mechanism of hypertension in T2 DM [60]. This finding raise the possible blood pressure lowering and renoprotective effect of GLP-1 and based thearpies. Improved endothelial function and anti-oxidant effects of GLP-1 may be another contributory effect in their renoprotective action.

Favorable effects on lipids is another important metabolic action of GLP-1. Preliminary studies reveal that GLP-1 decreases triglyceride, apo B-48 and cholesterol levels [61].

GLP-1 is proposed to be a new therapeutic option for neurodegenerative diseases with its neuroprotective effects which has been shown in animal studies [62].

3. Contribution of incretin system in the pathogenesis of diabetes

Diabetes is the state of compromised insulin secretion which resulted with hyperglycemia. Incretin effect is reduced or almost absent in T2 DM [63]. Although the secretion of GIP is nearly normal, its insulinotropic effect has been shown to be lost in T2 DM [27]. Secretion of GLP-1 is decreased in contrast to GIP, but its favorable effects on endocrine pancreas and extrapancreatic sites are preserved in T2 DM [20, 64]. In conclusion, deterioration of both the effect and secretion of incretin hormones are involved in the pathogenesis of T2 DM. It is not clear whether the deterioration of incretin effect is a primary defect in the pathogenesis of diabetes or not. Studies suggest that incretin hormone deterioration is a secondary defect during progression of diabetes. Another important fact is the restoration of insulin secretion with GLP-1 replacement is possible and improve hyperglycemia [65, 66].

There are several mechanisms of action of GLP-1 in T2 DM. The first one is the augmentation of glucose induced insulin secretion, resulting with improvement in hyperglycemia. Near-normal improvement in β -cell response to glucose, improvement in the first phase insulin secretion and completely normalisation of second phase insulin secretion by GLP-1 has been exactly defined [67]. Although the induction of insulin secretion is lost during chronic GLP-1 administration, glucose lowering action with maintained insulin levels tend to persist. Reduction in glucagon secretion is another mechanism of antiglycemic effect of GLP-1 [68]. Administration of GLP-1 delays gastric emptying significantly, and results with reduced postprandial glucose levels [69, 70]. The latter mechanism seems to be lost in chronic fashion. Based upon these mentioned antiglycemic effects of GLP-1, several pharmacological agents are developed for the treatment of diabetes, which will be talked about elsewhere in this chapter.

4. Incretin based therapies and their role in the management of type 2 diabetes

Effects of incretin hormones on glucose metabolism and contribution of incretins in the pathogenesis of T2 DM, make these hormones ideal therapeutic targets. Decrease in appetite, reduction of body weight, improvement in insulin secretion and delay in gastric emptying are among several favorable effects of GLP-1 infusion [71]. Rapid degradation of bioactive GLP-1 by DPP-4 shortens half life, and limits anti-diabetic effects of GLP-1 [73]. Two treatment strategies have been developed to overcome this problem, first to develop DPP-4 resistant GLP-1 analogs, and the second to inhibit the degrading enzyme DPP-4. These two groups of medications will be discussed in detail.

4.1. Dipeptidyl peptidase-4 inhibitors

These oral agents are approved for treatment of diabetes whose hyperglycemia do not improve with monotherapy with sulphonylurea, thiazolidinedione and metformin or their dual combinations. They exert their effects by inhibiting the enzyme which cleaves the incretins and increase GIP and GLP-1 levels. Sitagliptin, saxagliptin, linagliptin and alogliptin are available

in US, and vildagliptin is used in outside US. They have the advantage of being weight neutral and do not cause hypoglycemia except for combinations with sulphonylureas. They have been shown to be effective and safe when combined with sulphonylurea, thiazolidinedione or metformin in patients with T2 DM [73]. Usual dose of sitagliptin is 100 mg once daily, and renal dysfunction necessitate dose reduction (50 mg for patients who have glomerular filtration rate 50 mL/min and 25 mg for patients with <30 mL/min) [74]. Saxagliptin is used 2.5-5 mg once a day and the dose should be reduced to 2.5 mg for moderate renal insufficiency. It is also an effective agent in combinations like sitagliptin [75, 76]. Vildagliptin is used 50 mg twice daily in T2 DM. Dose adjustment is not necessary in mild renal insufficiency, 50 mg daily dose is suggested in case of moderate and severe renal dysfunction. Linagliptin is used 5 mg daily, and it differs from other DPP-4 inhibitors with its completely hepatic elimination, which makes it possible to use in renal dysfunction. Efficacy and safety of linagliptin have been proven in monotherapy and combination studies [78-80]. Alogliptin is used 25 mg daily and dose adjustment is necessary in renal dysfunction. It has similar efficacy and safety profiles with other DPP-4 inhibitors [80].

All of the members of DPP-4 inhibitors seem to have similar efficacy, but their enzymatic affinity may be different [81, 82]. Their side effects include headache, increased risk of nasopharyngitis, urinary tract infection, and skin reactions [83]. There are reports about hepatic dysfunction with alogliptin and vildagliptin. Although the incidence of pancreatitis is not increased, a population based data suggested an increased frequency of hospitalisation for pancreatitis among sitagliptin users [84]. There is concern about whether DPP-IV inhibitors cause pancreatic cancer development or not, but a causal relationship has not been established yet.

Cardiovascular safety of DPP-4 inhibitors is the matter of concern, since cardiovascular diseases are the most common cause of death in T2 DM patient population and there are several antidiabetic drugs which have been withdrawn from marketing due to their cardiovascular safety problems. In a study which cardiovascular events was an endpoint, saxagliptin and metformin showed similar cardiovascular safety pattern, but patients in saxagliptin group hospitalised more frequently for heart failure when compared with metformin group [85]. Two other studies showed that neither alogliptin, nor sitagliptin have beneficial or adverse cardiovascular effects in short term use [86, 87]. Although these studies showed increased or decreased risks for cardiovascular events with DPP-4 inhibitors in short term use, their long term cardiovascular safety need to be further evaluated in long term clinical trials.

4.2. GLP-1 receptor agonists

There are two approved synthetic GLP-1R agonist molecules in the marketing. First one is Exenatide and the second one is Liraglutide. They are approved for T2 DM as an add-on drug for patients whom glycemic regulation is failed with one or two oral anti-diabetic medication [88]. Lower hypoglycemia risk is an important advantage of these molecules, which make them an excellent choice of therapy in patients whom hypoglycemia is of concern. Although they are as effective as other older anti-diabetic agents in comparison trials, data about their long term safety, effects on mortality and weight reduction is lacking [89]. Their effects on weight

reduction has been proven by several studies, in which weight reduction was a secondary endpoint [90].

4.3. Exenatide

It is the synthetic analog of GLP-1, and it naturally occurs in the saliva of Gila monster (*Heloderma spectrum*) as Exendin-4. It has 53% aminoacid homology with original GLP-1 molecule and has a long half-life because of its resistance to DPP-4 mediated degradation. It is approved for T2 DM, as single or an add-on agent with other oral anti-diabetics in US. It can be combined with all of the oral anti-diabetics except for DPP-4 inhibitors.

It binds to GLP-1R and shows insulinotropic effects of GLP-1 on β -cells in the presence of glucose. It slows gastric emptying, lowers plasma glucose levels and reduces weight by inducing satiety like GLP-1 [91, 92]. Insulinotropic effects has been shown in animal models [93, 94].

Beneficial effects on hyperglycemia, weight reduction, lipids and blood pressure has been shown with clinical trials, which has less than 30 weeks of duration [71, 95-99]. Exenatide reduces a1c levels by approximately 1%, has lower hypoglycemia risk and hypoglycemia risk is increased with concurrent use of sulphonylurea. Exenatide causes a significant weight loss, which seems independent from its nausea inducing effect. Of note, patients experience lose more weight compared with patients who do not have [83, 100]. Preceding type of drug is another important factor on weight loss during exenatide use. Patients using metformin show much more weight loss when compared with patients using sulphonylurea and thiazolidinediones [100-103].

The most common side effect of exenatide is gastrointestinal, predominantly nausea and rarely vomiting, which wane with ongoing therapy. Starting with 5 mcg and increasing the dose after one month to 10 mcg help to overcome nausea. Although risk of pancreatitis among patients who use incretin based drugs has been shown to be similar to the diabetic patients who do not use incretin based therapy, hospitalisation for acute pancreatitis may be increased [84, 104-106]. Insulinotropic effects of GLP-1 raised concerns about the possibility of pancreatic cancer and neuroendocrine tumor risk among patients using incretin-based therapies [107-110]. There is no data which prove or unprove these issues, so it is suggested to monitor patients for possible adverse effects affecting pancreas [111]. Although acute renal failure following exenatide use has been reported, it is difficult to prove direct relationship with exenatide use and renal failure in this patient population, which is prone to develop acute renal failure because of concurrent use of nephrotoxic drugs and underlying diabetic nephropathy [112]. Exenatide is contraindicated in severe renal impairment (creatinine clearance below 30 mL/min), and close follow up for serum creatinine is suggested when initiating therapy and after the dose titration from 5 to 10 mcg in patients with moderate renal impairment (creatinine clearance 30-50 mL/min). Gastroparesis and history of past acute pancreatitis are the other contraindications for exenatide use.

Although Exendin-4 is a GLP-1R analog, it shares a %53 homology with human GLP-1, which leads to development of anti-exendin antibody. It has been shown that anti-exenatide antibody

development occur in about %40-57 of treated group [103, 113]. In one study the frequency of anti-exenatide antibody was reported to be more than %70 at the end of 24 weeks, and %40 of these antibody positive patients did not show further a1c reduction [114]. Although these mentioned studies have some limitations, ineffectiveness of exenatide due to blocking antibodies in long term use is possible.

The usual administration schedule is starting with 5 mcg sc twice a day within 1 hours before breakfast and dinner, and titration to 10 mcg twice a day 1 month later. Exenatide once weekly sc formulation is also available in US and Europe, and efficacy on hyperglycemia has been shown [115]. There are studies which compare the efficacy of daily and weekly formulations of exenatide. The improvement in a1c level seem to be better achieved with weekly formulation when compared with daily formulation, with similar body weight reduction [116, 117].

4.4. Liraglutide

Liraglutide is a GLP-1 analog which is produced by a recombinant DNA technology. Substitution of lysine at position 34 by arginine, and attachment of palmitic acid side chain to lysine group at position 26 of original GLP-1 produce liraglutide. The lipid side chain lead to formation of a non-covalent bond with albumin, which in turn slows degradation of the molecule, allowing it to be used once a day sc. Liraglutide shares 97% amino acid homology with GLP-1.

Clinical indications are similar with exenatide. Once daily administration of 0.6 mg sc for one week reduce gastrointestinal side effects. The dose should be increased to 1.2 mg once daily for one week, and to 1.8 mg once daily if blood glucose remains above the goals [118]. Liraglutide monotherapy and combination with one or two oral agents are efficacious in reducing blood glucose and a1c, causing significant weight reduction compared with placebo, glimepiride and sitagliptin [119-121].

Nausea, vomiting and diarrhea are the most common adverse events [119]. The relationship between liraglutide use and pancreatitis is controversial. Animal studies have shown a relationship between liraglutide use and benign and malignant parafollicular C-cell tumors [122]. It may be a species specific effect and GLP-1R expression of human C-cell has been shown to be very low [122]. Short term human studies did not show any elevation in calcitonin levels with liraglutide, but this issue need further evaluation, since it takes a long time for a malignant transformation. Liraglutide is not recommended for use in patients who have medullary thyroid carcinoma or a related syndrome, or a family history of these diseases.

4.5. Is one GLP-1 receptor agonist superior to the other?

In a 26 week trial comparing the effects of liraglutide and exenatide showed a better glycemic control with liraglutide compared with exenatide, with similar weight loss and adverse effects [123]. In another study the effects of both analogs on hyperglycemia was similar, with slightly better weight reduction in liraglutide group [124]. One potential superiority of liraglutide to exenatide may be its molecular homology to GLP-1, which is not associated with development of blocking antibodies causing drug ineffectiveness during chronic use.

Besides their beneficial effects like weight reduction and low frequency of hypoglycemia, long-term safety data, effect on diabetic macro and microvascular complications and mortality of these GLP-1R analogs are still lacking.

5. Summary

The role of comparatively older drugs such as insulin, insulin secretagogues, metformin, thiazolidinediones and alpha glucosidase inhibitors in the management of diabetes are familiar aspects of diabetes therapy. These medications target insulin secretion, insulin sensitivity and glucose absorption, which may be interpreted as having limited targets in the pathogenesis of diabetes. Definition of incretin hormones and their role on β -cell function and survival are the new aspects of the pathogenesis of diabetes, and management of hyperglycemia. Besides the novelty of incretin based therapies in the management of diabetes, their roles on β -cell function and regeneration, which are really promising effects for an anti-diabetic agent are so interesting and need to be observed in long term clinical practice. Possible effects of these drugs that is associated with their pleiotropic effects, which have been shown in invitro studies on diabetes related complications are the new era in diabetology. In our opinion the role of incretin based therapies in the progression of diabetes and diabetic complications will be determined in the future, although favorable or not.

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