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OVERVIEW OF GLP-1 AND ITS PHYSIOLOGY

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ABSTRACT

Diabetes mellitus is most prevailing and pervasive metabolic disorder across the globe, out of all these, cases 90% are suffering from diabetes mellitus type 2. Two peptide hormones basically released from the enteroendocrine cells, K-cells present in duodenum release Glucose Dependent Insulinotropic Polypeptide (GIP) and L-cells present in pancreas, ileum and colon release Glucagon Like Peptide-1 (GLP-1), both GIP and GLP-1 are enzymatically fragmented by Dipeptide Pepidase-4 (DPP-4). Monosaccharides get absorbed by the intestinal cells through membrane transporter Sodium Glucose Co-transporter-1 (SGLT-1) which further promotes liberation of GLP-1 from intestinal L-cells. Many investigations have revealed that high protein diet releases more amount of GLP-1 in contrast with the normal calorie diet. Incretin effect leads to release of insulin by the GLP-1, and GLP-1 gets released by the oral ingestion of nutrients. Together, glucose and GLP-1 close the Potassium-ATP channel. It was searched that the potassium-ATP channel was phosphorylated by GLP-1-induced PKA activation, contributing to its closure. GLP-1 also reduces blood sugar by preventing glucagon secretion**.** According to preclinical research examining the mechanism by which GLP-1 receptor agonists cause weight loss, the primary mechanism is a decrease in food intake without modifications in activity level or energy expenditure.

Keywords: GLP-1 Secretion, Insulinotropic Effect, Glucagon Inhibition, Obesity

INTRODUCTION

Metabolic disorder such as diabetes is prevalent and widespread in almost every part of the society and maximum number of people who have diabetes mellitus suffer

from diabetes mellitus type 2 **[1, 2, 3]**. GLP-1 and GIP show their potential by releasing the insulin from the beta cells after having high carbohydrate, protein, and fat intake **[4, 5]**. GLP-1 has turn up to have a wide range of impacts on glucose metabolism, despite the fact it was supposed that it only affects insulin secretion. Within minutes of a meal, intestinal part like colon and ileum having high success rate for release of incretin hormones (GLP-1) has appeared to increase the production and release of insulin through glucose activated GLP-1.

GLP-1 release show decrease in the production of glucagon and increase glycogen synthesis and glucose absorption in the muscles. It prolongs the stomach clearance time and further increase its fullness. Consequently, diabetes can be cured by the prospective and specific aim of GLP-1 **[6, 7]**. It appears that one and the other endocrine and neuronal components stimulates the release of GLP-1 from the L cells, when small intestines get in contact with the processed and digested food **[8, 9]**. Within minutes of consuming food, GLP-1 scores get elevated quickly in the blood **[10, 11]**. It is found that DPP 4 having half-life of 2 minute can enzymatically breakdown the intact molecule of GLP-1 and produce its metabolite [9e36] amide and both get remove from circulation **[12]**. GLP-1 also seems to function physiologically as an appetite and food intake regulator. Owing to these effects, type 2 diabetes nowadays medicated with glucagon like peptide. Obesity may be increased by reduced GLP-1 secretion, whereas postprandial reactive hypoglycaemia may result from excessive GLP-1 secretion **[13]**.

SYNTHESIS, SECRETION AND DEGRADATION

SYNTHESIS

Yield of proglucagon peptide in L-cells and beta cells in controlled by prohormone convertase isoforms that are indicated tissue specifically. Thus, enteroendocrine cells having convertor of prohormone 1/3, cleaves proglucagon to release GLP-2 and GLP-1 along with the peptides having glucagon, oxyntomodulin and glicentin **[14, 15]**.

A mid-sequence glucagon epitope was the target of previous investigations on GLP-1 secretors, which led to the identification of glicentin/oxyntomodulin (also known as enter glucagon or gut glucagon-like immunoreactivity) along with glucagon. Glicentin/oxyntomodulin are put together and released in the proportion of 1:1 along with the GLP-1 **[16, 17]**. GLP (17-36) amino acid unit and GLP (17-37) unit are the two equipotent and bioactive units which are present in the blood stream.

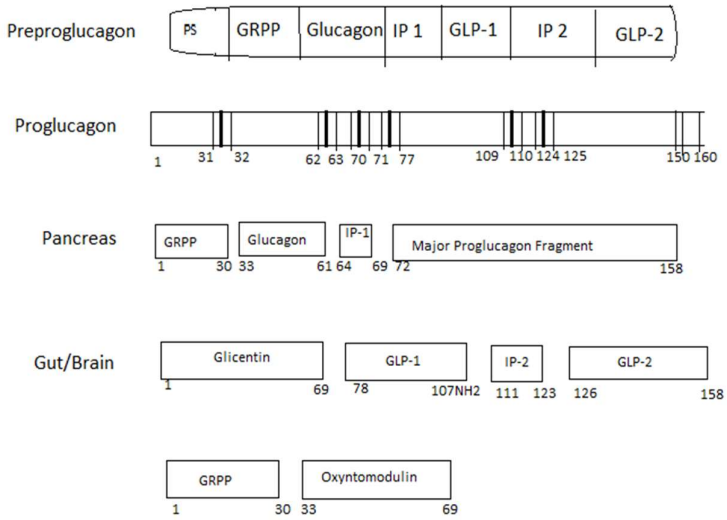

Figure 1: Different proglucagon-derived peptides are released by proglucagon's tissue-specific posttranslational processing

SECRETION

Release of GLP-1 is potentially induced by the nutrient present in the intestine (although other neurological or endocrine processes may be practical at work), and the release of insulin is closely connected with GLP-1 secretion throughout the day **[18]**. When delivery of glucose is done through intravenous route which means without going through the digestive system's absorptive process, plasma GLP-1 concentrations are unaffected. In difference, there is a brisk release of GLP-1 through oral administration as it is good impulse for its release, typically range from 5 to 15 p mol/l in the baseline state to 20 to 60 p mol/l following oral glucose or meals **[19, 20, 21]**. GLP-1 secretion is unquestionably related to meals.GLP-1 level are quite low in blood during fasting. Release of GLP-1 is not limitless as it is revealed that somatostatin can reduce starving concentration in people, indicating a normal range of secretion. Despite the fact there is a wide range of GLP-1 analogues drugs to the market having the same procedure for the release of GLP-1 and are the evolution for the treatment of diabetes **[22]**.

DEGRADATION

DPP 4 presence is seen in CD26 antigen on T-cell, which is also referred as Ectoenzyme, can appear on the plasma membrane of a variety of tissues, like in membranes of intestine, kidney, liver cells and in cells of blood vessels. It can also arise in plasma in soluble form. It has severe substrate specifications, N-terminal of the peptide is only cleaved from the amino acid chain and must be in the series of alanine and proline **[23, 24]**. Given that physiological action of incretin hormones is control by their cleavage point and its

regulation is governed by the activity of DPP 4.

DPP4 broken metabolites of the GLP-1, N terminal part is greatly circulated in the blood stream of humans, showing the major role in the breakdown of the incretin hormones. Small amount(picomolar) of GLP-1 in the plasma has proven that it has broken down by the DPP 4 **[25, 26]**.

MODULATION OF GLUCAGON LIKE PEPTIDE-1 SECRETION BY NUTRITION

CARBOHYDRATE INDUCED GLP-1 SECRETION

Digestible carbohydrates are burst down by enzymes after ingestion and are mostly soak up as glucose, with some fructose and galactose as well. Membrane of small intestines produces transport protein known as SGLT-1appears to be the mediator of absorption of glucose by membrane along with the release of GLP-1 from enteroendocrine cells **[27-32]**. Binding of glucose to SGLT-1 causes the potassium channels that are sensitive to ATP to close, which causes the membrane to depolarize and increases the levels of intracellular calcium. These studies demonstrate the significance of intestinal SGLT-1 absorbed glucose mediated GLP-1 production and luminal monosaccharide absorption **[33]**. Consequently, it was established that throughout a 6-hour postprandial period, there was a reduction of GLP-1 release in the starting period in a normal glucose concentration but later there is a brisk release of GLP-1 in blood having low glucose level **[34]**. Both unprocessed and indigestible carbohydrates get fermented in the last part of the intestine which further increase in short chain fatty acid (SCFA) yield, and this increased carbohydrate to get in contact with the intestinal L-cells are potential explanations.

Fructose transporter and Na+/glucose transporter present in the rat, intestinal GLP-1 ileum was supposed to increase the level of intestinal GLP-1 induce by monosaccharides. One study from 2017 found that SGLT-1 and GLUT-2, but not KATP channels, were critical to increase the synthesis of GLP-1. A high quantity of glucose (300 nmol/L) enhanced GLP-1 release in intestine of human and this process is not present when there is no Na^+ or taken into consideration along with the GLUT2 inhibitor phloretin or phlorizin **[35]**. Dietary fibre that can ferment and its by products, the SCFAs, appear to encourage the production of intestinal GLP-1 after associating with the fatty acid receptors namely FFAR2, FFAR3 **[36-39]**. Biological level of butyrate, acetate, propionate meet to release GLP-1 secretion in colonic cell cultures. Intestinal cells that don't have FFAR3 and FFAR2 don't release the GLP-1served as evidence of the role as it shows its role in GLP-1 secretion by short chain fatty acids **[40]**.

According to a randomised crossover research, galactose (50 gm) and guar gum (2.5 gm) combined in the company with the typical meal increased plasma GLP-1 concentrations by 57% in women of normal weight. Chitosan is usually used as a dietary supplement in medical nutrition treatment and could aid with diabetes management. Low molecular mass chitosan present in the intestinal endocrine cells dramatically boost the release of GLP-1 in the concentration dependent manner via MAPK dependent signalling route **[41, 42]**.

PROTEINS AND AMINO ACIDS INDUCED GLP-1 SECRETION

Edible proteinaceous food is typically considered as the most satisfying food and their role moderately conciliated the release of GLP-1 and GIP. Acid hydrolysis and proteases break down proteins after consumption to create tripeptides, peptones, single amino acids and dipeptides **[43, 44, 45]**. Products of protein get breakdown by the two pathways which further stimulate GLP-1 secretion are by getting bind with calcium sensing receptor and the second is group 6, class 6 GPCR subtype which is present on the L cells. The amino acids tryptophan, phenylalanine, arginine, asparagine, histidine, and glutamine, as well as tripeptides, peptones, and dipeptides, are among those that calcium sensing receptors binds to **[46-50]**.

A recent study using the isolated perfused gut of rat revealed GLP-1 secreted by the protein highly depend on its absorption in intestine and further calcium sensitive receptor activation. Contrary to the hypothesis peptides present on the intestinal membrane act on the calcium sensitive receptor which is present on the apical side of the L cells to release GLP-1 **[51]**. In many studies it is proven that in contrast to normal calorie meal, meal higher in protein amount strongly release GLP-1. Since the test meals used in each of the investigations was isocaloric, variations in the energy ratio of the food cannot account for the variance in findings. Variations in meal volume may have influenced the release of GLP-1**[52, 53]**.

Potential mediators of peptone secreted GLP-1 induce the G protein coupled receptor (calcium sensing receptor) and the peptide transporter 1 (Pept1) **[54]**. GLP-1 amount was found to be higher in healthy women after consuming high protein diet and further compared for the energy level. 30%, 30%, and 40% were sourced from the protein, fat, and carbohydrate independently and this was compared to the normal protein diet the energy level was 10%, 30%, and 60% for protein fat and carbohydrate respectively. Different amino acids and proteins have varying degrees of success in promoting GLP-1 release.

According to their findings, isoleucine, leucine, casein, and skim milk all enhanced GLP-1 secretion to varying degrees. 2% leucine, isoleucine, casein (not whey), and skim milk increased the release of GLP-1 by 1.6, 2.5, 4.7, and 2.6 folds, respectively **[55, 56]**. Glutamate **[57, 58]**, phenylalanine **[59]**, arginine, and tryptophan have encountered to be some of most efficient amino acid promoting the release of GLP-1. In one study, isolated loops of the small intestine of rat were perfused with various amino acids (all 10 mM) to promote the release of GLP-1. Arginine > glutamine > tryptophan > asparagine is supposed to be the possible amino acids that stimulated GLP-1 production with the greatest potency, according to the results **[60, 61, 62]**.

FATTY ACIDS INDUCED GLP-1 SECRETION

Triglycerides, which is made up of three fatty acid molecule and one glycerol forms most of the dietary lipids. Following ingestion, lipids having long chain fatty acids digested by lipases in the duodenum and absorbed by enterocytes as glycerol and free fatty acids **[63]**. After interacting with both the fatty acid receptor FFAR4 and FFAR1, fatty acid chains powerfully stimulate the release of GLP-1 **[64, 65]**. When a substance binds with the fatty acid receptors, phospholipase C gets activated which then triggers calcium release via inositol triphosphate into the cytoplasm **[66]**. It is demonstrated that GLP-1 is highly secreted by the fatty acid long chains.

In healthy and diabetic rat models, some investigations found that colonic injection of polyunsaturated α-linolenic acid abruptly elevated level of GLP-1 in blood which release insulin that shows its role in lowering glucose level in the blood **[67]**. Close to this, α-linolenic acid when provided for long period used to promote the number of cells in rodents while also raising blood levels of GLP-1 **[68]**. Because GLP-1 is used to increase pancreatic neogenesis and reduce apoptosis, the authors hypothesised that the rise in GLP-1 level brought on by consuming α-linolenic was the mechanism by which the increased beta-cell proliferation was mediated. Oleoylethanolamide which is long chain fatty acid in a concentration of 10 micromoles /L reduces GLP-1 secretion from the intestinal enteroendocrine cells via acting on the fatty acid's receptor GPR119 **[69]**. In contrast, the vehicle or oleic acid provided to the control group didn't show GLP-1 release but, in another case, volunteers provided with 2-oleoyl glycerol significantly increase the GLP-1 plasma level in 0-25 minutes **[70]**. Therefore, intestinal, and pancreatic L cells having GPR119 can be the potentially target for curing the type 2 diabetes mellitus by increasing the GLP-1 release.

Moreover, metabolite of omega 5-hydroxyeicosapentaenoic acid (5-HEPE), was supposed to be the powerful tool for the GLP-1 secretion as sourced as GPR119 agonist, suggesting that it can help in the treatment of diabetes **[71]**. The pancreas and gut have high levels of GPR120 expression **[72]**. Intestines have large number of GPR120 which functions target for long chain free fatty acid as it can release GLP-1 from L cells can be the therapeutic aim for curing diabetes **[73]**. Blood glucose maintained can be regulated by short chain fatty acids as it has the capability to increase the release of incretin hormones by the process of interaction with FFA2/FFA3 **[74]**. Future treatments for T2DM may be made possible by the creation of impressive and FFA3 and FFA2 agonists, which will make it easier to understand the effects of these fatty acids on metabolism. Investigations are being directed to determine how the FFARs affect glucose absorption, stimulate GLP-1 secretion, contractility, and motility of colon along with the leukocyte activation **[75, 76]**.

INSULINOTROPIC ACTIONS OF GLP-1

In clinical terms, the capacity of incretin hormones to increase the release and secretion of insulin and maintaining blood glucose homeostasis and low blood glucose level is their most crucial characteristic. GLP-1 exerts its glucose-dependent characteristic on the β-cell of pancreas by attaching to a particular target that is associated to glucose absorption and digestion **[77, 78]**. GLP-1 has several recognised and potential pancreatic activities. In beta-cells, the GLP-1 receptor is indicated, and stimulation of this receptor is belief to have both immediate and long-term effects **[80]**. Respecting cell function, GLP-1 potently and quickly increases insulin secretion, which is a well-known effect that will be enfolded in more detail below. However, GLP-1 also promotes neogenesis, islet cell development, and transcription of the insulin gene—additional possibly significant processes which therapeutically associated in the curing of diabetes **[79]**.

Meaning of incretin effect is that after the absorption of glucose from the intestine and its release the insulin from islet of Langerhans by stimulating beta cells by the process of activation of GLP-1 and GIP **[81]**.

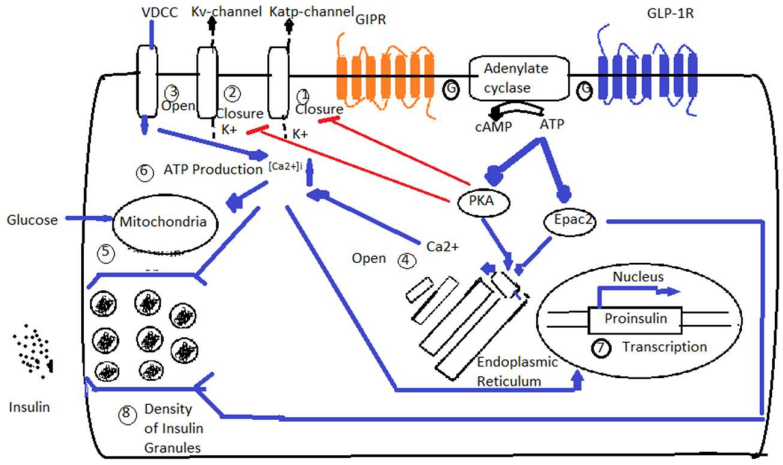

Figure 2: The molecular mechanisms by which incretin hormones show insulinotropic actions. After binding to incretin hormones to the GIP receptor and GLP-1 receptor adenylate, cyclase is activated which further increase the cAMP levels intracellularly. Then, as cAMP levels rise, PKA and Epac2/cAMP-GEFII are activated. K_{ATP} channels close when PKA is activated, facilitating membrane depolarization. Action potentials are prolonged because of PKA's suppression of K^+ channel, which is a negative regulator of insulin secretion in beta cells. Calcium level increases by the depolarisation of the voltage gated calcium channels, by Epsc2 and PKA dependent pathways. Insulin production from the β cells and the binding of granules having insulin with the plasma membrane are ultimately brought on by the elevated Ca^{2+} concentrations. Elevated calcium levels also encourage the proinsulin gene's transcription, which raises the β cell's insulin concentration. It has been demonstrated that activation of Epac2 causes an increase in concentration of insulin granules, which enhances the β cell's ability to release insulin. Epac2 has also been linked to increased K_{ATP} channel ATP sensitivity. The synthesis of mitochondrial ATP is also increased when GLP-1R is activated

GLP-1 RECEPTOR SIGNALLING IN THE HUMAN BETA CELLS

When blood glucose levels are high, G proteins get activated by the activation of GLP-1 receptor, which results in the activation of adenyl cyclase by the cAMP, accompanying calcium increase and ERK1/2 phosphorylation **[83]**. cAMP production is directly involved in the increasing the bar of insulin secretion along with proinsulin gene transcription factor. It also increases protein kinase A and exchange the protein activated by it **[82]**. Insulin is secreted by both the phases by glucose induced GLP-1 activation in the pancreas of rat and human **[84, 85]**. Glucose and GLP-1 work together to shut the KATP channel. It was brought to light that GLP-1-induced PKA activation phosphorylated the KATP channel, aiding in its closure. Moreover, it has been displayed that GLP-1 blocks KATP channels by activating the Epac2/Rap1/PIC signalling network **[86, 87]**.

Furthermore, PKA phosphorylates L-type calcium channels, increasing the likelihood of them opening. Together, these processes promote Ca2+ influx and membrane depolarization in -cells. The Ca2+ influx triggers activation of PKA and Epac2-dependent molecular pathways, which mobilises Ca2+ from intracellular storage.

PKA manage the release of inositol 1,4,5-triphosphate receptor (IP3R), and the ryanodine receptor (RYR), which is turn on by Epac2, are the mechanisms by which GLP-1 elevates [Ca2+]c **[88]** According to studies, the Ca2+ mobilisation increases mitochondrial ATP production, which encourages additional membrane depolarization by closing KATP channels **[89]**.

SAD-A is another mechanism through which GLP-1 induces insulin release. AMP activated protein kinase known as SAD-A which is only manifested in the brain and pancreas work by activating PAK1 plays a role in the insulin exocytosis by the glucose stimulation **[90]**. Glucose stimulated GLP-1 release from L cells which shows that SAD-A is responsible in insulin release through auto inhibitory phosphorylation site which releases GLP-1. Furthermore, these effects prove that SAD-A kinase get activated by GLP-1 through cAMP signalling pathway **[91]**.

CHALLENGES WITH USING GLP-1 FOR TARGETING PANCREATIC BETA CELLS

Several problems, including cytotoxicity, nonspecific binding, the lack of beta cell-specific targets, radioisotope accumulation, and the need for probes with the ability to attach to intracellular insulin, must be set on to accomplish successful pancreatic beta-cell imaging **[92]**. Due to the physiological differences between rodent and human islets of Langerhans, such as lower concentrations of alpha cells and higher concentrations of beta cells in rodent islets contrast to human pancreas **[93]**, it is challenging to make an exact probe for imaging of beta cell mass.

GLP-1 EFFECTS ON GLUCAGON SECRETION

As well, GLP-1 lowers blood sugar by inhibiting secretion of glucagon from pancreatic alpha cells **[94]**. Isolated perfused pancreas of the rat, mice, dogs, pigs, and human significantly shows that glucagon get inhibited by GLP-1 secretion **[95]**. Studies using clamps on people having diabetes show reduced glucagon secretion and GLP-1 augmentation of insulin release are both crucial for decreasing blood glucose. The methods by which glucagon is are intricate. Pancreatic cells also produce somatostatin which powerfully inhibit the glucagon secretion in response to GLP-1. Somatostatin blocks glucagon secretion via paracrine pathway. When somatostatin receptor antagonist (PRL-2903) is given with GLP-1 eliminates inhibitory effect of GLP-1 itself in the pancreas of the rat. These observations highly shows that somatostatin plays role in GLP-1 release for glucagon production.

GLP-1's insulinotropic impact on β-cells may potentially indirectly limit glucagon release. Consequently, GLP-1 increases the production of somatostatin from the beta

cells as well as insulin, amylin, zinc, and GABA from the b cells, all of which inhibit the release of glucagon. Insulin stops the release of glucagon in IN-R1-G9 cells produced from a-cells by activating phosphatidylinositol 3-kinase (PI3K). Wortmannin's inhibition of PI3K counteracts insulin's ability to inhibit glucagon production. GABA-A get translocated by the insulin present on the alpha cells while beta cells produced GABA produce glucagon inhibition **[96]**. When there is hyperglycaemia, Zn2+ and insulin are co-secreted. Insulin and Zn2+ co-crystallize in the beta cell granules. Moreover, in a paracrine manner zinc inhibits glucagon secretion by acting on the alpha cells **[97]**.

GLP-1 EFFECTS ON OBESITY

Decrease in the feeding capacity by both animals and in humans is provided by the strong supporting role of GLP-1, different species respond differently to GLP-1's effects on energy expenditure. GLP1RA enhances energy expenditure, according to studies on mice and rats, which contributes to the weight loss shown in preclinical investigations **[98]**. However, preclinical studies investigating the mechanism by which GLP1RA produces no changes in the energy expenditure and reduce food intake and provide weight loss **[99]**. Despite the potential of GLP-1-managed energy utilizations pathways, it doesn't seem such as this mechanism significantly contributes to the weight loss that occurs after GLP1RA treatment in humans **[100]**.

Subcutaneous and oral semaglutide were developed to induce satiety and decrease food intake when the processes underlying GLP-1-mediated weight loss were measured **[101]**. Liraglutide and semaglutide have been indicate in animal experiments to have access to the precise brain regions responsible for controlling hunger **[102]**. Semaglutide had an impact on both hedonic (food preference, control) and homeostatic (appetite, hunger, satiety) brain pathways in rodents, which led to reduce weight within effecting energy utilization **[103]**. The oral administration of GLP-1 can prolong satiety and lessen postprandial glucose excursions by delaying stomach clearance. Twain obese people with diabetes and those without it still have this impact. Pharmacologically simulating these effects might help people consume low fat food, hence promoting weight loss and maintenance **[104]**.

It is shown in the clinical trials that weight loss is seen for around 3 kg with the use of GLP-1 receptor agonist, diabetic patients' losses weight about 2.8 kg and patient without diabetes losses 3.2 kg in trials **[105]**.

GLP-1 EFFECTS ON CARDIOVASCULAR SYSTEM

Committed studies of cardiovascular outcomes with agonists of GLP-1 receptor doubtlessly have been proven to have

curative potential of GLP-1 effect in cardiovascular system, which is summed up as complex, positive affect on cardiovascular function as well as an inhibitory effect on the genesis, progression, and rupture of atherosclerosis plaques **[106, 107]**.

As per a study GLP-1 agonist have shown cardioprotective effect on subjection of palmitate on neonatal rat's cardiomyocytes, which illustrates increase in β-catechin signalling due to GLP-1 agonists, which further causes increase in surviving protein with the help of protein kinase β-glycogen synthase kinase 3β pathway and preventing apoptosis activation **[108]**.

There is decrease in cardiovascular event and acute cerebral events of mean of 65 year of age and 8.7% of mean HbA1c as well as same mortality rate due to Semaglutide **[109, 110]**.

CONCLUSION

GLP-1 analogues have a broad pleiotropic effect on metabolism, based on the substance and the delivery technique. GLP-1 receptor agonist provides a variety of beneficial effects including regulation of blood sugar, reduction of stomach utility and lowers body weight through inhibiting food intake. Sustained activity and enhanced pharmacokinetics of the recombinant GLP-1 analogues are effective in the treatment of diabetes. Peptides along with the GLP-1 are being tested in clinics to treat diabetes and obesity. In comparison to currently available GLP-1 receptor agonist, we might be cautiously optimistic that improved GLP-1 based pharmacology can one day be employed to further reduce body weight.

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