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The Role of GLP-1 Receptor Agonists in Obesity Management and Weight Loss:A Systematic Review

Saba Babar*, Kiran Aslam, Eman Fatima, Mahnoor and Ayesha Shahzad

Government Graduate College of Home Economics, Faisalabad

*Corresponding Author: mmirzababar182@gmail.com

ABSTRACT

Globally obesity is the most prevailing condition but GLP1 agonists is the major revolution in past 40 years dealing with weight management This review paper will evaluate the mechanism and working of glp 1 in our body and, peliotropic effect of glp 1 on multiple organs like pancreas brain heart kidney liver and Adipose tissues that help in our weight management Various research studies have been conducted on the effect of the glp 1 supplements and results have shown that the under the supervision of Endocrinologist and in a suitable amount these would be beneficial by delaying stomach emptying rate and by increasing sateity, While on the other hand there are some mild initial Gastrointestinal symptoms including vomiting nausea And diarrhoea which could be manage after sometime. In short terms Glp 1 therapeutic intervention act as a revolutionary bridge between the traditional Lifestyle modification and the invasive bariatric surgery.

Keywords: Obesity, weight management 1 agonist receptor, appetite regulation

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Introduction

GLP-1(glucagon like peptide) is an incretin hormone that produce naturally by our intestinal L cells(gut) when we eat something. The most significant functions of GLP1 is that it is appetite suppressor it delays the process of food digestion in stomach by acting on the part of brain that control hunger(hypothalamus) it also control insulin secretion by Beta cells of pancreas in this way it helps in blood glucose regulation in diabetic patient dealing with Type 2 and weight loss reduction in obese patients having BMI ≥ 30 kg/m2. Paradoxically coexisting with under nutrition Obesity is also the most chronic and prevailing condition and becoming a global epidemic,frequently known as Globesity by World Health Organization.Mortality and morbidity rate is being risen drastically.5 millions death rate and 160 million disability-adjusted life is being reported by a survey that was conducted in 2019. Obesity is being measured by an anthropometric tool that assist us to classify human beings on the basis of their weight to height ratio known as body mass index BMI having formula BMI=weight (kg)/height m2 and unit is kg/m2in adults and percentile in below 18 years.

In early century obesity was just managed by lifestyle modification,behavioral therapies and dietary changes.but this was not a result achieving approach because 90% people try with their great potential but unable to stick with these conditions in a long run.The pharmacotherapy used in earlier time has limited effect and multiple side effects so medication not minimized the weight loss process but also leads toward serious complications of kidney and liver due to their(medications) complex and unfamiliar mechanisms and chemical structures within human body.

This is the time which leads to the emergence of major discovery in the last 40 years that is GLP1 agonists which means supplements that have similar effect like GLP 1 when they introduced inside human body, usually through injections under supervision of specialized endocrinologist and experienced physicians.thay have positive impact on weight management [1].

Underlying mechanism of GLP 1 Agonist in Weight Loss:

GLP 1 receptor agonists:

GLP 1 receptor agonists are **synthetic molecule**s that bind with receptors like natural hormone and mimic their effects but they work in our body for a long time because they do not degrade easily by DPP 4 a molecule that degrade natural incretine hormone GLP 1 within 2 minutes.

Multi Organ Pleiotropic effect:

The main procedure of glp 1 agonist receptor starts when you eat something the food that you intake goes to your stomach then to your intestine and inside your intestine there are specialised cells that are L-cells also called entero endocrine cell that are responsible for the secretions of glp 1 it Is an incretine Hormone that is produced by the these L-cellsthese cells have specialised receptors and that can sense amino acids ,fats and glucose and when they sense that food is coming these secrete hormone and this glp 1 hormone is a messenger that gives message to the whole body that food has come and there should be some settlement for the by product of food.

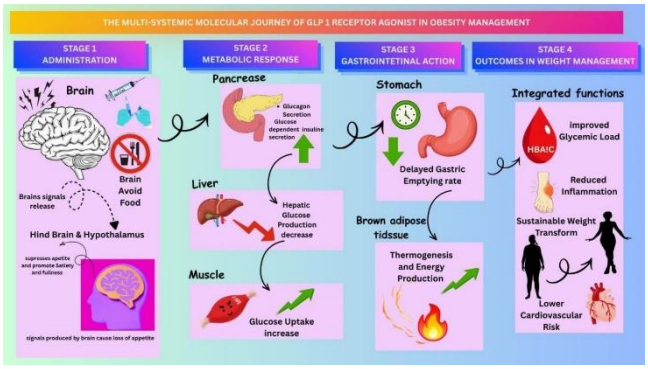


Fig. 1: Mechanism of Glp 1 agonist and peliotropic effect in body

Pancrease:

Glp 1 goes inside pancrease islets and acts on the Beta cells of the pancreas and gives signals for the entrance inside beta cells and bind with G protein that is present inside the beta cell by combining with G protein adenyline cycles start to form cyclic amp that is called cAMP this cyclic amp promote the function PKA (Protein Kinase A) aur EPAC2 (Exchange Protein Activated by cAMP 2) these two molecules are responsible for the opening of the calcium Gates and the excretion or elimination of insulin from the Beta cells because the insulin is inside the cell and their are Lot of packages of insulin that are present inside the beta cell so the PKA and EC A2 act like 2 switches that control insuline secretion by blocking the potassium Gate because during normal condition potassium Gates become open and potassium moves outside the cell and th ecell remains shunt and there will be nagivte charge along membrane but when the potassium channels gets blocked potassium ratio is getting increase inside the Beta cells so due to the increase amount of potassium inside the cell create a de polarization stage or create a voltage around the cell membrane and due to this voltage a specific condition at which enable opening of calcium channels and this opening of Calcium channel enable calciums ions CA2+ to goes inside the cell and bind with the SNARE protein (a protein helps small vesicles to bind with target membrane) and when the calcium come inside the cell and combining with these protein it will create insulin to get attach to the membrane and when Insulin gets attached with the cell membrane then insuline goes outside in the blood with the aid of process called exocytosis and insulin goes to the Transporter(blood) this insulin move all around the body and take glucose and gives to the cell for the final fate of glucose either storage in the form of glycogen in liver or utilization by cells [2].

Brain:

Glp 1 Agonist working is not stop here after this it will goes to the brain with the help of blood and then to the control centre of the brain that is called hypothalamus that have two contradictory neurons POMC (Pro-opiomelanocortin) and NPY (Neuropeptide Y), AgRP (Agouti-Related Peptide) Specialised opposite neuron population Located in arcuate nucleus

together they act as a switch board in melanocortin system that control our hunger, Metabolism, sotiety and weight.
The first one is a appetite suppressor and the second one is appetite promoter glp 1 excite the appetite suppressor and try to deactivate the appetite promoter and due to this appetite supression the body don't want to eat further and the person stop because these neurons secrete signals of fullfillness and their would be no craving and no extra intake of food.

Stomach:

Glp 1 don't stop there rather this it will go to the stomach lining and And give signals to the internal muscular wall of the stomach that you should delayed food and you should increase the delaying process of food so that the stomach empyting rate will be slow down and food remains in stomach for very long period of time so there will not hidden anger or there will be a feeling of fullfilness.

Liver:

Glp 1 in liver act in a both way directly or indirectly firstly it signals the pancreas Alpha cells to stop secreting the enzyme glucagon and suppress its secretion secondly with the help of Vegas nerve it signals the liver that you don't release extra glucose in the blood so there should not be sudden glucose Spikes in the blood In this result fasting blood sugar level goes down.[3]

Heart health:

There are glp one receptors that are present inside the endothelial lining of the heart cells and when glp bind with these receptors it will allow the secretion of nitric oxide against that not only dialate our blood vessel but also keep the flow of the blood in a smooth way and also decrease pressure on our heart and ultimately reduced the risk of heart attack, heart stroke or other CVD related issue that are very prevalent in present situations .

Adipose tissues:

When glp 1 goes to adipose tissues there are two types of fats white fat and brown fat the white fat store extra energy but the brown fatburn calories generate heat by the process calle d non shivering thermogenesis. It also regulate our blood glucose level.Firstly the glp 1 goes to hypothylamus in activate we VMH receptor this receptor than goes to sympathetic nervous system and release hormone and take this nonepinephrine into fat cells and enable their conversion of white fat into brown fat Another major factor of fat conversion is ucp protein found in white fat this UN coupling protein force white fat To convert into brown fat by producing heat despite of ATP.

Kidney:

Glp 1 when comes to Kidneys it will block the pump that is called NH3 (sodiumHydrogen exchanger 3) that is located on the proximal tube of the nephron due to this blockage the Sodium and water excreted out by urine from our body and levels of sodium goes down that will also very helpful in blood pressure regulation . It is also helpful in the patients that are dealing with CKD (chronic kidney disease).

Clinical efficacy:

Semaglutide(Brand Name:Wegovy,Ozempic)

Wegovy is used for weight management and ozempic is for Type 2 diabetes treatment but salt that is semaglutide is present in both. Week 1-4:2.4mg once in a week if tolerable week 5-8:0.5mg Week 9-12:1mg/week week13-16:1.7mg

Trizepatide(Brand Name:Manjaro and Zepbound)

It is a dual receptor agonist and in clinical trials it is more efficient than semaglutide first 4 week :2.5mgthan 5mg than 7.5mg than 10mg,12.5 mg.

Gastrointestinal Effects:

The most common and recurring side effects of GLp 1 agonist are :Nausea,vomiting, diarrhoea and ,constipation.[4]

GLP 1 Agonist supplements and their daily value

It is crucial to know that it is not a dietary supplement,powder aur pills or an OTC (over the counter medicine) that can be given to any one without proper guideline rather it is prescription based powerful medicine/peptides can be given only if recommended by specialized endocrinologist and experienced physicians.

As far as its dosage concern so according to STEP(Semaglutide treatment effect in people with obesity)this clinical trial conducted by major program named as Novo Nordisk the main purpose of this study is to check the weight loss and health outcomes after giving 2.4 mg dosage of semaglutide to obese pateints.the findings show that there is 14%-15% loss in weight without serious complications after that it get official approval for universal usage. On the other hand SORMOUNT(Study of understanding relative to metabolic outcomes with unicellular/dual agonist treatments)is a clinical trial conducted by a program name as Eli Lilly by a company in which trizepatide efficacy was analyzed.according to clinical research mentioned above there dosages usually given according to specific titration schedule so that body can adjust according to it or there should be minimum side effects.[5]

Body Composition:

When a person lose weight along fat loss there is also muscle loss if we neglect doors of the supplements If there is only fat loss and there is no lean mass lost then that would be an ideal weight loss but if the doors and quantity of these supplements is higher then serious consequences can be seen even it can be proved fatal The weight loss that is done with the help of glp 1 receptors agonist he is about 20 to 40% due to lean mass loss Due to this muscle loss metabolic rate of patient would be decreased And patient me feel weakness Two void this a high protein diet and sterness exercise these two things are recommended strictly when glp 1 is administrad [6]

The weight regain challenge:

Obesity is not a temporary issue rather it is a chronic disease like diabetes and And blood pressure according to recent studies Step 4 and s u r mount When patient Leave their medicine after 1 year there would be two by three increase in their weight It is very Crusher to understand that glp on Is not a permanent treatment or cure of vesity rather it is a management that helps us to maintain a healthy body weight and liver healthy life When you stop taking medicine your appetite will goes again you feel hunger slidely greater than the last one Like hypertension for obesity management these medicines maybe taken lifelong [7]

Prohibition in certain cases:

Scientific research has been conducted on rodents and it would be seen clearly that the rodents that have thyroid issue leads to cancer because glp 1 more stimulate the c cells of the thyroid and it would become rather it was rare in human beigs but due to security concerns FDA wecarcinoma ekly band to individuals that are dealing with meduallry Thyroid carcinoma MTC and labelled as Black Box warningPerson having medullary thyroid carcinoma and MEN 2 (Multiple endocrine neoplasia syndrome) disease are strictly prohibited to take this medicines for obesity management.
In case of pregnant and lactating women and type 1 diabetes [8.

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