

COMMENTARY

Benefits of GLP-1 Agonists

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Introduction

Glucagon-like peptide-1 (GLP-1) agonists, are a class of medications which are utilized in the treatment of type 2 diabetes, and obesity. The body naturally produces the hormone GLP-1 when the gut is stimulated by the consumption of food.¹ Type 2 diabetes can cause many health issues such as heart disease, foot problems and chronic kidney disease (CKD).² GLP-1 drugs work by mimicking the GLP-1 hormone that the body would naturally produce in three ways. First, stimulates release of insulin from the pancreas after eating. Second, inhibits the release of a hormone called glucagon, which stimulates the liver into releasing sugars that have been stored in the bloodstream. Third, it slows absorption of glucose into the blood by reducing the speed at which the stomach empties after consuming food, which makes you feel satisfied, extending the sensation of feeling full after eating.³ These effects combine, keeping your blood sugars down, supporting other benefits of taking a GLP-1 drug.

Metabolic Benefits

Metabolism is a balancing act involving two kinds of activities that go on at the same time. The first is a build-up of body tissue and energy stores, known as anabolism. The second activity consists of

storing energy to get more fuel for the body's functions, known as catabolism. Metabolism is focused on building and storing. It supports the growth of new cells, storing all energy for future use. In anabolism, small molecules transform into larger, more complex molecules of carbohydrates, protein, and fat. The use of GLP-1Ras (glucagon-like peptide-1 receptor agonists) has significantly increased cardiovascular activity in patients with type 2 diabetes. This new antidiabetic drug class has decreased cardiovascular mortality and promotes lifespan. Some benefits include decreased blood pressure values, weight reduction, and improvement of dyslipidemia (abnormal amount of lipids in the blood), improvements of blood circulation potentially increasing nitric oxide levels inhibiting clotting factors, such as thromboxane A2, selectins, and vascular cell adhesion molecules.² Reducing hepatic lipogenesis and augmenting mitochondrial oxidative capacity increases energy expenditure and brown adipose tissue. A study done by Holst JJ showed that Tirzepatide dose-dependently lowered triglyceride, apoC-III, and apoB levels over time as well as reduced the number of large triglyceride-rich lipoprotein particles and small low-density lipoprotein particles compared to dulaglutide and/or placebo. These findings indicate increased insulin sensitivity and a shift toward a less atherogenic lipoprotein profile in subjects with T2D treated with tirzepatide, with potential implications for cardiovascular safety.

Cardiovascular Benefits

Glucagon-like peptide-1 (GLP-1) has been linked to being beneficial in aiding the improvement in the human body. One of those benefits is helping cardiovascular health. The GLP-1 receptor has been found in all four chambers of the heart. It has been shown that GLP-1 is favorable in lowering triglycerides and cholesterol in the blood.³ The wide variety of benefits have been shown to improve the quality of life of those with and without diabetes, each with varying cardiovascular diseases, killing thousands of people every year. Cardiovascular disease (CVD) or heart disease, continues to be the predominant cause of mortality in the United States. It claimed the lives of 928,741 individuals in 2020 and took approximately 695,000 lives in 2021, representing 1 out of every five deaths nationwide, this computes to one death every 33 seconds.⁴ Cardiovascular disease affects all ethnicities, but some groups are more at risk than others, such as African Americans, and Hispanic Americans are more likely to develop CVD than Caucasians. Both men and women are at risk of CVD but men can develop it at a younger age than women. However, for women, the risk of CVD increases after menopause.⁵ Moreover, the mortality rate of men and women who succumb to cardiovascular disease is significantly correlated to the high cost of treatment for these diseases.

Finding alternative treatments for cardiovascular disease, such as the GLP-1, can aid clinicians in improving patients' health and relieving the potential financial burden placed on a patient and their overall quality of life. This combined with healthy lifestyle choices can further improve the patient's health outcome resulting in a change in the condition of the patient when they finish their treatment. The Agonism of the receptor has been shown to improve the endothelial function. The theoretical mechanisms of the anti-atherosclerotic effects of the agents would change the amount of force the heart would have to exert to pump blood throughout the cardiovascular system. Clinical studies have shown a reduction in intracellular calcium overload of high stress and glucose-induced apoptosis. This means that patients would have a reduced risk of heart related conditions and diseases. It does not have an effect on hospitalization admission based on heart complications. Overall, this evidence suggests that Glucagon-like peptide-1 (GLP-1) can be an effective treatment to improve cardiovascular health.

Neurological Benefits

The nervous system is one of the most important systems in the human body due to its many functions such as sending signals to the rest of the body to maintain homeostasis. The benefits of glucagon-like peptide-1 on the nervous system are numerous including, but not limited to, prevention of conditions such as Alzheimer's, anti-addictive properties, and affects the relationship that the body has with food.

Alzheimer's

Alzheimer's is a brain disorder in which neurofibrils, which are responsible for sending messages in the brain, get tangled due to an overproduction of beta-amyloid peptides.¹⁰ It is usually characterized by the loss of memory that people experience. After studies conducted on male rats, it was determined that GLP-1 improved spatial memory in mice.¹⁰ Spatial means relating to space in an environment; spatial memory functions as a remembrance of objects in relation to a room as well as correlating objects to others based on function. This means that administration of a GLP-1 agonist could potentially improve memory function in persons with Alzheimer's disorder. Moreover, GLP-1 agonist liraglutide has been shown to cross the hematoencephalic barrier where, besides the GLP-1 receptor activation, it has pleiotropic neuroprotective effects which could represent a viable use for the treatment of neurodegenerative diseases and after intra- cerebral hemorrhage. The regulation of GLP-1 agonists indirectly nourishes cells through the process of glycolysis; models of astrocytes in persons with Alzheimer's disease show that they are lacking this process which is why they develop the disease in the first place.¹⁰

Anti-addictive properties

There are copious amounts of research into the effect that GLP-1 agonists have on addictions such as alcohol use disorder, or AUD, primarily done on non-human mammals. The GLP-1 agonists that have shown the most promising results are exenatide and liraglutide. A human clinical trial, which was terminated due to the then ongoing COVID-19 pandemic, on the effects of Exenatide on substance use disorders, such as alcohol and nicotine, has shown promising results.¹¹ Some of the results that could be analyzed showed that when exposed to GLP-1 agonists such as exenatide, dulaglutide, and liraglutide many subjects in the clinical trial reported a decrease

in their use of their preferred substance to abuse of.¹¹ The results from recent clinical trials show favorable results against substances such as cocaine and alcohol. However, most of the studies that have been conducted are either ongoing or are not conducted on human subjects, which limits the availability of information.

Relationship with food

The human body is constantly working to maintain homeostasis through the different body systems. In order to maintain proper levels of nutrients and energy, the nervous system releases hormones that make a person feel 'hunger' so that food can be ingested. Once there are enough nutrients or food to be digested there is a decrease in hormone levels which leads to someone feeling 'full' or satiated.¹² One of the peptide hormones that is released is GLP-1 agonists. This is why this peptide is normally recommended for obesity and weight loss. GLP-1 agonists mobilize the afferent vagus nerve in order to release the nucleus tractus solitarius preproglucagon (NTS PPG) and nucleus tractus solitarius dopamine beta-hydroxylase (NTS DBH).¹² NTS PPG is used in order to generate major hormones and NTS DBH starts the process of altering dopamine into norepinephrine. Norepinephrine is used to maintain proper blood levels in the body. This in turn reduces the quantity of food consumption as well as meal portions.

Endocrine Benefits

The endocrine system is made up of the hypothalamus, pituitary gland, thyroid gland, adrenal glands, parathyroid glands, pineal gland, thymus, and pancreas. It has important functions like releasing hormones that can control metabolism, growth, reproduction, and sleep.¹³ Yet, its interaction with the GLP-1 hormone has shown to have benefits including weight loss, increased fertility in women with Polycystic ovary syndrome (PCOS), and strengthening the immune system against diseases.

Reduced risk of cancer

The endocrine system is intricately linked with other systems of the body, including the nervous and immune systems. For example, the thymus is an organ associated with the immune system that helps fight off infections by controlling white blood cells, while the brain, specifically the hypothalamus, maintains homeostasis by sending a signal to the pituitary gland to correct that abnormality.¹⁴ As a result of this homeostatic loop, the pituitary gland releases hormones that cause the body's temperature

to rise to fight off the infection. Antigens entering the body through the environment or via vaccines, trigger a response by immune cells by activating "natural killer" (NK) cells. These play the role of a natural vaccine that is produced by the body's immune system, without the prior introduction of foreign antigens to trigger that immune response.¹⁵ They do this by spotting and destroying mutated cells throughout the body, in effect also helping to prevent the spread of cancer cells. In this scenario, obesity can be problematic by disrupting these cells, putting overweight individuals at higher risk of cancer. Although GLP-1 drugs are traditionally prescribed to people with type 2 diabetes, it has also been shown to cause weight loss, which has a positive effect on patients with obesity by restoring "natural killer" (NK) cells that improve the immune system. In a study done at Mayo Clinic, researchers followed the progress of twenty obese participants who were prescribed a semaglutide (GLP-1) once weekly for over six months. The results of this study found that these patients had improved NK cell function.¹⁶ Separate from just weight loss, GLP-1 agonists have preventative benefits by helping to reduce the risk of cancer, one of the many detrimental complications associated with obesity.

Increased fertility

Obesity can lead to many other health complications, including its association with polycystic ovary syndrome (PCOS). Polycystic ovary syndrome is an endocrine disorder where the hormone androgen is secreted excessively, producing cysts within the ovaries. PCOS affects females and can cause infertility, weight gain, insulin resistance, and heart issues, among other medical difficulties.¹⁷ Insulin resistance in some women with PCOS puts them at higher risk for developing type 2 diabetes due to the body not being able to use the insulin produced by the pancreas effectively. The etiology behind this is complex, with one reason thought to be related to pancreatic beta cell dysfunction, but a combination of many genetic factors and metabolic processes in the body are thought to be involved.¹⁸ Fairly new, but limited, shows that GLP-1 agonist semaglutide aids in not only weight reduction in PCOS patients but also is correlated with the reproductive system.¹⁹ This by extension increases fertility since it helps reduce inflammation and fibrosis in the ovaries.¹⁹

Although limited, this research is an encouraging start that proves more studies are needed to investigate GLP-1 and how it has far-reaching benefits beyond the scope of treating diabetes and can

be used to treat other complex endocrine disorders such as PCOS as well.

Reduction of diabetes risk

Due to the necessity for the normal developmental process and maturity of vertebrates as well as its ability to control metabolism, growth, and development, the thyroid is a significant gland in the system known as the endocrine system. Thyroid hormones exhibit a variety of effects on the heart, muscles, and digestive system. The rate of heartbeat and cardiac contraction is increased by the thyroid, which enhances both the systolic and diastolic activity of the heart. This prolongs life expectancy and lowers the risk of myocardial infarction while also enhancing the quality of life.²⁰

A main condition people get from their endocrine system tends to be diabetes. Diabetes comes in two different types: The likelihood of acquiring type 1 diabetes is increased by geography, age, genetics, and family history. With type 2 diabetes, on the other hand, the human body either becomes resistant to insulin or stops generating sufficient insulin; another difference is that type 2 diabetes develops mostly through genetics, advanced age, sedentary lifestyle, bad dietary lifestyle, and obesity.

Despite the fact that it might seem like a person has no symptoms or visible indicators of the condition, it may take weeks, months, or even years before one can be certain that they have type 1 diabetes. It can happen as a result of an autoimmune reaction in which beta cells assault the pancreas and destroy insulin. Since human bodies convert food into glucose after eating and release it into the blood, insulin is crucial to the human body. Then, insulin aids in transferring the glucose from the blood into cells, where it can be used as an energy source now or in the future. Patients with type 1 diabetes do not produce enough or any insulin, which prevents the glucose from entering the cells and accumulating in the bloodstream rendering the energy useless.

Since insulin is so important to humans, type 1 diabetes's lack of it disrupts the entire process of how humans obtain energy. Many GLP-1 users report feeling more invigorated after taking the drug; this experience indicates that the drug is working as intended to increase glucose in human bodies. Conversely, Type 2 diabetes has an adverse effect on a number of important organs, the kidneys, blood vessels, nerves, eyes, and heart.²⁰ Additionally, risk factors for diabetes may raise the chance of other

serious illnesses. Controlling blood sugar and managing diabetes can reduce the risk of these problems and other illnesses. Despite the many risk factors, there are several approaches to fight this illness, including raising the standard of living, more physical activity, and the intake of semaglutide. Semaglutide is prescribed to some individuals who are at risk of getting diabetes because it aids in weight loss, which lowers the risk of developing diabetes. When blood sugar levels start to rise after eating, these medications may also encourage the body to produce more insulin. The extra insulin helps lower blood sugar levels. Lower blood sugar levels can aid in the management of type 2 diabetes.²¹

Benefits for the Liver

The liver is both an organ and a gland that is roughly the size of a football and the color is reddish-brown, however, the size changes according to a person's weight and height. The liver is a vital organ that carries out numerous tasks required for life support. Since it produces proteins and hormones that are required by other bodily components, this makes it a gland. The liver is the biggest internal organ, weighing about three pounds in an adult. The liver is located in the upper abdomen and is responsible for several biological processes such as removing all toxins from the body's blood, helping regulate blood sugar, and helping blood clotting.³⁰ Fatty liver disease is one of the most common diseases that can harm the liver. Obesity, diabetes, and heavy alcohol consumption are among the components that can lead to fatty liver. Toxin-like effects of fatty liver can cause inflammation in the liver cells and lead to the development of cirrhosis.

Anyone who suffers from liver disease or in particular "Non-Alcoholic fatty-liver disease" can get benefits from taking GLP-1 agonists. The fatty liver disease is a disease that builds up fat around the liver which causes several health issues within the whole body. Symptoms of fatty liver disease often include, Abdominal pain or a feeling of fullness in the upper right side of the abdomen (belly). Nausea, loss of appetite or weight loss. Yellowish skin and whites of the eyes (jaundice). Swollen abdomen and legs (edema). To diagnose NAFLD and distinguish between NAFL and NASH, doctors employ blood testing, imaging tests, and occasionally liver biopsies. For blood testing, you give a blood sample, then send that specimen to a lab. If your blood test results reveal an elevated amount of the liver's enzymes alanine aminotransferase, or ALT, and the aminotransferase

aspartate (AST), your doctor may assume you have NAFLD.²⁷

Another liver disease is cirrhosis. Cirrhosis mainly affects people who are overweight, drink too much alcohol, and have viral hepatitis. Fatigue, bruising, bleeding, appetite decrease, nausea, edema, weight loss, rough skin, jaundice, ascites, spider-like blood vessels, red palms, pale fingernails, clubbing, menopause, sex desire, testicular atrophy, gynecomastia, breast enlargement, and fuzziness can all be symptoms of this condition.

A previous study observed mice with NASH and were given cotadutide which led to improvements in liver histology, including decreases in steatosis, inflammation, and fibrosis.³³ This evidence suggests that GLP-1 Agonists can have a positive effect on liver disease and can directly lower hepatic lipogenesis and increase mitochondrial oxidative capability while also indirectly improving the clinical components of NASH. GLP-1 can enhance liver function, fat content and distribution, and lipid metabolism while lowering the activity of inflammatory cytokines and the signal transduction pathways connected to the hepatocytes which helps the liver decrease the chance of leading to Cirrhosis. Additionally, since adipose liver poses a risk to life, lowering the fatty tissue, GLP-1 can even improve the conditions of fatty liver by reducing steatosis. The liver has repeatedly been reported to be a target for GLP-1.³¹ GLP-1 receptor agonists are a new medication that mimics insulin in the human body. They have great effects such as reducing inflammation and improving insulin in the body. This medication is often given by injection and well tolerated, it can also have side effects more commonly as nausea and vomiting.³²

Gastrointestinal Benefits

The gastrointestinal (GI) system, also known as the digestive system, is a vital part of the human body that plays an important role in maintaining overall health and well-being. Its importance consists of several specific functions that human bodies need, such as digestion, nutrient absorption, gut microbiota balance, and hormone production.³⁸ The gastrointestinal system's proper functioning is essential for the maintenance of good health, immune function, energy production, and overall vitality. Any disruptions or disorders in this system can lead to various health issues and impact the body's ability to function correctly, such as a leaky gut affecting gut permeability as well as overall intestinal barrier function.

Colonic Permeability Improvement

GLP-1 may play a role in maintaining the integrity of the gut barrier. This could involve supporting the tight junctions between the cells of the intestinal lining, which prevent the leakage of harmful substances into the bloodstream.³⁵ Conditions such as leaky gut, where the lining of the intestines becomes more permeable than normal, allowing substances such as bacteria, toxins, and undigested food particles to leak from the intestines into the bloodstream, can benefit from the administration of the GLP-1 agonists.³⁵ The connection between the brain and the GI tract, also known as the blood-brain-barrier, is accessed through a hormone called Orexin that is released when administered the GLP-1 agonist. Although orexin is a naturally produced hormone by the brain's hypothalamus which controls the body's energy, appetite, and wakefulness, injection of the GLP-1 agonist aids in orexin action potential, which in turn helps support decrease colonic hyperpermeability.^{34,36} Through this action potential, the brain can affect the function of gut microbiota through the autonomic nervous system, by balancing regional gut motility, intestinal transit and secretion, and gut permeability, and potentially through the secretion of hormones, such as epinephrine, that proportionally affect microbial gene expression, which shows promise of aiding in both the symptoms from an individual with leaky gut syndrome, involving stomach bloating and intestinal permeability, as well as someone with Irritable bowel syndrome, consisting of bowel inflammation and constipation or diarrhea.^{37,39}

Conclusion

Many individuals considered low-income as the lower-middle class will not have as much availability to medications such as GLP-1 agonists due to the cost and the type of health insurance they may have. Additionally, while there are many benefits there are also risks that are associated with this medication, however, more research needs to be done to accurately assess how much it can damage a person's body as well as if the effects are reversible or permanent. Moreover, this form of medication used on the human body is recent so the effects that this medication may have as a person's age progresses is still unknown. Furthermore, there is also a judgment that may be passed by society due to the implications that taking medication may have. However, there is also a need for more studies to fully grasp this medication's effect on the entire human body. For instance, there are still

organs that need to be studied to successfully record the effects of medications such as GLP-1 agonists

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