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RESEARCH ARTICLE

Effects of Obesity on Human Health and the Emerging Role of GLP-1 Based Therapies

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ABSTRACT: Obesity is a chronic disease whose effects are growing daily. The effects of the disease spread through the entire body, making it one of the leading causes of death internationally. Recent drug discoveries have found new pathways in the gastrointestinal tract that can be targeted to promote weight loss and reduce the effects of obesity on the population. This is a novel addition to the current weight loss treatments. This paper will review the biological mechanisms behind Glucagon-like peptide-1 (GLP-1) based therapies and their effects on obesity treatment. We will begin by discussing the emergent need to research the field of obesity through a global health lens. We will discuss the economic impacts as well as the causes and effects of this disease. Then, we will discuss the current treatment landscape, addressing any disparities and drawbacks with current treatment options. Following this the paper will go in-depth about different gastrointestinal hormones, such as GLP-1, GIP, and Glucagon, being used to treat this chronic disease. This article is intended to give an overview of GLP-1-based therapies and the effect it has on various biological activities relating to obesity.

KEYWORDS: Transitional Medical Sciences, Disease Treatment and Therapies, Obesity, Endocrine system, GLP-1, Weightloss.

Introduction

Obesity is one of the most prevalent diseases worldwide. This chronic illness is characterized by an excess accumulation of adiposity, which can arise from a long-term excess of positive energy intake over expenditure, driven by a complex interaction between the Endocrine System and the Central Nervous System. The World Health Organization categorizes a person as overweight if their body weight is above the ideal range where their Body Mass Index (BMI) is between 25 and 30, while a BMI greater than 30 is considered obese. Moreover, a study done by WHO showed that 2.5 billion adults are overweight, and 890 million people suffer from obesity. Since the 1990s, the number of adults with obesity has doubled, and the number of adolescents with the disease has more than quadrupled.[1] The effects have found that close to 2.8 million people die each year due to obesity-linked diseases.[2] Many countries with rising Gross Domestic Product (GDP) and socioeconomic situations are seeing a rise in obesity rates as the increasing income of the population allows them to purchase greater amounts of energy-dense food. Economic growth leads to an increase in overweight and obesity in developing countries, where a 1% increase in income leads to around a 0.2 and 0.3% increase in overweight and obesity prevalence.[3] The World Health Organization's research further indicates that in countries with income in the upper to high-income ranges, 20-30% of the population have obesity, as seen in Figure 1. In contrast, lower-income countries see a much lower percentage, around 10%. It has become clear that as the world becomes more affluent, so does the number of people with obesity.[4] World-renowned news outlets like the New York Times and NPR have written articles about the obesity epidemic that the world is confronted with. Obesity is now a major global public health issue. This has led to research and investment from scientists and the government to develop strategies to prevent and treat this burgeoning epidemic. One newly emerging treatment for obesity comes in the form of peptide drugs, working to mimic the role of essential hormones such as Glucagon-like peptide-1 found in the digestive system. Part of its revolutionary essence is due to the strong results it yields and the vast room for further development.[5] It is currently one of the most prescribed drugs on the market and is steadily growing in popularity.

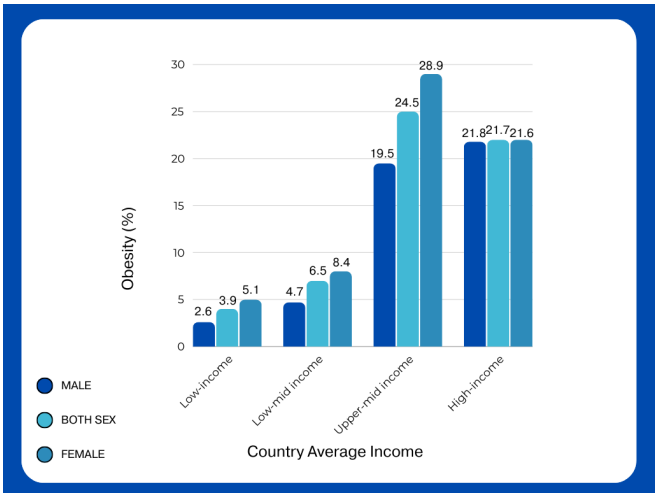

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Figure 1: Counties Average Income Versus the Percentage of Obesity in the Nation. This figure depicts the prevalence of obesity across countries with varied income levels, showing higher obesity rates in upper and high-income countries compared to significantly lower rates of obesity in low-income countries. The figure visually highlights the relationship between a nation's economic status, measured by the average income made by families in the nation, and the proportion of the country affected by obesity. Adapted from Bhurosy, T., & Jeewon, R. (n.d.). Overweight and obesity epidemic in developing countries: a problem with diet, physical activity, or socioeconomic status? Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4212551/. Created by Canva.

Genetic Links to Obesity:

Over the past two decades, there have been studies that have found that there are polymorphisms and genetic mutations that cause a predisposition for being overweight. Genetic conditioning of obesity has created three different types of obesity: monogenic, polygenic, and syndromic. [6]

Monogenic obesity is caused by a gene mutation that alters the leptin-melanocortin pathway.[7] The leptin-melanocortin system (LMS) exerts major control on appetite and insulin production. Leptin is an appetite-controlling hormone that is secreted by adipocytes and β-cells. It is signaled to the melanocortin 4 receptor (MC4R). This is how the signal crosses the blood-brain barrier and promotes a sense of satisfaction in the body. People with high levels of fat cells can eventually develop leptin resistance, which signals to the hypothalamus that the body still needs food.[8] Monogenic mutations cause severe obesity starting at a young age and feature hyperphagia (extreme hunger). A medication called Setmelanotide is an MC4R agonist that has been found effective in managing the symptoms of monogenic obesity as it helps promote satisfaction signaling in the body.[9] Polygenic obesity is caused by simultaneous genetic mutations that have a conglomerative effect on the body. Some of the common mutations include that in the minor alleles of the polymorphisms coding for isoleucine instead of valine at amino acid position 103 (103I) and for leucine instead of isoleucine at position 251 (251L) of the receptor protein are negatively associated with obesity.[10] Many of these genes affect the insulin cycle in the body and play a part in the nervous and digestive systems. Each mutation causes a small effect, but their build-up can harm the body in the wrong environment. Syndromic obesity is characterized by developmental disorders, often caused by disruptions in neurodevelopment, and involves a variety of genes and biological pathways that can cause dysmorphic features[11] and organ abnormalities.[12] Since there are so many different combinations of genetic factors that can make a person predisposed to obesity, there is a lack of drugs targeted at genetics to solve this issue. Instead, Researchers are working to tackle obesity using drugs that mimic hormones found naturally in the body.[8]

Other factors also contribute to obesity, including physical inactivity, excessive caloric intake, and intrauterine development.[7] Previous research about obesity showed that the disease was a simple imbalance of energies, meaning more calories were going in than out. However, the energy-based model of obesity was quickly disproven as scientists developed the carbohydrate-insulin model. This model shows how the digestion of carbohydrates, through the production of insulin and hormones, can cause an increase in fat deposits.[13] Excess levels of adiposity are vastly influenced by controllable and uncontrollable factors, but the effects of inflammation in the gut are pernicious.

Diseases Linked to Obesity:

Obesity leads to various complications, such as diabetes, cardiovascular diseases, and even some types of cancers, which lead to high mortality rates. The correlation between high adiposity and inflammatory cytokines is high since when excess nutrients are in the system, adipocyte cells release more cytokines such as IL-6, TNFα, C-reactive protein (CRP), IL-18, resistin, and visfatin. [14] These cytokines affect many of the body's organ systems and cause cellular function deterioration due to their signaling power. Cytokines are proteins that move chemicals and send signals to the immune system. An excess of cytokines can lead to autoimmune disorders, causing the body to attack its healthy cells.[15]

Heart disease, in any form, whether that be heart attacks, heart failure, or angina (chest pain due to a lack of oxygen-rich blood), can be exacerbated by obesity. This is due to raised levels of leptin, which causes high blood pressure, or overconsumption of food, which causes lipid abnormalities.[16]

Some forms of cancer have been linked to obesity, as the disease is caused by the abnormal and uncontrolled growth of cells in the body. Adipose tissue is a known producer of estrogen, high levels of which have been seen to cause breast cancer.[17] Additionally, obese women are at an increased risk for developing cancers of the endometrium (uterine lining) and gallbladder, while obese men have higher susceptibility to cancers of the colon, rectum, and prostate.[18] These risks are partly due to the inflammatory processes associated with visceral fat, which can disrupt hormone regulation and alter cellular life cycles, increasing the likelihood of malignant transformations.[19]

Many studies have shown that people affected by obesity are at greater risk of developing Type 2 Diabetes (T2DM). T2DM is caused by multiorgan insulin resistance in parallel with β-cells secreting less insulin. β-cells in the pancreas typically secrete insulin directly to the portal vein, which travels to the liver effectively to control the liver's glucose metabolism. People with obesity typically have an impairment in the ability of insulin to suppress liver glucose production. Increased liver glucose production occurs when the increased secretion of insulin is inadequate to compensate for insulin resistance.[20]

Obesity and T2DM also have adverse effects on liver fat metabolism and are a major cause of fatty liver disease. In fact, around two-thirds of adults with either obesity or T2DM are diagnosed with nonalcoholic fatty liver disease (NAFLD), largely due to an increase in triglyceride production.[21]

Circulating insulin also plays a crucial role in the movement of glucose into the cells, enabling the formation of ATP molecules that can be used as energy in the body. Obesity leads to insulin resistance, so the circulating insulin cannot act upon the cells effectively. This inhibits the entry of glucose into cells, which are depleted of energy, and a rise in blood glucose levels, resulting in diabetes. While initially, insulin resistance results in a compensatory increase in insulin secretion, the pancreatic β-cells ultimately become exhausted. This leads to a combina-

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tion of insulin resistance and deficiency, resulting in progressively worsening diabetes.[22]

People with higher numbers of adipocytes have the metabolic flexibility to adjust to changes in energy balance. They can adjust to more long-term changes in energy balance, and adipose tissue can expand or shrink accordingly. Studies suggest that excess abdominal fat causes fat cells to release 'pro-inflammatory' chemicals, which can produce insulin resistance. Thus, having excess abdominal fat (i.e. a large waistline) is known as central or abdominal obesity, a particularly high-risk form of obesity.[23]

Obesity is a disease with widespread impacts across multiple physiological systems, including the nervous and muscular systems, as illustrated in Figure 2 below. This comprehensive influence on the body's systems underscores the importance of targeted medical interventions, which hold significant potential to improve quality of life and long-term health outcomes.

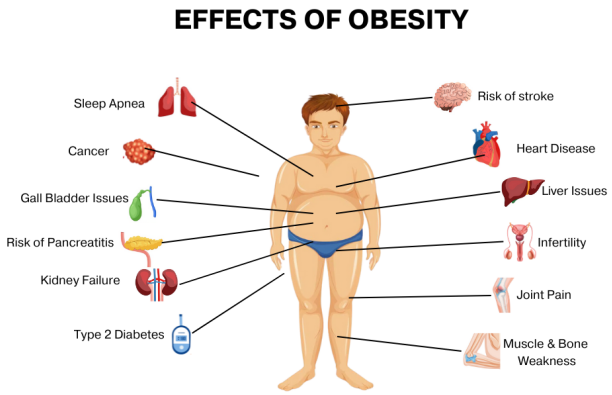

Figure 2: Effects of Obesity on Different Body Systems. This figure highlights the extensive health risks associated with obesity, showcasing its impact on multiple organ systems. The figure underscores the systemic nature of obesity as a chronic illness and its role as a major contributing factor to a wide range of comorbidities. Created by Canva and Biorender, information gathered by https://pmc.ncbi.nlm.nih.gov/articles/PMC3096264/

Current Treatment Landscape:

Due to the detrimental effects of excess fat on the body, researchers have worked to create and test drugs and strategies since the 1990s that assist individuals in reducing weight and subsequently decreasing their risk of certain illnesses. Many of these drugs have different mechanisms of action, so patients can take the drug most appropriate to their situation.

A major function of weight loss treatments is appetite suppression. Drugs such as Benzphetamine stimulate the nervous system, specifically the hypothalamic and limbic areas of the brain, which together control satisfaction while also increasing the amount of energy used by the brain. These medications are typically prescribed alongside a reduced-calorie diet and daily exercise. These are prescribed more for short-term use due to their addictive nature.[24] Historically, obesity was seen as only a cause of overeating with little to no pathological ties, which is why drugs that have previously been approved to fight the disease are used short-term. These drugs have dosing that will last around 12 weeks, which is about the time it takes to build a new habit.[25]

One of the most effective treatments that is available for obesity, and consequently diabetes, is bariatric surgery. There are several types of bariatric surgery. In one popular method, the surgeon divides your small intestine and connects the shorter part to the stomach. In turn, the body will absorb less calories from the food. This surgery also changes the hormonal levels and bacteria in the digestive system, which affects metabolism and appetite. Patients who have received this surgery can see results that show immediate stabilization of insulin levels, resulting in diabetic markers such as blood sugars returning to normal range. This surgery is also reversible if needed.[26]

Drugs with high lipophilicity (highly soluble compounds that have permeate properties allowing them to transfer through the body effectively)[27] can be used as a treatment for obesity because they function as lipase inhibitors. Lipase is an enzyme responsible for breaking down fats in the digestive system. By inhibiting lipase, these drugs reduce the fat absorbed from the diet. So, when a drug with high lipophilicity acts as a lipase inhibitor, it can effectively reduce fat absorption in the intestines. This means that less dietary fat is absorbed into the body, which can help reduce overall calorie intake and promote weight loss. The inhibitors use a compound called tetrahydrolipstatin, which disrupts the body's process of breaking down triglycerides. Many gastric lipases found locally in the stomach and the small intestines covalently bond with the compound, restricting triglyceride from breaking down into fatty acids. [28]

Role of Gastrointestinal Hormones :

Hormones in the Gastrointestinal Tract (GI) play a pivotal role in controlling insulin and glucose actions. In response to food intake, Glucagon-like peptide-1 (GLP-1) is released, stimulating insulin secretion and regulating blood glucose levels by delaying gastric emptying, which maintains a steady supply of nutrients and glucose to the bloodstream, creating glucose homeostasis. This helps control postprandial (postmeal) glucose levels and promotes satiety, thus limiting further food intake.[29] GIP and GLP-1 promote β-cell proliferation and inhibit apoptosis (cell death), thereby increasing pancreatic β-cell mass. GIP enhances postprandial glucagon response, while GLP-1 suppresses it. In adipose tissues, GIP but not GLP-1 facilitates fat deposition.[30] The final essential protein in the GI tract is glucagon, which signals the liver and muscle cells to convert the stored glycogen back into glucose.[31] Drugs that use these pathways are very effective in weight loss and T2DM treatments.

GLP-1 Therapeutics:

GLP-1, an incretin hormone, stimulates insulin secretion after food is consumed, delaying gastric emptying.[32] Gastric emptying is the process of food moving from the stomach into the duodenum, ensuring that the nutrients and glucose consumed are delivered through the digestive system in a limited and consistent way. By slowing gastric emptying rates, GLP-1 produces a lingering sense of fullness in the stomach and restrains further food intake. Gastric motor functions are also impacted by acute changes in blood glucose levels. There is an inverse relationship between blood glucose levels and the rate of gastric emptying. During hyperglycemia (high blood sugar),

GLP-1 is secreted, and gastric emptying slows down, thus preventing further movement of glucose into the bloodstream.[33]

In addition, GLP-1 can inhibit glucagon production from the α-cells in the pancreas. If blood glucose levels are out of normal range, the presence of glucagon helps ensure they drop back to normal levels. Glucagon triggers the liver to convert stored glucose into a usable form and release it into the bloodstream by a process called glycogenolysis.[34] A summary of these processes can be seen in Figure 3. The various mechanisms of GLP-1 can be used to decrease caloric intake and stabilize energy creation in the body, helping reduce weight.

As seen previously, there is a clear link between T2DM and Obesity. Many T2DM treatments currently on the market are revolutionary since GLP-1 targets both the stabilization of blood sugar and a decrease in appetite.

Drugs like semaglutide, available by the brand names Ozempic® and Wegovy®, are GLP-1 receptor agonists (RA) that mimic GLP-1 and can activate GLP-1 receptors.[35] For obesity, these drugs have been shown to cause substantial weight loss, often about 15% of one's body weight. This amount is drastically more than other weight loss techniques and medication used in the past to battle obesity.[36] More importantly, this class of drugs has been seen to lower both systolic and diastolic blood pressure while also decreasing total cholesterol, all of which assist in shielding the body from heart disease caused by excess adipose tissue.

Some additional functions of GLP-1 drugs include increased glucose intake in muscle cells, decreased glucose production in the liver, and increased neural satiety due to stimulation of the hypothalamus.[37]

Mechanism of action

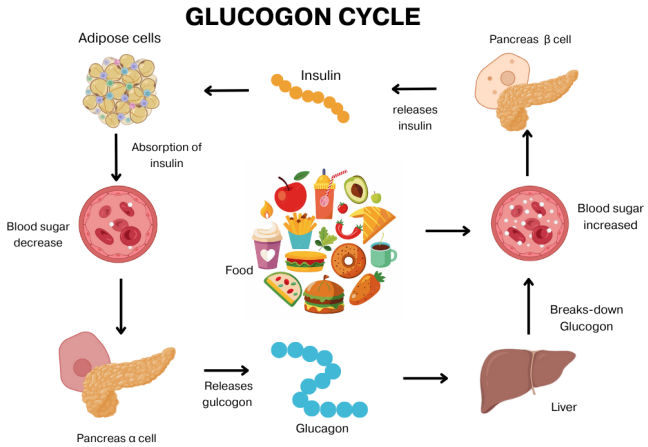

Figure 3: The Functions of the Glucagon Cycle. This figure illustrates the glucagon cycle, depicting the dynamic interplay between insulin and glucagon in regulating blood sugar levels, providing a visual aid for understanding the systems and pathways through which Obesity drugs impact the human body. Adapted from https://old-ib.bioninja.com.au/standard-level/topic-6-human-physiology/66-hormones-homeostasis-and/insulin-and-glucagon.html. Created by Canva and Biorender.

Metabolism:

Semaglutide, a generic name for the drugs Ozempic and Wegovy, uses GLP-1 RA channels to target various aspects of glucose metabolism. The drug is mainly given subcutaneously, allowing rapid absorption into the bloodstream, with peak concentrations reaching within hours. Once absorbed, GLP-1 RAs exhibit a low volume of distribution, meaning they primarily remain within the bloodstream, which is critical for their targeted effects. These medications selectively bind to GLP-1 receptors located in tissues involved in glucose regulation. Their ability to remain concentrated in the bloodstream and selective binding allows the drug to yield effective results. Native GLP1 is naturally broken down in the body through various pathways. Enzymes such as Dipeptidyl Peptidase-4 (DPP-4) and Neutral Endopeptidase (NEP) have proven to play roles in this metabolic process, leading to the formation of smaller, biologically inactive fragments that are subsequently eliminated. The drug semaglutide is resistant to the action of the DPP4 enzyme. Being a polypeptide, it is metabolized into individual amino acids by serum and tissue proteases, ensuring complete breakdown without residual active metabolites. The kidneys play a pivotal role in clearing GLP-1 medications from the body, and the rate of renal excretion significantly influences their duration of action and dosing frequency. Unlike other GLP-1 medications, Semaglutide stands out due to its extended-release (ER) profile, which provides a significantly prolonged half-life compared to shorter-acting formulations like Exenatide.[37]

Blood-Brain Barrier:

Native GLP-1 has been found in the Central Nervous System (CNS), showing that the hormone and the drug replicating it also have the power to pass the Blood Brain Barrier (BBB). BBB is a selective semipermeable membrane between the blood and the interstitium. It is comprised of capillary cells covered by various connective tissues such as tight junctions, basal lamina, pericytes, and tightly packed astrocytes. Tight Junctions (TJs) restrict the movement of substances through the paracellular aqueous diffusion pathways between adjacent endothelial cells. Their adhesive properties function to seal microvessels, thereby limiting the passive diffusion of proteins and polar solutes. Pericytes, located in the capillary basement membrane, play a crucial role in angiogenesis, supporting the formation and stability of blood vessels. They contribute to microvessel integrity by regulating endothelial cell function, promoting the formation of TJs, and controlling vascular permeability. Astrocytes are types of Glial cells found on the axon of neurons and allow for the passage of informational signals. This assists in regulating material passing between nerves and blood vessels that ultimately connect the brain and spinal cord to the body and help the brain maintain homeostasis. The semipermeable nature of BBB restricts the movement of large molecules from passing through to protect the brain from unwanted molecules and bacteria from entering. However, many GLP-1 drugs have been designed to meet the sizing standards by increasing levels of circulating free fatty acids, inflammatory cytokines (TNF-α, IL-1β, IL-6), and chemokines, which increase BBB permeability. GLP-1 is also expressed in the arcuate nucleus and paraventricular thalamic nucleus of the hypothalamus, both of which control food intake. The crossing of GLP-1 RA through the BBB promotes weight loss by

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acting on those nuclei, signaling satiety earlier, thus causing appetite reduction.[38]

Side Effects:

Medications that yield such high success rates of weight loss also have many side effects. It is often up to the doctor to prescribe the medication and the patient to decide what is best for them. Gastrointestinal side effects include nausea, vomiting, diarrhea, and constipation. These are the most common and mild effects, and they can be controlled with increased water intake or little changes in diet. There are, however, more serious side effects, some of which are pancreatitis, inflammation of the pancreas causing abdominal discomfort; gastroparesis, the slowing or stopping of the food movement in your stomach; bowel obstruction; gallstones; and bile duct blockages. These would need to be treated by a medical professional and may entail the patient stopping the mediation for a period of time.[5]

Dual Pathway Medication:

Tirzepatide is a dual antigen medication that works to promote weight loss and insulin stabilization through two pathways: GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. It has been found to maximize benefits similar to GLP-1 medications and is typically used second in line with GLP-1 drugs. The FDA approved this medication in May 2022 for the treatment of T2DM.[39]

GLP-1 and GIP are very similar incretin hormones. GIP is a 42-amino-acid hormone secreted from K-cells in the small bowel; however, it significantly affects the gastrointestinal (GI) tract. Both hormones attach to their respective receptors. [40]

Metabolism:

Tirzepatide is currently administered intravenously (IV) and has not yet been converted to oral form. Some companies are currently formulating an oral version of this medication to serve as an easier form of weight management. After injection, the body will absorb about 80% of the medication and will reach its peak absorption in 8 to 72 hours. When injected, the peptide structure of the medication undergoes a process of Metabolization, which breaks down peptide bonds in proteins using enzymes called proteases, peptidases, or proteolytic cleavage enzymes, which evenly distribute it and get absorbed by the body. The waste is cleared from the body about five days after injection.[39]

Future Research:

As the prevalence of T2DM and obesity grows in the human race, scientists in the field are working to make more developments in the drug world. While the most recent breakthrough has been the discovery of GLP-1 drugs and even dual pathway medication, work is being done to release Triple–Hormone-Receptor Agonists for public use. Retatrutide is a drug in Phase 2 of clinical trials and works on three hormone pathways: GLP-1, GIP, and the new edition, glucagon.[41] During clinical trials, this triple agonist resulted in a mean weight reduction of 24.2% after 48 weeks, which is more effective than single or double-antigen drugs.[42] In addition to this, Retatrutide has shown immense reducing weight in individuals with nonsyndromic obesity, which is a condition characterized by early onset severe obesity due to genetic mutations.[43] This drug has the potential to save lives when research on it is completed. Additionally, other novel pathways that may yield similar results are ones that work on Amylin. This hormone is secreted alongside insulin and acts on amylin receptors in the brainstem in response to nutrient stimuli. It is elevated in T2DM patients and regulates gastric emptying. It may be possible to activate the release of this hormone and its receptor, which may cause a decreased rate of gastric emptiness, a similar effect that GLP-1 RA drugs create. Thus, it may make the pipeline more efficient and promote more significant weight loss in patients with obesity.[44] Other emerging therapies that may become more prevalent in this field include nanotherapy: the application of biological molecules smaller than 100 nm in size. They would have the power to target the same GI pathways in a more selective manner, exceeding the abilities of current pharmaceutical drugs. However, at present, no Nanotherapy drugs have been approved for clinical testing.[45] As researchers gain a deeper of the ever-growing field of the Endocrine System, it will serve as a preemptive step in solving one of the world's most prominent diseases— Obesity.

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References

1. World Health Organization. *Obesity and overweight*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2. World Health Organization. *Obesity*. World Health Organization https://www.who.int/news-room/facts-in-pictures/detail/6-facts-on-obesity.
3. Bu, T.; Popovic, S.; Huang, H.; Fu, T.; Gardasevic, J. Relationship between National Economic Development and Body Mass Index in Chinese Children and Adolescents Aged 5–19 from 1986 to 2019. *Frontiers in Pediatrics* **2021**, *9*. https://doi.org/10.3389/fped.2fped.2021.671504.
4. Bhurosy, T.; Jeewon, R. Overweight and Obesity Epidemic in Developing Countries: A Problem with Diet, Physical Activity, or Socioeconomic Status? *The Scientific World Journal* **2014**, *2014*, 1–7. https://doi.org/10.1155/2014/964236.
5. Catanese, L. *GLP-1 diabetes and weight-loss drug side effects*: Harvard Health. https://www.health.harvard.edu/staying-healthy/glp-1-diabetes-and-weight-loss-drug-side-effects-ozempic-face-and-more.
6. Loos, R. J. F.; Yeo, G. S. H. The Genetics of Obesity: From Discovery to Biology. *Nature Reviews Genetics* **2021**, *23* (23), 1–14. https://doi.org/10.1038/s41576-021-00414-z.
7. Masood, B.; Moorthy, M. Causes of Obesity: A Review. *Clinical Medicine* **2023**, *23* (4), 284–291. https://doi.org/10.7861/clinmed.2023-0168.
8. Baldini, G.; Phelan, K. D. The Melanocortin Pathway and Control of Appetite-Progress and Therapeutic Implications. *Journal of Endocrinology* **2019**, *241* (1), R1–R33. https://doi.org/10.1530/joe-18-0596.
9. Pressley, H.; Cornelio, C. K.; Adams, E. N. Setmelanotide: A Novel Targeted Treatment for Monogenic Obesity. *Journal of Pharmacy Technology 2022, 38* (6), 368–373. https://doi.org/10.1177/87551225221116010.

10. Hinney, A.; Vogel, C. I. G.; Hebebrand, J. From Monogenic to P olygenic Obesity: Recent Advances. *European Child & Adolescent Psychiatry* **2010**, *19* (3), 297–310. https://doi.org/10.1007/ s00787 -010-0096-6.
11. Machado, L.; Augusto, A.; Débora Romeo Bertola; Cristina, A.; Rosenberg, C. A Comprehensive Review of Syndromic Forms of Obesity: Genetic Etiology, Clinical Features and Molecular Diag nosis. *Current Obesity Reports* **2024**. https://doi.org/10.1007/s136 79-023-00543-y.
12. Chung, W. K. An Overview of Mongenic and Syndromic Obesit ies in Humans. *Pediatric Blood & Cancer* **2011**, *58* (1), 122–128. h ttps://doi.org/10.1002/pbc.23372.
13. Ludwig, D. *The carbohydrate-insulin model: a physiological perspecti ve on the obesity pandemic*. Science Direct. https://www.sciencedire ct.com/science/article/pii/S0002916522005172#:~:text=In%20th e%20%20carbohydrate%2d%20Insulin%20model,drive%20a%20 %20positive%20energy%20%20balance.
14. Khanna, D.; Rehman, A.; Welch, B. S. *Pathophysiology of Obesity*. PubMed. https://www.ncbi.nlm.nih.gov/books/NBK572076/.
15. Cleveland Clinic. *What are Cytokines? Types and Function*. *Clevela nd Clinic*. https://my.clevelandclinic.org/health/body/24585-cyto kines.
16. Artham, S. M.; Lavie, C. J.; Milani, R. V.; Ventura, H. O. Obesity and Hypertension, Heart Failure, and Coronary Heart Disease—Risk Factor, Paradox, and Recommendations for Weight Loss. *The Ochsner Journal* **2024**, *9* (3), 124.
17. National Cancer Institute. *Obesity and Cancer*. National Cancer Institute. https://www.cancer.gov/about-cancer/causes-preventio n/risk/obesity/obesity-fact-sheet.
18. National Institute of Diabetes and Digestive and Kidney Disease s. *Health risks of overweight & obesity*. National Institute of Diabet es and Digestive and Kidney Diseases. https://www.niddk.nih.go v/health-information/weight-management/adult-overweight-ob esity/health-risks.
19. Underferth, D. *How does obesity cause cancer?* MD Anderson Can cer Center. https://www.mdanderson.org/publications/focused-o n-health/how-does-obesity-cause-cancer.h27Z1591413.html.
20. Fabbrini, E.; Sullivan, S.; Klein, S. Obesity and Nonalcoholic Fat ty Liver Disease: Biochemical, Metabolic, and Clinical Implicatio ns. *Hepatology* **2010**, *51* (2), 679–689. https://doi.org/10.1002/he p.23280.
21. National Institute of Diabetes and Digestive and Kidney Disease s. *Definition & Facts of NAFLD & NASH*. National Institue of Di abetes and Digestive and Kidney Diseases. https://www.niddk.ni h.gov/health-information/liver-disease/nafld-nash/definition-fac ts.
22. Klein, S.; Gastaldelli, A.; Yki-Järvinen, H.; Scherer, P. E. Why D oes Obesity Cause Diabetes? *Cell Metabolism* **2022**, *34* (1), 11-20. https://doi.org/10.1016/j.cmet.2021.12.012.
23. Hardy, O. T.; Czech, M. P.; Corvera, S. What Causes the Insulin Resistance Underlying Obesity? *Current Opinion in Endocrinology & Diabetes and Obesity* **2012**, *19* (2), 81–87. https://doi.org/10.10 97/med.0b013e3283514e13.
24. *Are Prescription Appetite Suppressants Right for You?* Cleveland Cl inic. https://my.clevelandclinic.org/health/treatments/9463-appe tite-suppressants.
25. Coulter, A. A.; Rebello, C. J.; Greenway, F. L. Centrally Acting A gents for Obesity: Past, Present, and Future. *Drugs* **2018**, *78* (11), 1113–1132. https://doi.org/10.1007/s40265-018-0946-y.
26. National Institute of Diabetes and Digestive and Kidney Diseas es. *Types of Bariatric Surgery | NIDDK*. National Institute of Diab etes and Digestive and Kidney Diseases. https://www.niddk.nih.g ov/health-information/weight-management/bariatric-surgery/ty pes.
27. Stoner, C.; Troutman, Matthew; Laverty, C. *Pharmacokinetics and ADME optimization in drug discovery.* Science Direct. https://ww w.sciencedirect.com/science/article/abs/pii/B9780123694485500 094.
28. Fyfe, M. N*on-systemic Intestine-Targeted Drugs*. Science Direct. Direct. Non-systemic Intestine-Targeted Drugshttps://www.sci encedirect.com/science/article/abs/pii/S0079646815000168.
29. Shah, M.; Vella, A. Effects of GLP-1 on Appetite and Weight. *R eviews in endocrine & metabolic disorders* **2014**, *15* (3), 181–187. ht tps://doi.org/10.1007/s11154-014-9289-5.
30. Khan, R.; Tomas, A.; Rutter, G. Effects on pancreatic *Beta and ot her Islet cells of the glucose-dependent insulinotropic polypeptide.* Scien ce Direct. https://www.sciencedirect.com/science/article/abs/pii/ S0196978119301792#:~:text=GIP%20stimulates%20insulin%20 secretion%20through,MAPK%20and%20arachidonic%20acid% 20pathways.
31. Susan York Morris. *How Insulin and Glucagon Work*. Healthline. https://www.healthline.com/health/diabetes/insulin-and-glucag on#working-together.
32. Horowitz, M.; Wishart, J. M.; Jones, K. L.; Hebbard, G. S. Gastr ic Emptying in Diabetes: An Overview. *Diabetic Medicine: A Journ al of the British Diabetic Association 1996, 13* (9 Suppl 5), S16-22.
33. Collins, L.; Costello, R. A. *Glucagon-like peptide-1 receptor agonis ts*. PubMed. https://www.ncbi.nlm.nih.gov/books/NBK551568/.
34. Cleveland Clinic. Glucagon: *What It Is, Function & Symptoms*. C leveland Clinic. https://my.clevelandclinic.org/health/articles/22 283-glucagon.
35. *The Medical Minute: What to know about Ozempic and weight loss drugs*. Penn State Health News. https://pennstatehealthnews.org/ 2024/07/the-medical-minute-what-to-know-about-ozempic-an d-weight-loss-drugs/.
36. T*he Ozempic Effect: Everything You Need to Know About Medical Weight Loss | Columbia Surgery*. Columbiasurgery.org. https://colu mbiasurgery.org/news/ozempic-effect-everything-you-need-kno w-about-medical-weight-loss#:~:text=Drugs%20like%20Ozemp ic%20may%20help.
37. Collins, L.; Costello, R. A. *Glucagon-like peptide-1 receptor agonis ts.* PubMed. https://www.ncbi.nlm.nih.gov/books/NBK551568/.
38. Dong, M.; Wen, S.; Zhou, L. The Relationship between the Blood-Brain-Barrier and the Central Effects of Glucagon-like Peptide-1 Receptor Agonists and Sodium-Glucose Cotrans porter-2 Inhibitors. Diabetes, Metabolic Syndrome and Obesity: *Targets and Therapy* **2022**, *15*, 2583–2597. https://doi. org/10.2147 /DMSO.S375559.
39. Farzam, K.; Patel, P. *Tirzepatide*. PubMed. https://www.ncbi.nl m.nih.gov/books/NBK585056/.
40. Seino, Y.; Fukushima, M.; Yabe, D. GIP and GLP-1, the Two In cretin Hormones: Similarities and Differences. *Journal of Diabetes Investigation* **2010**, *1* (1-2), 8–23. https://doi.org/10.1111/j.2040-1124.2010.00022.x.
41. Naeem, M.; Imran, L.; Banatwala, U. E. S. S. Unleashing the Po wer of Retatrutide: A Possible Triumph over Obesity and Overwe ight: A Correspondence. *Health Science Reports* **2024**, *7* (2), e1864. https://doi.org/10.1002/hsr2.1864.
42. Jastreboff, A. M.; Kaplan, L. M.; Frias, J. P.; Wu, Q.; Du, Y.; Sirel Gurbuz; Coskun, T.; Haupt, A.; Milicevic, Z.; Hartman, M. L. Tr iple–Hormone-Receptor Agonist Retatrutide for Obesity —a Ph ase 2 Trial. *The New England Journal Of Medicine* **2023**, *389* (6). https://doi.org/10.1056/nejmoa2301972.
43. *Orphanet: Genetic non-syndromic obesity*. Orpha.net. https://www. orpha.net/en/disease/detail/98267#:~:text=Disease%20definition (accessed 2024-09-07).
44. Ludvik, B.; Kautzky-Willer, A.; Prager, R.; Thomaseth, K.; Paci ni, G. Amylin: History and Overview. Diabetic Medicine: *A Journ*

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al of the British Diabetic Association **1997**, *14 Suppl 2*, S9-13. https://doi.org/10.1002/(sici)1096-9136(199706)14:2+3.3.co;2-4.
45. Angelidi, A.; Belanger, M.; Kokkinos, A.; Koliak, C.; Mantzoros, C. *Novel Noninvasive Approaches to the Treatment of Obesity: From Pharmacotherapy to Gene Therapy*. Oup.com. https://academic.oup.com/edrv/article/43/3/507/6407704?login=false (accessed 2024-11-12).

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