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Review Article

Exploring Semaglutide Effects on Osteoarthritis in Obesity: Emphasis on Weight Management and Inflammatory Responses

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ABSTRACT

Obesity frequently makes Osteoarthritis (OA), a degenerative joint disease, worse by increasing systemic inflammation and mechanical stress. Semaglutide is a medicine that helps people with type 2 diabetes and obesity. It works by making people lose weight. Recently, many researchers have been looking into how it might help in other ways. They want to know if it can be used for more than just weight loss and diabetes treatment. Semaglutide dual function in slowing the course of OA by encouraging substantial weight loss and modifying inflammatory pathways is examined in this review. Recent data indicates that semaglutide - induced weight loss reduces joint load, and its anti-inflammatory qualities may have a direct impact on the pathophysiology of OA. Gaining insight into these processes may help develop combined therapy plans that address OA and obesity.

Keywords: Semaglutide, Osteoarthritis, Obesity, Weight loss, T2DM.

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INTRODUCTION

Osteoarthritis (OA) is a common degenerative joint disease that is marked by the deterioration of cartilage, changes in the subchondral bone, and ongoing inflammation, which considerably affects the quality of life in affected individuals. Obesity is a well-established risk factor for OA, not only due to increased mechanical load on weight-bearing joints but also due to systemic metabolic and inflammatory changes. Obese people have more fat tissue in their bodies. This fat tissue releases chemicals called pro-inflammatory cytokines. Two important ones are Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α). These chemicals make joint inflammation worse. They also help break down cartilage in the joints. This leads to more pain and problems for people with Osteoarthritis (OA).[1] Semaglutide is a new drug that helps treat obesity. It works by acting on a specific receptor in the body. This drug is called a long-acting glucagon-like peptide-1 receptor agonist, or GLP-1 RA for short. One of its key features is its long half-life. This means it stays in the body for a long time. Because of this, patients can take it through a simple injection under the skin. This makes it easier to use and helps many people manage their weight better, and its mechanism include promoting insulin production in response to glucose, inhibiting glucagon, delayed stomach emptying, and controlling appetite. When these effects are combined, obese patients experience significant and long-lasting weight loss.[2] Recent research shows that semaglutide helps with weight loss. It also has a positive effect on inflammation in the body. This means it can reduce swelling and pain. People who take semaglutide may feel better overall. It is an exciting discovery for those looking to manage their weight and improve their health, positioning it as a beneficial addition to the treatment of osteoarthritis related to obesity. Its capacity to reduce systemic inflammation by modulating adipokine levels and the production of inflammatory cytokines could ease joint pain and decelerate the progression of OA.[3] This review delves into the potential therapeutic benefits of semaglutide for treating osteoarthritis in obese patients, highlighting its mechanism, its success in encouraging weight loss, and its new role in reducing inflammatory mechanisms involved in OA development.

PATHOPHYSIOLOGY OF SEMAGLUTIDE

Semaglutide is a medication that belongs to a group called GLP-1 receptor agonists. The incretin effect happens when certain hormones in your gut are released after you eat. These hormones are called incretins. They help your pancreas make more insulin. Insulin is important because it helps control your blood sugar levels. So, when you eat, incretins boost insulin production to keep your body balanced. DPP4 is an enzyme that works fast. It quickly turns off two important hormones called incretins.

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These hormones are released by K-cells and L-cells. The two incretins are gastric inhibitory peptide, or GIP, and glucagon-like peptide-1, known as GLP-1.[4] These incretins are released into the bloodstream and attach to their receptors after meals. The location of GIP and GLP-1 receptors in different tissues and organs is directly related to their physiological effects. The pancreas, brain, and adipocytes are among the tissues and organs that express GIP Receptors (GIPRs), of which the gastrointestinal tract, brain, and pancreas are rich in GLP-1 receptors. These tissues and organs are essential for controlling glucose and lipid metabolism.[5] While both incretins increase the production of insulin, GLP-1 is more efficient at doing so. It also inhibits the production of glucagon, lowers hepatic gluconeogenesis, increases insulin sensitivity, delays the emptying of the stomach, and increases satiety, all of which help people lose weight.[6] GLP-1 helps your body make more insulin when you eat. It does this by working with a special receptor in your cells. This process also reduces the chance of having low blood sugar. So, GLP-1 is important for keeping your blood sugar levels stable that is found on pancreatic α- and β-cells as well as other tissues. In addition, GLP-1 decreases apoptosis, boosts β-cell mass, and either directly or through the stimulation of insulin and somatostatin, inhibits glucagon secretion. Furthermore, GLP-1 inhibits fast glucose absorption by slowing stomach emptying, which is essential for controlling postprandial glucose levels.[7]

MECHANISM OF ACTION

Through a cAMP-dependent PKA mechanism, semaglutide mainly promotes glucose-dependent insulin synthesis and secretion by supplying two insulin signaling pathways: the PI3K/AKT pathway in combination with the AMPK/SIRT1 route and the PI3K/PKA/mTOR pathway in β-cells. Together, GIP and GLP-1 maintain healthy adipocytes, decrease ectopic fat distribution, and increase adipocyte synthesis and secretion of adiponectin by directly stimulating lipogenesis and indirectly promoting lipolysis.[8] In people with type 2 diabetes and obesity, two incretins help maintain metabolic homeostasis by preventing hyperglycemia and hypoglycemia, reducing dyslipidemia, and lowering the risk of cardiovascular illnesses.[9]

GLP-1 and the incretin effect are frequently decreased in T2DM patients, whereas GIP secretion may be elevated. A decrease in β-cell function, susceptibility to incretins, and/or hyperglycemia are associated with this lowered impact. The antidiabetic benefits of GLP-1 are not enhanced by GIP, although exogenous GLP-1 increases insulin secretion in T2DM. Incretin-based treatments extend GLP-1 activity by targeting DPP4 inhibitors and GLP-1 mimetic.[10]

OBESITY ASSOCIATED OSTEOARTHRITIS

Osteoarthritis (OA) associated with obesity is a complicated biopsychosocial disorder that raises patient morbidity and mortality rates and puts more financial strain on the health care system. By increasing the load and impact on the knee's articular cartilage, obesity may be causing fibrillation and degradation, according to the biomechanical mechanism. Conversely, metabolic pathways imply that systemic metabolic variables may also contribute to knee osteoarthritis in addition to mechanical load.[11]

Biomechanical mechanism

Mechanical stress on joints

The homeostatic balance between the anabolic and catabolic processes is maintained by chondrocytes, which is why the Extracellular Matrix (ECM) of cartilage changes slowly under normal physiological conditions. Joint tissues, like articular cartilage and subchondral bone, can change in many ways. They can change in composition, shape, metabolism, and mechanical properties. These changes can happen due to one strong impact or from repeated stress over time. Both types of loading can affect how joints work. ECM splitting, subchondral bone remodeling, increased cellular activity, and tissue hydration are all results of impact stress.[12] By increasing the expression of cytokines, growth factors, and metalloproteinases, mechanical stimulation of these mechanoreceptors may result in the production of mediators, including prostaglandins and nitrous oxide. These procedures could result in further tissue deterioration, inflammation, and oxidative stress at the knee joint.[13] In chondrocytes and cartilage, pro-inflammatory cytokines, including IL-1 and TNF-α, are momentarily elevated following traumatic injury. While fluid shear stress promotes the creation of proteoglycans, mechanical stress leads to the production of Nitric Oxide (NO), PGE2, and IL-6 by chondrocytes. It is noteworthy that chondrocytes in their native Extracellular Matrix (ECM) show higher levels of pro-inflammatory mediators during stressful situations, in contrast to those in an agarose matrix, highlighting the impact of ECM interactions. Furthermore, fibroblast-like synoviocytes that are mechanically stretched release pro-inflammatory factors (COX-2, PGE2, and IL-1β).[14]

Muscle weakness

Muscles help preserve joint stability by absorbing shock during joint action. Joint stability is impacted by muscle weakness because it causes high articular contact stress, dissipates joint loads, and reduces shock absorption. Because the quadriceps muscle was weaker, the articular cartilage may have been under more stress, which might cause the joint to gradually deteriorate.[15]

Metabolic Mechanism

Obesity and osteoarthritis in the knee may be related through metabolic processes. Adiponectin, resistin, and leptin are among the adipokines that mediate inflammation. Plasma had greater amounts of adiponectin and resistin than synovial fluid, although synovial fluid had higher levels of leptin than plasma.[16]

Adipocytokines

Bioactive substances called adipocytokines are mostly secreted by WAT. Adipocytokines play a crucial part in the pathophysiology of metabolic syndrome and in the metabolism of bone tissue, helping to differentiate bone marrow cells into osteoblasts. Certain adipocytokines may also directly contribute to the maintenance of an inflammatory state (referred to as a low-grade inflammatory state) in obese people's joints. Patients with OA have been found to contain these proteins in their plasma and Synovial Fluid (SF). Adipocytokine secretion in the knee joint region may be attributed to the Infrapatellar Fat Pad (IPFP). The state of the joint is then further deteriorated by the combination of the exterior action and the adipocytokine production inside the joint.[17]

Leptin

Leptin is a hormone that comes from fat cells. The name "leptin" comes from the Greek word for "thin." It was the first hormone discovered that comes from fat cells, also called adipocytes. Most leptin is made in white adipose tissue, or WAT. This protein is about 16 kDa in size and is not modified by sugars. It is produced by a gene known as the obese gene. Leptin acts like other hormones that help regulate the body. Higher amounts of body fat and a higher body mass index, or BMI, usually mean more leptin in the body. However, its production can also be affected by inflammation in the body.[18] It was initially identified as a hormone that regulates appetite and satiety. It causes people to eat less, which stimulates the hypothalamus to produce anorexigenic factors and suppresses orexigenic factors, which results in a feeling of fullness. By lowering blood glucose levels, it also promotes thermogenesis and energy expenditure. A higher risk of developing OA is associated with obesity, mostly because of excessive joint loading. Long-term obesity affects how leptin works in the body. This change can harm the subchondral bone. However, it does not change the levels of inflammatory cytokines. Thus, leptin activity is linked to the pathophysiology of OA through leptin-mediated inflammatory processes. Leptin affects cells in both humans and mice. It increases the levels of important proteins and enzymes. These include Phosphoinositide 3-Kinase (PI3K), IL-1b, and inducible Nitric Oxide Synthase (NOS2). Leptin also boosts certain Mitogen-Activated Kinases (MAP). These are MEK1, Extracellular Signal-Regulated Kinases (ERK) 1/2, p38, and c-Jun N-terminal Kinases (JNK). This means that leptin plays a big role in how these cells work. Leptin can boost the production of certain proteins in human cartilage. It does this by activating key pathways in the body. These pathways are called NF-kB, PKC, and MAP. When leptin activates these pathways, it increases the levels of MMP-1, MMP-3, and MMP-13. These proteins are important for cartilage health, especially in Osteoarthritis (OA). All of these findings suggested that the leptin axis, which controls the immunological and musculoskeletal systems, is a crucial mediator between obesity and OA.[19]

Adiponectin

The polypeptide adiponectin is made up of 244 amino acids. It is also known as AdipoQ, GBP28, apM1, or Acrp30. It is produced by the liver, placenta, adipocytes, myocytes (in reaction to oxidative and/or metabolic aggression), epithelial cells, osteoblasts, and pituitary cells. There are three types of adiponectin in the blood. The first type is called trimer. It has a low molecular weight. The second type is hexamer, which has a mid-molecular weight. The last type is dodecamer, and it has a high molecular weight.[20] The two main adiponectin receptors are AdipoR1 and AdipoR2. The brainstem, pituitary gland, muscles, and hypothalamus have a lot of AdipoR1. On the other hand, the liver, astrocytes, and cortex show higher levels of AdipoR2. AMPK, p38-MAPK, JNK, nuclear factor-κB, and PPAR-α are more closely connected to AdipoR1 activation. These connections are important for understanding how the body works. The development of OA has been linked to adiponectin. Adiponectin levels in serum and plasma were noticeably higher in OA patients. There was a correlation found between local synovial inflammation, OA biomarkers, and blood levels of adiponectin. Aggrecan breakdown has been linked to the detection of adiponectin in OA synovial fluids. IPFP, osteophytes, cartilage, bone tissues, and synovial fibroblasts may all release this adipokine. Adiponectin increases the production of several important substances in Osteoarthritis (OA) cartilage and human chondrocytes. These substances include Nitric Oxide (NO), interleukins IL-6 and IL-8, VCAM-1, tissue inhibitor of Metalloproteinases (TIMP)-1, and Matrix Metalloproteinases (MMP)-1, -3, and -13. This means that adiponectin plays a significant role in how these cells behave and respond in OA.[21]

Resistin

Resistin is a small protein that weighs 12.5 kDa. It comes from fat tissue and is rich in cysteine. Scientists call it by different names, like XCP1 and ADSF. This protein is important for certain immune cells. The RETN gene provides the instructions to make resistin. It belongs to the "FIZZ (discovered in the inflammatory zone) or "resistin-like molecules" family. Human resistin exists in two quaternary forms: a less common but highly bioactive trimer and a high molecular weight hexamer.[22] Chondrocytes are a type of cell found in cartilage. When they resist a protein called resistin, they produce more cytokines and chemokines. Cytokines and chemokines are important for cell signaling in the immune system. Some of the key ones they produce are TNF-a, IL-6, and IL-12. This process is controlled by two

proteins: NF-kB and C/EBP beta. Together, these proteins help chondrocytes respond better to resistin. In human OA, low shear stress regulated the expression of COX-2 produced by resistin. Chondrocytes are special cells found in cartilage. They respond to signals from AMPK, SIRT1, NF-kB, and CREB. These signals show how resistin activity connects with mechanical shear stress. This means that when there is movement or pressure, these cells react in specific ways. Understanding this interaction is important for studying cartilage health. In SF from OA patients, resistin levels were elevated and corresponded with the amount of resistin released by OA cartilage. In SF, SF resistin has a positive correlation with MMP-1, MMP-3, and IL-6 levels. Given its pro-inflammatory characteristics, correlation with obesity, and impact on chondrocyte activity and bone metabolism, another possible connection between inflammation, OA, and obesity could be this adipokine.[23]

SEMAGLUTIDE AND WEIGHT LOSS IN OBESE PATIENTS

Semaglutide helped adults with obesity and type 2 diabetes lose weight in a phase 2 trial. The results were promising, which led to more studies. Now, there is a large phase 3 study called the Semaglutide Treatment Effect in People with Obesity (STEP). This study aims to see how safe and effective semaglutide is for people who are overweight or obese. It will give the medication at a dose of 2.4 mg once a week through an injection.[24]

Semaglutide helps people lose weight over time. In studies, people taking semaglutide lost more weight than those taking a placebo. This study focused on adults who are overweight or obese but do not have diabetes. It looked at how safe and effective semaglutide is when taken once a week for long-term weight loss.[25] Semaglutide reduces calorie intake, regulates eating, suppresses appetite and hunger, and lessens the relative preference for fatty, high-energy foods. Furthermore, semaglutide's association with obesity has been extensively studied, and the majority of this research shows that semaglutide is effective at helping people lose weight. Overall, semaglutide's pharmacokinetics indicate a decrease in total body weight and glycosylated Hemoglobin A1c (HbA1c).[26]

SEMAGLUTIDE ROLE IN ANTI-INFLAMMATORY EFFECTS

Among other physiological processes, Glucagon-Like Peptide-1 (GLP-1) is linked to hunger, inflammation, and cardiovascular health. Both host healing mechanisms and *in vivo* responses to various threats, such as bacterial and viral infections, depend on acute inflammation. Chronic inflammation can lead to serious health problems. It is linked to type 2 diabetes and metabolic syndrome. It can also cause obesity and cancer. People with arthritis often suffer from chronic inflammation. Additionally, it is related to bowel disorders such as Crohn's disease and ulcerative colitis. GLP-1RAs have anti-inflammatory properties because they affect immune cell signaling, which is mediated by molecular mechanisms.[27] GLP-1 RAs can help control inflammation in the body. This is because immune cells like macrophages, monocytes, and lymphocytes have GLP-1 receptors. When GLP-1 RAs connect with these receptors, they change how immune cells send signals. This change can help reduce inflammation and improve health. GLP-1R stops immune cells from making pro-inflammatory cytokines. These cytokines include IL-6, IL-1β, and TNF-α. By inhibiting these substances, GLP-1R helps reduce inflammation in the body. This can be important for overall health. GLP-1RAs help make anti-inflammatory substances. One of these substances is IL-10. IL-10 reduces inflammation in the body. It also helps bring the immune system back to balance.[28] Inflammatory responses may be triggered by oxidative stress, among other causes. Chronic inflammation and tissue damage can happen when there are too many reactive oxygen species, or ROS. GLP-1RAs help reduce inflammation. They also lower oxidative stress by decreasing the amount of ROS produced. GLP-1RAs lessen inflammation and oxidative stress by lowering the generation of ROS.[29] Inflammation is controlled by a system called the NF-κB pathway. This system also helps create pro-inflammatory genes. GLP-1RA is a treatment that lowers the production of inflammatory substances. It does this by blocking the NF-κB activation. When NF-κB signaling is reduced, the body makes fewer pro-inflammatory cytokines, adhesion molecules, and chemokines. As a result, GLP-1RAs can help decrease inflammation. One reason GLP-1RA is good at reducing inflammation is that it stops the production of pro-inflammatory cytokines.[30]

THERAPEUTIC MANAGEMENT

Adults with a Body Mass Index (BMI) of 30 or higher, or 27 and above with at least one related health issue, can get help for obesity-related osteoarthritis. This includes conditions like high cholesterol, high blood pressure, or type 2 diabetes. They can receive a treatment called semaglutide. It is given as an injection under the skin once a week. This treatment is available in Canada, Europe, the UK, and the USA.[31] For subcutaneous administration, adhere to the following schedule: Begin with 0.25 mg once weekly during weeks 1 to 4, then increase to 0.5 mg once weekly for weeks 5 to 8. For weeks 9 to 12, the dose should be 1 mg once weekly, followed by 1.7 mg once weekly during weeks 13 to 16. Starting from week 17, a maintenance dose of 2.4 mg once weekly should be administered. If a patient is unable to tolerate the maximum dose, consider delaying dose escalation for an additional four weeks.[32]

CONCLUSION

Semaglutide, a GLP-1 receptor agonist, has shown encouraging potential in the treatment of Osteoarthritis (OA) in people with obesity. Its main advantages come from considerable weight loss and the modulation of systemic inflammation-both key

elements in the development and severity of OA. Evidence from both clinical and pre-clinical studies indicates that by reducing mechanical stress on joints and lowering pro-inflammatory cytokines, semaglutide may enhance symptomatic relief and slow down disease progression.[33] Future investigations should focus on randomized controlled trials that evaluate both structural and symptomatic results in OA, differentiated by obesity types and metabolic profiles. Furthermore, looking into combined approaches that integrate semaglutide with physical or regenerative therapies may provide additional benefits. Enhancing our knowledge in this domain could transform treatment approaches for OA in relation to obesity, tackling both mechanical and metabolic factors contributing to disease progression.[34]

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AMPK: Adenosine Monophosphate- activated protein kinase; **BMI:** Body mass index; **cAMP:** Cyclic Adenosine Monophosphate; **COX 2:** Cyclooxygenase; **CREP:** cAMP Response Element Binding protein; **DPP4:** Dipeptidyl peptidase; **ECM:** Extracellular matrix; **ERK:** Extracellular signal/regulated kinases; **GIP:** Gastric inhibitory peptide; **GLP:** Glucagon like peptide; **GLP-1-RA:** Glucagon like peptide -1- receptor agonist; **HbA1C:** Glycosylated hemoglobin A1c; **IL:** Interleukin; **IPFP:** Infrapatellar fat pad; **JNK:** c-Jun N- terminal Kinase; **mTOR:** Mechanistic target of Rapamycin; **MAP:** Mitogen- activated kinases; **MMP:** Matrix Metalloproteinases; **NO:** Nitric oxide; **NOS:** Nitric oxide synthase; **OA:** Osteoarthritis; **PGE2:** Prostaglandin E -2; **PKA:** Protein Kinase A; **ROS:** Reactive oxygen species; **SF:** Synovial fluid; **SIRT:** Sirtuin; **STEP:** Semaglutide Treatment Effect in People with Obesity; **T2DM:** Type 2 diabetes mellitus; **TIMP:** Tissue inhibitors of metalloproteinases; **TNF-α:** Tumor Necrosis Factor-alpha; **UK:** United Kingdom; **USA:** United States of America; **VCAM:** Vascular cell adhesion molecule; **WAT:** White adipose tissue.

SUMMARY

Obesity significantly contributes to the development and progression of Osteoarthritis (OA) by increasing systemic inflammation and mechanical stress on joints. This review explores the emerging therapeutic role of semaglutide, a Glucagon-Like Peptide-1 (GLP-1) receptor agonist, in the management of obesity-associated OA. The semaglutide supports its efficacy in inducing substantial weight loss, thereby reducing joint loading. Additionally, semaglutide exhibits anti-inflammatory properties by modulating adipocytokines such as leptin and resistin, suggesting a potential disease-modifying effect in OA. By targeting both biomechanical and metabolic pathways involved in OA pathophysiology, semaglutide presents a promising dual-action treatment approach. This review also addresses dosing schedules, storage requirements, and clinical considerations, highlighting semaglutide potential for integration into comprehensive management strategies for patients with coexisting obesity and OA.

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