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Review

Obesity, diabetes, and inflammation: Pathophysiology and clinical implications

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SUMMARY

Obesity and its related disorders, including type 2 diabetes and liver, kidney, and cardiovascular diseases, are now recognized as chronic inflammatory conditions. Here, we review the mechanisms underlying inflammation in these settings and how they may contribute to pathology. Nutrient excess triggers immune activation through pattern recognition receptors and the NLRP3 inflammasome, leading to interleukin (IL)-1β production and downstream cytokine cascades. Initially adaptive, this inflammation promotes tissue remodeling and metabolic compensation, but chronic activation contributes to insulin resistance, β cell dysfunction, and end-organ damage. We discuss the current therapeutic options, with a focus on glucagon-like peptide-1 (GLP-1) receptor agonists, which, alone or combined with additional bioactive moieties, exert notable anti-inflammatory effects. Some effects of GLP-1 medicines are independent of glucose control or weight loss, and they are attributed to direct signaling via the immune GLP-1 receptor (GLP-1R) and, indirectly, via central nervous system circuits. Understanding these mechanisms may unlock further therapeutic potential in chronic inflammatory diseases.

INTRODUCTION

It has long been debated whether obesity is a disease or just a risk factor. Recent advances in research emphasize that obesity is a disease in itself, resulting from a combination of physical inactivity, an unhealthy diet, psychosocial and genetic contributions, and poorly understood environmental factors. Obesity is associated with a number of comorbidities, although the far-reaching consequences of obesity are often underestimated. Obesity is one of the major risk factors, along with aging, for type 2 diabetes (T2D) and related cardiovascular diseases, metabolic-dysfunction-associated steatohepatitis (MASH), chronic kidney disease (CKD), retinopathy, and neuropathy.[1] Obesity is also associated with an increased risk for numerous malignancies such as breast, colorectal, endometrial, hepatocellular, and pancreatic cancer as well as multiple myeloma.[2] Obesity also underlies the susceptibility to many chronic diseases, including Alzheimer's disease, gout, sleep apnea, type 1 diabetes, multiple sclerosis, chronic fatigue, and osteoarthritis. This susceptibility extends to infectious diseases, exemplified by COVID-19, the mortality rate of which is dramatically higher in patients living with obesity, and is reduced by medicines that improve metabolic health.[3]

The discovery and widespread clinical use of medicines based in part on enhancing glucagon-like peptide-1 (GLP-1) include GLP-1 receptor (GLP-1R) agonists or GLP-1R agonists combined with one or more additional biologically active components, such as glucose-dependent insulinotropic polypeptide and glucagon receptor ligands, herein termed GLP-1 medicines.[4] These drugs were developed based on the physiological role of GLP-1, an incretin hormone secreted by intestinal L cells. GLP-1 enhances glucose-stimulated insulin secretion, suppresses glucagon release, and slows gastric emptying.[5] GLP-1 also protects insulin-producing β cells from apoptosis. It also has appetite-suppressing effects. Together, these properties provided the rationale for developing GLP-1 medicines for the treatment of T2D and obesity.[4–6]

The robust actions of these medicines to reduce blood glucose and body weight has provided a highly effective medical treatment for obesity and its comorbidities. These drugs have not only changed treatment approaches but have also reduced the stigma associated with obesity. Indeed, the recognition of obesity as a disease and the strong desire of those affected to have access to effective treatment has shown that, in most cases, treatment failure is not simply due to lack of motivation.

Despite the impressive success of GLP-1 medicines in controlling obesity, approximately 10%–20% of patients lose very little weight or do not respond to treatment at all.[7] Furthermore, for the vast majority, it appears that lifelong treatment will be necessary. Even in people who succeed in losing and maintaining their weight, some consequences of obesity persist. This means that even with improved treatment for obesity, its consequences cannot always be completely eliminated.

Obesity and T2D are associated with chronic activation of the immune system.[8] There is increasing evidence that this inflammation plays a critical role in the pathogenesis of obesity and associated complications. In this review, we will discuss the underlying mechanisms of inflammation; how it may contribute to obesity, diabetes, and related disorders; and explain the success of current therapeutic options, with a particular focus on

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the anti-inflammatory effects of GLP-1 medicines independent of weight loss.

MECHANISMS OF ACTIVATION OF THE IMMUNE SYSTEM DURING OBESITY

The immune system functions as a dynamic sensor of both internal and external disturbances, continuously monitoring the body for signs of infection, injury, or metabolic stress. Upon detecting such disruptions, it initiates a coordinated response designed to neutralize the threat and limit tissue damage. This involves the activation of inflammatory pathways, the recruitment of immune cells to affected sites, and the orchestration of repair mechanisms. Ultimately, the goal of the immune response is to reestablish tissue homeostasis, ensuring the proper functioning and integrity of the organism. When this process is well regulated, it is essential for survival and recovery; however, if the response becomes chronic or dysregulated, it can contribute to pathological conditions.[9]

This general concept applies to overnutrition, which causes metabolic stress, i.e., an excess of cellular nutrients. The molecular mechanisms mediating immune activation in obesity are likely to be multifactorial. Some may be tissue specific, whereas others may occur throughout the body with organ-specific development. Initially, macrophages (resident in the tissue and monocyte-derived) play a critical role, but other players, such as neutrophils, platelets, pericytes, and endothelial cells, also contribute.[10–12]

Intracellularly, the NLR family pyrin domain containing 3 (NLRP3) inflammasome appears to be a key sensor of metabolic stress.[13,14] It is primed by signals from Toll-like receptor 4 (TLR4) or interleukin (IL)-1 receptors, initiating nuclear factor κB (NF-κB)-mediated transcription of pro-IL-1β and NLRP3. Saturated fatty acids and lipopolysaccharide (LPS) from a leaky gut, as observed in obesity, activate TLR4. A second activation signal, triggered by the increased metabolism of glucose and other nutrients, is released by overactivated mitochondria.[14–18] This includes ATP or reactive oxygen species (ROS). Hypoxia in rapidly expanding adipose tissue will also lead to ROS production. Crystalline substances formed from cholesterol, uric acid, or human amyloid polypeptide can also act as secondary signals.[19–24] These secondary signals trigger the assembly of the NLRP3 inflammasome, leading to caspase-1 activation, cleavage of pro-IL-1β, and secretion of active IL-1β. In turn, IL-1β induces other cytokines, such as IL-6, IL-8, IL-33, tumor necrosis factor (TNF), and several chemokines.[12,25–27] Several immune cells are then expanded or recruited, the most important of which are key players in innate immunity, namely granulocytes and monocytes.[10,12] These monocytes differentiate into macrophages, which adopt a pro-inflammatory M1-like phenotype, while anti-inflammatory M2-like macrophages and regulatory T (Treg) cells decrease in abundance.[10,12] Other cells, such as type 2 innate lymphoid cells (ILC2s) and other lymphocytes, are numerically less prominent, but this does not mean that their contributions are not important.

Once inflammation is initiated by metabolic stress, persistent epigenetic remodeling—such as enhancer activation and histone modifications—sustains the transcription of pro-inflammatory genes, including IL-1β, IL-6, and TNF, thereby contributing to chronic inflammation.[28,29] Additionally, genetic variants located within enhancer regions can exacerbate this response by modifying transcription factor binding, further amplifying inflammation in obesity-associated metabolic disease.

The consequences of inflammation are primarily physiological and will contribute to the expansion, differentiation, and adaptation of pancreatic islets, adipose tissue, liver, and muscle to metabolic stress.[30,31] This is mediated by cytokines, but also by other factors such as insulin growth factor (IGF)-1, which appears to be a critical mediator of macrophage action in the context of metabolic adaptation.[31] This acute inflammation initially increases insulin secretion, as in the case of IL-1β.[32,33] Indeed, IL-1β acutely stimulates insulin release directly via the abundantly expressed IL-1 receptor in β cells and indirectly via neuronal stimulation. It also stimulates IL-6 production, promoting the expression and release of GLP-1, which has a trophic effect on young β cells.[34] Several other cytokines contribute to this physiological regulation of metabolism, including IL-22 and IL-33, which promote insulin secretion.[35–37] Similarly, cytokines are key players in the differentiation and expansion of adipose tissue.[30]

In addition to adapting to metabolic stress by increasing the storage capacity of tissues, inflammation will also limit the consequences of continued nutrient excess and the subsequent threat of tissue intoxication. Indeed, excessive concentrations of glucose and fatty acids are deleterious to cells. To protect tissues from this metabolic toxicity, inflammation will reduce insulin secretion and action over time. Although reduced insulin secretion and insulin resistance are typically perceived as harmful because they lead to hyperglycemia, they have the advantage of protecting tissues from intracellular intoxication.[38] It also limits obesity because insulin resistance protects against fat accumulation. When the excess of nutrients is stopped, either by reduced food intake or increased physical activity, insulin secretion and action are restored.[39,40] The short-term reversibility of these "lipo-glucotoxic" effects supports the concept that this initial inflammation-regulated impairment of insulin secretion and insulin resistance is a physiological adaptation.

Although the importance of sustained lipo-glucotoxicity for the pathophysiology of T2D remains uncertain,[41] chronic inflammation is typically detrimental, and this is also true in the context of metabolism. If over-nutrition and obesity persist, inflammation becomes deleterious, with the subsequent development of T2D and related diseases, as discussed below.

INFLAMMATION IN THE PROGRESSION OF OBESITY-ASSOCIATED DIABETES AND COMORBIDITIES

Obesity leads to systemic disease with organ-specific manifestations (Figure 1). This is triggered by metabolic disturbances, including hyperglycemia and dyslipidemia. Diabetes develops, with the occurrence of insulin resistance and impaired insulin secretion. While not exclusively due to inflammatory pathways, insulin resistance is in part mediated by TNF-α[27] and defective insulin secretion by IL-1β.[13] Although these two cytokines are key players in the context of metabolic disease, they are part of a complex inflammatory network involving multiple cytokines and immune cells, as detailed previously.[8]

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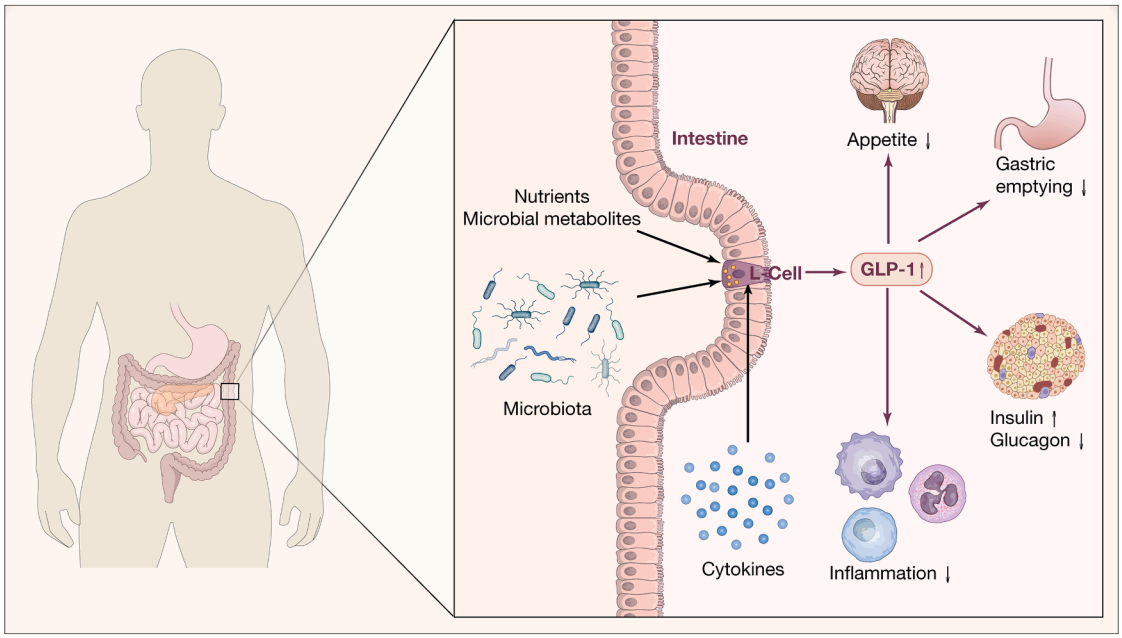

Figure 1. The physiology of GLP-1 activation and action

GLP-1-producing L cells, located in the distal small intestine and colon, respond to nutrients, viruses, fungi, microbiota, and their metabolites. Their activity is modulated by cytokine signaling. Upon stimulation, L cells release GLP-1, which acts to reduce appetite, delay gastric emptying, suppress inflammation and glucagon secretion, and enhance insulin secretion.

In terms of impaired health and prognosis, the most important consequence of this inflammation is cardiovascular disease. Indeed, atherosclerosis was first described as an inflammatory disease in the 19th century by Rudolf Virchow. Monocyte adhesion and foam cell formation are initiated by activation of the NLRP3 inflammasome by cholesterol crystals and free fatty acids (FFAs).[42–46] Beyond vascular disease, increasing evidence points to cardiac inflammation as a major disturbance contributing to heart failure and arrhythmia.[47]

Another important consequence of metabolic stress is liver inflammation (steatohepatitis, described as MASH), whereby hepatic lipid accumulation results from insulin-resistant adipocytes releasing excess FFAs, dietary fat via chylomicrons, increased *de novo* lipogenesis, and reduced fatty acid oxidation.[48,49]

Skeletal muscle is responsible for the majority of insulin-stimulated glucose uptake, making its insulin resistance critical for the development of T2D. Although insulin resistance protects against glucose overload in the short term, chronic lack of insulin signaling leads to muscle wasting, with dramatic consequences, particularly in the elderly. The precise contribution of inflammation in this context is less well studied but is likely to play a role. An interesting feature of skeletal muscle is that exercise induces the production of large amounts of IL-6, which is thought to contribute to energy mobilization during physical activity.[50] This physiological feature of IL-6 adds to the debate as to whether IL-6 is a "good or bad cytokine" in diabetes due to its pleotropic effects.[51–53] It is likely that the pleiotropic effects of IL-6 arise from its signaling mechanisms. IL-6 exhibits strong pro-inflammatory activity when its receptor is cleaved by metalloproteinases, forming a soluble complex that drives trans-signaling. Inhibition of this process effectively resolves inflammation. In contrast, IL-6 family proteins such as ciliary neurotrophic factor (CNTF), which signal via a leukemia inhibitory factor (LIF) receptor heterodimerizing with the membrane-bound IL-6 receptor, cannot induce trans-signaling, resulting instead in beneficial membrane-bound signaling. This distinction has fueled the development of IL-6 chimeric proteins, which are showing promising therapeutic potential.[54]

Inflammation is also seen in microvascular dysfunction and obstruction—microangiopathy, i.e., retinopathy, nephropathy, polyneuropathy—and in wound healing, although this remains correlative. However, there is strong evidence for a causal contribution of inflammation, particularly in diabetic retinopathy, macular edema, and vascular leakage, where high concentrations of cytokines such as IL-1β, IL-6, IL-8, and TNF-α are observed.[55,56] Furthermore, vascular endothelial growth factor (VEGF), which mediates much of the vascular dysfunction in the retina, is strongly induced by IL-1β.[55] Most data linking inflammation to distal sensorimotor polyneuropathy are cross-sectional.[57] However, two cohort studies reported that increases in multiple cytokines and chemokines preceded the onset of polyneuropathy.[58,59] Notably, these profiles reflected activation of both the innate and adaptive immune systems.

Obesity is also associated with a large number of diseases where the role of inflammation is well documented and is potentiated by metabolic stress. Thus, during Alzheimer's disease, amyloid plaques activate the inflammasomes, further enhancing metabolically induced inflammation.[60] Other disorders where inflammation precipitates disease progression include rheumatoid arthritis, psoriasis, and hypogonadism.[61–63]

The exact role of inflammation in cancers for which obesity is a risk factor is unclear, but it is likely to be significant. Indeed, some cytokines, such as IL-6, are potent inducers of cell proliferation. In addition, an intact immune system is crucial for immune

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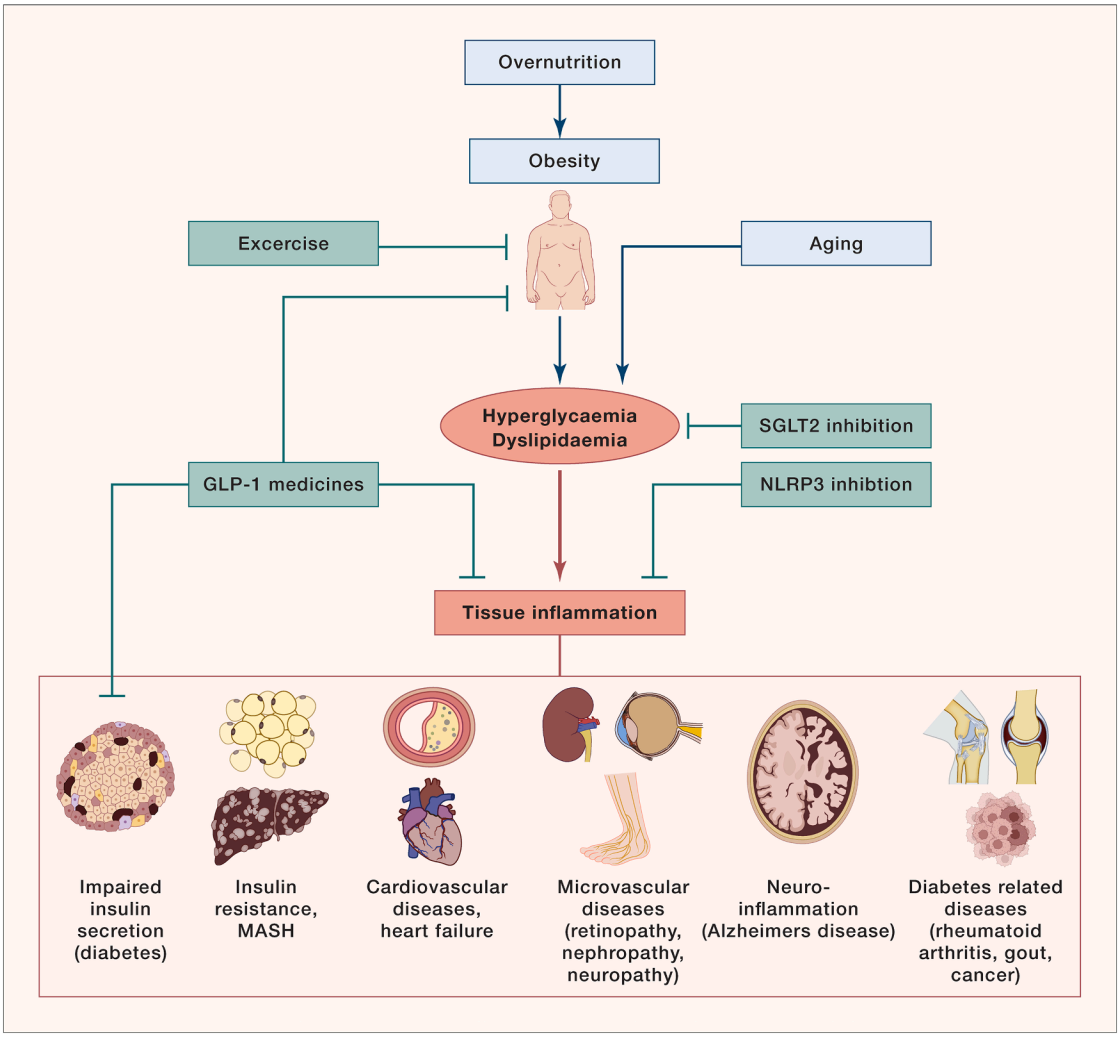

Figure 2. Pathophysiology and therapeutic approaches to obesity, T2D, and inflammation

Obesity, caused by an unhealthy diet, physical inactivity, and aging, leads to hyperglycemia and dyslipidemia, with subsequent tissue inflammation and obesity-related diseases. Possible treatments based on clinical trials include exercise; GLP-1 medicines that reduce food intake, improve diabetes, and have immunomodulatory effects; SGLT-2 inhibitors that reduce glucose accumulation and thereby prevent inflammation; and NLRP-3 inhibitors that prevent IL-1β activation.

surveillance, which can be compromised by obesity. Specifically, obesity increased expression of programmed cell death protein 1 (PD-1) expression on macrophages, thereby impairing anti-tumor immunity.[64]

Finally, obesity itself may be precipitated by the induction of neuroinflammation and subsequent reduced satiety. Whether neuroinflammation contributes to the lack of response to treatment with GLP-1 medicines in some patients remains to be shown.

TARGETING INFLAMMATION TO TREAT OBESITY, DIABETES, AND RELATED CONDITIONS

Understanding the role of inflammation in obesity, as well as in T2D, cardiovascular disease, and related conditions, provides a strong rationale for anti-inflammatory treatments (Figure 2).[65] The advantages of such approaches are that they target the pathogenesis of the diseases and have a systemic benefit, with the potential to improve multiple conditions caused by metabolic dysfunction. However, therapies targeting inflammation alone do not address the etiology of obesity, which reflects an imbalance of energy intake and storage in genetically predisposed individuals. Over time, obesity hastens the onset of T2D and its complications, to which we must add the aspect of aging, which seems to be partly driven by inflammation, giving rise to the concept of "inflammaging." Indeed, there is an age-related increase in the activity of innate immunity.[66]

Therefore, the first focus in the treatment of obesity should be on lifestyle modification, i.e., limiting calorie intake and increasing activity and energy expenditure. This will reduce systemic inflammation and effectively prevent obesity-related diseases. However, the suboptimal success of lifestyle interventions reflects major societal and psychosocial barriers as well as the genetic predisposition to gain weight in the setting of

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energy excess. In very rare cases, monogenic causes have been identified for obesity, and some of these disorders have been successfully treated with leptin[67] or melanocortin 4 receptor (MC4R) agonists,[68] with impressive success. However, for the vast majority of the population, the genetic predisposition appears to be polygenic, with no etiology-based treatment option.

A pioneering approach in the treatment of obesity has been bariatric surgery, now more commonly referred to as metabolic surgery. It was the first obesity intervention to demonstrate cardiovascular benefits in large-scale clinical outcome studies.[69] Notably, in the context of this review, bariatric surgery markedly reduces activation of the innate immune system.[70] However, despite its impressive metabolic and cardiovascular benefits, bariatric surgery remains an invasive procedure associated with significant short- and long-term complications, and it necessitates lifelong monitoring of micronutrient status.

GLP-1 medicines represent an extraordinary advance, transforming the medical treatment of obesity.[4] These therapies have dramatically improved the success of reducing body weight and, thus, metabolic load, with the consequences of preventing or improving T2D, cardiovascular disease, and other obesity-associated diseases. Mechanistically, a fundamental question is whether these effects of GLP-1 medicines are secondary to glucose control and/or weight loss, which, in turn, reduces metabolic stress and inflammation, or whether there are weight-independent anti-inflammatory effects at play. Emerging evidence suggests that GLP-1 medicines exhibit weight-loss-independent anti-inflammatory effects that may indirectly contribute to the reduction of cardiometabolic complications.[71]

Supporting the hypothesis of a reduction in metabolic-stress-induced inflammation due to weight loss is that treatments leading to weight reduction independently of GLP-1 medicines are also associated with reduced signs of systemic inflammation, such as decreased levels of C-reactive protein (CRP), IL-1β, IL-1Ra, IL-6, and TNF.[70] Importantly, the reduction in inflammation caused by GLP-1 medicines is associated with a significantly lower risk of major adverse cardiovascular events.[72] However, the putative anti-inflammatory benefits of GLP-1 medicines are seen very early after the start of treatment, before any weight loss is seen. For example, a reduction in major adverse cardiovascular events is seen after a few weeks of treatment with semaglutide in people with obesity studied in the SELECT cardiovascular outcomes trial, before there is a significant reduction in body weight.[73] However, GLP-1 medicines rapidly reduce appetite, so the reduction in nutrient influx into immune cells is immediate. Therefore, this early beneficial effect might still be attributable to attenuation of nutrient-induced inflammation.

Considerable preclinical and clinical evidence links endogenous and pharmacological GLP-1 action to the control of inflammation. The localization of GLP-1 producing L cells in the distal small bowel and colon makes these cells well suited to sense and respond to enteric pathogens such as viruses, fungi, microbiota, and their metabolites. Indeed, well before the discovery of GLP-1 ensuing from the cloning of the proglucagon cDNAs and genes in the 1980s, circulating levels of gut glucagon-like immunoreactivity had been shown to be increased in the setting of gastrointestinal infection,[74] and levels of GLPs are increased in patients with inflammatory bowel disease.[75] Several decades of research have solidified the view that L cells function as pathogen sensors, responding to cytokines, bacterial cell wall products, and microbial metabolites with increased secretion of L cell peptides, including GLP-1[34,76–78] (Figure 1). Consistent with these findings, plasma GLP-1 levels are elevated in patients with sepsis and correlate with disease severity and outcomes.[79,80] Furthermore, L cells also sense and respond to sterile inflammation, with plasma GLP-1 levels rising in the context of myocardial infarction, correlating with the severity of outcomes.[81]

GLP-1 acts locally within the gut to suppress inflammation by targeting GLP-1Rs expressed on intestinal intraepithelial lymphocytes (IELs).[82] The GLP-1R agonist exendin-4 directly increases cyclic AMP in IELs and attenuates cytokine secretion from activated IELs *ex vivo*. Moreover, dysregulated expression of immune-related genes in the gut of *Glp1r*$^{-/-}$ mice is substantially normalized following bone marrow transplantation of wild-type donor bone marrow, consistent with restoration of the intestinal IEL GLP-1R.[82] Studies of mice with genetic inactivation of the IEL GLP-1R treated with GLP-1 medicines reveal the importance of the gut IEL GLP-1R system for attenuation of local and systemic inflammatory responses arising pursuant to T cell activation.[83] In contrast, the gut IEL GLP-1R was not required for the actions of GLP-1 medicines to suppress systemic inflammation arising in mice following LPS administration, implicating one or more additional pathways conveying anti-inflammatory signals following activation of GLP-1R signaling.[84] Surprisingly, despite the importance of gut mucosal T cells for the development of intestinal injury in graft vs. host disease (GVHD), gain vs. loss of GLP-1R signaling does not modify the severity of intestinal GVHD in mice.[85]

Restoration of glucose control and achievement of weight loss may be secondary, indirect contributors to the anti-inflammatory actions of GLP-1 medicines. However, several lines of evidence support GLP-1R-dependent anti-inflammatory pathways that are active in the absence of hyperglycemia and weight loss. For example, GLP-1 medicines acutely reduce biomarkers of inflammation within hours in animals, prior to the achievement of calorie restriction or weight loss.[84,86]

Interrogation of the anti-inflammatory effects of GLP-1 medicines compared with those induced by weight loss alone, reveals similar weight-loss-independent mechanisms contributing to the suppression of inflammation. Analysis of the effects of oral vs. injectable GLP-1R agonist semaglutide in people with T2D reveals a consistent reduction in circulating levels of high-sensitivity CRP (hsCRP), findings only partially correlated with the extent of reduction in glucose and body weight.[87] For example, in a randomized controlled trial comparing the actions of empagliflozin, an inhibitor of sodium-dependent glucose transporter 2 (SGLT-2), which causes renal glucose loss, vs. oral semaglutide in patients with T2D, circulating levels of hsCRP were significantly lower in subjects treated with oral semaglutide, despite similar levels of weight loss with empagliflozin vs. semaglutide.[88] Assessment of individuals with prediabetes or diabetes treated with lifestyle management or the once-daily injectable GLP-1R agonist liraglutide over several months revealed significantly greater reduction in sCD163 levels in the liraglutide treatment arm, despite the achievement of comparable weight loss with lifestyle management.[89] Analysis of the circulating plasma proteome in patients with overweight or obesity treated with

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semaglutide in the STEP-1 and STEP-2 trials revealed substantial changes in circulating biomarkers of inflammation with semaglutide therapy, with changes in a subset of inflammation-related biomarkers not dependent on changes in glucose control and body weight.[90] Consistent with these findings, proteomic signatures of semaglutide action that associate with improvements in metabolic liver disease, including proteins regulating inflammation, are substantially independent of weight loss in clinical trials.[91]

Interrogation of the mechanisms linking GLP-1R signaling to the control of inflammation is challenging due to the low levels of GLP-1R expression in most immune cells beyond the gut, as well as limitations and pitfalls in identification of immunoreactive GLP-1R protein expression with suboptimally validated antisera.[92–95] Although treatment with the peptide GLP-1R agonist exenatide or liraglutide decreases expression of inflammation-related genes in circulating white blood cells (WBCs),[86,96] *GLP1R* mRNA transcripts are not detected in circulating WBCs,[89] and the GLP-1R agonist exendin-4 (identical in sequence to exenatide) fails to directly reduce TNF-α secretion in LPS-treated murine splenocytes or blood cells *ex vivo*.[84] Collectively, these findings support indirect mechanisms, likely through inter-organ communication, for pathways linking GLP-1R activation to the suppression of inflammation in some tissues.

GLP-1Rs are widely expressed within the central nervous system (CNS), raising the possibility that central GLP-1R-dependent signals attenuate inflammation in peripheral organs through neural pathways. Indeed, a range of pro- and anti-inflammatory cytokines communicate states of systemic inflammation to the brain through vagal pathways, and activation of specific groups of hindbrain neurons in turn attenuates systemic inflammation.[97] Consistent with these findings, CNS GLP-1R signaling is essential for a subset of the acute anti-inflammatory actions of GLP-1 medicines in mice. Induction of systemic inflammation using LPS or a polymicrobial cecal slurry was attenuated by exenatide or semaglutide, findings requiring neuronal GLP-1R signaling. Interestingly, the anti-inflammatory action of tirzepatide, a GLP-1 medicine that also activates glucose-dependent insulinotropic polypeptide receptor (GIPR) signaling, was preserved in mice with a reduction of CNS GLP-1R activity. Collectively, these findings add further complexity to the direct and indirect pathways linking GLP-1 medicines to the control of inflammation.[84]

GLP-1 medicines produce benefits in a range of disorders frequently associated with T2D or obesity. These include atherosclerotic cardiovascular disease, heart failure with preserved ejection fraction (HFpEF), diabetic kidney disease, peripheral artery disease, obstructive sleep apnea, and metabolic liver disease.[98] Whether the anti-inflammatory actions of GLP-1 medicines contribute to the reduction of heart and kidney disease, arthritis, and metabolic liver disease observed in clinical trials[71] will require further analysis of trial outcomes, stratified by the extent of achieved weight loss.

Another class of drugs that changes cardiorenal outcomes in people with obesity and diabetes is the group of SGLT-2 inhibitors, which reduce all-cause mortality and protect against heart failure and nephropathy. There are several explanations for these effects. The most obvious is that urinary glucose excretion itself may be beneficial. Indeed, SGLT-2 inhibitors promote glucosuria, with 50–80 g of glucose being excreted daily or about 2 kg/month. By preventing excess glucose from entering the tissues, SGLT-2 inhibitors reduce metabolic stress and thus inflammation; in an animal model of diabetes, SGLT inhibition prevented glucose-induced IL-1β.[13] Notably, people with obesity without diabetes treated with SGLT-2 inhibitors also excrete a significant amount of glucose, preventing intracellular glucose excess and subsequent inflammation. Nevertheless, SGLT-2 inhibitors improve renal and cardiovascular outcomes in individuals without T2D, highlighting their pleiotropic mechanisms of action.[99] Furthermore, a subset of the cardiovascular actions of SGLT-2 inhibitors may reflect actions independent of the SGLT-2 protein.[100] The traditional anti-diabetic drug metformin could also work in part by reducing inflammation. Metformin inhibits complex I in the mitochondria, thereby reducing ROS production and inflammasome activity.[101]

In addition to these somewhat speculative mechanisms of action of glucose-lowering drugs, direct immunomodulatory drugs can prevent obesity-related diseases. Metabolic improvement by a purely immune intervention was achieved with the IL-1 receptor antagonist IL-1Ra.[102] Indeed, in a proof-of-concept study in patients with T2D, IL-1Ra improved insulin secretion and glycaemia and reduced systemic inflammation, as reflected by decreased WBC, CRP, and IL-6. Importantly, CRP is a well-validated marker of cardiovascular disease. Accordingly, in a subsequent study using an IL-1β antibody—the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) trial—this approach prevented cardiovascular disease.[103] It is important to note that the CANTOS study was not a diabetes trial. Anti-diabetic drugs were adjusted accordingly, which explains why the significant improvement in blood glucose seen in the first 6–9 months of treatment was not seen in the latter period.[104] Consistent with this, anti-IL-1β decreased hemoglobin A1c (HbA1c) in non-diabetic patients for the entire duration of the study. Importantly, a meta-analysis of almost 3,000 patients with T2D confirmed that IL-1 antagonists significantly reduced HbA1c.[105] Other anti-inflammatory approaches, including salsalate, have beneficial effects in patients with T2D.[106] However, due to patent expirations, and the competitive environment, together with the achieved effect size, pharmaceutical companies are unlikely to pursue IL-1 antagonism and salsalate for the treatment of diabetes and its complications. Nevertheless, several NLRP3 inhibitors are in clinical development, including small, orally active molecules. The most advanced candidate, dapansutrile, is currently in a 6-month trial for T2D and its complications (ClinicalTrials.gov NCT06047262). Intriguingly, preclinical studies in high-fat-diet-fed mice administered a brain-penetrant NLRP3 inhibitor (NT-0796) demonstrated additive weight-loss effects when combined with semaglutide, and NT-0796 limited weight regain following cessation of semaglutide therapy,[107] findings associated with a reduction of systemic inflammation and hypothalamic astrogliosis.

CONCLUDING REMARKS

Obesity and T2D are now firmly recognized as chronic inflammatory diseases. Initially adaptive, this inflammation becomes pathogenic when sustained, contributing to the progression of metabolic disease, including insulin resistance, β cell dysfunction, and damage to organs such as the liver, heart, kidney, and CNS.

The clinical success of GLP-1 medicines marks a paradigm shift in the treatment of obesity and diabetes, offering substantial improvements in glycemic control and weight reduction. Importantly, these drugs also exhibit direct and indirect anti-inflammatory effects, some of which occur independently of weight loss. This supports the notion that inflammation itself is a therapeutic target of GLP-1 medicines. Remarkably, despite suppression of immune activity, GLP-1 medicines are not associated with an increased risk of infection or cancer.

Progress toward targeting inflammation in metabolic disorders is impeded by limited commercial incentives for the development of anti-inflammatory therapies specifically for diabetes and obesity, particularly for agents like IL-1 antagonists, which are no longer patent protected. Moreover, disentangling weight-dependent from weight-independent effects in clinical trials remains methodologically challenging, and any new therapeutic strategy would need to show benefits on top of existing therapies such as SGLT-2 inhibitors and GLP-1 medicines.

Future research must aim to dissect the molecular basis of the anti-inflammatory actions of metabolic drugs and rigorously evaluate emerging immunomodulatory compounds, including NLRP3 inhibitors, in clinical settings, ideally in patients with considerable residual risk of inflammation-driven complications. A better understanding of the immunometabolic interface will be essential for developing therapies that not only control weight and glucose levels but also modify the underlying disease process. This may also improve other inflammatory diseases driven by metabolic stress, such as Alzheimer's disease, gout, sleep apnea, type 1 diabetes, multiple sclerosis, and osteoarthritis.

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