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Review Article

Type 2 Diabetes Mellitus: Understanding the Role of Inflammation and Oxidative Stress in Disease Progression

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Abstract

Obesity has become a global epidemic, affecting approximately one-third of the world's population and serving as a primary risk factor for Type 2 Diabetes (T2D) and related metabolic disorders. This review examines the intricate relationship between obesity, inflammation, and insulin resistance, highlighting White Adipose Tissue (WAT) as a crucial player in this process. Elevated body fat triggers a low-grade, chronic inflammatory response characterized by the recruitment and activation of pro-inflammatory macrophages, leading to the release of cytokines like TNF-α and IL-6, which disrupt insulin signaling and promote systemic inflammation. We explore the role of various immune cells in adipose tissue, the phenotypic switching of macrophages from anti-inflammatory to pro-inflammatory states, and the resultant impact on metabolic health. Additionally, we discuss emerging therapeutic strategies targeting inflammatory pathways as potential interventions for managing obesity-related conditions. These include pharmacologic agents like salsalate, TNF-α inhibitors, IL-1β antagonists, and anti-inflammatory properties of established diabetes medications such as thiazolidinediones and metformin. By elucidating the mechanisms underlying obesity-induced inflammation and its effects on glucose metabolism, this review aims to inform future research and clinical approaches to mitigate obesity and its associated metabolic complications.

Keywords: Adipose tissue; Salsalate; Thiazolidinediones; Diabetes

Introduction

Excess weight and fatness are the result of a persistent disturbance between energy consumption and discharge, leading to the deposition of fat in AT. About one third of the habitancy of our world suffers from excess weight or fatness which means that the global sickness rate has increased since 1980 [1,2].

Heaviness is a composite state including genetic and living constituents and corresponds to a few morbid disturbances leading to significant consequences for personal and public health. Changing of habits and a standard of living (e.g., enhanced sports activity and reduced fattening consumption) are the basic for the check of weight [3,4]. The enhancement of β-cell features and insulin susceptibility in Adipose Tissue, liver, and skeletal muscle can happen after slow reduction of weight reaching 16% from the initial body weight [5-7]. Glycemic control is better after the reduction of weight because of uncontrolled transformation genetic information in protein switched in cholesterol flux, lipid synthesis, ECM remodeling, and oxidative stress. Taking into consideration the information above, fatness is the widest spread endocrine disease in the world and an initial trigger for IR and diabetes mellitus [8-11].

According to American Diabetes Association diabetes mellitus is in a cluster of illnesses in which sugar is not assimilated properly. The sickness rate of diabetes mellitus deceased has grown significantly for the last three decades so that it has become the main cause of death in the world. T2D is supposed to be a sequela of fatness in 2025 for more than 300 million people [12,13].

Persistent illness with a high rate of glucose because of insufficient insulin generation (i.e., β-cell disturbance) and IR (no cell reaction on insulin) is T2D. It is a dominant form of diabetes mellitus [14-17].

Fatness is one of the conditions for IR appearance and the full insight into linkage obesity and IR will improve our impression of T2D etiology and help us better treat fatness-related conditions A few studies have been done on

people and genetically modified animals, showing a link between overeating and the activation of both the inborn and adaptive immune systems in body parts that regulate overall energy balance in the body [18-20].

The first evidence suggesting that inflammation is linked to obesity and diabetes comes from studies on humans and animals in the early 1990s. These studies showed that fat tissue in obese rodents and humans undergoes inflammatory changes and releases more of the pro-inflammatory molecule TNF-α, which can cause insulin resistance by immobilization of IRS-1 [21-24]. The key role of TNF-α is considerably supported by findings that blocking TNF-α in obese mice enhances insulin sensitivity and glucose metabolism. Weak persistent inflammation in fat tissue, also known as meta-inflammation, is closely linked to a surplus body fat. This condition is marked by the presence and activation of pro-inflammatory macrophages and other immune cells, which generate and release pro-inflammatory cytokines and chemokines [25-27].

In the course of obesity not only does the quantity of macrophages in fat tissue grow (achieve 40% of all cells in fat tissue), but their position and inflammatory behavior also change. In people of normal weight, macrophages have anti-inflammatory properties [28]. However, in obese individuals, these macrophages (called AT macrophages or ATMs) move to a pro-inflammatory state. In obesity, macrophages cluster around dead fat cells, forming structures known as crown-like structures, and release pro-inflammatory cytokines. This contributes to both local and systemic inflammation and insulin resistance [29-31].

The exact triggers of inflammation are still largely unknown, but changes in fat tissue caused by obesity, such as fat cell death, lack of oxygen, and mechanical stress, can start an inflammatory response. Because inflammation plays a key role in the development of T2D and its related metabolic problems, there is an increasing interest in targeting inflammatory pathways or molecules to impede and cure the disease [32,33].

In this study, we focus on how the loss of immune regulation contributes to inflammation in fat tissue and the development of obesity-related disorders, with an emphasis on the molecular details. We discuss the cellular and molecular factors that trigger inflammation due to obesity and provide an overview of new anti-inflammatory treatment strategies.

The inflammatory phenotype of white adipose tissue

WAT primarily stores fat and acts as a major endocrine organ that releases signaling molecules called adipokines and cytokines into the bloodstream. Adipokines play key roles in regulating various metabolic processes, including insulin signaling, glucose uptake, and fatty acid oxidation. Cytokines manage inflammation and support tissue repair and blood vessel formation [34,35].

When a person gains weight and becomes obese, WAT undergoes changes that include the development of inflamed, dysfunctional fat cells and an increase in immune cells in the tissue. These inflamed fat cells release proinflammatory cytokines, which can break up both the normal function of WAT and affect other organs in the body [36,37]. In this context, WAT can be seen as both an immune and secretory organ, and obesity can be viewed as an inflammatory immune condition [38,39].

Researches of either animals or humans have confirmed that increased body fat and inflammation in adipose tissue are linked to a surplus calorie consumption. The research by Lee, et al. used immunocompromised mice to show that inflammation plays a crucial role in developing insulin resistance from a long-term Western-style diet. One notable aspect of the inflammation in expanding WAT is its persistent, low-grade nature, which is not possible to be resolved and is referred to as “metaflammation” [40-42].

Inflammation generally wastes energy, increasing energy outgo and decreasing energy consumption through straight and devious methods. Directly, inflammatory cytokines like TNFα, IL-1, and IL-6 provide energy expenditure by interacting with receptors in the central nervous system and metabolic organs. These cytokines have effects similar to leptin, a hormone that promotes energy outgo [43-45].

Leptin production increases in adipose tissue during inflammation, triggered by hypoxia and inflammatory signals. Additionally, TNFα boosts leptin receptor expression, enhancing leptin’s role in increasing energy expenditure and reducing appetite. Thus, leptin contributes to higher energy expenditure indirectly through its effects on appetite and metabolism [46-49].

Interestingly, the inflammation in adipose tissue caused by overnutrition does not lead to a significant increase in energy expenditure. This allows inflammation and weight gain to coexist in obese individuals. Despite this, the inflammatory response in adipose tissue shares similarities with traditional inflammation [50,51]. It involves the infiltration of immune cells from the bone marrow and the release of inflammatory mediators, such as chemokines and cytokines, by both adipocytes and resident immune cells. Additionally, even in people who are otherwise healthy and normal-weight, inflamed adipose tissue can trigger widespread systemic inflammation through the release of cytokines [52,53].

Due to its location and structure, white adipose tissue WAT exhibits various inflammatory profiles. Research shows that obesity causes a more severe inflammatory response in visceral WAT Visceral Fat (VAT) compared to Subcutaneous WAT (SAT). VAT in obese individuals has more macrophages and greater adipocyte hypertrophy than SAT [54-56]. Additionally, inflammation in VAT is linked to lower expression of lipogenic markers, likely because more cells adopt an inflammatory rather than a lipid storage role. This shift contributes to metabolic issues, including abnormal fat accumulation in the liver and muscles. Since fat buildup in the wrong places reduces the body’s ability to use insulin, inflammation in VAT is believed to greatly influence obesity-related problems like insulin resistance and Type 2 diabetes [57,58]. Although research suggests VAT inflammation is a major factor, many studies also high-

light the role of inflammation in subcutaneous fat SAT in metabolic issues. The debate over how different fat types contribute to inflammation has been partly studied in mice. To understand how VAT and SAT affect metabolism differently, Rytka, et al. [59] increased fat mass in mice by transplanting epididymal VAT into areas draining into the caval or portal systems [60,61]. The procedure caused inflammation in Adipose Tissue (AT) in both groups of transplanted mice. However, only the mice with fat transplanted into the mesenterium had higher levels of IL-6 and Free Fatty Acids (FFA) in the portal vein and showed impaired glucose tolerance. Human studies further confirm that VAT and SAT metabolize differently [62,63]. For the same amount of AT, VAT takes up more meal FFA than SAT in both men and women. Additionally, omental fat (a type of VAT) takes up more plasma FFA compared to abdominal subcutaneous fat in women. This suggests that VAT's location and structure allow it to more directly affect important organs, like the liver, which are crucial for regulating insulin and overall metabolism [64,65].

What is the role of inflammation? What is the role of macrophages? Are they central mediators of obesity-induced adipose tissue inflammation and insulin resistance?

In obesity, expanded AT produces high levels of proinflammatory cytokines, which activate the IKKβ/NFκB and JNK pathways. This leads to insulin resistance in both fat cells and liver cells. The inflammatory response in AT is key to obesity-related insulin resistance, with various immune cells in AT playing roles in regulating inflammation and insulin resistance. While adipocytes (fat cells) are important for managing inflammation and tissue remodeling through cytokine release and antigen presentation, evidence also highlights the critical role of macrophages in these processes [66-69].

Macrophages are immune cells found in AT that have a versatile role. They help with removing dead cells, remodeling the extracellular matrix, regulating blood vessel formation, and maintaining AT balance. In obesity, there is an increased influx of monocytes and macrophages into AT. In lean human visceral AT, macrophages make up about 10% of the stromal vascular cells, but this proportion rises to about 40% in obese individuals [70-72].

A model called "phenotypic switching" of macrophages in AT during obesity has been suggested. In this model, macrophages shift from an anti-inflammatory state (M2 macrophages) to a proinflammatory state (M1 macrophages). M2 macrophages, which are induced by Th2 cytokines like IL-4, IL-10, and IL-13, are common in lean AT and play a role in maintaining normal adipocyte function by promoting tissue repair and angiogenesis [73-75]. They express high levels of arginase-1, which inhibits nitric oxide synthase activity, and secrete anti-inflammatory cytokines such as IL-10. However, in obesity, M1 macrophages, which are activated by signals like Lipopolysaccharide (LPS) and Th1 cytokine IFN-γ, become more dominant. These M1 macrophages produce proinflammatory factors such as TNF-α and IL-6 and are associated with increased insulin resistance. Initially, the "phenotypic switching" model of macrophages in AT during obesity was helpful [76-78]. However, as our understanding of macrophage activation has grown, this model's accuracy in living organisms has been questioned. It is now clear that macrophages in obesity are highly adaptable, with their characteristics depending on the specific stimuli they encounter. The exact roles and numbers of these macrophages in obese AT are still being studied, and the mechanisms behind their unique activation states are not fully understood [79-81]. What is evident, though, is that more than one type of macrophage exists in obese AT. These macrophages may not fit neatly into the M1 or M2 categories but instead show a state of "Metabolic Activation" (MMe), driven by various metabolic stimuli like free fatty acids, high insulin, and high glucose levels [82-84]. Transformations in the microenvironment and inflammatory state cause macrophages to infiltrate tissues and adopt a metabolic activation state, a process known as macrophage polarization. This involves the induction of proteins related to lipid metabolism, enabling these macrophages to manage excessive lipids in their environment [85-87]. These recruited macrophages vary from resident macrophages in their allocation, gene expression, and function. Proteomic analysis of MM1, MM2, and metabolically activated macrophages (MMe) has shown that MMe cells have clear surface markers. Specifically, MMe macrophages overexpress proteins such as ABCA1, CD36, and PLIN2, all of which play crucial roles in lipid metabolism [88-90].

The penetration of macrophages into expanding AT may play a crucial role in triggering inflammation in obesity and causing insulin resistance. These macrophages are thought to create conditions that allow the negative effects of AT expansion to occur. However, other research suggests that inflammation in adipose tissue might actually be a result of insulin resistance, rather than the cause of it [91,92].

Inflammation as a therapeutic target for metabolic diseases

Chronic inflammation, especially in AT, is now recognized as a key factor in the development of T2D and its related complications. The link between obesity, AT inflammation, and metabolic diseases has made targeting inflammatory pathways an attractive strategy for treating these conditions [5,25]. Inflammation is seen as a central cause of these common health issues. Although a few anti-inflammatory treatments have been tested in obese individuals with Insulin Resistance (IR), more clinical trials are needed to confirm their effectiveness. The amount of drugs available that target various parts of the immune system and improve different aspects of metabolism is growing rapidly [93-95].

Therapeutic approaches to targeting inflammation in IR and T2D can be categorized basing on their mechanism of action into two main groups: (i) pharmacologic approaches that directly target inflammation, and (ii) diabetes drugs that also possess anti-inflammatory properties [96-98] (Table 1).

Table 1: Therapeutic strategies targeting inflammation in obesity.

Therapeutic approach	Mechanism of action	Clinical evidence
Salsalate	Inhibits NF-κB pathway	Improves insulin sensitivity; lowers HbA1c in T2D
TNF-α Inhibitors	Neutralizes TNF-α	Mixed results in T2D; lowers fasting glucose in non-T2D
IL-1β Antagonists	Blocks IL-1 receptor	Improved blood sugar control; beneficial in RA+T2D
Thiazolidinediones (TZDs)	PPARγ agonists, anti-inflammatory effects	Reduces AT macrophages, enhances insulin sensitivity
Metformin	Reduces liver glucose production, inhibits inflammatory cytokines	Lowers CRP levels; improves metabolic outcomes

Salsalate

Salsalate is a derivative of salicylate and is part of the Non-Steroidal Anti-Inflammatory Drug (NSAID) class. Research has shown that salsalate can help improve blood sugar control in patients with T2D. The mechanism by which salsalate reverses hyperglycemia in obese mice involves the inhibition of the NF-κB pathway, a discovery made by Shoelson and colleagues in 2001 [99,100].

Goldfine expanded on the initial findings by conducting clinical studies that showed salsalate can lower fasting glucose and triglyceride levels, increase adiponectin levels, enhance glucose utilization during hyperinsulinemic-euglycemic clamps, and improve insulin clearance in diabetic patients. These results were verified in two interdisciplinary, randomized, placebo-controlled trials involving patients with T2D [101].

In the first study, salsalate treatment improved insulin sensitivity and reduced HbA1c levels by 0.5% compared to placebo over 14 weeks. The second study, which lasted 48 weeks and involved 283 participants (with 146 receiving salsalate and 137 receiving placebo), found a smaller reduction in HbA1c levels (–0.33%) and serum triglycerides with salsalate treatment. Additionally, salsalate treatment was associated with reduced levels of glycation end products [99-101].

Other studies also indicate that the metabolic improvements from salsalate treatment are due to the activation of AMPK. While its impact on blood sugar control is modest, salsalate is affordable and has a strong safety profile [102,103].

TNF-α inhibitors

In 1993, a preclinical study demonstrated the role of TNF-α in the development of insulin resistance in adipose tissue. This led to the hypothesis that blocking TNF-α could have therapeutic benefits [104]. However, clinical study results have been disappointing. Although TNF-α neutralizing antibodies are effective for treating many other inflammatory diseases and have shown slight improvements in blood sugar control in some patients, results in patients with T2D have been inconclusive [105,106]. Despite promising effects in mice, a human clinical trial found that anti-TNF-α therapy did not improve insulin sensitivity in T2D patients. On the other hand, a study on obese individuals without T2D showed that inhibiting TNF-α for 6 months could lower fasting glucose and increase adiponectin levels [107,108].

IL-1β antagonists

IL-1β is a key driver of obesity-related inflammation and plays a role in the development of T2D by contributing to the harmful effects of high blood sugar on pancreatic β-cells. In a proof-of-concept study, blocking the IL-1 Receptor (IL-1R) for 13 weeks in T2D patients led to improved blood sugar control, better pancreatic β-cell function, and reduced markers of systemic inflammation [109,110]. A follow-up study on the same group showed that even 39 weeks after the last IL-1R antagonist dose, β-cell insulin secretion remained elevated and C-Reactive Protein (CRP) levels were still lower. These long-term effects are likely due to the blocking of IL-1β's self-reinforcing mechanism. Additional studies have also suggested that using antibodies against IL-1β could be beneficial in treating T2D, as it significantly lowers HbA1c levels [111]. Pathological activation of IL-1β also plays a role in the development of other diseases associated with T2D, such as Crohn's disease, gout, and Rheumatoid Arthritis (RA). Recently, a multicenter randomized controlled trial was conducted to specifically evaluate the effects on blood sugar control in participants with both RA and T2D over a 6-month period [112,113]. Thirty-nine participants were randomized to receive either an IL-1 receptor antagonist (anakinra) or TNF inhibitors (TNFi) to compare the effectiveness of these treatments in managing blood sugar levels in T2D. After 3 and 6 months of treatment, anakinra led to a significant progress in metabolic outcomes, with a reduction in HbA1c by more than 1%, while TNF inhibitors did not show any improvement [114,115]. Both groups experienced a gradual reduction in RA disease activity. In conclusion, the results of this study highlight the specific effectiveness of IL-1 inhibition in patients with both RA and T2D, achieving therapeutic targets for both conditions and improving the primary outcomes for participants. The more pronounced reduction in HbA1c, compared to previous studies on T2D alone, may be due to the theory that the pathogenic mechanisms of T2D are

more severe in the context of RA. This suggests that the IL-1 pathway may be a common pathogenic mechanism in both diseases, and a single treatment targeting this pathway could be a promising approach for managing both RA and T2D [116,117].

Thiazolidinediones

Thiazolidinediones (TZDs) are antidiabetic drugs that enhance insulin sensitivity and improve blood sugar levels by acting as agonists for the PPARγ nuclear receptor. In addition to their metabolic effects, TZDs also possess anti-inflammatory properties; they inhibit NF-κB activity and decrease the expression of genes regulated by NF-κB [116,117].

Inhibiting the NF-κB pathway decreases the content of Adipose Tissue Macrophages (ATMs), helps to restore the anti-inflammatory M2 macrophage phenotype, and promotes the recruitment of anti-inflammatory regulatory T cells in adipose tissue [118-120].

Moreover, the ability of TZDs to lower circulating inflammatory mediators like CRP and MCP-1 appears to be independent of their effects on glycemic control. Therefore, TZDs likely operate through multiple mechanisms, and their anti-inflammatory properties are not yet fully understood [121,122].

Metformin

The exact mechanism by which metformin works is not fully understood, but it lowers blood sugar levels by decreasing glucose production in the liver and increasing glucose consumption in peripheral tissues. Beyond its well-known metabolic effects, metformin also possesses anti-inflammatory properties; it directly inhibits the production of reactive oxygen species in the mitochondria and can reduce the production of various cytokines. Emerging evidence suggests that metformin may have immune-modulatory effects [123-125]. It has been extensively reviewed how metformin impacts various immune cells such as T cells, B cells, monocytes/macrophages, and neutrophils that play a role in autoimmune and inflammatory diseases. Inside these immune cells, metformin temporarily inhibits complex I of the mitochondrial electron transport chain, leading to an increased AMP/ATP ratio. Decreased ATP levels lead to the activation of AMPK, which then inhibits the Mammalian Target Of Rapamycin (mTOR). mTOR is essential for various cellular processes, including metabolism, cytokine responses, antigen presentation, macrophage polarization, and cell migration, through its interaction with the STAT3 pathway [126-128]. Metformin also affects other pathways relevant to immune cells, such as NF-κB and JNK. Specifically, metformin has been shown to inhibit TNF-α-induced activation of the NF-κB pathway and IL-6 production through PI3K-dependent AMPK phosphorylation. Additionally, metformin reduces IL-1β production in lipopolysaccharide-activated macrophages in a dose-dependent manner, and this effect is independent of AMPK activation [129,130]. Metformin also reduces circulating inflammatory proteins, such as CRP, in patients with impaired glucose tolerance and type 2 diabetes. Its anti-inflammatory effects, similar to those of TZDs, seem to be independent of glycemic control. In animal models, reducing inflammation has been effective in improving obesity-induced insulin resistance. However, ongoing clinical trials are needed to confirm the therapeutic potential of metformin in humans. This step is crucial for establishing the translational relevance of these findings [131,132].

T2D is a heterogeneous disease, and the lack of clinical biomarkers indicating whether treatments have anti-inflammatory effects in adipose tissue complicates the analysis. Identifying and profiling these biomarkers in T2D patients would help predict which individuals are most likely to benefit from anti-inflammatory therapies [133-135].

Conclusion

In summary, the surge in obesity prevalence worldwide is intricately linked to the development of insulin resistance and type 2 diabetes, with chronic inflammation in adipose tissue serving as a pivotal mechanism behind this association. The transition of macrophages within white adipose tissue from anti-inflammatory to pro-inflammatory states exacerbates metabolic dysregulation, highlighting the role of immune dysregulation in the pathology of obesity. Addressing the inflammatory processes associated with obesity presents a promising avenue for therapeutic intervention. Emerging strategies, including the targeting of specific inflammatory pathways and the use of existing diabetes medications with anti-inflammatory properties, offer hope for improving metabolic outcomes in obese individuals. Future research should focus on elucidating the complex interactions between immune responses and metabolic health, as well as identifying biomarkers that predict response to anti-inflammatory therapies. By advancing our understanding of these relationships, we can develop more effective treatments to combat obesity and its extensive health consequences.

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