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Physiopathological mechanisms related to inflammation in obesity and type 2 diabetes mellitus

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Abstract

Overweight, obesity, and type 2 diabetes mellitus pose global health problems that are ever-increasing. A chronic low-grade inflammatory status and the presence of various pro-inflammatory markers either in circulation or within dysfunctional metabolic tissues are well established. The presence of these factors can, to some extent, predict disease development and progression. A central role is played by the presence of dysfunctional adipose tissue, liver dysfunction, and skeletal muscle dysfunction, which collectively contribute to the increased circulatory levels of proinflammatory factors. Weight loss and classical metabolic interventions achieve a decrease in many of these factors' circulating levels, implying that a better understanding of the processes or even the modulation of inflammation may alleviate these diseases. This review suggests that inflammation plays a significant role in the development and progression of these conditions and that measuring inflammatory markers may be useful for assessing disease risk and development of future treatment methods.

INTRODUCTION

Overweight and obesity represent a significant, ever-increasing global public health challenge^[1-4]. Obesity is a complex multifactorial disorder linked to a high risk of developing type 2 diabetes mellitus (T2DM), cardiometabolic diseases and most

recently COVID-19 [2,5-10]. Excess and ectopic adiposity and adipose tissue (AT) dysfunction, characterized by a state of low-grade inflammation, underline the pathophysiology of obesity and its consequences to a great extent [8, 11-18]. The presence of inflammation in obesity and related metabolic diseases is well established and is proposed to be linked to insulin resistance and/or its further exacerbation, as inflammatory mediators appear to interfere with insulin signal transduction in important metabolic organs (AT, liver, and muscle)[15,19]. Inflammatory markers may be indicators of disease development, allowing us to potentially predict the transition and/or development of complications such as T2DM and cardiovascular diseases [2021]. Consequently, by achieving an improved understanding of the changes in metabolic and inflammatory processes in these various tissues and organs, and unveiling their properties, we could achieve a better understanding of the pathophysiology of obesity-related complications, including T2DM, and develop better prevention and treatment strategies[22-24]. In this mini-review, we will present evidence of obesity and T2DM-related inflammation, explore the underlying mechanisms in selected tissues and organs, and present potential therapeutic options based on the current literature.

CIRCULATING INFLAMMATORY MARKERS

Systemic inflammation in overweight and obesity

Excess adiposity is related to modestly raised levels of many circulating cytokines and inflammatory factors in both mice and humans; hence, obesity is usually defined as a condition of persistent low-grade systemic inflammation[15,16,25]. Evidence suggests that many of these factors are produced in AT, collectively referred to as adipokines, including hormones (leptin, adiponectin), hormone-cleavage enzymes like dipeptidyl peptidase 4 (DPP-4), components or factors regulating the clotting cascade like plasminogen activator inhibitor-1 (PAI-1), and chemoattraction/pro-inflammatory factors including interleukins 1, 6, and 8 (IL-1, -6, -8), tumour necrosis factor alpha (TNF- α), and monocyte chemoattractant protein-1 (MCP-1)[11,22,26-30]. Adipokine expression and/or secretion is altered in states of AT dysfunction and may contribute to

obesity-associated diseases^[11,26]. Leptin circulating concentrations are elevated in individuals with obesity, and its concentrations are generally strongly and positively correlated with white AT mass^[31,32]. At the same time, hypoadiponectinemia is another hallmark of obesity, suggesting a loss of its positive insulin-sensitizing and anti-inflammatory properties^[33–35]. In a recent meta-analysis of 60 studies with 45,210 participants, positive correlations with C-reactive protein (CRP), IL-6, and TNF- α were observed for leptin but not for adiponectin, implying an important association between AT hormonal function and inflammatory biomarkers with potentially pathophysiological implications^[36]. Moreover, acute-phase proteins, including CRP and serum amyloid A (SAA), and white blood cell (WBC) count, are also elevated in obesity and related metabolic diseases^[21,29,37–40].

Several genome-wide association studies (GWAS) have been conducted to explore the link between obesity and various conditions, as well as the potential cause-and-effect relationship^[41]. These studies have identified over 300 single-nucleotide polymorphisms (SNPs) that are associated with different measures of obesity, such as BMI, WHR, and other indicators of adiposity^[41]. In a large-scale genome-wide association study involving a total of over 40,000 individuals of European descent, genetic variants associated with higher BMI were strongly associated with higher high-sensitive CRP levels, indicating a causal relationship between adiposity and inflammation, however the opposite was not recorded^[42].

Notably, pro-inflammatory markers were also strongly associated with insulin resistance in most individuals, regardless of the degree of adiposity, implicating either a role or at least a relationship between these molecules and the transition to more insulin-resistant states like T2DM^[21,43,44].

Inflammation in T2DM and related cardiovascular complications

Subclinical chronic inflammation appears to be a distinct contributor to the development of T2DM^[21,45]. Independent of the initial degree of insulin resistance and obesity, elevated levels of several inflammatory biomarkers at baseline in different

human populations are predictive of T2DM occurrence^[21,45]. Elevated levels of IL-6 and CRP are significantly associated with an increased risk of T2DM^[46–48]. An elevated WBC count is also associated with a worsening of insulin sensitivity and predicts the development of T2DM^[38]. Increased circulating concentrations of pro-inflammatory cytokines IL-1 β , IL-18, TNF- α , (apart from IL-6 and CRP) and low levels of adiponectin are strongly associated with T2DM^[49]. Among the markers of blunted fibrinolysis, increased PAI-1 appeared to predict T2DM development independent of insulin resistance and other known risk factors for diabetes^[50]. Furthermore, biomarkers indicative of inflammation and endothelial dysfunction, including intercellular adhesion molecule 1 (ICAM-1) and E-selectin, were positively associated with the incidence of T2DM^[51]. Based on these observations, it could also be claimed that these changes may be associated with the various cardiovascular complications often related to T2DM and obesity^[52,53].

Finally, a plethora of GWAS has been conducted more recently regarding the association and causality between T2DM and inflammatory biomarkers^[54]. Of these IL-1 and IL-6 pathways appeared to be positively associated, however evidence remains elusive^[55,56].

PATHOPHYSIOLOGICAL BACKGROUND

As mentioned already, inflammation appears to be linked to insulin resistance and/or its worsening in obesity since it was shown to interfere with insulin signal transduction in critical metabolic organs (AT, liver, and muscle) and potentially contribute to the development of T2DM^[15,19,48]. In this section, we will present potential mechanisms driving obesity-related inflammation, primarily in the AT, and the implications of circulatory inflammatory factors on various metabolic and regulatory organs. A summary can be found in Figure 1.

Adipose tissue dysfunction

Excess adiposity, AT dysfunction (characterized by a state of low-grade inflammation), body fat distribution, and ectopic fat deposition, particularly visceral fat deposition, are all central figures in the pathophysiology of obesity and its complications^[8,11,14].

Dysfunctional AT is distinguished by adipocyte hypertrophy, which is associated with chronic low-grade inflammation, pro-inflammatory immune cell infiltration, adipokine dysregulation, hormonal resistance, blunted metabolism, reactive oxygen species (ROS) production, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and altered oxygenation, all of which contribute to ectopic fat accumulation and related complications ^[13,15,57,58]. The location of lipid storage is a key factor in determining an individual's overall health, as obesity-related complications such as hypertension and the risk of T2DM relate to abdominal (upper body) fat accumulation^[14,59–63]. In contrast, fat accumulation in the lower body (gluteofemoral AT) is linked to a lower risk of cardiometabolic disease^[59,64–67]. Lower body cell composition, including immune cells, is thought to be primarily associated with enhanced anti-inflammatory properties^[17,18]. In accordance with that theory, IL-6 release (as determined by an arteriovenous difference technique model) was much lower in femoral adipose tissue than in matched abdominal tissue^[60].

Obesity-related lipid accumulation in non-adipose tissues has significant metabolic effects since it is linked to insulin resistance and, potentially, through molecular mimicry, lipid moieties may trigger inflammatory pathways^[11,22,68]. Furthermore, hypertrophic adipocytes are shown to possess a pro-inflammatory phenotype, which may exacerbate insulin resistance, resulting in a vicious cycle^[69,70]. Adipocyte and AT inflammation, on the other hand, appears to be required for healthy AT growth and remodeling^[71]. That observation implies that inflammation is more than just a harmful process, maybe contributing to AT adaptation to stressors, including excess calorie intake. It is worth noting that drugs used to treat T2DM may reduce inflammation by lowering hyperglycemia. However, these medicines' anti-inflammatory effects are inconsistent, and it is unclear if their favorable metabolic effects are mediated by regulation of chronic low-grade inflammation^[72]. Finally, in addition to white AT

inflammation in obesity, it appears that brown AT inflammation also exists, at least in animal models of obesity, implicating that dysregulation of this tissue aggregates the obesity-related inflammatory status^[73].

Liver

Liver dysfunction linked with obesity, which encompasses the Metabolic Associated Fatty Liver Disease (MAFLD) spectrum, is characterized by complex pathophysiological processes that are currently under vigorous investigation and involve several pathways^[74]. It has been postulated that an inability to sufficiently enhance subcutaneous AT triglyceride (TAG) storage capacity in response to increased caloric consumption and body weight reroutes lipids towards other organs, such as the skeletal muscle and the liver, resulting in ectopic lipid accumulation and lipotoxicity at the cellular level, which leads to insulin resistance (IR) and inflammatory responses in these organs^[75–79]. Interestingly, fat molecules appear to serve as ligands for substantial inflammatory signaling pathways in Kupffer cells in the liver and AT macrophages *via* the toll-like receptor 2 and 4 (TLR2/TLR4) signaling cascade^[80]. Numerous ³ previous studies have shown that pro-inflammatory cytokines, specifically TNF- and IL-6, play an important role in the development and progression of NASH^[81,82]. TNF- and IL-6 Levels are elevated in the livers and blood of NASH patients, but blocking these mediators improved MAFLD in animal models^[81, 83].

Muscle

Several pro-inflammatory cytokines have been reported to be overexpressed apart from AT and the liver, also in the skeletal muscle of individuals with obesity and insulin resistance as well as in animal models^[84,85]. Obesity progression increases inflammation in skeletal muscle in two ways: indirectly through AT inflammation and adipocytokines dysregulation, which affect skeletal muscle function and may also augment IR, and directly through ectopic lipid deposition within the skeletal muscle, which initiates several pro-inflammatory pathways^[81,86,87]. Myocytes stimulate the production of

several hormones and cytokines, collectively called myokines, including IL-6 and IL-15, as well as other molecules like fibroblast growth factor 21 (FGF21) and irisin^[75,82]. All these molecules can regulate potential inflammatory processes, and the imbalance of their production in IR, obesity, and T2DM could further aggregate this overall inflammatory status^[88]. Sarcopenic obesity, which is more common in older patients, may also cause an increase in unfavorable pro-inflammatory status and impair insulin sensitivity *via* a loss of favorable myokines^[9]. Finally, as in the AT and other organs, immune cell infiltration with pro-inflammatory activation in skeletal muscle has been observed, **resulting in the release of pro-inflammatory markers such as IL-1, IL-6, and TNF- α** ^[89,90].

Other important tissues and organs dysfunction/inflammation

Evidence exists that several other tissues and organs in obesity, T2DM, and insulin resistance states are affected by or involved in systemic inflammation. For example, it is well established that macrophage infiltration is associated with islet inflammation and cell abnormalities in T2DM and obesity^[91-93]. Furthermore, the western diet and cultural habits may be part of a vicious cycle that promotes oxidative stress and inflammation in the gut and even the brain^[94]. Obesity-related inflammation is enhanced by diminished mucosal barriers and intestinal immune homeostasis^[95]. These findings could be attributed to effects on the gut microbiome^[96]; the importance of diet on organ-specific and systemic inflammation is apparent in diet-induced models of obesity in which even parts of the brain, in particular the hypothalamic arcuate nucleus, have been affected *via* infiltration of macrophages and increased expression of pro-inflammatory markers^[16,97-99]. Finally, even non-metabolic or metabolic regulatory organs seem to be affected, as obesity appears to induce ovarian and kidney inflammation, respiratory hyperresponsiveness, and various hematological consequences^[100-103].

IMPACT OF CLASSICAL METABOLIC TREATMENTS ON INFLAMMATION AND THE THERAPEUTIC POTENTIAL OF INFLAMMATORY MODIFICATIONS IN METABOLIC DISEASES

Strategies to tackle obesity, diabetes, and related cardiometabolic diseases include a variety of combinations, including lifestyle changes with dietary and exercise options, anti-obesity, anti-diabetic, and anti-hyperlipidemic medications, bariatric or metabolic surgery, and potentially the use of drugs with anti-inflammatory properties [72,104–107].

Current medicinal therapies for T2DM act in a multitude of ways to improve glycemic control, but they can also be beneficial for the treatment of obesity and related cardiometabolic diseases[23,24,72,107]. Many of these medications, for instance, metformin, may possess anti-inflammatory properties that can be exerted indirectly *via* metabolic control of hyperglycemia and hyperlipidemia and weight loss or by directly impacting the immune system and inflammatory responses[72,107]. Weight loss per se and therapeutic interventions that achieve it, including anti-diabetic and anti-hyperlipidemic medication use, resulted in reduced circulating concentrations of IL-6, IL-8, CRP, and MCP-1 and increased adiponectin concentrations[39,40,108–110]. A recent meta-analysis of the effect of intermittent fasting dietary patterns on plasma concentrations of inflammatory biomarkers found a decrease in CRP in individuals with overweight or obesity, but no changes in IL-6 or TNF-[111]. A meta-analysis of 116 studies[112], however, found that serum concentrations of CRP, IL-6, and TNF- were significantly lower after bariatric surgery.

Targeting inflammation or inflammatory pathways in general has emerged as a viable alternative to traditional metabolic therapeutic options[72,107]. Anti-TNF therapy has produced contentious results in the treatment of T2DM in humans[72,113]. In animal models of IR and T2DM, inhibition combining anti-TNF and IL-1 was shown to be more effective[107,114]. Favorable effects were recorded with IL-1 blockage alone in a human study[115]. Moreover, salsalate, a prodrug of salicylate, diacerein, an anti-arthritis medication, and hydroxychloroquine, usually used for the treatment of autoimmune diseases, appeared to be beneficial; however, long-term safety profiles for these

metabolic diseases are still to be elucidated^[72]. Finally, the option of directly altering the pro- or anti-inflammatory activation and the balance of the immune cells within the AT arises as a potential therapeutic option^[107].

CONCLUSION

In this brief review, we have demonstrated that inflammatory biomarkers reflecting underlying processes and pathway activations are present in obesity and type 2 diabetes mellitus. The impact of obesity and T2DM on inflammatory pathways appears to be linked to disease progression. Achieving a better understanding of the connection and causality between these factors and the disease risk and progression could give us the opportunity to potentially predict, follow up on, and modify their risk. Further studies are warranted to better understand the underlying pathophysiology and the use of predictive biomarkers in everyday clinical practice. It is necessary to conduct *in vivo* physiological studies to investigate the sequence of events underlying pathophysiological events in various metabolic and regulatory tissues, such as adipose tissue. Such studies can help elucidate whether inflammation precedes metabolic derangements or is mainly a result of perturbations caused by increased adiposity. Furthermore, it is essential to conduct randomized clinical trials that precisely target inflammatory pathways in diverse populations to either confirm or refute these findings.

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