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Review Article

Obesity and Systemic Inflammation: Pathophysiological Mechanisms and Management Strategies

Ayesha Abdul Raoof [1]

[1]Department of Internal Medicine, Adam Hospital, Ministry of Health, Sultanate of Oman

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***Corresponding author:** Ayesha Abdul Raoof
Email: ayesha.raoof001@gmail.com

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ABSTRACT

The worldwide increase in the prevalence of obesity marks the beginning of the global public health crisis that it unparalleled in human history. Obesity is the second major public health problem after tobacco use. Obesity is the central problem underlying the other epidemics of chronic diseases such as cardiovascular diseases, type 2 diabetes, and non-alcoholic fatty liver disease. Obesity is the key underlying problem. The systemic and chronic inflammation fuels the associated co-morbid conditions and obesity itself. I will devote the remainder of this review to the mechanistic aspects of the systemic inflammation induced by obesity. I will begin with the primary source: the adipose tissue itself, and expansion of the fat tissue, and infiltrating immune cells, along with the various forms of insulin resistance. Then I will review the evidence of the adipocytes' secretion of pro-inflammatory and inflammation perpetuating cytokines and adipokines as the central activators of the chronic and systemic fuel to the metabolic dysfunction of inflammation. The exit of the obesity and inflammation cycle needs a management plan. The lifestyle changes targeting diet and physical activity focus on the inflammation axis and assist in fat mass decline, along with the use of some prescribed anti-inflammatory medications, and drugs such as GLP-1 agonists and SGLT-2 inhibitors. For patients with severe morbid obesity, the impact of immune-modulating fat mass reduction and bariatric surgery and gastric bypass is chronic and systemic. This review highlights the importance of integrating lifestyle modifications, medications, and surgical options in the management of obesity and inflammation to optimize health outcomes and mitigate the complications associated obesity.

Keywords: Obesity, systemic inflammation, adipose tissue, lifestyle interventions, pharmacological treatments

BACKGROUND

As one of the most important global public health challenges of the 21st century, the World Health Organization contends that obesity results from the excessive accumulation of body fat and reflects a disequilibrium between the expenditure of and the

consumption of energy [1]. Obesity causes and complicates numerous other diseases, particularly type 2 diabetes, cardiovascular disease, some malignancies, and other inflammatory diseases. It is the systemic inflammation that obesity provokes and sustains that complicates the pathophysiology of the aforementioned conditions [2].

Obesity is also accompanied by systemic inflammation that is characterized by the activation of the disease fighting component of the immune system in the absence of an acute provoked infection or acute injury [3]. Adipose tissue is the only inflammatory tissue of the body that functionally operates as an endocrine tissue, releasing pro-inflammatory cytokines and other inflammatory mediators. It is the excess visceral adipose tissue that causes inflammation as cytokines cross the vascular endothelium of the systemic circulation, triggering and perpetuating the chronic inflammatory state of other organs in the body [4]. Although the dysfunction of the adipose tissue is the primary instigator of the inflammatory cascade, it also involves the liver, skeletal muscle and vasculature [5].

The proposed mechanistic pathways that interrelate obesity and systemic inflammation at the cellular and molecular levels have become a major interest of study. The main cause of inflammation in obesity is the excessive accumulations of adipose tissue, and more specifically, visceral adipose tissue [6]. Visceral adipose tissue is a metabolically active tissue and releases pro-inflammatory substances like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). The aforementioned inflammatory components lead to the activation of pro-inflammatory circulating immune cells like macrophages and neutrophils [7]. The hypoxic state of adipose tissue, common in obesity, leads to the activation of hypoxia-inducible factors (HIFs) and increased production of pro-inflammatory cytokines [8].

Insulin resistance is yet another central and driving factor in the inflammation of obesity. Insulin resistance that develops with excessive adipose tissue leads to hyperglycemia, the inability of cells to uptake glucose and further glucose modulated hyperinsulinemia [9]. Insulin further exacerbates inflammation with the over secretion of pro-inflammatory cytokines and adipokines. This cycle of excessive inflammation, metabolic dysfunction, and hyperglycemia is pernicious and self-sustaining [10].

The inflammatory response associated with obesity becomes an enduring issue, resulting in complications such as cardiovascular disease, type 2 diabetes, and fatty liver disorder. The connection between obesity and cardiovascular disease has been long established, with inflammation being a central mechanism driving atherogenesis and endothelial dysfunction [11]. Inflammation of the liver contributes to fat accumulation, resulting in NAFLD which can progress to NASH and cirrhosis. The obesity-diabetes link is complicated by the presence of insulin resistance and systemic inflammation, where, in the case of type 2 diabetes, inflammation further deteriorates β-cell function, contributes to insulin resistance, and systemic inflammation to expedite the progression of diabetes [12].

The consequences of inflammatory illness tied to obesity demonstrate the need for new therapeutic approaches. While diet and exercise remain essential, there is growing focus on obesity therapy that incorporates anti-inflammatory treatment [13]. The systemic inflammatory illness associated with obesity outlines the necessity for new therapeutic approaches, since anti-inflammatory strategies hold great potential for the management of obesity and associated inflammation [14].

This review investigates the mechanisms by which obesity leads to systemic inflammation and assess the contributions of adipose tissues, immune cells, and inflammatory pathways.

REVIEW

Mechanisms of Obesity-Induced Systemic Inflammation

Obesity triggers a complex network of cellular and molecular pathways that contribute to systemic inflammation. The key mechanisms involve:

1. Adipose Tissue and Inflammation: Inflammation associated with obesity is principally mediated by adipose tissue and visceral fat. Adipocytes and immunity cells that reside or infiltrate adipose tissue produce and release several pro-inflammatory cytokines and adipokines that maintain and propagate systemic inflammation [15]. Table 1 lists and describes the primary pro-inflammatory mediators of inflammation released by adipose tissue.

Table 1: Pro-inflammatory Mediators and Their Sources

Pro-inflammatory Mediators	Source	Effects on Inflammation
Tumor Necrosis Factor-alpha (TNF-α)	Adipocytes, Macrophages	Activates immune cells, induces insulin resistance, increases vascular permeability
Interleukin-6 (IL-6)	Adipocytes, Macrophages	Stimulates liver production of C-reactive protein (CRP), amplifies immune response
C-Reactive Protein (CRP)	Liver (induced by IL-6)	Serves as a marker of systemic inflammation, contributes to atherosclerosis
Leptin	Adipocytes	Stimulates inflammatory pathways, enhances endothelial dysfunction
Adiponectin	Adipocytes (lower in obesity)	Anti-inflammatory, reduces insulin resistance

2. Immune Cell Activation and Infiltration: The presence of excess adipose tissue in obesity creates a microenvironment that facilitates the unsolicited entry of immune cells into the adipose tissue. Signals released from hypertrophic adipocytes and tissue hypoxia lead macrophages, neutrophils, and T-lymphocytes to infiltrate the adipose tissue [16].Table 2 presents the roles of immune cells in obesity-induced inflammation and their impact on health.

Table 2: Immune Cell Activation in Obesity-Induced Inflammation

Immune Cell Type	Role in Obesity-Induced Inflammation	Impact on Health
Macrophages	Release cytokines (e.g., TNF-α, IL-6), polarize towards M1 phenotype	Drive systemic inflammation, insulin resistance
Neutrophils	Contribute to oxidative stress, release proteases	Aggravates endothelial dysfunction, promotes atherosclerosis
T-cells	Promote chronic inflammation, modulate immune responses	Contribute to inflammatory processes in insulin resistance and atherosclerosis

3. Insulin Resistance and Inflammation: As obesity progresses, insulin resistance becomes more pronounced. Elevated insulin levels in response to insulin resistance can amplify the inflammatory response, further promoting a cycle of inflammation and metabolic dysfunction [17].Table 3 outlines the mechanisms through which insulin resistance contributes to systemic inflammation and its consequences.

Table 3: Insulin Resistance and Inflammation

Mechanism	Effect on Systemic Inflammation	Consequences
Elevated Insulin	Stimulates inflammatory cytokine release	Aggravates insulin resistance, increases pro-inflammatory cytokines
Hyperglycemia	Increases reactive oxygen species (ROS) production, enhancing oxidative stress	Further insulin resistance, contributes to endothelial dysfunction
Adipokine imbalance	Reduced adiponectin and increased leptin levels	Heightened inflammation, impaired fat metabolism

Consequences of Obesity-Induced Systemic Inflammation

The chronic inflammation seen in obesity leads to numerous health complications. These include:

1. Cardiovascular Diseases: Systemic inflammation contributes to the development of atherosclerosis and endothelial dysfunction, two key factors in the onset of cardiovascular diseases [18].Table 4 outlines the effects of inflammation on cardiovascular health and the resulting consequences.

Table 4: Inflammation and Cardiovascular Diseases

Inflammatory Mediators	Effect on Cardiovascular Health	Consequences
TNF-α, IL-6, CRP	Stimulate endothelial cells, promote plaque formation	Increased risk of heart attacks, strokes
Adipokines (e.g., leptin)	Impair nitric oxide production, increase arterial stiffness	Hypertension, atherosclerosis, cardiovascular disease

2. Type 2 Diabetes: Chronic inflammation disrupts normal insulin signaling, contributing to the development and progression of insulin resistance, a hallmark of type 2 diabetes [19].Table 5 provides a summary of the impact

of inflammatory mediators on insulin resistance and the consequences for type 2 diabetes.

Table 5: Inflammation and Type 2 Diabetes

Inflammatory Mediators	Effect on Insulin Resistance	Consequences
IL-6, TNF-α	Impair insulin receptor function, promote β-cell dysfunction	Elevated blood glucose levels, diabetic complications
Adipokines (e.g., leptin)	Block insulin signaling pathways, exacerbate insulin resistance	Increased risk of metabolic syndrome, hyperglycemia

3. Non-Alcoholic Fatty Liver Disease (NAFLD): Obesity and inflammation are closely associated with the development of NAFLD, which can progress to more severe liver diseases such as cirrhosis [20]. Table 6 illustrates the inflammatory mediators involved in liver health and their consequences in the context of NAFLD.

Table 6: Inflammation and Non-Alcoholic Fatty Liver Disease (NAFLD)

Inflammatory Mediators	Effect on Liver Health	Consequences
IL-6, TNF-α, CRP	Stimulate hepatocytes, enhance fat accumulation	NAFLD, fibrosis, non-alcoholic steatohepatitis (NASH)

Management Strategies for Obesity and Systemic Inflammation

Given the detrimental effects of chronic inflammation in obesity, effective management strategies are essential. These strategies focus on reducing obesity itself, addressing inflammation, and improving metabolic outcomes.

Lifestyle Interventions: The indications that lifestyle changes, especially including certain dietary modifications and exercise, have a considerable impact on obesity and associated inflammatory states are presented in Table 7. The goal of the first dietary intervention entails the incorporation of low-calorie, anti-inflammatory food items, which are known to mitigate fat accumulation and alter cytokine (inflammation-mediating proteins) production [21]. Since the fatty tissue mass is associated with the production of pro-inflammatory cytokines, the reduction in fatty tissue will lead to a reduction in overall systemic inflammatory response. In addition to the reduction of fatty mass, the positive change in the dietary pattern triggers the metabolic health to improve, especially the more manageable glucose and insulin levels which are important in obesity and associated inflammatory state [22].

The second intervention of exercise improves insulin sensitivity and lowers visceral fat, which is a major contributor to inflammation in obesity. With regular exercise, the body's insulin utilisation improves, and there will be a reduction of the oversecretion of insulin, which is characteristic of obesity and inflammation [23]. Exercise also lowers the secretion of adipokines and enhances the secretion of anti-inflammatory cytokines, thus addressing inflammation triggered by excess adipose tissue. Overall, these lifestyle changes suggest to not only promoting positive weight changes but also improving the inflammatory state and overall metabolic health of the individual [24].

Table 7: Lifestyle Interventions for Obesity and Inflammation

Intervention	Impact on Obesity and Inflammation	Outcome
Diet (low-calorie, anti-inflammatory foods)	Reduces fat accumulation, modulates cytokine production	Decreases systemic inflammation, improves metabolic health
Physical Activity	Enhances insulin sensitivity, reduces visceral fat	Reduces adipokines, promotes anti-inflammatory cytokines

Pharmacological Interventions: The past few decades have seen a culmination of research on the inflammatory component of obesity leading to the creation of Plans for the pharmacological management of obesity and its inflammatory consequences. Drugs like TNF-α inhibitors help ease the effects of obesity and increase insulin sensitivity by lowering systemic inflammation and insulin resistance. Such medication target the inflammation directly whereby inflammation cascades and metabolic consequences such as hyperglycemia and insulin resistance become significantly improved [26].

DISCUSSION

The pharmacological intervention of the GLP-1 agonist class of drugs also improves the management of obesity. GLP-1 agonists aid in weight loss by increasing insulin sensitivity and assisting in the reduction of fat deposition; as a result, blood sugar levels are controlled, and inflammatory markers, markers of obesity, become less numerous. The importance of these drugs also lie in their ability to manage type II diabetes and their effects on the inflammation of obesity in peripheral fat, thus improving long term metabolic health [27].

SGLT-2 Inhibitors is yet another class of drugs which help with glycosuria and help with weight reduction as well. These agents help with both the metabolic and inflammatory components of obesity and assist with the reduction of bodily inflammation and metabolic profile improvement for the better responding to obesity with type 2 diabetes. Collectively, such pharmacological measures tackle the problem of the inflammatory and insulin resistance state, and the weight reduction attempts in a more comprehensive and organized manner [28].

The overview of surgical treatment options for severe obesity and associated inflammation, such as bariatric surgery and gastric bypass. The surgery for obesity which is most frequently performed is bariatric surgery which works by decreasing fat mass and altering gut hormones that regulate hunger and satiety. The result is a significant decrease in pro-inflammatory cytokines which are primarily produced by adipose tissues. During the metabolic state, insulin sensitivity improves, fat tends to resolve and be eliminated, and other conditions such as type 2 diabetes are positively impacted [29].

Another surgical option which is gastric bypass, invokes revision of food intake and changes the way the body absorbs nutrients which is also one of the major mechanisms to undergo significant visceral fat loss as inflammation. Gastric bypass surgery improves the inflammatory state associated with obesity by altering the hormonal interplay governing lipids and the immune system [30].

In summary, gastric bypass, as well as both other types of bariatric surgery which promote significant weight loss, decrease obesity inflammatory syndrome. All three surgeries present severe obesity patients with lifetime benefits. Although more invasive than lifestyle modifications and pharmacotherapy, these surgical approaches do provide a viable and meaningful option for patients suffering from morbid obesity, resulting in weight loss, a decrease in inflammatory states, and improvement in overall metabolic health.

FUTURE AIMS AND SCOPE

One promising approach involves modulating the release of anti-inflammatory adipokines or targeting adipokines, since these are the molecules released by fat cells. In another promising line of investigation, modifying gut microbiota composition is proposed as a means to manage inflammation caused by obesity. There are also efforts to study gene therapy aimed at the genetic determinants of adipogenesis and inflammation to tackle the inflammation obesity. All of these efforts are aimed at developing strategies to address the inflammation related to obesity [31].

CONCLUSION

Obesity is associated with chronic inflammation which, in turn, perpetuates the cycle of inflammation related to diseases such as cardiovascular disease, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD). The presence of excess adipose tissue and insulin resistance give rise to and perpetuate the cycle of obesity and other associated metabolic disorders. The incorporation of new lifestyle techniques, which include nutrition and physical activity, can reduce fat mass, enhance insulin sensitivity, and mitigate inflammation. The course of inflammation and metabolic disorders improves with the use of anti-inflammatory medications and diabetes medications, i.e., GLP-1 agonists and SGLT-2 inhibitors. The use of bariatric surgeries in individuals with severe obesity aids in modulating the inflammatory response and alleviating obesity. The management of obesity and its associated inflammatory response is best achieved with the integration of lifestyle modification, pharmacotherapy, and surgical interventions.

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Ayesha Abdul Raoof : Conceptualized the study, developed the review design, and oversaw the entire project. She was responsible for all the preparation of this review article.

ABBREVIATIONS USED IN THE STUDY:

a) **TNF-α** - Tumor Necrosis Factor-alpha
b) **IL-6** - Interleukin-6
c) **CRP** - C-Reactive Protein
d) **GLP-1** - Glucagon-Like Peptide-1
e) **SGLT-2** - Sodium-Glucose Cotransporter-2
f) **NAFLD** - Non-Alcoholic Fatty Liver Disease
g) **NASH** - Non-Alcoholic Steatohepatitis
h) **HIFs** - Hypoxia-Inducible Factors
i) **β-cell** - Beta-cell (referring to insulin-producing cells in the pancreas)
j) **ROS** - Reactive Oxygen Species
k) **Adipokines** - Cytokines secreted by adipose tissue

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