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An Analysis of the Impact of Metabolic Changes Caused by Obesity on Immune Response

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Abstract. Currently, as obesity rates continue to rise globally, its complications are becoming increasingly detrimental to public health. Beyond its close association with chronic diseases such as cardiovascular disease and diabetes, obesity is also recognized as an important contributor to immune dysfunction. This study aims to investigate how obesity-induced metabolic changes interact with the immune response and increase the risk of infection and inflammation. Through a systematic literature review, this paper explores how obesity-induced metabolic changes affect the immune system through multiple pathways. The study specifically focuses on altered glucose and lipid metabolism, insulin resistance, and imbalances in adipokines and cytokines. It reveals how obesity-induced metabolic disturbances and chronic low-grade inflammation disrupt normal immune function, leading to increased susceptibility to infections, inflammation, and chronic diseases. It demonstrates a positive correlation between obesity and the risk of infection and inflammation, providing a comprehensive perspective on these interactions.

Keywords: Obesity, Metabolic Changes, Immune Response, Inflammation, Infection Risk.

1. Introduction

According to the WHO, as of 2022, more than 1 billion people will be obese globally, with 300 million classified as clinically obese [1]. Obesity has become a serious public health challenge worldwide, profoundly affecting the body's immune system in addition to being strongly associated with chronic diseases such as cardiovascular disease and diabetes [2]. Obesity-induced metabolic changes, such as insulin resistance and chronic low-grade inflammation in adipose tissue, have been shown to have a significant impact on immune function [3]. Although existing studies have revealed how obesity-induced metabolic disorders alter the function and number of immune cells, particularly macrophages and T cells, through multiple pathways, most obesity studies have focused on a single metabolic pathway or a specific immune cell type and have lacked systematic analyses of overall metabolic-immune interactions. This study utilized a systematic literature review. First, the authors conducted a literature search in databases like PubMed, Web of Science, and Google Scholar using the keywords “obesity,” “metabolism,” “immune response,” “inflammation,” and “chronic disease.” Screening criteria included peer-reviewed articles published within the last decade, studies involving obesity-related metabolic and immune interactions, and studies involving human and animal models. The final literature included in the analysis included 50 original studies. Based on the literature review, this study constructed a theoretical framework to systematically explore how obesity-induced metabolic changes

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affect the immune system through multiple pathways. This article specifically focused on insulin resistance, abnormal lipid metabolism, adipokines, cytokines, and changes in immune cell function. Through a comprehensive analysis of the existing literature, the collective impact of these changes on infection risk and chronic disease development is revealed, and potential mechanisms and influences are explored. Through this integrative perspective, this study not only deepens the understanding of the complex relationship between obesity and immune response, but also provides a new theoretical basis for future research, helps identify new therapeutic targets for obesity-related diseases, and provides strategies and directions for improving the health of obese individuals.

2. Obesity-induced metabolic changes

Obesity triggers a series of complex metabolic changes, and adipose tissue, beyond its role as an energy storage organ, functions as an active endocrine organ that produces a variety of adipokines, including leptin, lipocalin, endolipin, and resistin [4]. These adipokines interact in a complex manner with long-term energy regulators such as insulin. An increase in adipocyte mass and volume disrupts the balance of hormone secretion, leading to a series of metabolic disorders [4].

Firstly, altered glycolipid metabolism is one of the most striking features of obese individuals [5]. Excessive accumulation of lipids not only affects the function of adipocytes, but also disturbs the energy balance of the whole body, which is manifested by elevated fasting blood glucose levels and dyslipidemia [6]. Studies have shown that fasting blood glucose in obese individuals usually exceeds 100 mg/dL, while the normal range is 70-99 mg/dL, showing signs of impaired glucose tolerance or even pre-diabetes [7]. In addition, triglyceride levels in obese individuals usually exceed 150 mg/dL, while the normal range is below this threshold, and HDL cholesterol levels are often less than 40 mg/dL, which is below the normal recommended level [8]. These abnormal lipid levels indicate a serious disturbance of lipid metabolism in obese individuals, increasing the risk of atherosclerosis and cardiovascular disease [8]. This metabolic disorder is not only one of the manifestations of obesity, but also a precursor to the development of insulin resistance and increased cardiovascular risk [6].

Insulin resistance is another key metabolic change triggered by obesity. It is usually accompanied by the presence of chronic low-grade inflammation. In the obese state, excess lipid and glucose metabolites accumulated in adipose tissue interfere with insulin signaling, triggering a decrease in insulin sensitivity [6]. At the same time, these metabolites stimulate the release of inflammatory factors, such as TNF-α and IL-6. The accumulation of these pro-inflammatory cytokines in adipose tissue further exacerbates insulin resistance, creating a vicious circle that intensifies metabolic disorders [2,6].

Meanwhile, leptin and lipocalin proteins are key regulatory substances secreted by adipose tissue that play different roles in the body. Leptin is primarily associated with appetite regulation and energy homeostasis, whereas specific lipocalin, such as Lipocalin-2 (LCN2), plays important roles in anti-inflammatory responses and insulin sensitization [9,10].

In obese individuals, leptin levels are usually significantly elevated, often reaching several times that of normal weight individuals [11-13]. In contrast, levels of lipid carrier proteins, particularly Lipocalin-2 (LCN2), are significantly altered in obese individuals. In animal models (e.g., Lepr db/db mice), it has been shown that a 50% reduction in circulating LCN2 levels exacerbates metabolic dysfunction, including weight gain and fat accumulation [14]. Such variations in LCN2 levels impair its anti-inflammatory and insulin sensitizing functions, which can promote the development of inflammation and insulin resistance [14]. Imbalances in lipocalin levels exacerbate inflammation, manifested by increased release of pro-inflammatory cytokines (e.g., IL-1β, IL-6, and MCP-1), leading to a systemic inflammatory response [6]. This systemic inflammation not only affects the metabolic state of adipose tissue, but also has profound effects on other organ systems, laying the foundation for metabolic and immune dysregulation in the development of obesity-related diseases.

3. Effects on immune cells and function

The immune system protects the organism through a complex array of cellular and molecular mechanisms that accurately distinguish between its own cells and foreign pathogens, and effectively

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detect and destroy invading viruses [15]. However, the metabolic dysregulation induced by obesity impairs these immune responses, resulting in reduced infection-fighting capabilities and weakened immune surveillance. This phenomenon, known as immune dysregulation, increases the organism's susceptibility to infections [15].

In the state of obesity, adipose tissue, as an active endocrine organ, undergoes significant changes in the level and pattern of secretion of a variety of immune-related proteins (e.g., leptin, TNF-α, and IL-6) [2]. This change is driven by obesity-induced abnormal expansion and dysfunction of adipocytes, which enlarge as obesity worsens, leading to increased leptin secretion. However, due to the presence of leptin resistance, these elevated leptin levels fail to exert their normal regulatory effects, and the regulation of appetite and energy homeostasis is thus inhibited. In addition, the increased secretion of pro-inflammatory cytokines and decreased secretion of anti-inflammatory factors in adipose tissue further contribute to the formation and maintenance of a systemic inflammatory response, which in turn exacerbates immune dysfunction [2].

Besides, studies have shown that obesity leads to a significant accumulation of macrophages in adipose tissue, especially an increased proportion of pro-inflammatory M1-type macrophages [16]. Studies have shown that in obese individuals, the percentage of macrophages in adipose tissue rises from 5%-10% in lean individuals to as much as 40%-50% in obese conditions, indicating a strong link between obesity and increased inflammation within adipose tissue [17]. These M1-type macrophages secrete large amounts of pro-inflammatory factors (e.g., TNF-α and IL-6), which not only exacerbate the chronic inflammation in adipose tissue, but also affect other tissues and organs through the systemic circulation, leading to the development of a systemic inflammatory state [16]. This chronic inflammatory state not only damages the adipose tissue itself, but also further weakens the systemic immune function and reduces the body's ability to fight infection and tissue repair [18].

Moreover, obesity triggers significant changes in T-cell subsets. In the obese state, the activation of pro-inflammatory Th1 and Th17 cells is increased, whereas the function of regulatory T cells (Treg) is suppressed [19]. The over-activation of Th1 cells, which promote the inflammatory response mainly through the secretion of interferon gamma (IFN-gamma), and Th17 cells, which enhance inflammation through the secretion of IL-17, is closely associated with immune dysfunction in obese individuals [19].

Thus, a series of metabolic changes triggered by obesity leads to chronic low-grade inflammation and significantly impaired immune function, weakening the body's defenses against external pathogens and exacerbating the risk of infections, as well as the onset and progression of chronic diseases.

4. Increased risk of infection

The close relationship between obesity and immune system dysregulation significantly increases the risk of infection [20]. Obesity not only leads to an attenuated cell-mediated immune response, but also triggers a series of metabolic changes and dysregulation of immune function, which directly contribute to the increased susceptibility of obese individuals to various infectious diseases [20,21]. Studies have shown that obesity is a known risk factor for surgical site infections, nosocomial infections, periodontitis, skin infections, and respiratory tract infections [20,21].

Among respiratory infections, obese individuals are at particularly significant risk. Obesity-induced chronic low-grade inflammation and impaired immune cell function weaken the body's immune defences, making it difficult for obese individuals to respond effectively in the face of viral attack [22]. For example, a systematic review and meta-analysis encompassing data from 75 studies across various countries found that obese individuals were 46% more likely to test positive for COVID-19, had a 113% higher risk of hospitalization, and experienced a 48% increased mortality rate compared to those with a healthy weight. The studies included in the analysis covered a wide range of populations, from inpatients to the general community population, suggesting strong evidence that obesity significantly increases the risk of COVID-19 [23].

It has been shown that obese COVID-19 patients have higher SARS-CoV-2 viral loads in the upper respiratory tract, implying uncontrolled upper respiratory viral replication or ineffective immune responses in obese patients [23-25]. Notably, patients with high viral loads tend to face higher mortality

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and longer incubation periods [23,24]. In addition, excess subcutaneous adipose tissue in the chest and abdomen of obese individuals limits lung expansion, leading to decreased lung capacity, which in turn increases the risk of respiratory infections through shallow breathing [24-26]. Excess parapharyngeal fat is also associated with higher airway resistance, which may lead to upper airway obstruction or collapse, such as obstructive sleep apnoea [24-26]. As a result, obesity not only prolongs the duration of infection, but also significantly increases the incidence of severe illness and complications, such as respiratory failure and acute respiratory distress syndrome (ARDS) [24-26].

The risk of infection is also exacerbated by the negative impact of obesity on the wound healing process. Excess adipose tissue in obese individuals results in relatively poor blood circulation, leaving the wound site with an inadequate supply of oxygen and nutrients [27]. This insufficient oxygen supply slows down fibroblast activity and collagen synthesis, thereby slowing down the wound healing process [28].

The risk of infection in obese individuals is also reflected in a diminished vaccine response [24,29]. Obesity-induced immune dysregulation impairs immune memory formation following vaccination, making obese individuals unable to generate as effective an immune response as normal-weight individuals when confronted with the same pathogens [24,29]. Reduced vaccine effectiveness means that even after vaccination, obese individuals remain at a higher risk of infection [24,29]. To complicate matters, the diminished vaccine response may be linked to a multifactorial interaction of chronic inflammatory states, dysfunction of the immune system, and metabolic disorders in obese individuals, further suggesting a broader negative impact of obesity on the immune system [24,29].

5. Inflammation and chronic diseases

Inflammation is a physiological response of the body to noxious stimuli, whether physical, chemical or biological, and usually contributes to the re-establishment of homeostasis in the body [30]. However, obesity-induced metabolic changes not only lead to impaired immune function and increased risk of infection, but also drive the onset and progression of several chronic diseases through persistent chronic low-grade inflammation [30]. For example, obese individuals are twice as likely to develop coronary heart disease compared to those with normal weight [31]. And obese people have seven times the risk of developing type 2 diabetes than healthy weight people [32].

As fat continues to accumulate, it not only accumulates in adipose tissue, but is also deposited in other organs, especially in the liver, leading to the development of NAFLD and systemic insulin resistance [33]. In the context of obesity, multiple adipokines secreted in adipose tissue play a key role in the onset and development of these metabolic disorders [33]. Studies have shown that leptin and lipocalin act as adipokines, with the former promoting the production of pro-inflammatory factors such as TNF-α and IL-6 in obesity, exacerbating chronic inflammation [9,10]. The latter, on the other hand, has the opposite effect to leptin, which is anti-inflammatory, but its levels are usually low in obese individuals, thus creating a vicious circle [9,10].

As inflammation increases, these metabolic changes set the stage for the development of a range of chronic diseases. The metabolic syndrome, as a typical manifestation of these metabolic dysregulations, usually includes glucose intolerance, central obesity, dyslipidemia, and hypertension [34]. These metabolic abnormalities not only exist independently of each other, but also increase the risk of cardiovascular disease, type 2 diabetes, and certain cancers through complex interactions [34].

There is a direct link between obesity-related chronic inflammation and type 2 diabetes. Pro-inflammatory factors in adipose tissue, such as TNF-α and IL-6, interfere with insulin signaling and further exacerbate metabolic disturbances [35]. This inflammatory state not only contributes to the development of diabetes, but also complicates the management of the disease and increases the risk of complications.

Cardiovascular disease is also an important consequence of obesity-induced chronic inflammation[36,37]. The immune system disorders and chronic inflammatory state described above not only trigger inflammation locally in the adipose tissue, but also have a widespread effect throughout the body via the blood circulation, resulting in systemic inflammation [36]. These inflammatory factors,

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together with abnormalities of lipid metabolism common in obese individuals, accelerate the formation of atherosclerosis and increase the risk of cardiovascular events [37]. Thus, obesity disrupts the immune response while simultaneously contributing to cardiovascular pathology through a persistent inflammatory state.

6. Discussion

The profound effects of obesity on the immune system have been demonstrated in numerous studies. The metabolic disturbances triggered by obesity not only contribute directly to immune dysfunction but also significantly increase the risk of infection and inflammation. Obesity-induced chronic low-grade inflammation is thought to be a central driver of these immune abnormalities. This chronic inflammation not only weakens the body's ability to fight off infections, but also has a lasting impact on systemic metabolism. This systemic inflammation further triggers the development of other serious health problems, particularly type 2 diabetes, and cardiovascular disease. Taken together, obesity not only affects immune function by triggering metabolic disturbances, but also promotes the development of chronic diseases through complex metabolic-immune interactions. Therefore, the management and amelioration of obesity-associated metabolic disturbances should be prioritized.

Comprehensive interventions are essential to control and improve obesity-related metabolic disorders. Dietary modifications and physical activity are the basis for managing obesity, such as a very low-calorie diet or Mediterranean diet therapy [38]. By reducing energy intake and increasing energy expenditure, these interventions can help reduce weight and improve metabolic function [38]. Behavioral therapies also play a critical role in increasing patient compliance with lifestyle changes, thus leading to long-term weight management and metabolic improvement [39].

In terms of pharmacologic interventions, multiple drug classes can act synergistically to control and improve obesity-related metabolic disturbances. For example, insulin sensitizers (e.g., metformin) can effectively improve insulin resistance and lower blood glucose levels; lipid-lowering drugs (e.g., statins) reduce the risk of cardiovascular disease by regulating blood lipids; in addition, anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), can inhibit chronic low-grade inflammation and help improve the systemic inflammatory response induced by obesity [40][41][42]. This multipronged pharmacologic therapy provides a comprehensive strategy for the management of obesity-related metabolic disorders.

For patients with severe obesity who have not achieved satisfactory results with other methods, surgical interventions, such as gastroplasty, gastric banding, and Roux-en-Y gastric bypass can significantly reduce body weight, improve metabolic function, and reverse obesity-induced metabolic disorders [38].

7. Conclusion

This article provides insights into the metabolic changes triggered by obesity and further comprehends the impact of these metabolic changes on the risk of infection and inflammation and their progression. The findings suggest that obesity not only causes metabolic disorders but also serves as a significant driver of immune system dysregulation and multiple chronic diseases. Obesity-induced metabolic-immune interactions exacerbate systemic inflammation, increase the risk of infection, and significantly increase the incidence of type 2 diabetes and cardiovascular disease. However, there are shortcomings in this study. Firstly, it relies primarily on existing literature and theoretical analyses, lacking empirical data, particularly from clinical trials, which limits the extrapolation of the results. Second, the study did not delve into the effects of different types of obesity on immune responses and metabolism, nor did it adequately consider the role of individual differences such as gender, age, and genetic background. Future research should design more comprehensive clinical studies and experiments to validate theories and further explore whether there are deeper implications of different types of obesity in the specific mechanisms of metabolic changes on infection and inflammation.

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