

The Intriguing Relationship Between Obesity and Infection

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Abstract

The number of overweight people worldwide is steadily growing. Obesity has become a serious health problem even in developing countries where infectious diseases are still highly prevalent. However, the interactions between these two conditions are still unclear. It is known that, during obesity, lipid deposits induce metabolic alterations associated with increased pro-inflammatory status, which disrupts the body hemostasis and could impair the immune responses against microorganisms. Moreover, studies in humans and animal models with infectious diseases have demonstrated that obesity usually correlates with increased susceptibility to bacterial, viral and protozoa parasite infections. In this mini-review, we will discuss some few studies that characterized the interactions between obesity and infections to clarify why obesity-associated inflammation results in impaired protective immunity.

Introduction

Obesity has become a major health problem in the world, if the current trends continue, global obesity prevalence will reach 24% in men and will surpass 27% in women, by 2025¹. Considering the widespread occurrence of obesity and infections in the population, such interactions need to be identified and addressed. Obesity brings not only metabolic alterations but also induces a range of modifications in the immune response that can compromise the ability to deal with infections.

During obesity, there is a complex modification in adipose tissue (AT), with cell infiltration and pro-inflammatory cytokines secretion. Obesity-related alterations induce a status of chronic low-grade inflammation. It is known that this inflammation is often associated with unbalanced metabolism and differentiated immune response. This review will identify the impact of obesity in some infectious diseases.

Immune-Metabolic Consequences of Obesity

In normal condition (homeostasis), AT is a connective tissue of low density and high plasticity. However, in obese individuals, the content of connective fibers from AT increases, mainly collagen VI, making the extracellular matrix (ECM) more rigid and with less capacity to expand and store lipids, enhancing the free fatty acids (FFA) concentration². Those alterations favor ectopic deposit of lipids in some organs, such as liver, skeletal muscle, and pancreas, resulting in metabolic imbalance and lipotoxicity³. Obesity is also associated with stress in the endoplasmic reticulum (ER) in AT, that leads to adiponectin hypo-secretion and increased lipolysis, which

contributes to insulin resistance, endothelial dysfunction and atherosclerosis⁴.

Apart from AT, obesity impacts the modulation of intestinal microbiota, increasing intestinal permeability, bacteria and lipopolysaccharides (LPS) translocation to the circulation. These alterations in the intestinal mucosa increase cellular infiltration and amplify the contact between LPS and other pathogen-associated molecular patterns (PAMPs) with toll like receptors (TLRs), mostly TLR4^{5,6}. These receptors are known to trigger inflammatory signaling pathways in immune cells such as macrophages, dendritic cells and T cells⁷⁻⁹.

As first described by Hotamisligil (1993), TNF- α levels are increased in AT of obese subjects¹⁰. Later reports, showed a positive correlation between the adipocyte size and the TNF- α production¹¹. This cytokine also favors the activation of NF- κ B and stimulates the cell death-signaling pathway. Moreover, it acts inhibiting GLUT4 expression and enhancing the levels of FFA in the blood which leads to insulin resistance¹². The FFA excess, which activates IKK β , NF- κ B, JNK, and TLR pathways^{13,14}, also contributes to protein phosphorylation and commands the augment in TNF- α , IL-6, leptin, and resistin levels. Increased levels of inflammatory mediators, such as FFA, LPS, and proinflammatory cytokines act directly in monocytes differentiation to "classically activated" (M1) macrophages. These macrophages produce mostly inflammatory cytokines, reactive oxygen species (ROS) and nitric oxide, which could help the innate immune response against pathogens¹⁵. Due to increased cell recruitment and higher production of inflammatory cytokines, obesity establishes a chronic "low-grade" inflammatory response.

It has been shown that high-fat-fed mice, present higher number of TCD4⁺, TCD8⁺ and higher levels of IFN- γ and TNF- α when compared to the lean counterparts, mostly in the AT¹⁶. The TCD8⁺ infiltration in AT precedes the macrophage (M1) accumulation, which migrates towards the AT in response to higher amounts of FFA, glucose and apoptosis, increasing the inflammation. This scenario contributes to the production of more proinflammatory cytokines, release of monocyte chemoattractant protein-1 (MCP-1) and MCP-3, which creates a cycle of continuous cell recruitment and constant inflammation in the AT¹⁷. Obesity also helps to modify the adhesion capacity of leucocytes, adipocytes and endothelial cells by altering the expression of adhesion molecules, such as ICAM-1 and VCAM-1, chemokines such as C-C chemokine receptor type 2 (CCR2), impacting in antigen presentation by antigen-presenting cells (APCs).

The lipid deposit in ectopic tissues causes metabolic alterations during obesity. This affects the architecture and function of primary and secondary lymphoid organs¹⁸.

It has demonstrated that in leptin-deficient mice (ob/ob), there is increased lipids infiltration in bone marrow, which impacts severely in the hematopoiesis¹⁹. Leptin can stimulate the synthesis of T cell factors, such as IFN- γ and enhance macrophage effector functions. However, leptin deficiency reduces the numbers of naive T cells, decreases the production of IL-2, IFN- γ and favor Th2 immune response¹⁷. Leptin signaling modulate the hypo-responsiveness and exerts negative signal for the proliferation of Treg cells, decreasing their activity and abrogating the cells functions²⁰.

In mice with diet-induced obesity, there is a reduced thymopoiesis and restricted T-cell receptor repertoire diversity¹⁸. Yet, the peripheral immune response in obesity has reduced migration of APCs to peripheral lymph nodes and the number of T lymphocytes. These changes lead to dysfunction in the distribution of leukocyte populations and in lymphocyte activity²¹. Thus, these alterations could affect the immune response against infectious diseases.

Obesity and Infections

The low-grade inflammatory context of obesity and its systemic effects create a scenario where the relationship with infectious diseases is intriguing. Although obesity is associated with a systemic low-grade inflammation, studies correlating obesity in humans and animal models with infectious diseases usually demonstrate an impaired immune response and increased susceptibility to bacterial and viral infections (Table 1). The mechanisms by which obesity affects the immune response to diverse infective agents are not yet fully understood²².

Studies with ob/ob mice, were the first to demonstrate a negative relationship between obesity and airway bacterial infections, including *Klebsiella pneumoniae*²³ and *Mycobacterium tuberculosis*²⁴. In most cases, the worst outcome was associated with the inability of macrophages to clear bacteria in the compromised organ, due to impaired phagocytosis, leading to higher dissemination to peripheral blood and higher mortality of the host. Those first studies also noticed that ob/ob mice displayed a delayed efficient inflammatory immune response against to the airway pathogen, leading to enhanced lethality.

As cited above, leptin deficiency implicates in many alterations in the immune system by itself. Otherwise, diet-induced obesity models in rodents try to be more realistic to human obesity, in a sense that it promotes all the metabolic effects associated with obesity over an alteration in the nutritional habits of the animals. It has been shown that diet-induced obesity leads to the worst outcome infection by Influenza virus^{25,26}. Obese mice exhibited increased mortality, with decreased levels of important antiviral cytokines, such as IFN- α and IFN- β and concomitant reduction in the cytotoxicity of NK cells,

Table 1. Studies of infectious diseases, immune system and obesity

Infection	Animal model	Immune cells alterations	Impact of obesity	References
<i>Klebsiella pneumoniae</i> , <i>Streptococcus pneumoniae</i> ; <i>Mycobacterium tuberculosis</i>	ob/ob mice	Macrophages	↓ phagocytosis	21-23
Influenza virus	Diet-induced obesity	Innate cells and T cells	↓ IFN-α and IFN-β; ↓ NK; macrophages and memory T cell	22-23
<i>Staphylococcus aureus</i>	Diet-induced obesity	B cells	↓ IgG anti- <i>S. aureus</i>	24
<i>Porphyromonas gingivalis</i>	Diet-induced obesity	Innate and adaptive immune system	↓ TNF-α, IL1-β, and IL-6; macrophage phagocytosis	26
<i>B. burgdorferi</i>	Diet-induced obesity	macrophages and neutrophil	↓ phagocytosis	27
<i>Trypanosoma cruzi</i>	db/db mice	Innate cells	↑ IL-6 and TNF-α	33
<i>Trypanosoma cruzi</i>	Diet-induced obesity	Innate cells	↑ TNF-α and IFN-γ	37
<i>Plasmodium berghei</i> ANKA	MSG-obese-mice	T cell	↑ Th1 cells ↑ IL-12 and IFN-γ	38
<i>Leishmania infantum chagasi</i>	Diet-induced obesity	adaptive immune system	↑ TNF-α, IL-6 and IFN-γ	47

which are essential to control the infection by H1N1. They also showed inadequate macrophage activation, reflecting inefficient phagocytosis and impaired development of memory T cell²⁶. Studies with *Staphylococcus aureus*²⁷, *Porphyromonas gingivalis*²⁸, and *Borrelia burgdorferi*²⁹, have noticed that production of specific-inflammatory cytokines and antibodies are less efficient in obese mice. Diet-induced obese mice had more severe *S. aureus* infection with less survival than the lean counterpart, due mostly to a reduction of Anti-*S. aureus* IgG levels²⁷. In periodontal disease associated with *P. gingivalis*, the infection was more severe in high fat diet (HFD)-fed mice, leading to endothelial injury, partially by accelerating endothelial cell apoptosis. One of the hallmarks of obesity, the excess of FFAs contributed to the inflammation, characterized by the extensive release of TNF-α²⁸. Opposite to *P. gingivalis*, in Lyme disease, *B. burgdorferi* HFD-infected mice, had down-regulation of inflammatory cytokines, mostly TNF-α, which leads to an increased bacterial burden in the heart, due to an inefficient uptake by macrophages and neutrophils²⁹. Therefore, the chronic inflammatory state of obesity is characterized by an unbalanced production of TNF-α and other cytokines. This seems to be prejudicial to the tissue and insufficient to activate immune cells and control most of infectious diseases caused by bacteria and virus.

Observational studies and meta-analyses have been correlating obesity and infectious diseases in humans. Recently, Dhurandhar et al. (2015), have gone over a systematic review of Human studies that evaluated the effects of obesity on infections and vice-versa³⁰. Those studies were important to define the impact of obesity in H1N1 for example, being crucial to include obesity as a risk factor in cases of Influenza infection³¹. In other several bacterial³² and viral infections, such as Dengue³³ and HIV³⁴, obesity was linked to the worst prognosis in humans.

Obesity and Protozoan Infection

Protozoa infections are spread around the world and are classified as Neglected Diseases. Yet, it is still obscure how those parasites behave in an obese host. Some parasites such as *Trypanosoma cruzi* are capable to infect and persist inside adipocytes³⁵, even this environment being defined as pro-inflammatory in overweight individuals. On the other hand, AT could be considered a safe place for the parasite as well, because it is a major energetic reservoir, which can provide FFAs and lipids to the parasite, supporting its growth³⁶. Protozoa infection can cause systemic effects in the body as well, because it modulates metabolic pathways in the host such as lipid and glucose metabolism³⁷. Acute *T. cruzi* infection can induce lipolysis in the cell, which is important for the parasite survival. This event alters the lipid metabolism in the host, a process that is mediated by adiponectin, inflammatory cytokines and other AT-related substances which acts by altering the metabolic state of the host³⁸. *T. cruzi* infection also triggers a host response in infected cells that includes increased mitochondrial respiration, biogenesis and concomitant elevated glucose uptake into infected cells³⁹.

Tanowitz's group were the pioneers in defining how the *T. cruzi* interacts with the host, modifying its metabolism during Chagas disease. They were also the first to study the effects of obesity in the immune response during acute *T. cruzi* infection. They showed that mice deficient in the leptin receptor (db/db mice), have adverse consequences in *T. cruzi* infection, characterized by enhanced parasite load and severe inflammatory reaction in the heart and increased levels of IL-6 and TNF-α⁴⁰. Interestingly, taking advantage of HFD to induce obesity and type 2 diabetes in mice, they observed different results. Obese mice presented reduced mortality, parasitemia, myocardial parasite load and myocardial damage during acute *T. cruzi*

infection, in spite of higher parasite burden in the AT and overexpression of TNF- α and IFN- γ ⁴¹. It seems that diet-induced obesity represents a more “physiologic obesity” that leads to adipocytes expansion, which is excellent for *T. cruzi* infection. It is possible that AT sequesters parasites that would otherwise go to the heart⁴¹. Likewise, studies with a Brazilian cohort detected that high (body mass index) BMI levels were associated with improved survival rate in a population with a high prevalence of Chagas disease⁴².

The low-grade inflammatory status characteristic of obese individuals would be advantageous to control some infectious diseases, especially those that usually require a rapid and strong inflammatory response to remove the pathogen such as protozoan infections. New studies using different mice models have observed different outcomes in obese subjects infected with protozoans. Indeed, studies on cerebral malaria showed that ob/ob mice displayed lower cerebral damage and higher parasitemia than the control group⁴³. De Carvalho et al. (2015), using a model of obesity induced in neonatal mice through injections of monosodium glutamate (MSG) have found the opposite result. They observed that obese mice infected with *Plasmodium berghei* ANKA presented low parasitemia and severe brain damage due to increased production of Th1 pro-inflammatory cytokines IL-12 and IFN- γ in the brain⁴⁴. Recently, obesity was also identified as a risk factor for severe *Plasmodium falciparum* malaria in humans⁴⁵.

A few number of studies correlating obesity and other neglected parasite diseases were recently reported. *Leishmania* spp. is an intracellular parasite that infects mostly macrophages. The outcome of the disease depends largely on the capacity of macrophages to kill the parasite. Sarnáglia et al. (2016) showed that diet-induced obesity promoted susceptibility to visceral leishmaniasis, with higher parasite burden, hepatic and splenic tissue damage and greater inflammation characterized by systemic overexpression of TNF- α , IL-6 and IFN- γ during *L. chagasi* infection⁴⁶. Similarly, our group has observed that obese C57BL/6 infected with *L. major* in the ear are less resistant than the lean group, presenting more ulcerative lesions (unpublished results). Studies by other groups showed that obesity correlated with a higher parasitemia in individuals infected with *Toxoplasma gondii*⁴⁷ and *Neospora caninum*⁴⁸.

Conclusion

The studies on the interaction between obesity and different infectious agents are still controversial and show a very complex scenario. The outcomes of infection in obese animals and individuals change according to the extension of infection probably because it affects the metabolic pathways of immune cells in different manners. There are

several questions to be answered, for instance if parasites survive in adipose tissue; if obesity changes the metabolic pathways in the cells; if the host and vector microbiota will affect the outcome of infection; and many others.

In conclusion, obesity is a major factor that causes disruption of body homeostasis, altering immunometabolic pathways, which often results in a poor protective immune response to infections. The alterations in the immune response due to obesity are still obscure, and the relationship between immunity and parasites during obesity is a vast research field to be explored.

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