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 atherosclerosis.

Apart from AT, obesity impacts the modulation of intestinal microbiota, increasing intestinal permeability, bacteria and lipopolysaccharides (LPS) translocation to the circulation. This 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. These receptors are known to trigger inflammatory signaling pathways in immune cells such as macrophages, dendritic cells and T cells.

As first described by Hotamisligil (1993), TNF-α levels are increased in AT of obese subjects. Later reports showed a positive correlation between the adipocyte size and the TNF-α production. This cytokine also favors the activation of NF-kB 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 resistance. The FFA excess, which activates IKKβ, NF-kB, JNK, and TLR pathways, 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 pathogens. 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 AT. The TCD8 infiltration in AT precedes the macrophase (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 AT. 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 organs.

It has demonstrated that in leptin-deficient mice (ob/ob), there is increased lipids infiltration in bone marrow, which impacts severely in the hematopoesis. 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 naïve T cells, decreases the production of IL-2, IFN-γ and favor Th2 immune response. Leptin signaling modulate the hypo-responsiveness and exerts negative signal for the proliferation of Treg cells, decreasing their activity and abrogating the cells functions.

In mice with diet-induced obesity, there is a reduced thymopoiesis and restricted T-cell receptor repertoire diversity. 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 activity. 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 understood.

Studies with ob/ob mice, were the first to demonstrate a negative relationship between obesity and airway bacterial infections, including Klebsiella pneumoniae and Mycobacterium tuberculosis. 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. 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.
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 aureus27, Porphyromonas gingivalis28, and Borrelia burgdorferi29, 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.

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

<table>
<thead>
<tr>
<th>Infection</th>
<th>Animal model</th>
<th>Immune cells alterations</th>
<th>Impact of obesity</th>
<th>References</th>
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<tr>
<td>Klebsiella pneumoniae, Streptococcus pneumoniae, Mycobacterium tuberculosis</td>
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<td>Macrophages</td>
<td>↓ phagocytosis</td>
<td>21-23</td>
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<tr>
<td>Influenza virus</td>
<td>Diet-induced obesity</td>
<td>Innate and T cells</td>
<td>↓ IFN-α, IFN-β; ↓ NK, macrophages and memory T cell</td>
<td>22-23</td>
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<td>B cells</td>
<td>↓ IgG anti-S. aureus</td>
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<td>Porphyromonas gingivalis</td>
<td>Diet-induced obesity</td>
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<td>↓ TNF-α, IL-1-β, IL-6; macrophage phagocytosis</td>
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<tr>
<td>B. burgdorferi</td>
<td>Diet-induced obesity</td>
<td>macrophages and neutrophil</td>
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<td>db/db mice</td>
<td>Innate cells</td>
<td>↓ IL-6 and TNF-α</td>
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<td>Trypanosoma cruzi</td>
<td>Diet-induced obesity</td>
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<td>↓ Th1 cells; ↓ IL-12 and IFN-γ</td>
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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. 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 sequestrates parasites that would otherwise go to the heart. 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 disease.

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 group. 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 brain. Recently, obesity was also identified as a risk factor for severe Plasmodium falciparum malaria in humans.

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 infection. 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 and Neorospora caninum.

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.

References

44. de Carvalho IRH. Plasmodium berghei ANKA infection results in exacerbated immune responses from C57BL/6 mice displaying hypothalamic obesity. Cytokine. 2015; 76: 545–548.