Torres L, Martins VD, Faria AMC, Maioli TU. The Intriguing Relationship Between Obesity and Infection. J Infectiology. 2018; 1(1): 6-10

Journal of Infectiology

Journal of Infectiology

Mini Review Open Access

The Intriguing Relationship Between Obesity and Infection

Licia Torres[1#], Vinicius Dantas Martins[2#], Ana Maria Caetano Faria[2], Tatiani Uceli Maioli[1,2*]

[1]Departamento de Nutrição, Programa de Pós-Graduação em Nutrição e Saúde, Universidade Federal de Minas Gerais, Brasil

[2]Programa de Pós-Graduação em Bioquímica e Imunologia, Universidade Federal de Minas Gerais, Brasil

[#]Both authors contributed equally

Article Info

Article Notes
Received: May 16, 2018
Accepted: June 20, 2018

***Correspondence:**
Dr. Tatiani Uceli Maioli, Professor, Depto. de Nutrição, EE–UFMG, Av. Alfredo Balena, 190, St. Efigênia, Belo Horizonte, MG 30130-100, Brazil, Tel: (5531) 34099858
Email: tatianimaioli@gmail.com

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 2025[1]. 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) concentration[2]. Those alterations favor ectopic deposit of lipids in some organs, such as liver, skeletal muscle, and pancreas, resulting in metabolic imbalance and lipotoxicity[3]. 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[4].

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[5,6]. These receptors are known to trigger inflammatory signaling pathways in immune cells such as macrophages, dendritic cells and T cells[7–9].

As first described by Hotamisligil (1993), TNF-α levels are increased in AT of obese subjects[10]. Later reports, showed a positive correlation between the adipocyte size and the TNF-α production[11]. This cytokine also favors the activation of NF-κB 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[12]. The FFA excess, which activates IKKβ, NF-κB, 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 pathogens[15]. 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[16]. 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 AT[17]. 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[18]. It has demonstrated that in leptin-deficient mice (ob/ob), there is increased lipids infiltration in bone marrow, which impacts severely in the hematopoiesis[19]. 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 response[17]. Leptin signaling modulate the hypo-responsiveness and exerts negative signal for the proliferation of Treg cells, decreasing their activity and abrogating the cells functions[20].

In mice with diet-induced obesity, there is a reduced thymopoiesis and restricted T-cell receptor repertoire diversity[18]. 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[21]. 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[22].

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
Klebsiella pneumoniae, Streptococcus pneumoniae; Mycobacterium tuberculosi	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
Staphylococcus aureus	Diet-induced obesity	B cells	⇩IgG anti-*S. aureus*	24
Porphyromonas gingivalis	Diet-induced obesity	Innate and adaptive immune system	⇩TNF-α, IL1-β, and IL-6; macrophage phagocytosis	26
B. burgdorferi	Diet-induced obesity	macrophages and neutrophil	⇩phagocytosis	27
Trypanosoma cruzi	db/db mice	Innate cells	⇧IL-6 and TNF-α	33
Trypanosoma cruzi	Diet-induced obesity	Innate cells	⇧TNF-α and IFN-γ	37
Plasmodium berghei ANKA	MSG-obese-mice	T cell	⇧Th1 cells ⇧IL-12 and IFN-γ	38
Leishmania infantum chagasi	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 cell[26]. 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 levels[27]. 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-α[28]. 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 neutrophils[29]. 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-versa[30]. 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 infection[31]. In other several bacterial[32] and viral infections, such as Dengue[33] and HIV[34], 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 adipocytes[35], 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 growth[36]. Protozoa infection can cause systemic effects in the body as well, because it modulates metabolic pathways in the host such as lipid and glucose metabolism[37]. 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 host[38]. *T. cruzi* infection also triggers a host response in infected cells that includes increased mitochondrial respiration, biogenesis and concomitant elevated glucose uptake into infected cells[39].

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-α[40]. 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 sequestrates parasites that would otherwise go to the heart[41]. 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[42].

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[43]. 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[44]. Recently, obesity was also identified as a risk a factor for severe Plasmodium falciparum malaria in humans[45].

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[46]. 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 *Neorospora 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.

References

1. Di Cesare M. Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016; **387:** 1377–1396.
2. Khan T, Muise ES, Iyengar P, et al. Metabolic Dysregulation and Adipose Tissue Fibrosis: Role of Collagen VI. Mol Cell Biol. 2009; **29:** 1575–1591.
3. Kusminski CM, Bickel PE, Scherer PE. Targeting adipose tissue in the treatment of obesity-associated diabetes. Nat Publ Gr. 2016. doi:10.1038/nrd.2016.75
4. Torre-Villalvazo I, Bunt AE, Alemán G, et al. Adiponectin synthesis and secretion by subcutaneous adipose tissue is impaired during obesity by endoplasmic reticulum stress. J Cell Biochem. 2018. doi:10.1002/jcb.26794
5. Gomez-Hernandez A, Beneit N, Diaz-Castroverde S, et al. Differential Role of Adipose Tissues in Obesity and Related Metabolic and Vascular Complications. Int J Endocrinol. 2016; **2016:** 1216783.
6. Winer DA, Luck H, Tsai S, et al. The Intestinal Immune System in Obesity and Insulin Resistance. Cell Metab. 2016; **23:** 413–426.
7. Revelo XS, Ghazarian M, Chng MH, et al. Nucleic Acid-Targeting Pathways Promote Inflammation in Obesity-Related Insulin Resistance. Cell Rep. 2015; **16:** 717–730.
8. Boucard-Jourdin M, Kugler D, Endale Ahanda ML, et al. β8 Integrin Expression and Activation of TGF-β by Intestinal Dendritic Cells Are Determined by Both Tissue Microenvironment and Cell Lineage. J Immunol. 2016; **197,** 1968–1978.
9. Henao-Mejia J, Elinav E, Jin C, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature. 2012; **482:** 179–85.
10. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science (80-.). 1993; **259:** 87–91.
11. Winkler G, Kiss S, Keszthelyi L, et al. Expression of tumor necrosis factor (TNF)-α protein in the subcutaneous and visceral adipose tissue in correlation with adipocyte cell volume, serum TNF-α, soluble serum TNF-receptor-2 concentrations and C-peptide level. Eur J Endocrinol. 2003; **149:** 129–135.
12. Gï¿½mez-Hernï¿½ndez A, Beneit N, Dï¿½az-Castroverde S, et al. Differential Role of Adipose Tissues in Obesity and Related Metabolic and Vascular Complications. Int. J. Endocrinol. 2016; **2016.**
13. Baker RG, Hayden MS, Ghosh S. NF-kB, Inflammation, and Metabolic Disease. Cell Metab. 2011; **13:** 11–22.
14. Chiang S. The Protein Kinase IKK 3 Regulates Energy Balance in Obese Mice. Cell. 2009; **138:** 961–975.
15. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotipic switch

in adipose tissue macrophage polarization. J Clin Invest. 2007; **117:** 175–184.

16. Rocha VZ. Role for Adaptive Immunity in Obesity. 2009; **103:** 467–476.
17. Nishimura S, Manabe I, Nagasaki M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med. 2009; **15:** 914–920.
18. Yang H, Youm YH, Vandanmagsar B, et al. Obesity accelerates thymic aging. Blood. 2009; **114:** 3803–3812.
19. Pizzolla A, Oh DY, Luong S, et al. High Fat Diet Inhibits Dendritic Cell and T Cell Response to Allergens but Does Not Impair Inhalational Respiratory Tolerance. 2016; 1–18. doi:10.1371/journal.pone.0160407
20. De Rosa V, Procaccini C, Calì G, et al. A Key Role of Leptin in the Control of Regulatory T Cell Proliferation. Immunity. 2007; **26:** 241–255.
21. Andersen CJ, Murphy KE, Fernandez ML. Impact of Obesity and Metabolic Syndrome on Immunity. Adv Nutr. 2016; **7:** 66–75.
22. Karlsson EA, Beck MA. The burden of obesity on infectious disease. Exp. Biol. Med. (Maywood). 2010; **235:** 1412–1424.
23. Mancuso P, Gottschalk A, Phare SM, et al. Leptin-Deficient Mice Exhibit Impaired Host Defense in Gram-Negative Pneumonia. J Immunol. 2002; **168:** 4018 LP-4024.
24. Wieland CW, Florquin S, Chan ED, et al. Pulmonary Mycobacterium tuberculosis infection in leptin-deficient ob/ob mice. Int Immunol. 2005; **17:** 1399–1408.
25. Smith AG, Sheridan PA, Harp JB, et al. Diet-Induced Obese Mice Have Increased Mortality and Altered Immune Responses When Infected with Influenza Virus. J Nutr. 2007; **137:** 1236–1243.
26. Karlsson EA, Sheridan PA, Beck MA. Diet-Induced Obesity Impairs the T Cell Memory Response to Influenza Virus Infection. J Immunol. 2010; **184:** 3127 LP-3133.
27. Farnsworth CW, Shehatou CT, Maynard R, et al. A Humoral Immune Defect Distinguishes the Response to Staphylococcus aureus Infections in Mice with Obesity and Type 2 Diabetes from That in Mice with Type 1 Diabetes. Infect Immun. 2015; **83:** 2264–2274.
28. Ao M, Miyauchi M, Inubushi T, et al. Infection with Porphyromonas gingivalis Exacerbates Endothelial Injury in Obese Mice. PLoS One. 2014; **9:** e110519.
29. Zlotnikov N, Javid A, Ahmed M, et al. Infection with the Lyme disease pathogen suppresses innate immunity in mice with diet-induced obesity. Cell Microbiol. 2017; **19:** e12689.
30. Dhurandhar NV, Bailey D, Thomas D. Interaction of obesity and infections. Obes Rev. 2015; **16:** 1017–1029.
31. Louie JK, Acosta M, Samuel MC, et al. A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). Clin Infect Dis. 2011; **52:** 301–312.
32. Hegde V, Dhurandhar NV. Microbes and obesity-interrelationship between infection, adipose tissue and the immune system. Clinical Microbiology and Infection. 2013; **19:** 314–320.
33. Zulkipli MS, Dahlui M, Jamil N, et al. The association between obesity and dengue severity among pediatric patients: A systematic review and meta-analysis. PLoS Negl Trop Dis. 2018; **12:** e0006263.
34. Koethe JR, Hulgan T, Niswender K. Adipose tissue and immune function: a review of evidence relevant to HIV infection. J Infect Dis. 2013; **208:** 1194–1201.
35. Versiani A. Evidence for Trypanosoma cruzi in adipose tissue in human chronic Chagas disease. 2011; **13:** 1002–1005.
36. Tanowitz HB, Scherer PE, Mota MM, et al. Adipose Tissue: A Safe Haven for Parasites. Trends Parasitol. 2017; **33:** 276–284.
37. Cabalén ME, Cabral MF, Sanmarco LM, et al. Chronic Trypanosoma cruzi infection potentiates adipose tissue macrophage polarization toward an anti-inflammatory M2 phenotype and contributes to diabetes progression in a diet-induced obesity model. Oncotarget. 2016; **7:** 13400–13415.
38. Miao Q, Ndao M. Trypanosoma cruzi infection and host lipid metabolism. Mediators Inflamm. 2014; **2014:** 902038.
39. Shah-Simpson S, Lentini G, Dumoulin PC, et al. Modulation of host central carbon metabolism and in situ glucose uptake by intracellular Trypanosoma cruzi amastigotes. PLoS Pathog. 2017; **13:** e1006747.
40. Nagajyothi F, Zhao D, Machado FS, et al. Crucial role of the central leptin receptor in murine Trypanosoma cruzi infection. J Infect Dis. 2010; **202:** 1104–1113.
41. Nagajyothi F, Weiss LM, Zhao D, et al. High fat diet modulates Trypanosoma cruzi infection associated myocarditis. PLoS Negl Trop Dis. 2014; **8:** e3118.
42. Beleigoli AM, Ribeiro AL, Diniz M de FH, et al. The 'obesity paradox' in an elderly population with a high prevalence of Chagas disease: the 10-year follow-up of the Bambui (Brazil) Cohort Study of Aging. International journal of cardiology. 2013; **166:** 523–526.
43. Robert V, Bourgouin C, Depoix D, et al. Malaria and obesity: obese mice are resistant to cerebral malaria. Malar J. 2008; **7:** 81.
44. de Carvalho RVH. Plasmodium berghei ANKA infection results in exacerbated immune responses fom C57BL/6 mice displaying hypothalamic obesity. Cytokine. 2015; **76:** 545–548.
45. Wyss K, Wångdahl A, Vesterlund M, et al. Obesity and Diabetes as Risk Factors for Severe Plasmodium falciparum Malaria: Results From a Swedish Nationwide Study. Clin Infect Dis. 2017; **65:** 949–958.
46. Sarnáglia GD, Covre LP, Pereira FE, et al. Diet-induced obesity promotes systemic inflammation and increased susceptibility to murine visceral leishmaniasis. Parasitology. 2016; **143.**
47. Reeves GM, Mazaheri S, Snitker S, et al. A Positive Association between T. gondii Seropositivity and Obesity. Front Public Heal. 2013; **1:** 73.
48. Teixeira L, Moreira J, Melo J, et al. Immune response in the adipose tissue of lean mice infected with the protozoan parasite Neospora caninum. Immunology. 2015. doi:10.1111/imm.12440