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The Impact of Obesity on Immune Response to Infection and Vaccine: An Insight into Plausible Mechanisms

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Abstract

Though we know much about development of obesity and its associated complications like type II diabetes, cardiovascular diseases, hypertension and cancer, our knowledge is very limited about the impact of this metabolic syndrome on immune functions per se. Studies in obese humans and animal models have earlier shown, altered lymphocyte numbers, and reduced lymphocyte responsiveness to mitogen stimulation, dysregulated cytokine expression, decreased natural killer cells, macrophage and dendritic cell functions, leading to reduced resistance to infections involving a number of organisms such as Mycobacterium tuberculosis, Coxsackie virus, Helicobacter pyroli and influenza. Several obesity-associated hormonal changes such as leptin resistance, hyperinsulinemia, and metabolic changes such as excessive inflammation and altered glucose, amino acid and fatty acid metabolism which are required for the functionality of T cells could affect the immune response. This review tries to explore these possibilities and project them as plausible mechanism(s), which could affect the response to infectious diseases and vaccine in obese conditions.

Introduction

The immune system has two interconnected arms, innate immunity and acquired or adaptive immunity, both of which interact with each other to generate protective immunity to the organism. Such response, in essence requires, activation and propagation of immune cells and synthesis of molecules requiring DNA replication, RNA expression, and protein synthesis and secretion, all of which consuming considerable anabolic energy. Studies in bumblebee show that the energy cost of immunity impairs the fitness of an organism [1]. Thus, immune-competence is dependent on nutritional status and can be easily dysregulated in states of imbalanced nutrition such as under nutrition (malnutrition) or over nutrition (obesity). Though immune suppression in undernourished state is well known [2], the role of immune dysfunction happening in state of over nutrition (obesity) is poorly understood.

Obesity is a major health problem since excessive body weight constitutes a risk factor in a number of chronic diseases. The prevalence of obesity is increasing worldwide and as per the latest WHO estimates, approximately 500 million adults and nearly forty-three million children under the age of 5 years appear to be obese , showing a BMI ≥ 30 [3]. Obesity is defined as a state of excess adiposity due to prolonged positive energy imbalance and is multifactorial in origin. Several comorbidities exist for this metabolic syndrome such as diabetes, hypertension and cardiovascular diseases and latest in the list is immune dysfunction, which makes obese individuals vulnerable to infectious diseases and even seems to affect their response to vaccines. This review is an attempt to chronicle the vulnerability of obesity status on exposure to infectious diseases, and its delayed or non response to vaccine and the plausible mechanisms that might be involved in such an altered immunity status.

Obesity and Immune Status

Human studies

Most studies conducted so far were focused primarily on ex vivo cellular functions. Obese subjects showed either increased or decreased total lymphocytes in peripheral blood populations [4-7] and had decreased CD8^{+} T cell population along with increased or decreased CD4^{+}T cells [6,7]. Obese subjects also showed reduced lymphocyte proliferative response to mitogen stimulation and dysregulated cytokine expression [4,6-9]. In addition, both the NK cell number and its cytotoxic activity were diminished in obese individuals [10].

Animal studies

Altered immunity under obese condition is well documented in studies involving animal models. For example both, genetically leptin deficient (Ob/ob mice) and leptin receptor deficient obese animals (Db/db mice and fa/fa rats) demonstrate a global impairment in ex vivo immune function. Obese animal's show marked thymic atrophy, lower splenic and circulating T cells, decrease in mitogen stimulated lymphocyte proliferative capacity and cell mediated cytotoxicity [11-20]. Obese animals exhibited impaired innate immunity in terms of reduction in number and function of dendritic cells [21], displayed diminished development, differentiation and cytotoxicity of NK cells [22]. These genetically obese models provide insight into how excess adiposity may directly or indirectly alter immune cell function and host defense against infectious agents. However, these studies have limitations with reference to human obesity, since gene mutations in humans are rare. So, to mimic human condition, animals were made obese by feeding either high fat and/or sucrose for a period of time. Such DIO (diet induced obese) mice (induced by feeding high fat/Sucrose diet) had significantly reduced thymocyte counts, increased apoptosis of thymic T cell population and reduced splenic T cell proliferation in response to mitogen [8,18,23]. Further, high- fat

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dietary intake decreased NK cell numbers and function, impaired DC function and T cell responsiveness to antigen presentation [24-26]. DIO mice produced lower mitogen-induced interleukin (IL)-2 and high interferon (IFN)-γ and IL-4 cytokines [25]. DIO mice also had increased CD11b macrophage/monocyte population, mRNA levels of adipocyte derived monocyte chemo attractant protein-1 (MCP-1) and MCP-1 protein levels in the plasma [27].

Obesity and Vulnerability to Infectious Diseases

Immune dysfunction leading to increased morbidity and mortality from infectious diseases in obese human subjects and obese rodent models are well documented as given below.

Human studies

Several reports evince obesity to be a risk factor for post operative and surgical site [28], nosocomial [29], periodontitis [30] and respiratory infections [31].

Obesity and clinical settings

Retrospective and prospective studies showed obesity to be an independent risk factor for infection after trauma [32-34]. In a prospective cohort study of critically ill trauma patients, obese patients had more than two fold increased risk of acquiring a bloodstream, urinary tract or respiratory infection [32]. In one prospective observational study, obesity is shown to increase the risk of ICU acquired catheter and blood stream infections due to the relative difficulty in obtaining venous access [29]. In a large multicenter prospective study conducted in 200 ICUs in 24 European countries wherein BMI was measured at the time of admission, obese and morbidly obese patients frequently developed ICU-acquired infections in comparison to patients with lower BMI [35]. One risk-adjusted matched cohort study showed an association of obesity with increased risk of ICU-associated infections such as septic shock and ventilator-associated pneumonia. However, obesity is not a risk factor for infection-related case fatality [36]. One prospective multicenter matched epidemiologic study also indicated lack of association between obesity and the risk of catheter-related infection or ventilator-associated pneumonia. In this study, comparison between morbidly obese and non obese is done, leaving out the obese group [37]. The bias in this kind of studies is because of vascular fluid volume depletion in the patients which yield erroneous BMI at the time of admission.

Nosocomial and surgical infections

Cohort studies show an association between obesity and the risk of nosocomial infections [38,39]. A recent retrospective case–control study also showed obesity to be an independent predictor of nosocomial bloodstream infection in older adults [39]. Prospective and retrospective cohort studies suggest association between obesity and risk of skin and soft-tissue infection after surgery [40-43].

Periodontitis

Obesity is an independent predictor of risk factor for periodontitis [44]. Meta-analysis shows overweight and obesity to be associated with the development of periodontal disease [45]. However, it is not clear whether obesity is a risk factor for periodontal disease or periodontitis leading to obesity [46].

Pancreatitis

One large epidemiological study indicates obesity to be a risk factor for gallstones, gallbladder disease and pancreatitis [47]. Obesity increases the risk of severe pancreatitis by inducing local complications such as pancreatic pseudocysts, abscess and necrosis [48,49]. Visceral adipose tissue plays a role in the pathophysiology of severe diseases by secreting adipokines which help maintain systemic inflammation [50,51]. A meta-analysis published in 2004 and 2006 showed obesity to be associated with systemic and local complications in severe acute pancreatitis [48,49].

Skin infections and cellulitis

Obesity affects skin barrier function, the lymph system, collagen structure and function, wound healing, micro and macro circulation. Obesity leads to a wide range of skin diseases [52]. Several case-control studies indicated an association between obesity and the risk of cellulitis, and limited data also supported association of obesity and the outcome of skin infections [53,54].

Urinary tract infections

Several studies pertaining to the risk of Urinary Tract Infection (UTI) were conducted in obese individuals. One large epidemiological study conducted in 1980's indicated decreased risk of UTI with obesity. However, in this study, subjects with BMI ≥ 24 were considered which might explain the negative association [55]. Recent study showed an association between obesity and risk of UTI [56] and females are at high risk for pyelonephritis [56]. Obesity increases the risk of UTI in diabetic males in a cohort study [57]. Obesity also increases the risk of UTI during pregnancy and postpartum period [58,59]. Data on the effect of obesity on the outcome of UTI is lacking.

Viral hepatitis

Cohort studies indicate that obesity increases risk of hepatic steatosis and fibrosis in non-diabetic patients with chronic hepatitis C infection [60,61]. Overweight diminished response to antiviral therapy and affects the progression of chronic HCV (Hepatitis C virus) liver disease [60,61].

Influenza

The sudden spurt in influenza H1N1 pandemic in 2009 raised interest in the interaction between obesity and infection. Obesity affects the progression of the disease and increases the mortality rate. One prospective, observational and multicenter study conducted in 144 ICUs in Spain showed obesity to be associated with higher ICU resource consumption and longer ICU length of stay in H1N1 influenza [62,63]. Obesity is a risk factor for mortality in patients with H1N1 infection-related community-acquired bacterial pneumonia [64]. A recent systematic review and meta-analysis indicated obesity to be associated with higher risks of ICU admission or death in patients with influenza A (H1N1) infection [65]. One recent global study conducted by World Health Organization included 70,000 laboratory confirmed cases with H1N1 from nearly 20 countries reports a clear association between obesity and poor outcome of H1N1 [66].

Influenza enters the cell via endocytosis and subsequently replicates, resulting in the generation of Pathogen-Associated Molecular Patterns (PAMPs) that are detected by Pattern-Recognition Receptors (PRRs) such as the Toll-Like Receptors (TLRs), retinoic acid-inducible gene I receptors (RIG-I) and Melanoma Differentiation-associated protein 5 (MDA5), resulting in type I and type III IFN induction. Released IFN subsequently binds IFN receptors, resulting in Janus-activated kinase–signal transducer and activator of transcription (JAK–STAT) phosphorylation and complex formation with IFN regulatory factor 9 (IRF9). This complex translocates to the nucleus resulting in

upregulation of antiviral IFN-stimulated genes (ISGs), such as MxA, IFITM3, Oligoadenylate Synthetase (OAS) and viperin. Attenuated IFN response might cause diminished response to influenza infection. In agreement, DIO mice upon intranasal administration of mouse-adapted influenza strain A/Puerto Rico/8/34 (A/PR/8/34) had attenuated IFN response, reduced natural killer cell cytotoxicity and diminished lung proinflammatory cytokine (IL-6, TNF-α, IL-1β) and chemokines (MCP-1 and RANTES) mRNA expression [67]. One mechanism by which obesity may potentially attenuate the antiviral IFN response is by leptin-induced upregulation of Suppressor of Cytokine Signaling (SOCS), which inhibits JAK–STAT signal transduction. A recent study in diet-induced obese mice infected with A (H1N1) pdm09 suggested preexisting high levels of circulating leptin to be involved in mediating lung injury by producing excess proinflammatory cytokines and chemokines [68]. In infected DIO mice, administration of anti-leptin antibody led to decrease in proinflammatory cytokines and lung pathology and improved the survival rate [68]. Further studies are needed to elucidate the mechanisms behind diminished type I IFN and proinflammatory response.

Data on the impact of obesity on the outcome of influenza virus infections other than H1N1 virus are scanty. A recent cohort study conducted over 12 influenza seasons indicated association of obesity, morbid obesity and respiratory hospitalization [69].

Studies are rare on the affect of obesity on other respiratory tract infections. However, a recent study did suggest the impact of obesity on respiratory syncytial virus infection in children [70] and another study from Poland even reported BMI to be related to susceptibility to respiratory infections [32]. In clinically ill trauma patients also obesity or morbid obesity showed association with respiratory infections [30,33]. Conversely, few studies [71,72] also reported lack of association of obesity with the risk of respiratory infections. It was pointed out that obesity often complicates lung mechanics by restricting lung volume, and this could be increasing the risk for pneumonia or other infections in such cases.

In addition to the earlier mentioned infections, high BMI seemed to increase susceptibility to staphylococcus aureus nasal carriage, gastric infection by Helicobacter pylori [73,74]. A recent study also reported obesity to be associated with herpes simplex virus 1 infection and risk of clostridium difficile infection [75]. There are however no studies yet on the affect of obesity on fungal, tropical and HIV infections.

Rodent models of obesity and infection

Increased risk to infection was observed in obese animals also. Thus, leptin deficient Ob/Ob mice were sown to be susceptible to a number of different bacterial infections such as Mycobacterium abscesses, Klebsiella pneumonia, streptococcus pneumonia and Mycobacterium tuberculosis [76-79] while Db/db mice to staphylococcus aureus and H.pyroli [80,81]. Further, both ob/ob and db/db mice were shown to have increased susceptibility to Listeria monocytogenes [82]. Fa/fa Zucker rat was shown to have decreased ability to clear candida albicans [83].

Viral infections

Ob/ob mice showed increased susceptibility to viral myocarditis induced by coxsackie virus B4 and encephalomyocarditis virus [84,85]. Diet induced obese (DIO) mice were found to be susceptible to bacterial infections such as porphyromonas gingivalis and staphylococcus aureus-induced sepsis and viral infections such as influenza virus [67,86,87].

Drug dosing in obesity

Data on antimicrobial dosing in obesity is scanty. There is a need to determine dosage for maximum and effective therapy in obese individuals.

Pharmacodynamics of drugs in obese is variable and depends on multiple factors such as degree of obesity, organ function and drug characteristics. Obesity affects volume of distribution (Vd) of drugs and thus increases the Vd of lipophilic drugs (for example, fluoroquinolones) and decreases the Vd of hydrophilic drugs (for example, amikacin and tobramycin). Several studies indicate underdosing of antimicrobials in obese patients [88]. Earlier data showed impaired penetration of antimicrobials in the interstitial space fluid of obese subjects [89]. Few studies exist on the dosing of antimicrobials such as vancomycin and aminoglycosides. Vancomycin concentration reduced to 30% of the optimal therapeutic concentrations in obese patients [90]. However, plasma drug concentration does not reflect the tissue drug concentration. Further studies on other antimicrobials are needed. Morbid obesity affects the blood and tissue levels of prophylactic antimicrobials [91]. A recent study suggested the lack of dose adjustment in healthy, morbidly obese subjects upon administration of single dose of oseltamivir phosphate and its carboxylate metabolite [92]. However, there was no problem with antiviral therapy in obese animals, which responded well to the treatment [93]. Other studies suggested dosing of antimicrobials with high minimal inhibitory concentration at frequent intervals in the case of obese patients [94,95]. As these recommendations were based on single patient cases, randomized large sale studies are suggested that may yield data for appropriate drug dosage for obese individuals.

Obesity and Immune Response to Vaccination

Human studies

Weber et al. [96], conducted the first study to describe the relationship between vaccine response and obesity. His group found that, high BMI was associated with a failure to develop detectable antibody response to Hepatitis B vaccine in health-care workers [96]. Further, Simo Minnana et al. reported lower antibody response in adolescents with high BMI when administered a three-dose regimen of recombinant hepatitis B vaccine [97]. A randomized controlled trial compares triple-antigen vaccine vs standard single antigen vaccine administered in three doses over six months resulted in 71% and 95% protection rates in obese subjects when compared with lean subjects (91% & 99% respectively) [98]. Eliakim et al. [99], reported lower antibody response to tetanus immunization in overweight 13-year – olds than their age-matched controls with lower BMIs [99]. Reduced antibody response could be due to diminished B-cell numbers. Ob/ob mice show 21% and 12% decrease in pre-B and immature B-cells respectively and this was normalized upon leptin administration. This suggests the role of leptin in B-cell generation [100]. Non-immune factors such as the length of the needle also seemed affect the response to vaccination, since increasing the length of the needle was shown to enhance the immune response to vaccine [101].

Epidemiologic data identified obesity to be a risk factor for severe morbidity and increased mortality from A (H1N1) pdm09 virus influenza infection, suggesting the need for prophylaxis against influenza. Few studies have been conducted on the efficacy of influenza vaccine in humans. Obese individuals showed an initial increase in IgG response to 2009-2010 inactivated Trivalent Influenza Vaccine (TIV). However 12 months post vaccination titers were drastically reduced suggesting defective cellular immunity. In agreement, obese individuals showed decrease in expression and release of early activation marker

CD69 and IFNγ and granzyme B respectively by CD8+ T cells [102]. In contrast, to these findings Talbot et al., reported lack of association between obesity and either seroprotection or seroconversion [103]. However unlike the earlier study, the authors did not measure 12 months post vaccination response.

Animal studies

Animal studies on the effect of obesity on immune response to vaccine are rare. Studies from our lab showed reduced HBsAg specific IgG response in WNIN/Ob and WNIN/GR-Ob obese rats upon Hepatitis B vaccination. These obese rats showed impaired splenic lymphocyte proliferative response to HBsAg which is essential for the long term memory to the vaccine. In addition, WNIN/GR-Ob strain of obese rats also showed altered peritoneal macrophage function upon vaccination [104,105]. With the influenza pandemic, efficacy of influenza vaccine was analyzed in a DIO mice model. DIO mice vaccinated with commercial monovalent pH1N1 vaccine did not survive beyond 12 days from pH1N1 infection. DIO mice had impaired CD8 T cell function and high proinflammatory cytokine expression leading to diminished vaccine efficacy [106]. More such studies are warranted to decipher the effect of obesity on other common vaccines.

Table 1 depicts the studies conducted so far on the effect of obesity on response to vaccination in humans:

Vaccine and Cellular Immune Response

Efficacious vaccination against viral antigen generates long-lived, antigen-specific CD8+ memory T-cells leading to long-term immunity. Following infection, antigen-specific T-cells are activated and expanded. This expansion results in a large population of effector T-cells containing both Short-lived Effector Cells (SLEC) and Memory Precursor Effector Cells (MPEC) to clear infection. Following pathogen clearance, SLEC, composing 90–95% of the effector population, go through activation-induced cell death during the subsequent contraction phase of the response, leaving the smaller MPEC subset to form a long-lived, antigen-specific memory cell pool. These memory T-cells can then act to mount larger, faster and stronger responses to subsequent encounters with the same pathogen. Generation and function of CD8+ memory T-cells requires a balancing act between MPEC potential and terminal differentiation into SLEC. Both inherent programming during initial contact with an antigen-presenting cell and environmental factors such as inflammation can affect the balance between effector and memory potential [107]. This balance can be considered using the 'Goldilocks model' of generation [108]. Obesity may impair the inherent programming of T-cells and or environmental factors. In diet-induced obese C57BL/6 mice, a secondary H1N1 influenza challenge following a primary H3N2 infection led to a increase in mortality, lung pathology and

lung viral titer. Further, mRNA expression of IFN-gamma was >60% less in lungs of obese mice. Obese mice had lower influenza-specific CD8+ T cells producing IFN-gamma postsecondary infection. Memory CD8+ T cells from obese mice had a >50% reduction in IFN-gamma production when stimulated with influenza-pulsed dendritic cells from lean mice suggesting inherent defect of CD8+ T-cells [109]. High fat-fed obese mice showed aggravated inflammatory response upon immunization with H1N1 virus. The basal messenger RNA (mRNA) levels of 2 chemokines MCP-1 and RANTES were lower in immunized obese mice than in immunized controls. However, the mRNA levels of MCP-1 and RANTES were markedly increased at 3 and 8 days after viral challenge in immunized obese mice. Similarly the proinflammatory cytokines (TNFα, IL-1β, and IL-6) were also elevated upon immunization [106]. This high inflammatory response may tip the balance towards SLEC and diminished MPEC. Detailed mechanism leading to a decrease in cellular memory upon vaccination needs to be elucidated.

Suggested Mechanisms for the Observed Altered Immunity in Obesity

Studies have reported that White Adipose Tissue (WAT) is not only a storage organ, but produces close to 100 cytokines. These secreted adipokines are directly correlated to the increased adipose tissue mass and play an intricate role in various aspects of the innate and adaptive immune response and participate in a wide variety of physiological or physiopathological processes including food intake, insulin sensitivity and inflammation. In the obese status, secretion of these adipokines such as leptin and the proinflammatory cytokines like TNFα, IL-6 and IL-1β are bound to increase. When such proinflammatory cytokines are secreted into blood, they are likely to produce disastrous condition for the host. This proinflammatory excess energy milieu could have a definite impact on immune cell function under obesity. Such heightened pro-inflammatory cytokine expression, associated with increased tissue inflammation leading to increased mortality upon infection was seen in DIO animals. Further, enhanced proinflammatory cytokine expression was also associated with lower memory response in DIO animals. However, more studies are needed to delineate the mechanism by which this excess inflammatory response desensitizes the immune cells during an antigenic exposure.

Another adipokine which has gained much attention is leptin. Leptin has pleiotropic effects on immune cell activity as evidenced from the presence of leptin receptors on all immune cells of both the arms of innate and adaptive immunity [110]. Leptin promotes macrophage phagocytosis by activating phospholipase. Leptin increases secretion of proinflammatory cytokines such as TNF-α (early), IL-6 (late) and IL-1 by macrophages. Leptin stimulates monocyte proliferation and upregulates the expression of activation markers including CD38,

Author	Year	Vaccine	No. of subjects	Study outcome
Weber et al. [96]	1985	Hepatitis B vaccine	194	Redced HBsAg specific IgG response
Roome et al. [141]	1993	Hepatitis B vaccine	528	Reduced anti HBs with extreme obesity
Wood et al. [142]	1993	Hepatitis B vaccine	595	Lack of anti HBs associated with obesity
Simo Minana et al. [97]	1996	Hepatitis B vaccine	427	Post vaccination anti HBs were low
Averhoff et al. [143]	1998	Hepatitis B vaccine	2,213	Decreased immunogenicity was associated with obesity
Young et al. [98]	2001	Hepatitis B vaccine	303	Reduced response to HBV
Elikiam et al. [99]	2006	Tetanus	30	Anti-tetanus IgG antibodies were low; IL-6 was significantly higher and no change in TNF-a, IL-1b and IL-1ra cytokine levels.
Sheridan et al. [102]	2011	Influenza vaccine	499	Decreased 12 months post vaccination IgG production; Reduced CD69, IFNg and granzyme B in CD8+ T cells.
Talbot et al. [103]	2012	Influenza vaccine	415	No consistent relationship between antibody response and obesity

Table 1: Studies of immune response to vaccine in humans.

CD69, CD25 (IL-2 receptor a-chain) and CD71 (transferrin receptor) [111]. Leptin increases the expression of already highly expressed surface markers of activation on resting monocytes, such as HLA-DR, CD11b and CD11c [112]. leptin stimulates chemotaxis of polymorphonuclear cells by producing ROS [113]. Leptin is involved in the NK cell development, differentiation, proliferation, activation and cytotoxicity by activating STAT3 and increasing the expression of perforin and IL2 [114].

Leptin modulates adaptive immunity. Leptin activates lymphocytes when co-administered with non specific immunostimulants such as PHA (phytohemagglutinin) or ConA (concanavalin A). leptin induces early- (CD69) and late-activation markers (CD25, CD71) in both CD4$^+$ and CD8$^+$ lymphocytes [115]. Leptin differentially affects the naïve and memory T-cells. Leptin induces the proliferation of naı̈ve CD4$^+$CD45RA$^+$ T cells but inhibits the proliferation of memory CD4$^+$CD45RO$^+$ T cells [19,116]. At the functional level, leptin polarizes T helper (Th0) cytokine production towards a proinflammatory (Th1, IFN-γ, TNF-α). Leptin increases T lymphocyte survival by increasing the expression of antiapoptotic proteins such as Bcl-2 and T-bet [117]. Leptin suppresses the generation and proliferative capacity of Treg cells and increases susceptibility to autoimmunity [118,119].

Leptin mediates its action through JAK/STAT signaling pathway, resulting in the subsequent transcription of leptin induced genes including SOCS3 which acts as a negative feedback for leptin signaling [110]. Obesity is associated with high serum leptin levels [120]. DIO mice infected with influenza virus exhibits unchanged serum leptin levels, decreased OBR expression and increased expression of leptin signaling inhibitor such as SOCS 1 and 3 [109]. Further, increased mRNA expression of SOCS1 leads to leptin resistance which results in decreased effector memory T cells. These leptin resistant memory T cells are vulnerable to inflammation-induced apoptosis [109]. A recent study demonstrated high circulating leptin levels to increase lung proinflammatory cytokines and chemokines leading to severe lung pathology and mortality in influenza infected DIO mice [68]. Neutralization with anti-leptin antibodies improved the survival rate of these mice [68]. In addition, leptin resistance leads to increased T regulatory numbers (Treg) which suppresses immune response [121]. Despite, the presence of high percentage of Treg in the spleen of DIO, the extent to which this Treg cells affects the outcome of infection and vaccination remains unknown.

Obesity is also associated with hyperinsulinemia and insulin resissatnce. Insulin receptors are present on monocytes and activated T lymphocytes and insulin signaling modulates T cell activation and function by inducing glucose uptake, amino acid transport and lipid metabolism [122-125]. Further, as insulin has been shown to promote anti-inflammatory T helper type 2 cell phenotype insulin resistance enhances T helper type 1 cell development [124,126]. However, the effects of excess insulin on immunity remain relatively unexplored.

Role of Nutrients

Apart from altered hormonal profile, obesity harbors altered metabolic environment and immune cells require nutrients such as glucose, amino acids and fatty acids to meet their energy needs [127]. Glucose is required for T cell proliferation and survival. Upon stimulation, GLUT 1 and GLUT3 levels were increased on T cell and monocytes respectively [126,128,129]. Exposure to high concentrations of glucose results in Reactive Oxygen Species (ROS) generation and lipid peroxidation [130]. Further, Jacobs et al. demonstrated that overexpression of GLUT1 in mouse T cells resulted in altered T cell metabolism and cytokine production [131]. Studies from our lab in

WNIN/GR-Ob showed impaired glucose tolerance as an additional risk factor in obese in impairing immunity [105]. However, little is known of the in vivo effects of hyperglycemia on immune cell function.

Similar to glucose, fatty acids are also important in fueling an immune response, as they are readily available source of abundant energy. However, the impact of excess circulating Non-Esterified Fatty Acids (NEFA), a hallmark of obesity, on immune cells has not been well studied. Interestingly, Saturated Fatty Acids (SFA), such as palmitate, shares structural similarities in chemical structure to Lipopolysaccharide (LPS) and thus induces an inflammatory response by initiating Toll like Receptor (TLR) signaling pathways [132]. However, much less is known on the effect of NEFA on the TLR signaling in T cells, though there are studies on the effect of NEFA on macrophages and on insulin resistance and type II diabetes.

Recent studies have found that the metabolic state is extremely important for the functionality of immune cells, especially T cells. Non-proliferating quiescent T cells (naïve and memory T cells) use catabolic metabolism to fuel ATP generation [133]. Stimulation and co-stimulation results in a metabolic switch to glycolysis and anabolic metabolism, which supports proliferation and effector functions [134]. This switch is achieved by the activation of Akt, which then promotes the mTOR pathway and increased utilization of glucose and amino acids [135,136]. Though, the exact mechanism is not clear, reduced mTOR activity has been associated with increased generation of memory CD8$^+$ T cells [137]. Thus, it would be interesting to pursue how obesity can alter T cell metabolism and subsequent T cell fate as over-nutrition directly inhibits insulin signaling in muscle at the level of IRS1 through the hyperactivation of the mTOR pathway [138]. Additionally, leptin signaling also appears to alter AMPK/mTOR activation [139,140]. If at all, obesity hyper activates mTOR, memory T cell generation may be at a significant disadvantage. Future studies are needed to focus on the activation of metabolism in T cells from the obese and its effects on memory T cell generation as well as other cells of the immune response.

Implications

As stated in the introduction, the numbers of adults and children who are obese and overweight have reached epidemic proportions in many countries. Population based strategies to improve social and physical environmental contexts of healthy eating and physical activity are thus essential for the prevention of obesity, overweight and its related health risks. Further, life style changes that lead to weight reduction have been demonstrated to reduce the incidence of diabetes and hypertension, and WHO has come up with formulated national policies to meet such exigencies.

It may appear that increased susceptibility and the exact defect in immunity were documented only for a small number of infections under obese status. However, a significant number of other studies pertaining to other infections and the exact systemic impact of obesity to susceptibility for such infections seemed poorly understood. So, further studies are warranted in this area to focus on the impact of increased weight or obesity on susceptibility to diseases. Another, yet key consideration is how best to prevent and manage infections in such high-risk population. As body size characteristics of patients are essential for the optimization of drug therapy, there is need for newer anti-microbial dosing for obese individuals. Moreover, the impairment of immune dysfunction, which is more pronounced in obese status, upon vaccine challenge calls for a new approach in vaccine management in obese children, as they are totally incapacitated minimally at the basal level and the present vaccine inoculation strategies seem to worsen

the situation. A new health policy of augmenting the effectiveness of vaccine especially in obese children by adding novel adjuvants should be attempted, before the situation goes out of control.

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