Obesity and Type 2 Diabetes Mellitus Drive Immune Dysfunction, Infection Development, and Sepsis Mortality

Lynn M. Frydrych, MD*, Guowu Bian, MD*, David E. O'Lone, BS*, Peter A. Ward, MD#, and Matthew J. Delano, MD, PhD*†

*Department of Surgery, Division of Acute Care Surgery, University of Michigan
#Department of Pathology, University of Michigan

Key words: Immune dysfunction, sepsis, weight loss
Running Head: *obesity and T2D increase risk of infections*

Summary Sentence:

Review on how obesity and type 2 diabetes mellitus impact immunity and lead to poor clinical outcomes and the cellular changes observed after weight loss.

†**Correspondence should be directed to:**
Matthew J. Delano, M.D., Ph.D.
Assistant Professor of Surgery
University of Michigan
Department of Surgery
Division of Acute Care Surgery
University Hospital, 1C340D
1500 E. Medical Center Dr., SPC 5033
Ann Arbor, Michigan 48109-5033
Office: (734) 936-3662
Fax: (734) 936-9657
Email: mjdelano@med.umich.edu

Total character count: (not including spaces or reference section): 33,906
Total number of figures: 2
Total number of color figures: 2
Total number of references: 75
Total numbers of words in Abstract: 197
Total number of words in summary sentence: 25

Abbreviations:

Adipose Tissue Macrophages (ATMs)

Body Mass Index (BMI)

Conventional Dendritic Cells (cDCs)

Dendritic Cells (DCs)

Free Fatty Acids (FFAs)

Gamma Delta T Cells (yδ T Cells)

High-Fat Diet (HFD)

Inflammatory Dendritic Cells (inf-DCs)

Interferon Gamma (IFNγ)

Lipopolysaccharides (LPS)

Major Histocompatibility Complex (MHC)

Metabolic Syndrome (MetS)

Natural Killer (NK)

Natural Killer Cell Activity (NKCA)

Perivascular Adipose Tissue (PVAT)

Plasmacytoid Dendritic Cells (pDCs)

Regulatory T Cells (Tregs)

T Cell Receptor (TCR)

T Helper Cells (T_h Cells)

Tumor Necrosis Factor-alpha (TNF-alpha)

Type 2 Diabetes Mellitus (T2D)

Vertical Sleeve Gastrectomy (VSG)

Visceral Adipose Tissue (VAT)

Abstract:

Obesity and type 2 diabetes mellitus (T2D) are global pandemics. Worldwide, the prevalence of obesity has nearly tripled since 1975 and the prevalence of T2D has almost doubled since 1980. Both obesity and T2D are indolent and chronic diseases that develop gradually, with cellular physiologic changes occurring before the clinical signs and symptoms of the diseases become apparent. Individuals with obesity and T2D are physiologically frail

and have an increased risk of infections and mortality from sepsis. Improvement in the morbidity and mortality of these at-risk populations would provide a great societal benefit. We believe that the worsened outcomes observed in these patient populations is due to immune system dysfunction that is triggered by the chronic low-grade inflammation present in both diseases. As immune modulatory therapies have been utilized in other chronic inflammatory diseases, there is an emerging role for immune modulatory therapies that target the chronically affected immune pathways in obese and T2D patients. Additionally, bariatric surgery is currently the most successful treatment for obesity and is the only weight loss method that also causes a sustained, substantial improvement of T2D. Consequently, bariatric surgery may also have a role in improving immunity in these patient populations.

Introduction

Obesity was once considered a problem of high-income nations only, but it is currently also on the rise in low- and middle-income countries[1]. Globally there are now more people who are obese than underweight[1]. Obesity is the result of an energy imbalance, with excess caloric consumption leading to weight gain and metabolic disturbances that result in tissue stress and organ dysfunction[2]. It is defined as an excess of body-fat mass, expressed as an elevated body mass index (BMI). The upper limit of a normal BMI in adults is 25 kg/m^2, while a BMI between 26-30 kg/m^2 is considered overweight, and a BMI >30 kg/m^2 is classified as obese[3]. In the United States, over 35% of adults and 17% of children are obese[4]. Worldwide, obesity has nearly tripled since 1975, with 13% of the world's adult population now classified as obese[1]. This is significant because obesity is the leading cause of preventable death[2].

The clinical signs of obesity present as metabolic syndrome (MetS). MetS is characterized by 3 or more of the following: central adiposity, elevated blood glucose,

elevated plasma triglycerides, low plasma HDL cholesterol, and hypertension[2]. Additionally, obesity is associated with endothelial dysfunction, atherogenic dyslipidemia, insulin resistance, and chronic low-grade inflammation[2]. These underlying changes lead to an increased risk of developing chronic diseases and health conditions[2]. As such, obesity is an independent risk factor for developing hypertension, high cholesterol, stroke, heart disease, certain cancers, arthritis, and type 2 diabetes mellitus (T2D)[5].

T2D is a common and devastating disease, which frequently complicates the recovery of critically ill patients. With the increasing spread of the western diet and lifestyle globally, the worldwide incidence and prevalence of T2D is increasing. In the United States alone, the prevalence of T2D has almost doubled from 11.9 million in 2000 to 21.9 million in 2014, and the incidence has more than tripled from 1980[6]. In 2014, an estimated 422 million adults worldwide had T2D, compared to 108 million in 1980. Similar to obesity, T2D is no longer a disease of high-income countries, as the highest growth rates are in low- and middle-income nations[7].

Both obesity and T2D are associated with an increased risk of recurrent, nosocomial, and secondary infections that lead to sepsis, renal failure, and death. Obese individuals have a higher risk of community acquired pneumonia, biliary disease, cutaneous infections, and aspiration pneumonia during hospitalizations[8]. In the critically ill intensive care unit (ICU) population, obese patients have a higher risk of infectious complications that lead to sepsis, ventilator-associated pneumonia, central venous catheter–related infections, and increased mortality compared to normal weight patients[8]. Surgical site infections are also more common in obese patients due to a variety of factors, including increased quantity and under-perfusion of adipose tissue, increased retraction-related local tissue trauma, lengthened operative time, and decreased subcutaneous tissue oxygenation[8]. Additionally,

obesity is independently associated with high rates of *Staphylococcus aureus* nasal carriage, which is a proven risk factor for surgical-site infections[8].

Patients with T2D have an increased risk of developing infections that directly lead to sepsis. Although a few rare infections such as *Klebsiella* liver abscesses, malignant otitis externa, and emphysematous cholecystitis are strongly associated with T2D, most infections that occur in T2D patients are also common in the general population[9]. However, having T2D worsens infection prognosis, with these patients showing increased morbidity and mortality from sepsis compared to the general population[10]. There is some controversy in the literature about these findings[11-13], which many investigators suspect is due to the inability to account for all of the study confounders[14, 15]. It has been shown that adequate control of hyperglycemia is associated with improved outcomes during episodes of critical illness. Conversely, too tight of glycemic control has been associated with decreased patient survival[16]. This U-shaped curve between glycemic control and mortality suggest that the ideal glycemic control for T2D patients is at moderately elevated glycemic levels. However, it is unclear whether this effect is actually due to the specific glucose concentration, instead of confounding variables that lead to both lower glycemic levels and worse outcomes[17].

Patients with obesity and T2D are physiologically frail and comorbidly challenged individuals. They comprise the largest population of patients that experience post-infection complications and rising long-term mortality. As medical management strategies improve, patients with obesity and T2D live longer, accumulate more comorbidities, and require more medical care. This has resulted in a rapidly expanding patient population that requires an immense amount of medical resources. Subsequently, there have been substantial efforts initiated to try and more effectively treat these diseases. For most endocrine diseases, researchers have established effective therapeutic treatments based on the underlying disease mechanisms[3]. However, this is not the case with obesity, as there is a limited

understanding of its pathogenesis despite decades of research and billions of dollars spent each year on treatment strategies[3]. Bariatric surgery is currently the most successful treatment for obesity and is the only therapeutic option that also results in a sustained, substantial improvement of T2D[18], as well as a reduction in mortality[19]. Roux-en Y gastric bypass and vertical sleeve gastrectomy (VSG) bariatric surgery result in similar physiological and behavioral effects. They both alter gut hormones, bile acids, insulin sensitivity, and inflammatory markers in a manner that is independent of weight loss, and in a way that may significantly impact systemic metabolism[18].

Given the heightened clinical focus on weight loss to improve obesity-related complications, equal emphasis has to focus on investigating the changes in immune function following weight loss. Recently, investigators have focused on understanding the underlying innate and adaptive immune system derangements in obesity and T2D, which facilitate infectious complications, impair recovery from sepsis, and increase long-term mortality[20]. However, there has been limited investigations into the immune system after weight loss and the studies that do exist emphasize immune phenotypes, instead of investigating immune function. This mini-review will examine what we know about the immune dysfunction observed in obesity and T2D, and the impact that these changes have on bacterial surveillance. We will then examine what is known about the effects of weight loss on obesity-related immune dysfunction and highlight the need for further research in this area.

Immune Dysfunction in Obesity and T2D

Immune cells play a role in the physiologic dysfunction and clinical pathology of obesity[2]. The metabolic disturbances present in obesity lead to immune activation, as indicated by elevated plasma inflammatory markers in obese individuals[2]. There are alterations in lymphoid tissue architecture and integrity, as well as shifts toward inflammatory phenotypes

in leukocyte populations[2]. This immune dysfunction results in high rates of vaccine failure and infectious complications[2].

The immune system also plays a role in T2D. T2D is a complex clinical syndrome where individuals have persistent hyperglycemia in the setting of decreased insulin secretion and sensitivity. This results in a compilation of aberrant metabolic changes[10], including increased formation of advanced glycation end products, activation of protein kinase C isoforms, and increased flux through the polyol and hexosaine pathways[21]. These changes lead to increased production of superoxide, which activates inflammatory pathways and leads to immune system dysfunction[22]. Additionally, individuals with T2D have abnormal host responses, including disorders of humoral immunity, and defects in neutrophil function and T cell response[23].

A key point is that the immune dysfunction seen in these chronic diseases develop over time as the diseases evolve. The mechanism of weight gain leading to obesity is usually slow, with consistent excess caloric intake leading to increasing levels of adiposity. For T2D, there is a progression from normoglycemia to impaired glucose tolerance and/or elevated fasting glucose, and finally, T2D, with obesity exacerbating any degree of insulin resistance. A key point is that insulin resistance may be present for many years before the development of any abnormality in plasma glucose levels[24]. Subsequently, an estimated one in four people with T2D are unaware that they even have the disease[25] and underlying derangements of the immune system have begun before a person even recognizes they are at increased risk of the sequelae of obesity and T2D. Furthermore, given the increasing prevalence of childhood obesity and the increasingly young age at diagnosis of T2D, there is prolonged exposure to adipose tissue inflammation and hyperglycemic conditions resulting in sustained exposure to glucolipotoxicity, low-grade inflammation, and increased oxidative stress[26]. We believe that this chronic exposure to an abnormal metabolic milieu leads to

persistent derangements in innate and adaptive immunity, which is the root cause of obesity-related infection pathology and mortality.

Cellular Defects in Obesity and T2D

In the following sections, we will summarize the known physiologic alterations in innate and adaptive immune cells in obesity and T2D. We will also summarize how non-surgical (diet/exercise) and surgical (bariatric surgery) weight loss impact obesity- and T2D-associated defects. We acknowledge that bariatric surgery is currently the most successful treatment for obesity but given the limited investigations on this topic, we have chosen to include data after both surgical and non-surgical weight loss. Additionally, we recognize that different methods of weight loss may result in different immunological outcomes. The exact mechanisms for these varying results are unclear; however, it is related to the physiologic changes that are observed after bariatric surgery[18], but not after non-surgical weight loss.

Bariatric surgery alters gut hormones, bile acids, insulin sensitivity, and inflammatory markers in a manner that is independent of weight loss and is hypothesized to significantly impact immune cell metabolism[18]. Additionally, adipose tissue itself shows weight-independent changes after bariatric surgery, with alterations in inflammatory markers and adipokine secretion[18]. These weight-independent changes facilitate widespread systemic alterations that are not observed from diet and exercise alone. Additionally, bariatric surgery generally leads to a greater percentage of excess body weight loss, which accounts for some of these observed differences.

Innate Immunity (Figure 1)

A) Neutrophils

Neutrophils are critical for the containment and eradication of microbes[27]. They are the majority cell in bone marrow and are the first responders to microbial infections sites[28].

Their antimicrobial activity is based on specific proteins, such as myeloperoxidase and calprotectin, which are located in the cytoplasm or stored in granules[29].
Neutrophils in obese individuals have heightened chemotactic and random migration, increased released of basal superoxide, and no difference in phagocytosis or adherence ability compared to lean individuals[30]. This suggest that neutrophils in obese individuals are primed and have the capacity to fight infections; however, being chronically primed may facilitate the pathogenesis of obesity-related diseases[30]. The elevated basal superoxide production from unstimulated neutrophils indicates a low grade of inflammation, which coincides with obesity being a pro-inflammatory condition. The elevated basal superoxide production may be the result of neutrophils being activated by high levels of triglycerides[30].

On the other hand, neutrophils in individuals with T2D show defects in almost all functions, including migration to inflammatory sites, release of lytic proteases, phagocytosis, production of reactive oxygen species, and apoptosis[31]. In addition, a study evaluating cytokines from neutrophils in individuals with T2D showed increased amounts of TNF-alpha, IL-1β, and IL-8 in both the basal state and after stimulation by lipopolysaccharides (LPS). This excessive release may lead to tissue injury, cell death[31], and increased susceptibility to invasive microorganisms[32].

From these findings, it appears that both obesity and T2D independently lead to neutrophil dysfunction, contributing to the increased risk and persistence of infections. Additionally, during sepsis there is delayed neutrophil apoptosis[33], leading to ongoing neutrophil dysfunction. Correcting the dysfunction of neutrophils in obesity and T2D has the potential to improve outcomes following infections and sepsis; however, the mechanistic pathways necessary to target are unknown. After bariatric surgery with marked weight loss, part of the inflammatory cascade (calprotectin levels) decreases, while other products (myeloperoxidase) do not, indicating a partial reduction in neutrophil activation[30].

Additionally, weight loss through bariatric surgery has been shown to result in sustained improvements in T2D, while weight loss through diet and exercise has not shown similar improvements[18]. This indicates that bariatric surgery has a potential role in improving the neutrophil dysfunction observed in obese, T2D patients.

B) Monocytes and Macrophages

Monocytes and macrophages play a significant role in phagocytosis, clearing apoptotic and necrotic cells[27], and in adaptive immune cross talk. More specifically, they secrete pro- and anti-inflammatory cytokines and express major histocompatibility complex (MHC)-II molecules, allowing them to activate $CD4^+$ T cells[27]. They also participate in the regulation of glucose and lipid metabolism, and play a substantial role in adipose tissue inflammation[34].

Macrophages have the ability to display remarkable phenotypic heterogeneity depending on the extracellular milieu, leading to the establishment of M1 pro-inflammatory (CD11c+) and M2 anti-inflammatory (CD11c-) macrophages[35]. Functionally, M1 macrophages are characterized by the production of inflammatory mediators, including inducible nitric oxide synthase, TNF-alpha, and IL-1β, while M2 macrophages have increased production of IL-10, a potent immune regulatory cytokine[36]. In obesity, there is an accumulation of adipose tissue macrophages (ATMs), which have a M1 phenotype. These ATMs form crown-like structures around dead adipocytes[37]. The mechanisms behind the accumulation of these pro-inflammatory M1 macrophages is thought to occur through two main process. Traditionally, the accumulation of ATMs was considered to be a consequence of peripheral monocyte migration under inflammatory conditions. The adipocytes and resident tissue macrophages would promote recruitment of blood monocytes by secreting increased levels of chemokines: LTB3, MIP, MIF, and MCP-3[38]. Once the monocytes arrived, the surrounding milieu would then influence the monocytes to

differentiate into the pro-inflammatory M1 phenotype[36], as CD11c expression can be induced by immunological stimuli, including interferon gamma (IFNγ) and LPS, elevated glucose levels, and elevated triglycerides[36]. However, there is increasing evidence that accumulation of ATMs may also be due to local proliferation of macrophages[37]. One study that evaluated if monocyte migration or macrophage proliferation contributed to ATMs revealed that resident macrophage proliferation contributed to ATM accumulation during the early stages of obesity, while migrated monocytes contribute to ATM accumulation during late stages of obesity[37]. Both theories lead to an increased ratio of M1 pro-inflammatory macrophages in obese, diabetic individuals.

These findings raise the question of how monocytes and macrophages function in obese and T2D individuals after being exposed to infections and sepsis. At baseline, obese and T2D individuals have a shift toward pro-inflammatory macrophages; however, the fate of these recruited macrophages and their contribution to infection eradication is unknown. The chronic polarization to M1 macrophages likely contributes to the increased sepsis mortality seen in these patient populations; however, the manner in which the altered mechanistic pathways in these chronic disease states overlap and interact with an acute infection is not clear. What is not known is whether correcting this polarization back to a normal M1/M2 ratio would improve macrophage function. Lumeng et al looked at weight loss in mice after switching from a high-fat diet (HFD) to a normal-fat diet[39]. They found that weight loss improved glucose tolerance and reduced serum insulin; nonetheless, ATMs retained an inflammatory gene expression profile similar to those found during obesity[39]. Seeley et al looked at the immune cell population in epididymal and inguinal fat pads in mice after VSG bariatric surgery[18]. They found that VSG caused an increase in M2 ATMs, which brought the ratio between M1 and M2 macrophages back to control levels; however, macrophage cellular function was not assessed[18].

C) Natural Killer (NK) Cells

NK cells act as immune complex regulators. They have the ability to destroy target cells spontaneously, without prior exposure and without MHC restrictions[40]. In addition, they are important guards that survey tissues for infected, transformed, or stressed cells[41]. They have a number of activating and inhibitory receptors that are attuned to detect signs of cytopathology, while at the same time ensuring self-tolerance[41]. Downregulation of MHC class I molecules or upregulation of stress ligands stimulates NK cells to produce cytokines or mediate a cytolytic response[41].

In obesity, there is upregulation of ligands for NK cell-activating receptor 1 on adipocytes. This stimulates NK cell proliferation and IFN-γ production, with a corresponding increase in differentiation of M1 macrophages, adipose tissue inflammation, and insulin resistance[41]. In mice fed a HFD, the number of NK cells and the production of pro-inflammatory cytokines were increased[42]. Recent studies have shown that individuals with T2D have abnormal NK cell phenotypes, with significant decreases in NKp46, a NK receptor that recognizes influenza hemagglutinins, and tumor ligand NKG2D, an activating receptor on NK and $CK8^{+}$ T lymphocytes. Functionally, they also exhibit reduced degranulation[43]. Therefore, NK cell phenotypes and function are clearly altered in obesity and T2D.

Given that decreased NK cell activity (NKCA) is associated with increased sepsis lethality and an increased risk of cancer development, how NKCA is altered after weight loss is an important consideration. One study showed a decrease in the number of circulating NK cells after dietary weight loss, while another study showed a decrease in NKCA after weight loss from diet-alone compared to no change after weight loss from a combination of diet and exercise[44]. When evaluating NK and bariatric surgery, prior to surgery, obese individuals had a normal number of NK cells but decreased NKCA, which subsequently improved after bariatric surgery[45]. Nonetheless, it is unclear whether improvement in NKCA after bariatric

surgery allows NK cells to respond to infections and sepsis like they would prior to being placed in an obese and hyperglycemic milieu.

D) Dendritic Cells (DCs)

DCs are messengers between the innate and adaptive immune systems. They have the ability to either activate or suppress immune responses depending on their maturation state. Upon stimulation, DCs express surface molecules and produce cytokines that initiate the adaptive immune response and activate T-cells[46]. DCs are characterized as conventional DCs (cDCs), plasmacytoid DCs (pDCs), or inflammatory DCs (inf-DCs). cDCs secrete IL-12 and are comparable to monocytes. pDCs secrete IFNα and are comparable to plasma cells[46]. Inf-DCs are created from inflammatory monocytes and are associated with inflammation or infection[47].

Given limited unique surface markers, the role of DCs in obesity and T2D is not well understood. It is known that there is an increase in inf-DCs in adipose tissue, which contribute to adipose tissue inflammation, as well an increase in Th17 cells[47]. In T2D, elevated glucose levels induce a pro-inflammatory cytokine profile in DCs, with increased IL-17, leading to their maturation[48]. Additionally, advanced glycation end products induce maturation of DCs[49], while hyperinsulinemia promotes DC activation and upregulation of scavenger receptors on tissues involved in the macrovascular complications of T2D[50].

During infectious episodes and sepsis, DCs have enhanced apoptosis[27]. Recent investigations have demonstrated that inhibition of sepsis-induced DC apoptosis or amplification of DC function improves long-term survival after sepsis[51]. Given that DCs are already activated in obese, diabetic individuals, it is unclear how they would respond when challenged with an infectious process. It is also unclear if improving these comorbidities will lead to a decrease in the quantity of inf-DCs and/or improve DC function. One study looking

at murine bariatric surgery showed a decrease number of adipose tissue dendritic cells after surgery[18]; however, the overall clinical impact of this is still unknown.

Adaptive Immunity (Figure 2)

A) Gamma delta T cells (γδ T cells)

γδ T cells are a diminutive subset of T cells that have a T cell receptor (TCR) made up of one γ chain and one δ chain[52]. Stress signals after traumatic epithelial injury, malignancy, and infection activate γδ T cells. Once activated, γδ T cells repair tissue, induce inflammation, and recruit leukocytes[53]. Depending on their location and the surrounding milieu, they can be either pro- or anti-inflammatory[52]. γδ T cells activated in the periphery secrete inflammatory cytokines, such as INFγ, TNF-alpha, and IL-17[27]. γδ T cells have also recently been found in adipose tissue[52]. In a HFD murine model, γδ T cell null mice and mice treated with anti-TCR*γδ* antibody had decreased insulin resistance, M1 macrophages, adipose tissue inflammation, and inflammation in the liver and skeletal muscles[52].

Obese humans have a decreased amount of γδ T cells, which is inversely proportional to BMI, and the remaining γδ T cells have a reduced ability to secrete IFNγ[53]. These alterations likely contribute to the chronic, non-healing wounds and persistent infections seen in obese patients. In T2D individuals, hyperglycemia results in impaired skin γδ T cell proliferation, resulting in a decreased number of γδ T cell in the epidermis. The γδ T cells that do persist have altered metabolic and nutrient sensing pathways making them unresponsive to epithelial cell damage[54]. Additionally, during sepsis, the number of circulating γδ T cells is reduced[55] and this reduction has been correlated with high rates of sepsis lethality[55]. γδ T cells contribute to the worsened infection control observed in the obese, T2D population. If it was possible to increase the quantity of γδ T cells or increase their functional ability, it is probable that there could be an improvement in the persistent

infections observed in this patient population. However, it is unclear if this could be achieved through weight loss. To our knowledge, there are no studies investigating weight loss and its effects on γδ T cells during an infection.

B) T helper (T_h) cell subpopulations

T_h cells assist other cells with immunological processes. Antigen presenting cells present peptide antigens to $CD4^+$ T cells through MHC class II molecules and to $CD8^+$ T cells through MHC class I molecules. Upon activation, $CD4^+$ T cells have the capability to differentiate into specialized T cell subsets[27]. These subsets promote monocyte stimulation, B cell differentiation, and cytotoxic T cell activation[27].

T cells contribute to the chronic visceral adipose tissue (VAT) inflammation in obesity. As obesity increases, the number of $CD4^+$[56] and $CD8^+$ T cells in VAT tissue increases[57]. Several studies have shown a decline in naïve $CD4^+$ T cells, as well as an imbalance of $CD4^+$ T helper cells toward Th17 and Th22 pro-inflammatory subsets in obese individuals with T2D. This leads to a cytokine-induced hyperinflammatory response, which further activates the innate immune system[58]. This shift to a pro-inflammatory environment is of substantial importance in T2D patients, as there is an increased number of Th17 cells[57], and these pro-inflammatory T_h cells contribute to the clinic complications of diabetes[58]. Although a pro-inflammatory state could be beneficial for immune surveillance and bacterial eradication, there is no current data to support that notion. Moreover, the pro-inflammatory $CD4^+$ cell phenotypes could very well hinder bacterial clearance and enable infection persistence. Additionally, during sepsis, there is apoptosis of lymphocytes. Compared to individuals who survive an episode of sepsis, in humans that die from sepsis there is more lymphocytic, specifically $CD4^+$ cells, apoptosis[59]. $CD8^+$ T cells have been shown to precede macrophages into the VAT in obesity. In a murine model of diet-induced obesity,

$CD8^+$ T cell depletion resulted in decreased accumulation of macrophages and improved insulin sensitivity[57].

When T cells were evaluated after bariatric surgery in mice, epididymal adipose tissue had an increased frequency of T cells[18]. In the murine model, a HFD resulted in increased $CD8^+$ T cells, while bariatric surgery resulted in a weight-independent increase in $CD4^+$ cells[18]. However, how changes in $CD4^+$ and $CD8^+$ cell numbers impact adaptive immune function and contribute to infection control and wound healing is still unknown.

C) Regulatory T cells (Tregs)

Tregs are master regulators of the adaptive immune system. They can be induced from peripheral naïve $CD4^+$ T cells[60]. Tregs help maintain self-tolerance and suppress responses of effector T cells subsets[27]. They also induce M2 anti-inflammatory macrophage differentiation[61].

A small subset of Tregs have been identified as resident VAT Tregs. In lean individuals, the number of VAT Tregs increases with age. In obesity, the number of VAT Tregs decreases and this reduction is associated with inflammation and insulin resistance[60]. In T2D, there is also a decrease in the number of Tregs[62, 63], which is hypothesized to contribute to the clinical complications of T2D[61]. In the presence of inflammation, Tregs enhance $T_{effector}$ cell suppression, which subsequently prolongs recovery and predisposes one to increased complications[64]. This correlates with the worse clinical outcomes observed in the obese, T2D populations. It is unclear if improving these disease states with weight loss would lead to an increased number of Tregs and/or functional improvements. To our knowledge, there are no published studies on the effects of diet-induced or surgical weight loss on Tregs number or function in obese, T2D individuals. Hence, it is difficult to speculate if improvements in either would diminish the increased infection risk associated with obesity and T2D.

D) B cells

B cells are a very diverse immune cell population. Historically, B cell function was thought to only encompass producing antibodies and plasma cells for long-term antibody responses. Recent data has shown that B cells play a role in chronic inflammatory diseases and sepsis[27]. In obesity, B cells promote hypertrophic obesity leading to insulin resistance, as well as adipose tissue and systemic inflammation[65]. Obese mice B cells produce a pro-inflammatory cytokine profile, with decreased secretion of IL-10 and increased secretion of IL-6 and IFNγ[65]. Additionally, B cells accumulate in the VAT of diet-induced obese mice. When the B cells were depleted, the obese mice were protected against insulin resistance, despite weight gain[57]. In obese humans, there is a decreased percentage of anti-inflammatory B cell subsets (transitional B cells) and an increased percentage of pro-inflammatory (late/exhausted) memory B cells[66].

In the face of infection, B cell antibody generation plays a key role in microbial elimination. As both obese[66] and T2D individuals have impaired B cell function[65], illustrated by the altered pool of B cells available, this contributes to the poor outcomes observed in these patient populations when challenged with an infection. Similar to the other adaptive immune cells, it is unknown if these deleterious changes can be reversed if the surrounding milieu is altered through weight loss. To date the authors are unaware of any studies that evaluated the effects of weight loss on B cell immune function.

Metabolic Regulation of Immunity

Metabolism is the fuel behind all biological functions[67]. The immune system protects against foreign microbial invaders, maintains optimal tissue homeostasis, and facilitates wound healing. When there is tissue injury or an invading pathogen, innate immune cells secrete inflammatory mediators, cytokines, and chemokines, which subsequently activate adaptive immunity[27]. These processes carry a considerable

bioenergetic cost, as they are constantly changing to meet the needs of the organism[67]. Since immune cells do not store nutrients, immune responses are only upregulated and sustained when there is an active, increased uptake of nutrients from the local microenvironment[67].

Glucose, glutamine, and free fatty acids (FFAs) are all potential energy sources[68]. A successful innate effector response is dependent on glucose metabolism[69] and mitogen-driven proliferation of adaptive immune cells requires the utilization of extracellular glutamine[70]. Obesity and T2D are diseases with aberrant metabolic regulation and glucose metabolism. In T2D, insulin resistance is associated with inactivity, obesity, and ageing[71]. Initially, the pancreatic islet β cells respond to this decrease in insulin-stimulated glucose uptake by increasing cell mass and secretory activity. When functional expansion of the islet β cells fail to compensate for the insulin resistance, insulin deficiency and T2D develop. The hypothesized mechanisms behind insulin resistance and islet β-cell dysfunction include molecular changes secondary to lipotoxicity, glucotoxicity, oxidative stress, endoplasmic reticulum stress, amyloid deposition in the pancreas, and ectopic lipid deposition in the muscle, liver, and pancreas[71]. All of these cellular stresses are caused by over-nutrition[72] and are induced or exacerbated by an inflammatory response[73]. In obese and T2D individuals, homeostatic conditions are altered and the immune cells now exist in an environment consisting of chronic hyperglycemia, hypertriglyceridemia, and increased FFAs[74].This altered milieu leads to chronic dysregulation of the immune system, which alters its ability to respond in times of acute infections and sepsis. However, much more investigation is necessary to identify how the metabolic alterations contribute to the ongoing immune dysfunction. Nonetheless, the overall clinical outcome is known. Obese, T2D individuals have worsened long-term outcomes after infections and sepsis. These patient populations are at increased risk of recurrent, nosocomial, and secondary infections that

result in hospital readmissions and increased morbidity and mortality. Future exploration that leads to medical therapies that improve or reverse these deleterious immune cell metabolic changes is crucial.

Given that bariatric surgery is currently the most successful treatment for obesity and is the only therapeutic option that also causes a sustained, substantial reduction of type 2 diabetes[18] and mortality[19], we need to evaluate immune cell function after bariatric surgery. Is it possible to improve the chronic immune dysfunction that is present in obesity and T2D if one undergoes bariatric surgery? There is a paucity of information on this topic. The studies that do focus on immunity after weight loss either look at diet- or exercise-induced weight loss or focus solely on immune phenotypes. Being able to identify immune phenotypes is the first step, but now that we know phenotypic changes exist, we need to better understand if these changes result in functional immune improvements, better clinical outcomes, and improved quality of life.

In addition, given the growing knowledge in the field of metabolic-induced immune dysfunction in obesity and T2D, possible interventions that curb inflammation may also offer therapeutic benefits in these patient populations. Some current antidiabetic medications are known to have anti-inflammatory properties[75]. Moreover, immune modulatory therapies are commonplace in other disease states, such as severe burns, advanced cancers, and autoimmune diseases, where combinations of therapies are used to reduce inflammation, optimize metabolism, and decrease infections[27]. Immune modulatory therapies have not been used in obesity and T2D; however, given that these patients are at the highest risk of mortality from infections that lead to sepsis, immune modulatory therapies have a potential role[75]. Combinations of immune modulators that target the chronically affected pathways in obesity and T2D and the acutely affected signaling pathways in sepsis have the potential to offer meaningful clinical improvements in overall survival.

Concluding Remarks

Obesity and T2D are chronic diseases that lead to persistent immune dysregulation. This immune dysregulation develops over time and begins prior to an individual showing clinical signs of these diseases. Clinically, obese and T2D patients have an increased risk of and significant morbidity and mortality from infections and sepsis for reasons that are poorly understood. We need to focus our efforts on reducing infectious complications and improving outcomes in these patient populations. To do this, it is mandatory that we further identify and improve the chronic interdigitating immune derangements that are found in these disease states. As bariatric surgery is currently the most successful treatment for obesity and the only therapeutic option that causes a sustained reduction in T2D, we need to investigate if bariatric surgery leads to improvements in immune cell function. Furthermore, additional research on utilizing immune modulatory therapies in these physiologically frail and comorbidly challenged patient populations during infections and sepsis is scientifically necessary.

Authorship

All authors have made substantial contributions to all phases of manuscript development. LMF and MJD conceived the larger project. LMF wrote the manuscript and made the figures. DEO and PAW edited the manuscript. All authors provided substantive and editorial feedback on multiple revisions. We have all approved the final version prior to submission.

Acknowledgments

LMF would like to acknowledge T32 HL007517, which supported her during her research fellowship. MJD would like to acknowledge the 2016 Research Scholarship from the Shock Society and the 2017 Faculty Early Career Investigator Research Fellowship from the American Surgical Association Foundation. Additional support was provided by National

Institutes of Health grants, GM-29507 and GM-61656, and from the Godfrey D. Stobbe Endowment (PAW).

Conflicts of Interest Disclosure

The authors declare there are no commercial or financial conflicts of interest related to the study.

References

1. WHO. World Health Organization. Obesity and overweight. http://www.who.int/mediacentre/factsheets/fs311/en/. January 1.
2. Andersen, C. J., Murphy, K. E., Fernandez, M. L. (2016) Impact of Obesity and Metabolic Syndrome on Immunity. Adv Nutr 7, 66-75.
3. Schwartz, M. W., Seeley, R. J., Zeltser, L. M., Drewnowski, A., Ravussin, E., Redman, L. M., Leibel, R. L. (2017) Obesity Pathogenesis: An Endocrine Society Scientific Statement. Endocr Rev 38, 267-296.
4. CDC. Centers for Disease Control and Prevention. Overweight & Obesity. https://www.cdc.gov/obesity/data. January 1.
5. Malnick, S. D. and Knobler, H. (2006) The medical complications of obesity. QJM 99, 565-79.
6. Mokdad, A. H., Bowman, B. A., Ford, E. S., Vinicor, F., Marks, J. S., Koplan, J. P. (2001) The continuing epidemics of obesity and diabetes in the United States. JAMA 286, 1195-200.
7. Collaboration, N. C. D. R. F. (2016) Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 387, 1513-30.
8. Falagas, M. E. and Kompoti, M. (2006) Obesity and infection. Lancet Infect Dis 6, 438-46.

9. Muller, L. M., Gorter, K. J., Hak, E., Goudzwaard, W. L., Schellevis, F. G., Hoepelman, A. I., Rutten, G. E. (2005) Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis 41, 281-8.
10. Tiwari, S., Pratyush, D. D., Gahlot, A., Singh, S. K. (2011) Sepsis in diabetes: A bad duo. Diabetes Metab Syndr 5, 222-7.
11. Esper, A. M., Moss, M., Martin, G. S. (2009) The effect of diabetes mellitus on organ dysfunction with sepsis: an epidemiological study. Critical care 13, R18.
12. Esper, A. M. and Martin, G. S. (2009) Extending international sepsis epidemiology: the impact of organ dysfunction. Critical care 13, 120.
13. Moss, M., Guidot, D. M., Steinberg, K. P., Duhon, G. F., Treece, P., Wolken, R., Hudson, L. D., Parsons, P. E. (2000) Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Critical care medicine 28, 2187-92.
14. Kao, L. S., Todd, S. R., Moore, F. A. (2006) The impact of diabetes on outcome in traumatically injured patients: an analysis of the National Trauma Data Bank. Am J Surg 192, 710-4.
15. Ahmad, R., Cherry, R. A., Lendel, I., Mauger, D. T., Service, S. L., Texter, L. J., Gabbay, R. A. (2007) Increased hospital morbidity among trauma patients with diabetes mellitus compared with age- and injury severity score-matched control subjects. Arch Surg 142, 613-8.
16. Chin, T. L., Sauaia, A., Moore, E. E., Chandler, J. G., Harr, J. N., Johnson, J. L., Banerjee, A. (2012) Elderly patients may benefit from tight glucose control. Surgery 152, 315-21.
17. Park, J. I., Bae, E., Kim, Y. L., Kang, S. W., Yang, C. W., Kim, N. H., Lee, J. P., Kim, D. K., Joo, K. W., Kim, Y. S., Lee, H. (2015) Glycemic Control and Mortality in

Diabetic Patients Undergoing Dialysis Focusing on the Effects of Age and Dialysis Type: A Prospective Cohort Study in Korea. PLoS One 10, e0136085.

18. Frikke-Schmidt, H., Zamarron, B. F., O'Rourke, R. W., Sandoval, D. A., Lumeng, C. N., Seeley, R. J. (2017) Weight loss independent changes in adipose tissue macrophage and T cell populations after sleeve gastrectomy in mice. Mol Metab 6, 317-326.
19. Gulliford, M. C., Charlton, J., Prevost, T., Booth, H., Fildes, A., Ashworth, M., Littlejohns, P., Reddy, M., Khan, O., Rudisill, C. (2017) Costs and Outcomes of Increasing Access to Bariatric Surgery: Cohort Study and Cost-Effectiveness Analysis Using Electronic Health Records. Value Health 20, 85-92.
20. Hotchkiss, R. S., Monneret, G., Payen, D. (2013) Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nature reviews. Immunology 13, 862-74.
21. Brownlee, M. (2001) Biochemistry and molecular cell biology of diabetic complications. Nature 414, 813-20.
22. Hameed, I., Masoodi, S. R., Mir, S. A., Nabi, M., Ghazanfar, K., Ganai, B. A. (2015) Type 2 diabetes mellitus: From a metabolic disorder to an inflammatory condition. World J Diabetes 6, 598-612.
23. Geerlings, S. E. and Hoepelman, A. I. (1999) Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol 26, 259-65.
24. Caballero, A. E. (2003) Endothelial dysfunction in obesity and insulin resistance: a road to diabetes and heart disease. Obes Res 11, 1278-89.
25. Centers for Disease Control and Prevention. (2014) National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. U.S. Department of Health and Human Services. Atlanta, GA.

26. Kong, A. P., Xu, G., Brown, N., So, W. Y., Ma, R. C., Chan, J. C. (2013) Diabetes and its comorbidities--where East meets West. Nat Rev Endocrinol 9, 537-47.
27. Delano, M. J. and Ward, P. A. (2016) Sepsis-induced immune dysfunction: can immune therapies reduce mortality? J Clin Invest 126, 23-31.
28. Link, D. C. (2005) Neutrophil homeostasis: a new role for stromal cell-derived factor-1. Immunol Res 32, 169-78.
29. Nijhuis, J., Rensen, S. S., Slaats, Y., van Dielen, F. M., Buurman, W. A., Greve, J. W. (2009) Neutrophil activation in morbid obesity, chronic activation of acute inflammation. Obesity (Silver Spring) 17, 2014-8.
30. Brotfain, E., Hadad, N., Shapira, Y., Avinoah, E., Zlotnik, A., Raichel, L., Levy, R. (2015) Neutrophil functions in morbidly obese subjects. Clin Exp Immunol 181, 156-63.
31. Hatanaka, E., Monteagudo, P. T., Marrocos, M. S., Campa, A. (2006) Neutrophils and monocytes as potentially important sources of proinflammatory cytokines in diabetes. Clin Exp Immunol 146, 443-7.
32. Baggiolini, M., Dewald, B., Moser, B. (1997) Human chemokines: an update. Annu Rev Immunol 15, 675-705.
33. Hotchkiss, R. S. and Nicholson, D. W. (2006) Apoptosis and caspases regulate death and inflammation in sepsis. Nature reviews. Immunology 6, 813-22.
34. Lumeng, C. N., Bodzin, J. L., Saltiel, A. R. (2007) Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 117, 175-84.
35. Okabe, Y. and Medzhitov, R. (2014) Tissue-specific signals control reversible program of localization and functional polarization of macrophages. Cell 157, 832-44.
36. Torres-Castro, I., Arroyo-Camarena, U. D., Martinez-Reyes, C. P., Gomez-Arauz, A. Y., Duenas-Andrade, Y., Hernandez-Ruiz, J., Bejar, Y. L., Zaga-Clavellina, V.,

Morales-Montor, J., Terrazas, L. I., Kzhyshkowska, J., Escobedo, G. (2016) Human monocytes and macrophages undergo M1-type inflammatory polarization in response to high levels of glucose. Immunol Lett 176, 81-9.

37. Zheng, C., Yang, Q., Cao, J., Xie, N., Liu, K., Shou, P., Qian, F., Wang, Y., Shi, Y. (2016) Local proliferation initiates macrophage accumulation in adipose tissue during obesity. Cell Death Dis 7, e2167.

38. Surmi, B. K. and Hasty, A. H. (2010) The role of chemokines in recruitment of immune cells to the artery wall and adipose tissue. Vascul Pharmacol 52, 27-36.

39. Zamarron, B. F., Mergian, T. A., Cho, K. W., Martinez-Santibanez, G., Luan, D., Singer, K., DelProposto, J. L., Geletka, L. M., Muir, L. A., Lumeng, C. N. (2017) Macrophage Proliferation Sustains Adipose Tissue Inflammation in Formerly Obese Mice. Diabetes 66, 392-406.

40. Trinchieri, G. (1989) Biology of natural killer cells. Adv Immunol 47, 187-376.

41. Wensveen, F. M., Jelencic, V., Valentic, S., Sestan, M., Wensveen, T. T., Theurich, S., Glasner, A., Mendrila, D., Stimac, D., Wunderlich, F. T., Bruning, J. C., Mandelboim, O., Polic, B. (2015) NK cells link obesity-induced adipose stress to inflammation and insulin resistance. Nat Immunol 16, 376-85.

42. Lee, B. C., Kim, M. S., Pae, M., Yamamoto, Y., Eberle, D., Shimada, T., Kamei, N., Park, H. S., Sasorith, S., Woo, J. R., You, J., Mosher, W., Brady, H. J., Shoelson, S. E., Lee, J. (2016) Adipose Natural Killer Cells Regulate Adipose Tissue Macrophages to Promote Insulin Resistance in Obesity. Cell Metab 23, 685-98.

43. Berrou, J., Fougeray, S., Venot, M., Chardiny, V., Gautier, J. F., Dulphy, N., Toubert, A., Peraldi, M. N. (2013) Natural killer cell function, an important target for infection and tumor protection, is impaired in type 2 diabetes. PLoS One 8, e62418.

44. Scanga, C. B., Verde, T. J., Paolone, A. M., Andersen, R. E., Wadden, T. A. (1998) Effects of weight loss and exercise training on natural killer cell activity in obese women. Med Sci Sports Exerc 30, 1666-71.

45. Jahn, J., Spielau, M., Brandsch, C., Stangl, G. I., Delank, K. S., Bahr, I., Berreis, T., Wrann, C. D., Kielstein, H. (2015) Decreased NK cell functions in obesity can be reactivated by fat mass reduction. Obesity (Silver Spring) 23, 2233-41.

46. Sundara Rajan, S. and Longhi, M. P. (2016) Dendritic cells and adipose tissue. Immunology 149, 353-361.

47. Bertola, A., Ciucci, T., Rousseau, D., Bourlier, V., Duffaut, C., Bonnafous, S., Blin-Wakkach, C., Anty, R., Iannelli, A., Gugenheim, J., Tran, A., Bouloumie, A., Gual, P., Wakkach, A. (2012) Identification of adipose tissue dendritic cells correlated with obesity-associated insulin-resistance and inducing Th17 responses in mice and patients. Diabetes 61, 2238-47.

48. Lu, H., Yao, K., Huang, D., Sun, A., Zou, Y., Qian, J., Ge, J. (2013) High glucose induces upregulation of scavenger receptors and promotes maturation of dendritic cells. Cardiovasc Diabetol 12, 80.

49. Ge, J., Jia, Q., Liang, C., Luo, Y., Huang, D., Sun, A., Wang, K., Zou, Y., Chen, H. (2005) Advanced glycosylation end products might promote atherosclerosis through inducing the immune maturation of dendritic cells. Arterioscler Thromb Vasc Biol 25, 2157-63.

50. Kuliczkowska-Plaksej, J., Bednarek-Tupikowska, G., Plaksej, R., Filus, A. (2006) [The influence of diabetes mellitus and insulin resistance on receptor CD36 expression. Part II. The role of receptor CD36 in the pathomechanism of diabetes complications]. Postepy Hig Med Dosw (Online) 60, 152-62.

51. Scumpia, P. O., McAuliffe, P. F., O'Malley, K. A., Ungaro, R., Uchida, T., Matsumoto, T., Remick, D. G., Clare-Salzler, M. J., Moldawer, L. L., Efron, P. A. (2005) CD11c+ dendritic cells are required for survival in murine polymicrobial sepsis. J Immunol 175, 3282-6.

52. Mehta, P., Nuotio-Antar, A. M., Smith, C. W. (2015) gammadelta T cells promote inflammation and insulin resistance during high fat diet-induced obesity in mice. J Leukoc Biol 97, 121-34.

53. Fay, N. S., Larson, E. C., Jameson, J. M. (2016) Chronic Inflammation and gammadelta T Cells. Front Immunol 7, 210.

54. Taylor, K. R., Mills, R. E., Costanzo, A. E., Jameson, J. M. (2010) Gammadelta T cells are reduced and rendered unresponsive by hyperglycemia and chronic TNFalpha in mouse models of obesity and metabolic disease. PLoS One 5, e11422.

55. Grimaldi, D., Le Bourhis, L., Sauneuf, B., Dechartres, A., Rousseau, C., Ouaaz, F., Milder, M., Louis, D., Chiche, J. D., Mira, J. P., Lantz, O., Pene, F. (2014) Specific MAIT cell behaviour among innate-like T lymphocytes in critically ill patients with severe infections. Intensive care medicine 40, 192-201.

56. Shirakawa, K., Yan, X., Shinmura, K., Endo, J., Kataoka, M., Katsumata, Y., Yamamoto, T., Anzai, A., Isobe, S., Yoshida, N., Itoh, H., Manabe, I., Sekai, M., Hamazaki, Y., Fukuda, K., Minato, N., Sano, M. (2016) Obesity accelerates T cell senescence in murine visceral adipose tissue. J Clin Invest 126, 4626-4639.

57. Gerriets, V. A. and MacIver, N. J. (2014) Role of T cells in malnutrition and obesity. Front Immunol 5, 379.

58. Xia, C., Rao, X., Zhong, J. (2017) Role of T Lymphocytes in Type 2 Diabetes and Diabetes-Associated Inflammation. J Diabetes Res 2017, 6494795.

59. O'Sullivan, S. T., Lederer, J. A., Horgan, A. F., Chin, D. H., Mannick, J. A., Rodrick, M. L. (1995) Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. Ann Surg 222, 482-90; discussion 490-2.

60. Kucharska, A. M., Pyrzak, B., Demkow, U. (2015) Regulatory T Cells in Obesity. Adv Exp Med Biol 866, 35-40.

61. Zeng, C., Shi, X., Zhang, B., Liu, H., Zhang, L., Ding, W., Zhao, Y. (2012) The imbalance of Th17/Th1/Tregs in patients with type 2 diabetes: relationship with metabolic factors and complications. J Mol Med (Berl) 90, 175-86.

62. Qiao, Y. C., Shen, J., He, L., Hong, X. Z., Tian, F., Pan, Y. H., Liang, L., Zhang, X. X., Zhao, H. L. (2016) Changes of Regulatory T Cells and of Proinflammatory and Immunosuppressive Cytokines in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. J Diabetes Res 2016, 3694957.

63. Jagannathan-Bogdan, M., McDonnell, M. E., Shin, H., Rehman, Q., Hasturk, H., Apovian, C. M., Nikolajczyk, B. S. (2011) Elevated proinflammatory cytokine production by a skewed T cell compartment requires monocytes and promotes inflammation in type 2 diabetes. J Immunol 186, 1162-72.

64. Venet, F., Chung, C. S., Kherouf, H., Geeraert, A., Malcus, C., Poitevin, F., Bohe, J., Lepape, A., Ayala, A., Monneret, G. (2009) Increased circulating regulatory T cells (CD4(+)CD25 (+)CD127 (-)) contribute to lymphocyte anergy in septic shock patients. Intensive care medicine 35, 678-86.

65. DeFuria, J., Belkina, A. C., Jagannathan-Bogdan, M., Snyder-Cappione, J., Carr, J. D., Nersesova, Y. R., Markham, D., Strissel, K. J., Watkins, A. A., Zhu, M., Allen, J., Bouchard, J., Toraldo, G., Jasuja, R., Obin, M. S., McDonnell, M. E., Apovian, C., Denis, G. V., Nikolajczyk, B. S. (2013) B cells promote inflammation in obesity and

type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. Proc Natl Acad Sci U S A 110, 5133-8.

66. Frasca, D., Diaz, A., Romero, M., Vazquez, T., Blomberg, B. B. (2017) Obesity induces pro-inflammatory B cells and impairs B cell function in old mice. Mech Ageing Dev 162, 91-99.

67. Ganeshan, K. and Chawla, A. (2014) Metabolic regulation of immune responses. Annu Rev Immunol 32, 609-34.

68. Boothby, M. and Rickert, R. C. (2017) Metabolic Regulation of the Immune Humoral Response. Immunity 46, 743-755.

69. Levene, P. A. and Meyer, G. M. (1912) On the action of leucocytes on glucose. J Biol Chem 12, 265-273.

70. Newsholme, E. A., Crabtree, B., Ardawi, M. S. (1985) Glutamine metabolism in lymphocytes: its biochemical, physiological and clinical importance. Q J Exp Physiol 70, 473-89.

71. Goldfine, A. B., Fonseca, V., Shoelson, S. E. (2011) Therapeutic approaches to target inflammation in type 2 diabetes. Clin Chem 57, 162-7.

72. Prentki, M. and Nolan, C. J. (2006) Islet beta cell failure in type 2 diabetes. J Clin Invest 116, 1802-12.

73. Hotamisligil, G. S. and Erbay, E. (2008) Nutrient sensing and inflammation in metabolic diseases. Nature reviews. Immunology 8, 923-34.

74. Arner, P. (2002) Insulin resistance in type 2 diabetes: role of fatty acids. Diabetes Metab Res Rev 18 Suppl 2, S5-9.

75. Frydrych, L. M., Fattahi, F., He, K., Ward, P. A., Delano, M. J. (2017) Diabetes and Sepsis: Risk, Recurrence, and Ruination. Frontiers in Endocrinology 8.

Figure Legends

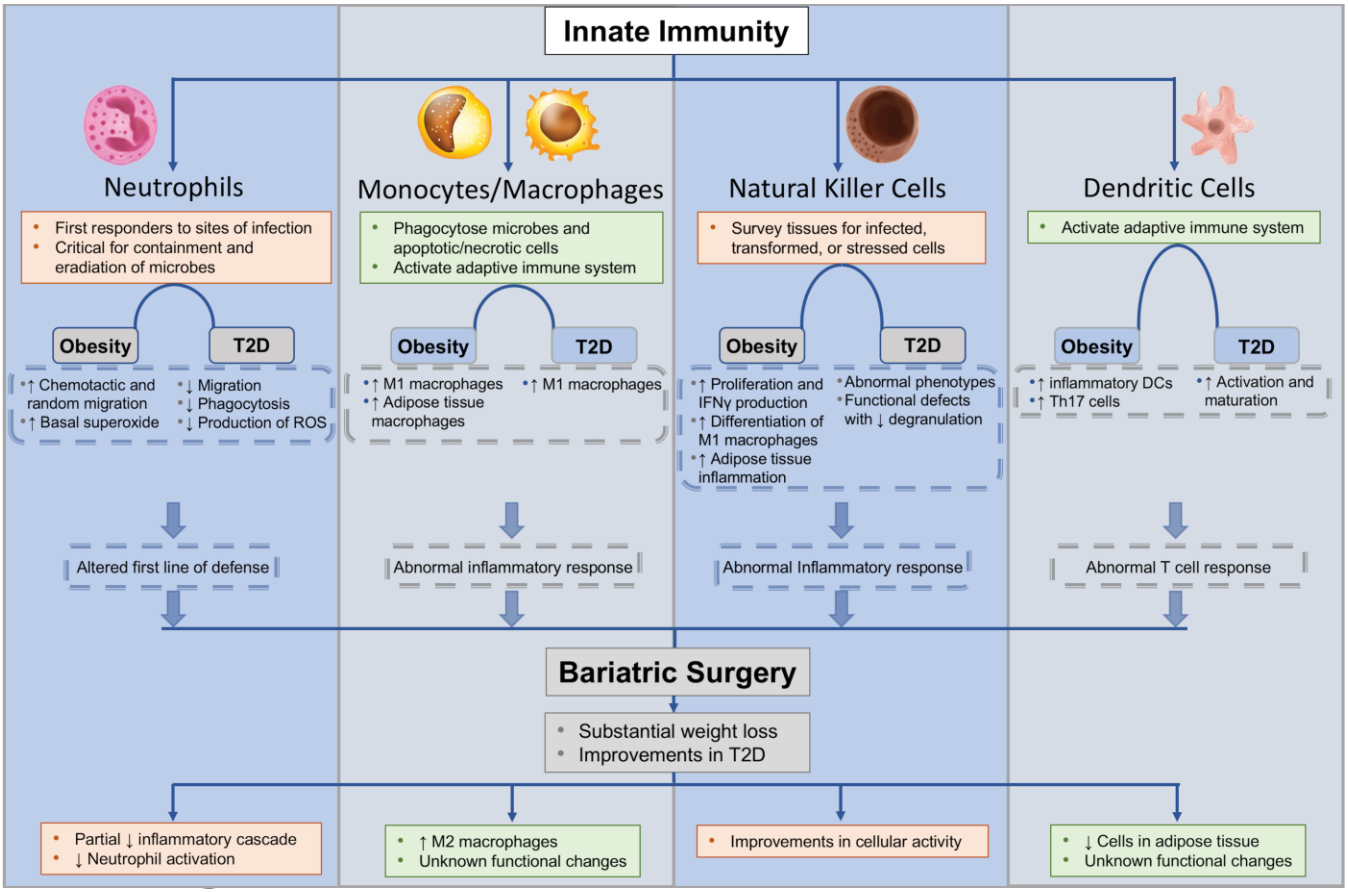


Figure 1. Altered innate immune function in obesity and type 2 diabetes mellitus. The innate immune response is altered in patients and in mice with obesity and type 2 diabetes. These alterations include altered neutrophil function, increased pro-inflammatory M1 macrophages, abnormal natural killer cell phenotypes, and increased inflammatory dendritic cells. These alterations are deleterious for the host as they lead to an altered first line of defense, increased inflammatory response, and abnormal T cell response. Bariatric surgery leads to substantial weight loss and improvement in diabetes; however, there is limited data on how bariatric surgery affects innate immune cellular function.

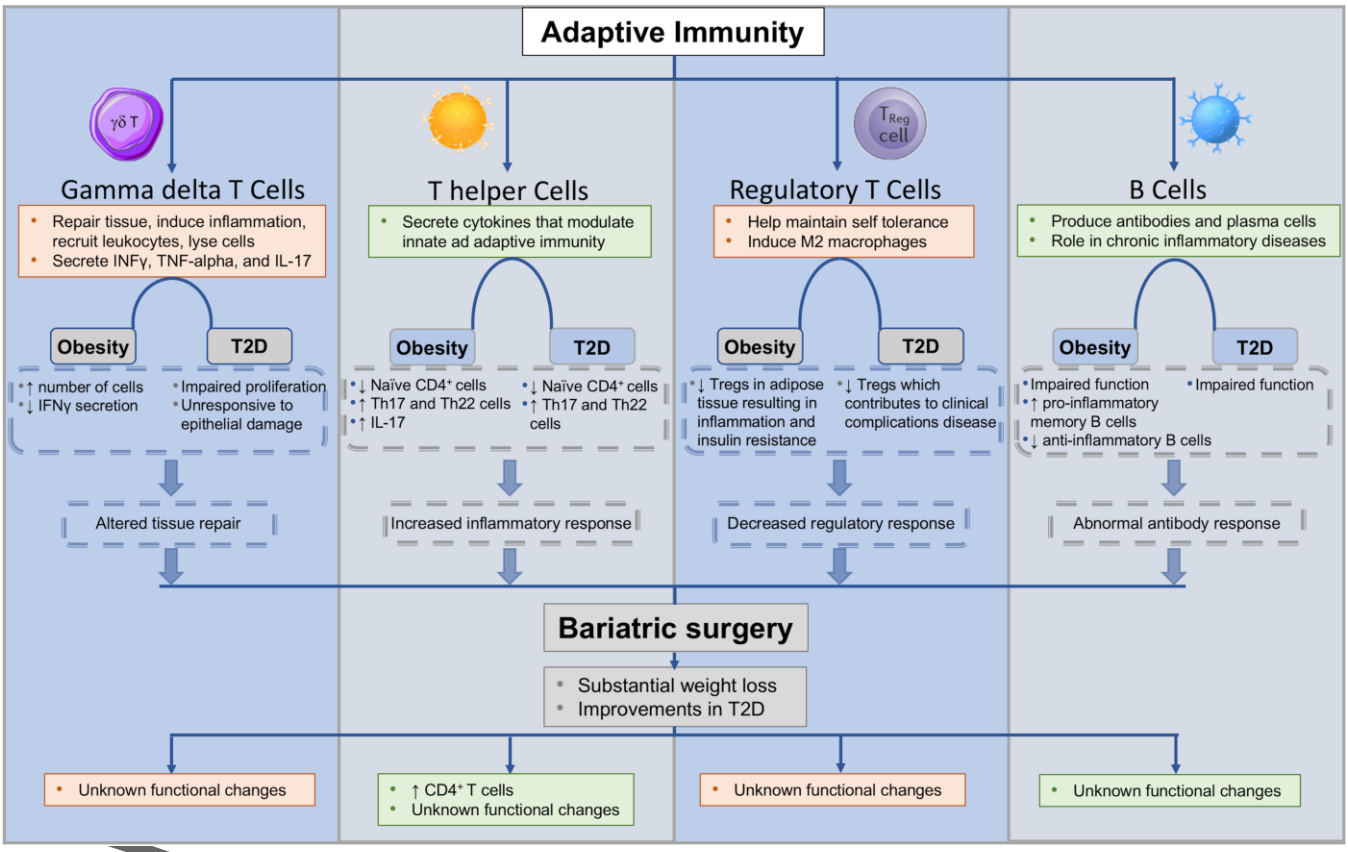
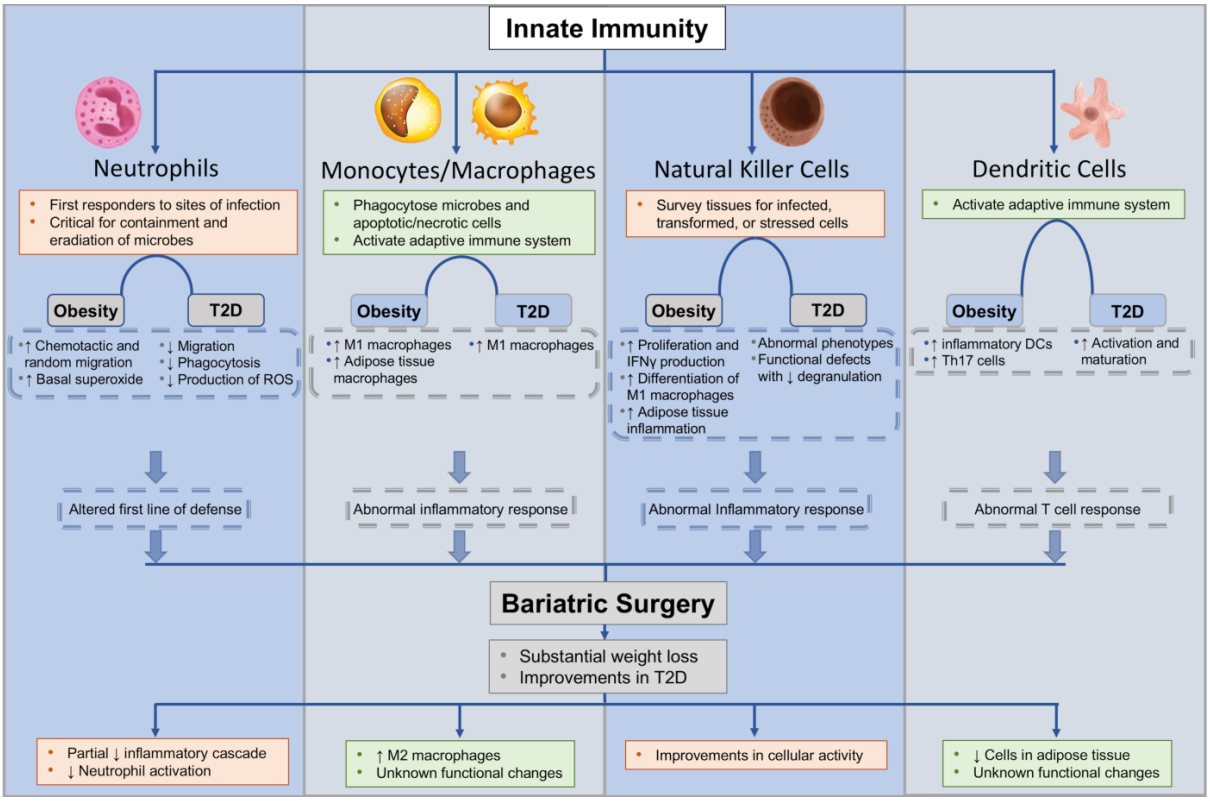
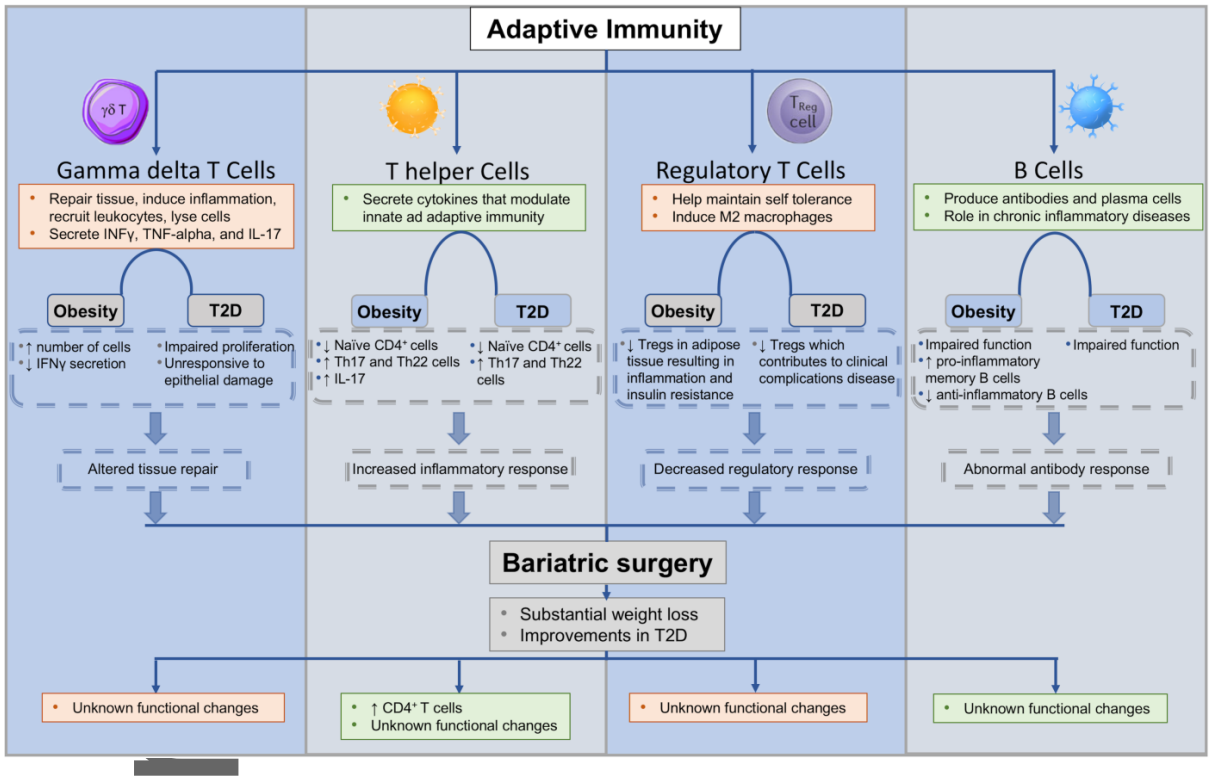


Figure 2. Altered adaptive immune function in obesity and type 2 diabetes mellitus.

The adaptive immune response is altered in patients and in mice with obesity and type 2 diabetes. These alterations include decreased gamma delta T cell function, increased inflammatory T helper phenotypes, decreased regulatory T cells, and impaired B cell function. These alterations are deleterious for the host as they lead to altered tissue repair, increased inflammatory response, decreased regulatory response, and an abnormal B cell response.

Bariatric surgery leads to substantial weight loss and improvement in diabetes; however, there is limited data on how bariatric surgery affects adaptive immune cellular function.





SSS