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The impact of obesity on immune response to infection: Plausible mechanisms and outcomes

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Summary

Emerging data suggest an association between obesity and infectious diseases. Although the mechanisms underlying this link are not well established, a number of potential factors may be involved. Indeed, the obesity-related vulnerability to infectious diseases could be due to chronic low-grade inflammation, hyperglycemia, hyperinsulinemia, and hyperleptinemia, which lead to a weakening of both the innate and adaptive immune responses. In addition, obesity results in anatomical–functional changes by the mechanical obstacle of excessive adipose tissue that blunt the respiratory mechanisms and predisposing to respiratory infections. Subjects with obesity are also at risk of skin folds and sweat more profusely due to the thick layers of subcutaneous fat, favoring the proliferation of microorganisms and slowing the repair of wounds down. All these factors make subjects with obesity more prone to develop nosocomial infections, surgical site, skin and soft tissue infections, bacteremia, urinary tract infections, and mycosis. Furthermore, infections in subjects with obesity have a worse prognosis, frequently prolonging hospitalization time as demonstrated for several flu viruses and recently for COVID-19. Thus, the aim of this manuscript is to provide an overview of the current clinical evidence on the associations between obesity and infectious diseases highlighting physio pathological insights involved in this link.

KEYWORDS
bacterial infections, fungal infections, obesity, viral infections

1 | INTRODUCTION

In the United States, the prevalence of obesity is over 40%, growing in the past 20 years from 30.5% to 42.4%.[1] Regarding childhood obesity, prevalence is 18.5% as it affects about 13.7 millions of children and adolescents in the United States.[1] In Italy, a prevalence of overweight of 35% and obesity of 13% has recently been estimated.[2] Moreover, about one in 10 people is obese and more than one in two men and one in three women are overweight in the same country, with projections indicating that overweight rates will increase by a further 5% within 10 years.[3] About childhood overweight in Italy, one in three children is overweight, one of the highest's rate in the Organization for Economic Co-operation and Development (OECD).[3] Obesity is often associated to chronic diseases such as type 2 diabetes, cardiovascular diseases, and osteoarticular diseases, which could represent an important burden for health national systems.[4] In particular, emerging data show that obesity could be a predisposing factor for infectious diseases increasing both the risk of getting an infection and/or of worsening the prognosis, thus increasing mortality once infection is established.[5] The exact mechanism according to which

obesity determines a vulnerability to infections is not yet known, although several hypotheses have been proposed. First of all, obesity causes dysregulation of the innate and adaptive immune system characterized by (i) impaired chemotaxis, (ii) altered differentiation of macrophages, (iii) dysregulated cytokine production, and (iv) imbalanced cross-talk between immune system and adipose cells.[6] In addition, subjects with obesity have a greater predisposition to develop respiratory infections and their complications due to alterations of the *obesity-related* anatomy and respiratory physiology such as pulmonary restriction, decreased pulmonary volumes, ventilation-perfusion mismatching, obstructive sleep apnea, and high risk of pulmonary embolism.[7] Obesity also carries an increased risk of surgical infections due to delay in wound healing, disrupted microcirculation and macrocirculation, and lymphedema.[8] In fact, prospective studies have shown that obesity is associated with a significantly increased risk of skin and soft-tissue infections after surgical procedures.[9,10] Waisbren et al. enrolled 591 elective surgical patients of which 69% had obesity founding that obesity and body fat percentage were significant predictors of surgical site infections (SSIs). In particular, they highlighted that patients with obesity had a fivefold higher risk for SSI than normal-weight patients and this risk increased the more the percentage of body fat was greater.[9] Similar results have been reported in an Australian large multicenter prospective study on 4474 patients undergoing coronary artery bypass graft (CABG) surgery. In this study obesity was found to be an independent predictor of SSIs following CABG, conferring a higher risk even compared with type 2 diabetes mellitus (odds ratio [OR] 1.8 vs. 1.6, respectively).[10] Some obesity-related comorbidities such as type 2 diabetes mellitus are known to be associated per se with immunosuppression and therefore could additionally aggravate the risk of infections when they coexist with obesity.[11] Nosocomial infections, periodontitis, and skin infections are also common findings in subjects with obesity.[12] Regarding nosocomial infections, most of the current data concern surgical patients reporting a significant increase in the number and percent of nosocomial infections such as pneumonia, wound infection, bacteremia, and *Clostridium difficile* colitis in the populations with obesity, with rates of 0.05% in normal weight, compared to 2.8% and 4.0% in groups of patients with obesity or severe obesity, respectively.[13] In addition, obesity makes the therapeutic management of infections extremely difficult altering protein binding, metabolism, and volume of distribution of antimicrobials. Currently, there are limited or no data on the dosage adjustment of antimicrobials in obesity, leading often to lack of efficacy of pharmacological treatments or in some cases to an increased risk of developing side effects.[14] Therefore, the aim of this manuscript is to provide an overview of the current clinical evidence on the associations between obesity and infectious diseases highlighting physio pathological insights involved in this link.

2 | SEARCH STRATEGIES

Articles were individually retrieved by each author up until April 2020 by search in PubMed (MEDLINE) using the following search terms: 'obesity', 'immunity', 'bacterial infections', 'viral infections', 'fungal infections', 'innate immunity', 'adaptative immunity', 'T cell s', 'CD4+ T-cells', 'CD8+ T-cells', 'Th1 cells', 'Th2 cells', 'Th17 cells', 'T-reg cells', 'B cells', 'Natural Killer cells', 'eosinophilis', 'macrophages', 'neutrophils', 'polymorphonuclears', 'proinflammatory cytokines", 'IL-1', 'IL-6', 'IL-17', 'IL-12', 'IL-10', 'IL-8', 'IL-33', 'TNF-α'. The reference lists of relevant articles and reviews were also searched manually. In order to address any bias, two authors independently screened the resulting articles for their methodology and appropriateness for inclusion. However, we did not use the Newcastle–Ottawa grading, which is used for assessing the quality of nonrandomized studies in meta-analyses because our manuscript is a narrative review.

2.1 | Bacterial infections and obesity: Clinical evidence and physiological mechanisms

In subjects with obesity, the innate immune response, which represents the first line of defense against pathogenic bacteria, is blunted probably due to the chronic low-grade inflammation state.[15,16] In fact, the equilibrium between proinflammatory and anti-inflammatory factors, which also plays an important role in the proper functioning of the immune system, is unbalanced due to the reduced production of anti-inflammatory molecules, such as adiponectin and the excessive production of proinflammatory adipokine and cytokines, such as interleukin (IL)-1, IL-6, IL-17, tumor necrosis factor-alpha (TNF-α), migration inhibitory factor (MIF), and leptin.[17] This latter plays a role in the innate and adaptive immune response with a protective action against infections in normal conditions, whereas in subjects with obesity, in which its levels is increased, it seems to have an opposite effect.[17,18] Indeed, leptin levels could influence the number and activity of natural killer (NK) cells, which participate to innate immune defense. In particular, it has been shown that short-term exposure to high leptin levels causes an increase in the activity and number of NK cells, whereas the prolonged exposure occurring in obesity has an opposite effect.[19] Furthermore, subjects with obesity also show an increased level of neutrophils and mast cells, decreased number of eosinophils in the adipose tissue,[20] and an accumulation in the adipose tissue of proinflammatory (M1) macrophages, responsible for the production of various inflammatory mediators, such as TNF-α, IL-6, IL-12, IL-17, and IL-1β. These mediators could contribute to the altered response of the immune system of subjects with obesity toward infections and to the increase in sepsis mortality observed in this population.[15] In particular, it was demonstrated that neutrophils from obese mice (ob/ob mice and in mice with diet-induced obesity DIO) during induced peritonitis produced high levels of the proinflammatory cytokine IL-17A compared with lean controls, this cytokine contributing to exacerbation and delayed resolution of peritoneal inflammation in obesity, being able to compromise the immune response to infections.[21]

Palmblad et al. observed, moreover, in patients with obesity a reduced polymorphonuclear (PMN) bactericidal capacity.[22,23] In support of this evidence, more recently, Kuwabara et al. demonstrated that neutrophils from diabetic rats and obese rats were tolerant to

lipopolysaccharide due to the impaired activation of Toll-like 4 (TLR4) receptors, which leads to lower production of cytokines and chemokines, migration, and myeloperoxidase (MPO) activity.[24] In fact, TLR4 are receptors expressed by innate immune cells that are activated following the recognition of the lipopolysaccharide, a component of gram-negative bacteria, promoting the early inflammatory and antimicrobial responses of the innate immune system.[25]

It would seem, therefore, that the immune response to infection in subjects with obesity is qualitatively lower than in normal-weight subjects, although further studies are needed to clarify the mechanisms underlying this association. Several studies have shown that nosocomial infections are among the most common bacterial infections in obesity.[26] Generally, obesity-related needs prolong hospitalization time thus increasing the chance of contracting hospital-acquired infections.[27] In this regard, Bishara et al. investigated the association between the risk of *C. difficile* infection, which is one of the main bacteria responsible for nosocomial infectious diarrhea, and body mass index (BMI) values in hospitalized patients, highlighting a positive association between obesity and Clostridium infections.[28] SSIs are among the most common bacterial nosocomial infections in obesity, especially in subjects who also have comorbidities related to obesity, such as type 2 diabetes mellitus, and after cardiac, vascular, orthopedic, and gastrointestinal surgical procedures.[26,29–32] In fact, Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) guidelines for the prevention of SSIs in acute care hospitals included obesity among the risk factors for SSIs.[26] Obesity seems to be also associated with an increased risk of bacterial urinary tract infections.[33–35] Semins et al. reported that subjects with obesity were up to 2.5 times more likely to be diagnosed with a urinary tract infection than people without obesity, mostly in females.[29] Obesity has been reported to be a risk factor for urinary tract infections also in pregnant woman and during the postpartum period.[24] Although the exact mechanisms responsible for the increased risk of urinary tract infections in people with obesity are still unclear, the reduced response of the innate immune system, which plays an important role in protecting the urinary tract from invasion by uropathogens, may be involved. In particular, the reduced bactericidal capacity of PMN cells, including neutrophils that play an important role in the antimicrobial defenses of the urinary tract, probably caused by the reduced activation of the TLR4 receptors present on their cell membrane, could favor bacterial invasion of the urinary tract.[22–24] Furthermore, obesity is often associated with other comorbidity such as diabetes mellitus. Type 2 diabetes mellitus could, in fact, increase the risk of urinary tract infections through several potential mechanisms that could promote bacterial growth including the high concentration of glucose in the urine in case of poor metabolic control of diabetes, incomplete bladder emptying due to autonomic neuropathy, impairment of the immune system, and increased adherence of bacteria to the uroepithelium.[36,37] In fact, it has been shown that in subjects with type 2 diabetes, there is a greater adherence of *Escherichia coli* with type 1 fimbriae to uroepithelial cells, which could be due to a different glycosylation of receptors for type 1 fimbriae on diabetic uroepithelial cells.[37] Furthermore, in men with obesity, a possible explanation for the increased risk of urinary tract infections could be that abdominal obesity is associated with an increase in estrogen synthesis, as well as free and total estradiol, and a reduction in free and total testosterone and serum globulin binding protein levels, which could influence benign prostatic enlargement.[38,39] Benign prostatic hyperplasia is in turn related to an increased risk of urinary tract infections as patients are unable to completely empty their bladder and the stagnant urine acts as a growth medium for bacteria.[34,40,41] As regards to the digestive system, subjects with obesity have been reported to have a higher risk of Helicobacter pylori infection than normal-weight subjects[22] that could be due to the compromised immune system, which could create suitable conditions for colonization of the stomach by this bacterium.[22]

Skin and soft tissue infections are also common findings in obesity due to changes in skin physiology such as the alteration of the skin barrier function, the alteration of sebum production, and the alteration of the skin microcirculation and microcirculation.[8] Moreover, due to excessive body fat, patients with obesity have skin folds that can favor the rubbing and maceration of the skin, creating an ideal environment for bacterial and fungal overgrowth.[42] Bacterial skin infections associated with obesity are usually different from those found in normal-weight subjects, being more common folliculitis, furunculosis erysipelas, and necrotizing fasciitis.[8,43,44]

Therefore, obesity could represent a risk factor for the development of bacterial infections due to anatomical and functional changes, which can promote bacterial growth, due to comorbidities associated with obesity, such as type 2 diabetes, and due to alteration of the immune system. In particular, subjects with obesity showed the impairment of the innate immune system, which represents the first line of defense against pathogenic bacteria, characterized by an increase in the level of neutrophils and mast cells and a decrease in the number of eosinophils in the adipose tissue, decreased number and activity of NK, reduced bactericidal capacity of PMN, and accumulation of proinflammatory macrophages (M1) in adipose tissue that produce inflammatory mediators, probably involved in increased susceptibility to bacterial infections.

The principal characteristics of studies are reported in Table 1.

2.2 | Viral infections and obesity: Clinical evidence and physiological mechanisms

Obesity is one of the most important condition that increases exponentially the susceptibility to viral infections.[54,55] Indeed, obesity significantly changes the adaptative immune responses through several mediators, and among them, leptin seems to be the one most involved.[56,57] In normal conditions, leptin sends prosurvival signals to double-positive and single-positive thymocytes during the maturation of T-cells[27] and, in the presence of a polyclonal stimulator, can increase T-cell proliferation and can modulate expression of activation markers on both cluster of differentiation (CD)4+ and CD8+ T-cells.[58] The adaptative immunity is the most involved in the antiviral response, and in obesity, it could be blunted by *leptin*

TABLE 1 Characteristics of principal studies between obesity and bacterial, viral, and fungal infection

Author	Experimental design	Country	No. of enrolled subjects	Age enrollment (years)	Types of infection	No. of obese subjects	Main findings
Waisbren et al.[9]	Cohort	USA	591	49.7 ± 10.1	Surgical site infection	409	Obesity, defined by % body fat, is associated with an increase of surgical site infection risk
Harrington et al.[10]	Cohort	Australia	4474	65.2 (20–95)	Surgical site infection	-	Obesity is an independent predictor of surgical site infection
Choban et al.[13]	Retrospective comparative study	USA	536	-	Nosocomial infection after surgery	313	There are significant increases in the number and percent of nosocomial infections in the populations with obesity
Bishara et al.[28]	Case-control	Israel	Cases: 148 Controls: 148	Cases: 64.6 (17) Controls: 64.2 (17.4)	*Clostridium difficile*	-	Obesity is a significant and independent risk factor for *Clostridium difficile* infection
Di Leo et al.[29]	Prospective study	Italy	1281	54 (8–97)	Surgical site infection	78	Obesity is a risk factor for SSI
Saliba et al.[34]	Cohort	Israel	153,439	59.3 ± 17.3	Urinary tract infection	43,884	Obesity is independently associated with urinary tract infection particularly in males
Semins et al.[35]	Cohort	USA	95,598	-	Urinary tract infection	32,987	Obesity is a significant risk factor for UTI. Subjects with obesity were up to 2.5 times more likely to be diagnosed with a UTI than were the nonobese.
Arslan et al.[22]	Cross-sectional	Turkey	214	Obese: 24.3 ± 5.4 Nonobese: 25.5 ± 5.4	Helicobacter pylori	103	*H. pylori* prevalence was higher in subjects with obesity compared with the control group. Obesity can be a risk factor for H. pylori infection
Kwong et al.[45]	Cohort	Canada	82,545	18–65	H1N1	58,634	Obesity increase hospitalization during influenza seasons for respiratory conditions
Louie et al.[46]	Cohort	California	534	46 (20–92)	H1N1	274	Extreme obesity increase odds of death
Diaz et al.[47]	Prospective, observational, and multicenter study	Spain	416	43.9 ± 12.3	H1N1	150	Obesity increase the duration of mechanical ventilation, intensive care unit length of stay, and hospitalization
ICNARC (8 May 2020)[48]	ICNARC report on COVID-19 in critical care	United Kingdom	8250	59.4 ± 12.1	SARS-CoV-2	2930	Obesity increase the need for support of advanced respiratory and renal
Simonnet et al.[49]	Retrospective cohort study	French	124	60 (51–70)	SARS-CoV-2	59	Obesity increase the severe acute respiratory syndrome and invasive mechanical ventilation

TABLE 1 (Continued)

Author	Experimental design	Country	No. of enrolled subjects	Age enrollment (years)	Types of infection	No. of obese subjects	Main findings
García-Hidalgoet al.[50]	Cross-sectional	Mexico	156	47.3 (16–89)	Fungal intertrigo	156	Prevalence of intertrigo increases according to obesity grade
Chan et al.[51]	Prospective epidemiologic survey	China	877	42.5 (1–93)	Fungal foot disease	-	In adults, obesity appeared to be the most frequently occurring factor coexisting with fungal foot disease
Chang and Chong[51]	Case–control	Taiwan	Cases: 375 Controls: 375	61.86 ± 10.68 61.70 ± 10.60	Onychomycosis	225	Metabolic syndrome, obesity, high triglycerides levels, and poor glycemic control were associated with onychomycosis
Elewski and Tosti[52]	52-week prospective multicenter randomized double-blind controlled study	USA, Canada, and Japan	1655	52.3	Onychomycosis	569	Efinaconazole topical solution 10% for onychomycosis is less effective in patients with body mass index >25 kg/m^2 compared with normal-weight patients and the complete cure rates at the end of the study are significantly lower in patients with obesity than nonobese subjects
Alobaid et al.[53]	Observational pharmacokinetics study	Australia	21	54 ± 15	Critically ill patients receiving fluconazole for prophylaxis or treatment	10	A fluconazole loading dose of 12 mg/kg and maintenance dose of 6 mg/kg/day achieved pharmacodynamics targets for higher

resistance-related mechanisms.[59,60] In this regard, Karlsson et al. reported that DIO mice infected with mouse-adapted influenza virus strain X-31 (H3N2) showed a reduced adaptive immune response characterized by a depletion of CD8 T memory lymphocytes compared with lean mice.[61] In particular, they state a significant reduced expression of leptin receptor mRNA at lung levels and, in addition, an increase in pulmonary suppressor of cytokine signaling 3 (SOCS3) mRNA expression that through the inhibition of the Janus kinase/signal transducer and activator of transcription (JAK–STAT) signaling pathway resulted in a negative feedback on the leptin signaling in DIO mice.[62] The role of leptin in the regulation of adaptative immune response is further pointed out by a study performed in children with severe obesity, congenitally deficient in leptin, in which the administration of recombinant human leptin reversed the immune alterations characterized by reduced numbers of circulating CD4+ T-cells and altered T-cell proliferation and cytokine release.[63] Furthermore, leptin resistance could have an impact on the function and distribution of regulatory T-cells (T_{reg}).[64] T_{reg} suppress effector T-cell responses in vitro and in vivo, mainly involved in the antiviral cytotoxic response.[64] Leptin resistance damages the anergic state of T_{reg} and allows for enhanced proliferation, contributing to greater T_{reg} number thus resulting in an oversuppression of T-cell responses.[65] Another mechanism that could contribute to increase the susceptibility to viral infections in obesity is represented by a damage of humoral responses. In adipose tissue of normal-weight subjects, there are mainly resident macrophages, eosinophils and T_{reg} that produce anti-inflammatory cytokines such as IL-10, whereas obesity leads to increased adipocyte expansion, hypoxia, and apoptosis with release of chemokines and proinflammatory cytokines. These latter attract and activate macrophage, T-cell, and B-cell whose cross-talk favors the presentation of antigen by B lymphocytes to T ones, which in turn produce proinflammatory cytokines.[66–68] This proinflammatory switch condition of B-cells also involves a reduction in their function and antibody production and would seem to be favored by high levels of leptin as occurs in obesity, since leptin is a regulator of maturation and activation of B-cells.[69,70] Regarding the innate immune responses to viruses in obesity, there are scarce evidence. Huang et al. investigate how the patient-related characteristics can affect the host's response to infection of Avian influenza A (H7N9) virus.[71] They pointed out that although obesity did not influence the viral replication in respiratory epithelial cells, it could amplify the secretion of cytokines. In particular, they detected higher IL-8 levels that is not only a principal chemokine involved in cytokine storm but also a chemokine of innate immunity, and high IL-8 levels were associated with more severe infection in subjects with obesity with confirmed (H1N1) infection compared with normal-weight individuals.[72] Another cytokine that could play a role in the response to viral infections in obesity is IL-33, a member of the IL-1 family originally described as a potent initiator of type 2 immunity found during allergic inflammation and parasitic infections, but currently involved in the regulation of tissue homeostasis, T-cell regulation, obesity, and viral immunity.[73]

Although the evidence so far present is limited and the results are not univocal, it has been shown that abundant IL-33 is expressed in adipose tissue endothelial cells[74] and that IL-33 drives influenza-induced asthma exacerbations by halting innate and adaptive antiviral immunity,[75] moreover that IL-33 correlated with severity of hemorrhagic fever and regulated the inflammatory response in Hantaan virus-infected endothelial cells.[76] In addition to the mechanisms already known, other factors also seem to be involved in increasing the predisposition to infections in obesity, including mitochondrial dysfunction. Mitochondria are the main cytoplasmic organs responsible for cellular respiration and production of ATP and reactive oxygen species, and it can also orchestrate immunity by modulating both metabolic and physiologic states in different types of immune cells. Among mitochondrial proteins, voltage-dependent anion channel (VDAC) participates actively in necrotic and apoptotic cell death processes, which involve changes in mitochondria membrane permeability.[77] Moreover, mitochondrial DNA (mtDNA) can be released into the cytosol and is a danger-associated molecular pattern that induces inflammasome oligomerization and activation in macrophages and T-cells, or it can also be released extracellularly as web-like structures for T and B lymphocytes and neutrophils activating antiviral defense or trapping larger pathogens.[77]

In this regard, recent evidence suggests a role of obesity in worsening mitochondria function: mice fed a high fat diet showed liver mitochondrial cholesterol accumulation, which disrupts mitochondrial functional performance and the organization of respiratory supercomplexes assembly, which can contribute to oxidative stress, worsening the immune response to infections.[78] Moreover, cellular infiltration by excess triglycerides can impair mitochondria function and can also lead to oxidative stress through increased ceramide formation, increased products of lipid peroxidation, increased nitric oxide synthase, and inflammatory cytokine production and excess formation of reactive oxygen species (ROS) contributing to the weakening of the immune response.[79]

Furthermore, obesity could also be associated with insulin resistance and compensatory hyperinsulinemia, which in turn has been shown to exert immunomodulatory functions. In fact, the resting T-cells have low metabolic requirements, whereas activated T-cell need an increase amount of energy; to reach this goal, they increase the insulin receptor expression and glucose transporter type 1-mediated glucose uptake (Glut 1). In fact, the lymphocytes primarily rely on the surface expression of Glut1, a ubiquitously expressed glucose transporter.[80] However, the insulin resistance in obesity may suppress insulin signaling, resulting in an insufficient T-cell activation in response to pathogens.[56,81] Moreover, insulin resistance may reduce T-cell-mediated resolution of inflammation; indeed, the normal signaling of insulin is necessary to promote anti-inflammatory T helper cell 2 (TH2) differentiation.[82]

The increase vulnerability of subjects with obesity to viral infections could be further worsened by obesity-related respiratory comorbidities such as chronic obstructive bronchopathy, asthma, hypoventilation syndrome, obstructive sleep apnea, and other mechanical anomalies due to excess of thoracic and abdominal fat mass that could be a "breeding ground" for viral infections.[83]

Several observational studies reported a higher prevalence of hospitalization and deaths for viral infections in subjects with obesity than in normal-weight subjects.[45,46] In particular, the most human influenza virus infections are limited to the upper respiratory tract, including the nasal, tracheal, and often bronchial epithelium, but, however, progression of the infection to the lower respiratory tract, which determines severe sequelae, occurs frequently in the population with obesity, leading to poorer infection resolution and recovery than in normal-weight subjects.[70] Animal studies have shown that obese mice exhibit increased viral spread to the lower respiratory tract compared with nonobese counterparts. In this regard, Easterbrook et al. investigated the role of obesity as an independent risk factor for severity of infection with 2009 pH1N1, seasonal H1N1, or a pathogenic H1N1 influenza virus in DIO mice and their nonobese control counterparts.[84] DIO mice had higher mortality (80%) than control mice (0%), and more viral antigen was expressed in the bronchiolar and alveolar regions in DIO mice inoculated with H1N1 virus than in the same regions of infected control animals.[84]

Indeed, data from many countries around the world reported that subjects with obesity were disproportionally represented among influenza-associated hospitalizations and deaths during the early phase of the 2009 influenza A (H1N1) pandemic.[45,85] During the same pandemic, half of Californians >20 years old hospitalized with the infection were individuals with obesity.[46] In particular, subjects with obesity appeared to be at increased risk of influenza-associated intensive care unit admission and deaths.[45,85] In fact, a prospective, observational multicentric study carried out in Spain reported that obesity was associated with higher intensive care unit admissions during H1N1 influenza.[47] A cohort study over 12 flu seasons (1996–1997 through 2007–2008) carried out in Canada pointed out that individuals with severe obesity, with and without chronic conditions, are at increased risk for respiratory hospitalizations thus suggesting that they should be considered a priority group for preventive flu measures.[45] A role for obesity has been also highlighted in the context of COVID-19.[83] In late 2019, the CoV infection, which was called 2019 CoV, has been reported in Wuhan, Hubei, China. On February 2020, the World Health Organization (WHO) renamed the CoV infection as CoVID-19. The National Center for Immunization and Respiratory Diseases (NCIRD) identified as risk factors for COVID-19: hospitalization or long-term care in nursing homes, advanced age (>65 years), immunosuppression, the presence of chronic renal, liver or heart disease not well controlled, type 1 or 2 diabetes mellitus, and severe obesity (BMI of 40 or higher).[86]

The Intensive Care National Audit & Research Centre (ICNARC) report on COVID-19 in critical care of United Kingdom (May 8, 2020) pointed out that 73.4% of 8250 patients with confirmed COVID-19 were subjects with overweight or obesity.[48] Similar results were found in a retrospective cohort study carried out in 124 consecutive patients admitted to intensive care for COVID 19.[49] In fact, 47.6% of subjects requiring invasive mechanical ventilation (IMV) had obesity (BMI > 30 kg/m^2) and 28.2% had severe obesity (BMI > 35 kg/m^2).[49] Although several studies are underway to clarify the mechanisms that explain the increased incidence, prevalence and mortality of COVID-19 in subjects with obesity, it would seem that the different mechanisms mentionated above contribute. In addition, COVID 19 showed a tropism for adipose tissue. This is because this virus uses human angiotensin converting enzyme 2 (ACE2) as putative receptor for the entry into the host cells and adipose tissue is particularly rich of these receptors. Thus, subjects with obesity having more adipose tissue had consequently an increased number of ACE2-expressing cells that could predispose the very same subjects to an increased gateway to the virus.[87]

The data identified obesity to be a risk factor for severe morbidity and increased mortality from virus influenza infection, suggesting the need for prophylaxis against influenza. However, the alteration of the immune system in subjects with obesity causes a delay or nonresponse to vaccine in this population. Studies on mouse models suggested that T-cell responses to Influenza A virus infection may be impaired in obesity.[61,88] The lower effectiveness of vaccines in subject with obesity is probably mediated by insufficient T-cell function. In this regard, in a human study, Sheridan et al. have valued peripheral blood mononuclear cells (PBMCs) in subjects with obesity 12 months after immunization with the 2010–2011 seasonal Influenza A virus infection vaccine. PBMCs from subjects with obesity (BMI 35.7 ± 4.5) had a significantly lower (p = 0.015) increase in the percentage of CD8+ T-cell surface marker CD69, a T-cell activation marker, than PBMCs from normal-weight subjects (BMI 22.2 ± 1.7). Besides, CD8+ T-cells from individuals with obesity expressed lower levels of interferon gamma (IFNγ) and granzyme B (GrB), two cytokines essential for proper CD8+ T-cell activity.[89] Another possible mechanism that could determine the lower efficacy of vaccines in individuals with obesity is a physical mechanism. In fact, some studies have demonstrated that as weight and BMI increase, longer needle lengths are needed to ensure intramuscular deposition of vaccines.[89–92] In fact, it is possible that vaccines deposited into fat pads are less immunogenic and may lead to greater local side effects than those deposited deeper into muscle tissue.[93]

Finally, obesity is a medical condition with complex pathophysiology including several mechanisms that are emerging as significant risk factors for viral infections. However, targeted epidemiological studies specifically oriented in order to reveal the impact of obesity on severity and mortality rates of viral infections are needed in order to determine specific therapeutic and prevention strategies for subjects with obesity. Therefore, the obesity could compromise the immune system and in particular the adaptative immune system by depletion of CD8 T memory lymphocytes, reduced number and functionality of CD4+ T-cells, increased level of T_{reg} cells, and decreased number and function of B-cells. Moreover, the obesity could contribute to worsen the prognosis once the viral infection is established, determining respiratory diseases and alterations of respiratory mechanisms due to fat excess.

The principal characteristics of studies are reported in Table 1.

2.3 | Fungal infections: Physiological mechanisms and clinical evidence

Regarding fungal infections in subjects with obesity, the data present in the literature to date are rather limited, compared to bacterial and

viral infections that have been most studied. Mycoses can be classified according to the site of infection into superficial, cutaneous, subcutaneous, or systemic (deep) depending on the type and degree of tissue involvement, or according to virulence of the pathogen. In particular, primary pathogens can establish infections in normal hosts while opportunistic ones cause disease in individuals with compromised host defense mechanisms.[94] Obesity is known to lead not only to an alteration of the innate immune response resulting in a dysfunction of monocyte–macrophage, dendritic and NK, a decreased response to antigen/mitogen stimulation, and cytokine production but also to a weakening of the cell-mediated immunity,[54] mainly involved in the susceptibility to fungal infections.[95] In fact, the proliferation and function of T-cells are influenced by leptin signaling, and the metabolic alterations typical of obesity can therefore determine functional impairments in the cell-mediated immune response.[96,97] Also, proinflammatory cytokines and adipocyte activation of T-cells typical of adipose tissue have been implicated in the reduction of T-cell populations.[98] In addition to obesity per se, some obesity-related conditions, such as type 2 diabetes mellitus, can also favor the onset of fungal infections compromising innate and adaptive immune system and creating an environment that promotes the survival and proliferation of the fungus: in particular mucocutaneous *Candida albicans* infections are often associated with type 2 diabetes due to hyperglycemia that in turn increase microbial virulence by allowing Candida spp. to express a protein enabling more avid adherence to surface epithelial cells and thus promoting infection.[99] Furthermore, the presence of skin folds such as inframammary, genitocrural, axillary, and abdominal folds, which develop macerated erythematous plaques due to increased friction and moisture, as well as the poor local hygiene that can occur in the subject with obesity, are predisposing factors for the onset of cutaneous mycosis, especially recurrent Candida intertrigo.[100] In particular, it has been demonstrated that skin surface pH was higher in the inguinal folds of diabetic women with BMI > 25 kg/m^2 compared with normal weight, increasing the risk of developing skin infections.[101] In a cross-sectional study carried out in 156 subjects with obesity, a positive trend between the severity of

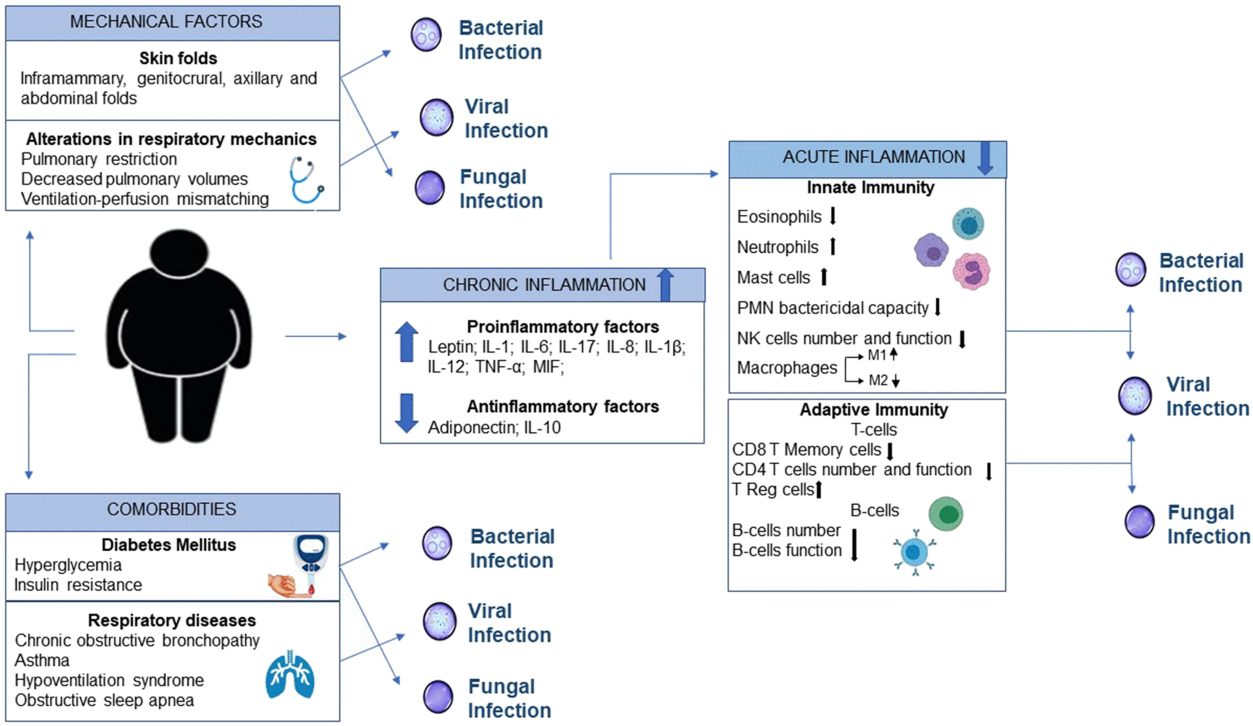

FIGURE 1 Obesity and infections: physio pathological mechanisms. Obesity could be associated with an increased risk of getting infections and/or a worsening prognosis in people with ongoing infections. There are several mechanisms that increase the vulnerability of people with obesity to infections. First of all, obesity-related chronic low-grade inflammation determines an imbalance between the production of proinflammatory factors, including leptin and numerous cytokines, and anti-inflammatory factors, such as adiponectin and IL-10. This could lead to changes in the functionality of the immune system, both innate and adaptative. In particular, the alterations of the innate immune system cells represented by increased level of neutrophils and mast cells and decreased number of eosinophils in the adipose tissue, reduced PMN bactericidal capacity, decreased number and activity of NK, accumulation of macrophages in adipose tissue, and switch from an anti-inflammatory phenotype (M2) to an inflammatory phenotype (M1) producing inflammatory mediators, such as TNF-α, IL-6, IL-12, and IL-1β, could be involved in the increased susceptibility to bacterial and viral infections. The alteration of the adaptative immune system, characterized by depletion of CD8 T memory lymphocytes, reduced number and functionality of CD4+ T-cells, increased level of T_{reg} cells, and decreased number and function of B-cells, may be predispose to viral and fungal infections. The risk of bacterial and fungal infections in subjects with obesity could also be increased by the presence of other obesity-related comorbidities such as type 2 diabetes mellitus, which causes impaired wound healing and the creation of an environment that promotes the survival and proliferation of fungal, and skin folds, which create an ideal environment for bacterial and fungal overgrowth. Respiratory diseases and alterations of respiratory mechanisms due to fat excess could predispose to respiratory viral infections in obesity or could contribute to worsen the prognosis once the infection is established

obesity and intertrigo has been reported.[50] Obesity is also one of the most important risk factors for onychomycosis. In fact, in a Chinese study conducted on 877 adult patients who went to dermatologic clinics for diseases other than foot problems, obesity appeared to be the most frequently occurring factor coexisting with fungal foot disease (9.6%), followed by diabetes mellitus (5.3%).[51] Similarly, in a study on 1245 diabetic Taiwanese patients, it has been observed that obesity, metabolic syndrome, high levels of triglyceride, and glycosylated hemoglobin (HbA1c) were associated with onychomycosis.[102] Obesity could also contribute to weaken the efficacy of antimicotic drugs. Data collected from a 52-week prospective study on the efficacy of efinaconazole topical solution 10% in the treatment of onychomycosis showed that the drug was less effective in patients with BMI > 25 kg/m^2 compared with normal weight ones and that the complete cure rates at the end of the study were significantly lower in patients with obesity than subjects without obesity.[52] The systemic mycoses that usually occur in patients with congenital or acquired immunodeficiency require an increased amount of oral or intravenous antimicotic treatment that still raises doubts in the subject with obesity. In particular regarding fluconazole, it has been observed that in patients with BMI > 30 kg/m^2, a fix dose of 200 mg daily was often insufficient to achieve an adequate plasma concentration and that therefore it is more useful to use a loading dose of 12 mg/kg and maintenance dose of 6 mg/kg/day to achieve pharmacodynamic targets.[53] In subjects with obesity, careful attention must be paid when calculating the dose of liposomal amphotericin B in the treatment of systemic mycosis because it has limited distribution into adipose tissue thus resulting in a high potential toxicity when the dose is calculated on body weight.[103] Therefore, obesity per se increases the risk of developing and worsening the prognosis of fungal infections due to physical and mechanical factors predisposing to skin and mucous membranes colonization and development of mycosis, as the development of inframammary, genitocrural, axillary, and abdominal folds, and due to alteration of the adaptive immune response. In particular, chronic inflammation, proinflammatory cytokine levels, and hyperleptinemia typical of obesity alter the finely tuned balance among Th1, Th17, and T_{reg} subsets, necessary for optimal clearance of fungi with limited tissue damage. This immunosuppression can be further exacerbated when comorbidities such as type 2 diabetes coexist with obesity. Finally, obesity can make the pharmacological therapeutic management complex, thus requiring specific dosage adjustments of antimycotic pharmacological treatments. The principal characteristics of studies are reported in Table 1.

The physio pathological mechanisms between obesity and infection (bacterial, viral, and fungal) were reported in Figure 1.

3 | CONCLUSIONS

In summary, obesity has been reported to blunt the immune system, which is involved in the defense against infectious agents. Thus, it is mandatory to carry out research studies in order to investigate the link among obesity, obesity-related metabolic derangements, and immune system. Another key point is to prevent and manage infections in subjects with obesity. Due to excess adipose tissue that could modify pharmacokinetic, antimicrobial drugs and vaccines may not work properly. Further research on how to customize the amount of antimicrobial drugs that should be administered to subjects with obesity are warranted.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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