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# The etiology of lower respiratory tract infections in people with diabetes

The authors declare no financial disclosure

## Abstract

Patients with diabetes mellitus (DM) are likely to develop many types of infections, which affect the transport of glucose into tissues. Diabetes increases the susceptibility to different kinds of respiratory infections, is often identified as an independent risk factor for developing lower respiratory tract infections. Pulmonary infections caused by *Mycobacterium tuberculosis*, *Staphylococcus aureus*, gram-negative bacteria and fungi may occur with an increased frequency, whereas infections due to *Streptococcus pneumoniae* or influenza virus may be associated with increased morbidity and mortality. During lung infection, there are changes in the local and ciliary epithelial lining. Increased susceptibility to pneumococcal infection by people with diabetes is the result of reduced defense capability of antibodies to protein antigens. The relationship between diabetes and pulmonary tuberculosis is well known, and the incidence of tuberculosis in diabetic individuals is 4–5 times greater than among the non-diabetic population. It is thought that malfunction of monocytes in patients with diabetes may contribute to the increased susceptibility to tuberculosis and/or a worse prognosis. Hospitalization of patients with diabetes due to influenza virus or flu-like infections is up to 6 times more likely to occur compared to healthy individuals, also diabetic patients are more likely to be hospitalized due to infection complications. Immunization with influenza and anti-pneumococcal vaccines is recommended to reduce hospitalizations, deaths, and medical expenses. Diabetes, especially the uncontrolled one, predisposes to fungal infection, the most common candidiasis and mucormycosis.

**Key words:** diabetes mellitus, *Streptococcus pneumoniae*, influenza, tuberculosis, mycosis**Pneumonol Alergol Pol 2015; 83: 401–408**

## Introduction

Lower respiratory tract infections (LRTI) are the most common diseases in the world [1]. In the United States, the incidence of lower respiratory tract infections and associated mortality rate are higher than of other infectious diseases. According to the WHO report, LRTI accounted for 6.9% of all deaths in 2002 [2]. High rates of lower respiratory tract infections contributed to the development of guidelines for the diagnosis and treatment of lower respiratory tract infections by European countries and the USA. These guidelines are subject to regular evaluation, which is based on review of multiple medical and epidemiological studies. The Ameri-

can Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA) and the British Thoracic Society (BTS) presented comprehensive guidelines [3]. Some of the most common respiratory tract infections in diabetics includes: acute bronchitis, sinusitis, otitis media, pneumonia. Etiological factors are bacterial, viral and fungal. Respiratory tract infections are the cause of increased hospitalizations in diabetic individuals compared to those without diabetes [4–6].

## Immunodeficiency in diabetes

The complement system is one of the main mechanisms of humoral immunity. It contains

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plasma proteins and cell surface proteins whose main functions are to promote opsonization and phagocytosis of microorganisms by macrophages and neutrophils and induction of lysis of microorganisms. Induction of the complement system mediates a B cell antibody production. Lowering the content of C4 in patients with DM may be associated with dysfunctional neutrophils and decreased response to cytokines. Mononuclear cells and monocytes of DM patients release lower amounts of interleukin-1 (IL-1) and interleukin-6 (IL-6) in response to stimulation by lipopolysaccharide (LPS), which is activated in the process of phagocytosis [7, 8]. The increased glycosylation may inhibit IL-10 production by lymphocytes and macrophages. Additionally, the amount of interferon gamma (IFN- $\gamma$ ) released by T cells and NK cells, and tumor necrosis factor (TNF- $\alpha$ ) released by T cells and macrophages is reduced. The process of glycation also reduces the myeloid cells expression of surface major histocompatibility complex class I (MHC), which impairs cell-mediated immunity [7, 8]. Hyperglycemia reduces the mobilization of polymorphonuclear leukocytes, chemotaxis and phagocytic activity. Hyperglycemic environment also prevents the antibacterial functions of the immune system, resulting in inhibition of glucose-6-phosphate (G6PD), which in turn stimulates apoptosis of leukocytes and reduces the transmigration of leukocytes across the endothelium. In tissues that do not consume insulin, hyperglycemic environment increases the intracellular concentration of glucose, which is then metabolized using NADPH as a cofactor. The decrease in concentration of NADPH prevents the action of molecules that play a key role in the mechanisms of antioxidant functions of a cell, which leads to an increase in tissue sensitivity to oxidative stress. With respect to the mononuclear cells, some studies have shown that

HbA1c < 8.0% results in the proliferative activity of T helper cells (CD4 +) and their response to antigens. Glycation of immunoglobulin occurs in diabetic patients in proportion with the increase in HbA1c, and this may harm the biological function of the antibodies (Table 1) [4]. In addition, infectious diseases in patients with DM may result in metabolic complications such as hypoglycemia, ketoacidosis, and coma. Table 2 shows the effect of diabetes on the immune dysfunction in diabetics.

### Community and hospital-acquired pneumonia

Community-acquired pneumonia (CAP) is one of the most common infections of the lower respiratory tract and accounts for 5–12% of all LRTI [9]. In Europe, the incidence of community-acquired pneumonia is estimated to be 5–12 per 1,000 persons per year. Mortality of outpatients with CAP does not exceed 1% of hospitalized cases [10]. Pathogens that cause CAP are viruses, bacteria and other unusual microbes. The microbial composition is complex and often depends on the geographical area, population and seasonal changes. The most common CAP pathogens include *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila* and *Haemophilus influenzae*. A high percentage of CAP cases in adults is due to mixed bacterial and atypical pathogens [10, 11]. CAP caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is still rare, however, it accounts for an increasing number of cases reported in the United States [12, 13]. It is generally accepted that MRSA causes more frequently infections of the skin and soft tissue than of the respiratory tract. CAP caused by *Escherichia coli* and *Klebsiella pneumoniae* is significantly more frequent in patients over 50 years of age [14].

**Table 1. Pathophysiological changes resulting from infection in patients with diabetes mellitus**

Diabetes mellitus			
Hyperglycaemia/ uncontrolled diabetes	Related metabolic consequences	Molecular and immunologic events	Impaired immunological defense
HbA1c > 8.0% Glycosuria	Glycation, cells hypoglycemia, ketoacidosis, coma	Inhibit: interleukin 10 (IL-10) interferon gamma (IFN- $\gamma$ ) tumor necrosis factor (TNF- $\alpha$ ) lower amounts of interleukin-1 (IL-1) and interleukin-6 (IL-6) increase in tissue sensitivity to oxidative stress	Polymorphonuclear dysfunction and reduction of C4 component reduces major histocompatibility complex class I (MHC) decreased function of the antibodies and T lymphocytes re-response abnormalities in neutrophil function, such as impaired chemotaxis, phagocytes, and bacterial killing

**Table 2. Pathophysiology of infections associated with diabetes mellitus**

Diabetes mellitus			
Decrease T lymphocytes response, decrease neutrophil function, lower secretion of inflammatory cytokines, anti-oxidant system depression, disorder of humoral immunity.	Hyperglycemia: increased virulence of infectious microorganisms and apoptosis of polymorphonuclear leukocytes . Glycosuria.	Large number of medical interventions, neuropathy, angiopathy	GIT-gastrointestinal tract: dysmotility

Hospital-acquired pneumonia (HAP) is lung inflammation that occurs at least 48 hours after hospital admission. This group of diseases refers to pneumonia infections associated with mechanical lung ventilation, i.e. it is inflammation occurring 48–72 hours of mechanical ventilation in patients, as well as pneumonia associated with exposure to health care-associated pathogens. The incidence in European countries is estimated to be 5–15 cases per 1,000 hospitalizations, with estimated mortality rate of 30–50%. The most common bacteria causing HAP during the first four days of hospitalization are: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* (methicillin-susceptible), and *E. coli*, *K. pneumoniae*, *Enterobacter*, *Serratia*, and *Proteus* [3, 10]. From the 5<sup>th</sup> day of hospitalization, there is a predominance of *Acinetobacter sp*, *Pseudomonas aeruginosa*, *E. coli*, *K. pneumoniae*, *L. pneumophila* and *Staphylococcus aureus* (methicillin-resistant MRSA) [10]. The most commonly isolated bacteria associated with HAP in European countries and the USA is MRSA strain *Staphylococcus aureus* [15].

The Danish researchers attempted to elucidate why type 2 diabetes increases the risk of death and complications in patients after hospitalization for pneumonia, and to evaluate the prognostic value of hyperglycemia occurring on hospital admission. Their study included 29,900 patients hospitalized for the first time due to pneumonia in the years 1997 to 2004, including 2,931 (9.8%) with type 2 diabetes mellitus (DM2). The mortality rate among patients with DM2 was higher than in patients without DM2, and the respective values after 30 days and 90 days of hospitalization were: 19.9% vs 15.1% and 27.0% vs 21.6%, which corresponds to 30 and 90 days to corrected MRR (mortality rate ratio) of 1.16 (95% CI 1.07–1.27) and 1.10 (1.02–1.18). Patients with pneumonia and DM2 were not at risk of pulmonary complications and bacteremia. High glucose concentration on admission was a predictor of death among patients with diabetes

and more so among non-diabetic patients: adjusted 30-day MRRs for glucose level  $\geq 14$  mmol/l were 1.46 (1.01–2.12) and 1.91 (1.40–2.61), respectively. In 60.2% of diabetic and 59.7% of other patients with pneumonia at least one blood culture was isolated [5]. *Streptococcus pneumoniae* accounted for 51.1% of all episodes of bacteremia. Among patients with pneumonia with available blood cultures, the adjusted relative risk (RR) for the occurrence of bacteremia in diabetic patients compared to patients without diabetes was 1.02 (0.78–1.33). Patients with diabetes compared with non-diabetic patients had RR similar for pneumococcal bacteremia (RR 1.17 [95% CI 0.84–1.62]), a greater risk of bacteremia due to gram-positive pathogens other than *S. pneumoniae* (1.69 [1.02–2.80]), and a lower risk for gram-negative bacteremia (0.72 [0.42–1.23]). The Danish researchers showed that patients with DM2 have an increased risk of death associated with pneumonia hospitalization. High glucose levels were related with increased mortality in all patients. The results showed that glucose level on admission is a very important clinical indicator among patients with pneumonia [5]. Ehrlich et al. also conducted a study assessing the risk of pneumonia, asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis in patients with and without diabetes. Retrospective longitudinal cohort study used the electronic records of a large health plan in northern California. The full cohort study included 77,637 patients with diagnosis of diabetes and 1,733,591 patients without diabetes. Significantly higher incidence of each pulmonary condition, except for lung cancer, was observed in patients with diabetes, compared with patients without diabetes. The prevalence of asthma, COPD, lung fibrosis and inflammation was significantly higher in patients diagnosed with diabetes (Table 3). The risk of pneumonia and COPD increased significantly with growing concentration of HbA1c (hazard ratio [HR] 1.03 [95% CI 1.01–1.04] and

**Table 3. Analysis of the relationship between diabetes and the occurrence of lung diseases [16]**

In diabetic patients adjusted for age, sex, race/ethnicity, smoking, BMI, education, alcohol consumption, and number of outpatient visits occurring in the 12 months before the baseline, health plan members with a diagnosis of diabetes	HRs and 95% CI for the association between each pulmonary condition and diabetes status
Asthma	1.08 (1.03–1.12)
COPD	1.22 (1.15–1.28)
Fibrosis	1.54 (1.31–1.81)
Pneumonia	1.92 (1.84–1.99)

COPD — chronic obstructive pulmonary disease

1.06 [1.05–1.07] respectively (both  $p \leq 0.002$ ), but no such associations were observed for asthma and fibrosis. Ehrlich et al. report that in all of the analyses (conducted among the full cohort or the sub cohort of survey responders, before and after adjustment for relevant confounders) there was a significant increase in the risk of COPD and pneumonia with raising baseline HbA1C among patients with diabetes. In patients with asthma and fibrosis, associations weren't observed, suggesting that these conditions might be related to factors other than glycemic control that are associated with diabetes [16].

According to recommendations of the American Diabetes Association (ADA), the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP), anti-pneumococcal and influenza vaccination is advisable for people with DM [4]. The Polish Diabetes Association recommends following the vaccination schedule, whereas against *Streptococcus pneumoniae*, 13-polyvalent vaccine is recommended [17]. The use of vaccines helps to reduce the number of respiratory infections, the frequency and length of hospitalizations, deaths caused by respiratory tract infections, and medical expenses related to pneumonia [4].

### Respiratory tract infections other than pneumonia

*Streptococcus pneumoniae* and influenza virus are the causes of frequent respiratory tract infections associated with diabetes mellitus (DM) [18]. Natural protection against invasive pneumococcal disease is largely conferred by anticapsular antibody. It is less clear whether they are necessary or they constitute the primary mechanism of natural development of resistance to pneumococcal infection. Natural pneumococcal immunity may originate through factors other than anticapsular antibodies like serotype-specific polysaccharides. These species antigens are

found in all or most serotypes that lie beneath or are interspersed within the capsular polysaccharide. These pneumococcal species antigens, e.g. pneumococcal surface protein A (PspA) and adhesin A (PsaA), are immunogenic early in life, and antibodies against them can be elicited by mucosal colonization (carriage), otitis media, or invasive disease [19]. Nasopharyngeal carriage can lead to the development of antibodies against specific capsular polysaccharide [20] and surface proteins [19–21]. Antibodies effectively opsonize pneumococci and stimulate macrophages or neutrophils to phagocytose [20]. Nam et al. [21] studied the function and the titre of protective antibodies. Their research aimed at determining whether susceptibility to pneumococcal invasion in people with diabetes is due to lower titers or low availability of antibodies to protective polysaccharide capsule and / or protein antigens. Mathews et al. [22] showed that diabetes is associated with poor response to anti pneumococcal surface protein (PspA), which was consistent with the results obtained by Nam et al. [21]. The researchers have shown that the positive results of cross-reacting antibodies to PspA in diabetic patients were lower compared to patients without diabetes. Mathews et al. identified reaction with protein antigen as abnormal in patients with diabetes. The response to protein antigens was compromised in individuals with diabetes, and the T cells play a significant role in response to protein antigens by activating B cells and initiating antibody class switching [22].

DM patients are six times more likely to be hospitalized during a flu epidemic compared to non-diabetic patients [6]. Diabetes is a common co-morbidity risk factor in patients with influenza virus infection. Type A and B influenza viruses are the common cause of human flu epidemic. The Type A virus is divided into subtypes based on the antigenic specificity of the hemagglutinin (H) and neuraminidase (N). The most common seasonal

flu viruses are H1N1 and H3N2 subtypes, sometimes H1N2 virus, and to a lesser extent the group B. The disease usually resolves spontaneously after 3 to 7 days, but cough and malaise can persist for up to two weeks [23]. Compared to typical seasonal outbreaks, the influenza virus A H1N1 virus penetrates deeper into the respiratory system. Some patients may rapidly develop progression from severe pneumonia to respiratory failure [21]. Miller et al. in their study of 43 patients with the current H1N1 virus pandemic, revealed that the proportion of patients with a flu pandemic with comorbid diabetes accounted for 18.6% of the cases [24]. Rodríguez-Valero et al. [25] studied the differences between early clinical symptoms of confirmed cases of H1N1 virus infection in hospitalized patients who had been tested negative for H1N1 infection. They found 1,024 patients with acute respiratory symptoms who were admitted to the emergency department of a general hospital in Mexico from April to December 2009. The patients had a confirmatory test for influenza A H1N1 performed using either real-time or reverse transcriptase polymerase chain reaction (RT-PCR). Of the 1,024 patients surveyed, H1N1 infection was confirmed in 36%. Diabetes was present in 6% of all confirmed hospitalized cases of infection. H1N1 infection was often mild and affected mostly younger patients. The sudden occurrence of symptoms such as pulmonary rales, wheezing and the sudden symptom onset were more frequent and statistically significant in confirmed patients. Influenza-like illness was more frequent in confirmed cases ( $p = 0.049$ ). Rodríguez-Valero et al. reported that the presence of H1N1 virus was confirmed by RT-PCR. Patients with diabetes should be identified to prevent and treat potentially severe and fatal cases [25]. Jain et al. described the clinical characteristics of patients in the United States who were hospitalized in 2009 due to the H1N1 flu. The study collected data from 272 patients treated for at least 24 hours because of flu-like symptoms and a positive result for the presence of the H1N1 virus on RT-PCR assay. Of the 272 patients, 73% had at least one of the comorbidities, particularly diabetes occurred in 40 (15%) hospitalized patients [26]. The World Health Organization (WHO) recommended vaccination against the H1N1 virus, in order to minimize the morbidity and mortality caused by the viruses. The coverage of anti-flu vaccinations in people with DM remains inadequate. The recommendation for compulsory immunization with anti-flu vaccines is essential because of their impact on the reduction of respiratory infections,

the number and length of hospitalizations and the number of deaths related to respiratory tract diseases [4]. In patients who were hospitalized with seasonal influenza, complications which included pneumonia, bacterial coinfection, and exacerbation of underlying medical conditions, such as congestive heart failure were frequently reported [26]. The Polish Diabetes Association recommends annual vaccination against influenza virus to children over 6 months of age and adults with DM [17].

### **Tuberculosis in patients with diabetes**

Approximately 9 million new cases of tuberculosis were reported in 2009 worldwide. 1.7 million people who were diagnosed died of tuberculosis infection [27]. Restrepo et al. conducted a prospective study on the impact of diabetes on clinical outcome of tuberculosis (TB). TB patients over the age of 20 from clinics in Texas and Mexico have been tested for diabetes. The risk of diabetes among TB patients was compared to data from a control adult population. The prevalence of diabetes among TB patients was 39% in Texas and 36% in Mexico. Diabetes contributed to 25% of tuberculosis cases. The authors recommended implementing international programs to control diabetes and facilitate the prevention of tuberculosis in patients with diabetes as well as earlier diagnosis of diabetes [27]. People with diabetes are at higher risk of developing active TB compared to people without diabetes [27, 28]. Some studies have shown that people with diabetes are more likely to develop drug-resistant tuberculosis and treatment failure; as a result, mortality is higher in these patients [29]. In addition, infection and treatment for tuberculosis (rifampicin activates the metabolism of oral antidiabetic agents) may hinder glycemic control [30].

It has been suggested that DM causes a reduction in the immune response (reduced chemotaxis, phagocytosis and antigen presentation in response to *Mycobacterium tuberculosis* infection and changes in the function and proliferation of T lymphocytes), thus facilitates infection and progression of the symptoms of the disease [27–29]. Patients with type 2 diabetes are at increased risk of developing tuberculosis, which can be attributed to the mononuclear phagocyte functional drawbacks, which play a key role in defending against infection with *Mycobacterium tuberculosis*. The cause of increased susceptibility to tuberculosis in patients with DM2 may be related to dysfunctional immunity [31]. Immune

**Table 4. Immune changes in patients with diabetes increasing incidence of infection with *Mycobacterium tuberculosis***

Molecular and immunologic events	Interaction between <i>m. Tuberculosis</i> and the host phagocyte in DM patients	Impaired immunological defense
Impaired T-cell proliferation reduced T-helper (Th)-associated chemokine receptors and cytokines	Monocytes migrate to sites in tissues infected by <i>M. tuberculosis</i> , which contribute to the local response	Decrease t lymphocytes response and reduced chemotaxis and antigen presentation in response to <i>Mycobacterium tuberculosis</i>
Reduced IFN- $\gamma$ production at the onset of disease	Opsonization of <i>M. tuberculosis</i> by serum components, with C3b, iC3b and natural antibodies to mycobacteria	Reduced association of <i>M. tuberculosis</i> with monocytes in patients with diabetes
Defective opsonization such as C3b/iC3b, and/or natural IgG and/or complement receptors CRS (CR1, CR3) and receptors Fc $\gamma$ Rs on the monocytes	Binding of opsonins to complement receptors (CR1 and CR3) or, Fc $\gamma$ receptors on the monocyte, which is followed by phagocytosis	Monocytes have a reduced activity binding and phagocytosis of <i>M. tuberculosis</i>

dysfunction in infected diabetes patients revealed reduced T-helper (Th)-associated chemokine receptors and cytokines, impaired T-cell proliferation and reduced IFN- $\gamma$  production at the onset of disease [7]. T cells, by the release of interferon- $\gamma$  (IFN- $\gamma$ ), induce autophagy, phagosomal maturation, the production of antimicrobial peptides and antimicrobial activity against *Mycobacterium tuberculosis* in macrophages [32]. Mononuclear phagocytes (monocytes and macrophages) play an important role in the immunopathogenesis of TB [33]. In macrophages infected with *Mycobacterium tuberculosis*, the pathogen accumulates in phagocytic vesicles or early endosomes, which fail to localize lysosomes as identified with the lysosomal marker [32]. Monocytes also migrate to sites in tissues infected with *M. tuberculosis*, which contributes to the local response. Given the importance of monocytes in the biology of *M. tuberculosis*, it is probable that the functional changes in the cells of patients with DM2 contribute to increased susceptibility to tuberculosis or in TB-infected individuals to infection [34]. In patients with DM2 who are yet to be treated, monocytes have a reduced activity (binding and phagocytosis activity towards *M. tuberculosis*) of *M. tuberculosis* compared to non-diabetic monocytes [35], suggesting defective serum opsonization routes (such as C3b/iC3b, and/or natural IgG) and/or complement receptors (CRs) and receptors Fc $\gamma$ Rs monocytes. Further experiments with the *M. tuberculosis* inactivated serum that opsonized, suggest that the defect is linked to the termolabile element. DM2 patients may have CRs changes that adversely affect the binding and phagocytosis by monocytes to *M. tuberculosis*: the defect may be associated with monocyte receptor (CR1, CR3) and/or their ligands in serum (complement protein C3b and its breakdown product iC3b). Restrepo et al. demonstrated that human monocytes

in DM2 patients have functional defects in the process of phagocytosis of *M. tuberculosis*, opsonization with serum, lanes intermediate and/or receptors CRs and Fc $\gamma$ Rs, which is correlated with chronic hyperglycemia. This disadvantage is independent of host opsonization with serum or plasma, and is not associated with reduced expression of CR3, R-I and-II-III, or upregulation of inhibitory receptor CD32B. Higher susceptibility of DM patients to such pathogens as *M. tuberculosis* is associated with activation of effector mechanisms for killing bacteria. It is probable that the defect is one of the factors involved in the higher sensitivity in patients with DM2 to pathogens such as *M. tuberculosis* (Table 4). In summary, these results indicate that the reduction in phagocytosis by CRs and Fc $\gamma$ Rs is at least partly linked to the drawbacks associated with the same monocytes in DM2. Further studies are needed to evaluate the relationship between the decrease in phagocytosis by monocytes in DM2 and its activation [35, 36].

### Respiratory mycosis

The analysis of clinical epidemiology of fungal infections in diabetic patients has shown that diabetes was associated with an increased incidence of fungal infections. The study included 221 patients with DM2 over 10 years, and it found that infections and pneumonia accounted for 22% of all deaths. It has been estimated that 50–75% of cases of fungal infections in diabetic patients are caused by *Mucorales*, while acidosis is a predisposing factor. The second microorganism responsible for onychomycosis in diabetic patients is *Aspergillus* [37]. *Aspergillus* is a ubiquitous fungus that causes many clinical syndromes, including: invasive pulmonary aspergillosis (IPA), chronic necrotic

form of aspergillosis, aspergillus mycetoma and allergic bronchopulmonary aspergillosis. IPA is a severe and often fatal disease that occurs in immunocompromised patients, and allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to *Aspergillus* antigens, which mainly affects patients with asthma. Although diabetes predisposes individuals to the development of fungal infections, aspergillosis is relatively rare in these patients [38, 39].

Mucormycosis can be categorized according to the site of infection, including nasal-cerebral, pulmonary, gastrointestinal, cutaneous and disseminated. In diabetic patients nasal-cerebral or pulmonary embolism are the most common forms of mucormycosis, which can occur after a lung infection [40, 41]. Pathogens associated with this disease include the *Zygomycetes* fungi (*Phycomycetes*), the most common family of *Mucoraceae*, including *Rhizopus*, *Absidia* and *Mucor*. Though acidosis is a predisposing factor, it only occurs in about 50% of diabetic patients with concomitant fungal infection [42]. These infections are caused mainly by the fungi of the genus *Rhizopus*. *Rhizopus* fungi cause inflammation of the middle ear, nasal cavity, paranasal sinuses, lungs and meninges. Hypotheses attempting to explain the increased incidence of mucormycosis include: increased availability of iron to the pathogen at lower pH values, lack of inhibitory activity in the serum of *Rhizopus* species at lower pH values and the presence of pulmonary macrophages in patients with DM, which reduced the ability to prevent germination of *Rhizopus* species [39, 41, 42]. The pathogenesis of the disease probably starts with the inhalation of the fungus to the paranasal sinuses. Initial symptoms may include fever, headache, and facial pain or swelling, pain in the eye or periosteum orbital edema or blocked nose. There is soft tissue swelling and bloody nasal discharge from the external nasal cannula. Infection can cause slight fever and impaired consciousness. The black scabs in the mucosa of the nose and palate, which occur in approximately 40% of patients, are due to tissue necrosis following vascular invasion of the fungus. Invasion is fast and can lead to exophthalmos, ophthalmoplegia, and blindness that are caused by the seizure of the orbit. Patients may also experience cranial nerve palsy caused by the seizure of the cavernous sinus or massive stroke caused by occlusion of the carotid artery. Early diagnosis and treatment of the condition in patients with diabetes mellitus is important to reduce the invasion of the fungus, and associated morbidity and mortality [42, 43].

## Summary

Inadequate blood glucose control in diabetes predisposes patients to pneumococcal pneumonia, but the degree of hyperglycemia in diabetes is not associated with an increase in disease severity. In contrast to non-diabetic patients with pneumococcal pneumonia, hyperglycemia is a marker for severe disease and increased mortality, probably because of mass release of proinflammatory cytokines and glucocorticoids during the infection process. Diabetic lung infection causes a change in the entire lung immune system of the host organism, with associated changes in the local and ciliated epithelial dysfunction and its mobility. The relationship between diabetes and pulmonary tuberculosis is linked to loss of function of the body's defense and antigen-presenting ability, which promotes the formation of clinical and radiological changes in patients with diabetes mellitus. Thus, worsening of tuberculosis appears to be important for the immune system and the severity of hyperglycemia. Particularly noteworthy is the incidence of diabetes in the case of influenza virus or flu-like infection. Complications such as pneumonia and even death, occur more often than in the general population. There is the empirical antiviral therapy in hospitalized patients with suspected H1N1 flu or pneumonia in patients at risk group like persons with diabetes. Some researchers relate the presence of elevated glucose levels in diabetic patients with increased development of infection and the resulting inability to control the infection. Although the optimal control of blood glucose levels helps to prevent the occurrence of life-threatening infections associated with diabetes, the increased susceptibility to infections is attributed to defective functioning of cellular and humoral immunity. In addition, an aging immune system is associated with an increased risk of bacterial, mycobacterial, fungal, and viral infections.

## Conflict of interest

The authors declare no conflict of interest.

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