

Diabetes and Infection: Is There a Link? – A Mini-Review

Sylvia Knapp

Center for Molecular Medicine of the Austrian Academy of Sciences, and Division of Infectious Diseases and Tropical Medicine, Department of Medicine 1, Medical University of Vienna, Vienna, Austria

Key Words

Diabetes · Infection · Neutrophil function · Hyperglycemia

Abstract

Diabetes mellitus is one of the most prevalent conditions in the elderly and is associated with considerable morbidity and mortality, mainly from cardiovascular and renal complications. Furthermore, common perception associates diabetes with a generally increased susceptibility to infectious diseases, although epidemiologic data that would prove this are surprisingly scarce. However, it seems to be confirmed that diabetes predisposes to certain types of infection and death thereof, but it is less well understood if metabolic disturbances in diabetes itself, associated hyperglycemia and hyperinsulinemia or diabetes-associated comorbidities provide the link between diabetes and susceptibility to infections. In this review, I will summarize published reports on the incidence and risk for infectious diseases in diabetic people and give a comprehensive overview of the molecular mechanisms that have been suggested to explain the potentially altered immune response to pathogens in patients with diabetes.

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Diabetes mellitus is one of the leading causes of morbidity worldwide and is anticipated to rise substantially over the next decades. While type 2 diabetes used to be mainly a disease of the elderly, early-onset diabetes is increasingly diagnosed in young adults in industrialized countries. In 2011, the diabetes incidence was reported to be 26.9% for people older than 65 years in the USA and as high as 11.3% for people older than 20 years [1]. Since Western diet and obesity are spreading rapidly around the globe, the number of young diabetic individuals is anticipated to further increase in the near future.

Diabetes is associated with several complications, including vascular diseases and renal failure, that ultimately impact the overall survival of these patients. It is furthermore a common belief that people with diabetes are generally more susceptible to infections. The difficulties associated with estimating the actual risk of infection in diabetic patients are mainly due to the fact that diabetes is not solely a disturbance of glucose metabolism but instead a chronic inflammatory condition characterized by multiple alterations in lipid profiles and neuropathy as well as chronic vascular and renal diseases, with each of these changes having been reported to alter the response to pathogens. Therefore, it seems near impossible to con-

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Sylvia Knapp, MD, PhD
Division of Infectious Diseases and Tropical Medicine
Department of Medicine 1, Medical University of Vienna
Währinger Gürtel 18–20, AT–1090 Vienna (Austria)
E-Mail sylvia.knapp@meduniwien.ac.at

clusively answer the question of whether 'diabetes' or diabetes together with all its metabolic and vascular complications predisposes to infection.

Diabetes as a Risk Factor for Infection-Related Mortality

While a few studies have actually investigated the general risk for infection, the majority of reports have focused on assessing the risk of dying from an infection in diabetic patients. A recent study analyzed the death rates of more than 800,000 participants and identified the presence of diabetes as a major risk factor for premature death [2]. In particular, the authors report an on average 6-year earlier death of a 50-year-old patient with diabetes as compared to a nondiabetic person of this age [2]. Of interest, this paper discussed in detail relevant causes of death associated with diabetes and showed that beside cardiovascular causes and cancer, infectious diseases substantially contribute to the reduced life expectancy of diabetic people. As such, the hazard ratio for a person with diabetes dying from any infection was 2.39, and for pneumonia, it was a modest 1.67 [2]. While this indicates that infections are a potentially fatal complication in diabetic subjects, it does not show that diabetes predisposes to infection itself. An earlier report by Bertoni et al. [3] examined the risk of infection-related death in more than 9,000 patients over a 12- to 16-year follow-up period and confirmed that diabetes is a predictor of infection-related mortality. However, they discovered that this excess risk of death was related to preexisting cardiovascular diseases associated with diabetes rather than the disturbances in glucose metabolism that are characteristic for diabetes itself. In agreement, the analysis of two multicenter cohort studies that focused on community-acquired pneumonia in the presence of diabetes mellitus concluded that diabetes was associated with poorer outcome, possibly based on a higher frequency of worsened preexisting vascular and renal conditions [4]. It has to be noted, however, that from multiple studies performed to identify risk factors for infection-related mortality, results were conflicting when focusing on diabetes. While some reports identified diabetes as an independent risk factor for infection-related mortality [2, 4], others found no association between diabetes and mortality in classical infections such as community-acquired pneumonia [5] or severe sepsis [6]. These differences might be explained by variable statistical analyses, as some studies corrected for comorbidities while others did not.

Diabetes and Infection Susceptibility

Despite the common belief of a higher susceptibility to infectious diseases in diabetic people, very few investigations exist that have conclusively explored the overall risk for infections in this population. The first such study was performed in Canada and retrospectively analyzed the rate of infection and/or death thereof in diabetic patients and age-matched controls, totaling more than 500,000 cases per group, over two independent time periods [7]. These data demonstrated a significantly higher rate of infections in people with diabetes; the highest rates were noted for bacterial infections such as osteomyelitis, pyelonephritis and cystitis, pneumonia, cellulitis, sepsis or peritonitis [7]. The second such study was performed in the Netherlands and prospectively evaluated the incidence of certain infections in patients with type I or type II diabetes compared to patients with hypertension [8]. The authors concluded that diabetes enhanced the susceptibility to lower respiratory tract infections, urinary tract infections and bacterial skin and mucous membrane infections. This is in line with the general observation of an increased risk for wound infections in diabetic patients, most likely based on the higher number of leg ulcers in these patients.

Beside the fact that diabetes seems to be an independent risk factor for bacterial infections, there are several additional aspects that link diabetes to infections: (1) patients with diabetes are more prone to acquiring selected types of (rare) infections and (2) diabetic subjects are more susceptible to certain complications while being infected with pathogens. As such, some rare infections are more prevalent in people with diabetes, including emphysematous pyelonephritis, invasive otitis externa, emphysematous cholecystitis or rhinocerebral mucormycosis [reviewed in 9]. Furthermore, diabetes seems to increase the likelihood of infections caused by certain bacteria such as *Staphylococcus aureus* [9] or *Mycobacterium tuberculosis* [9]. There is evidence suggesting that infections by some organisms, such as *Streptococcus pneumoniae*, are linked to higher rates of bacteremia [10], which was proposed to explain higher mortality rates from pneumococcal pneumonia in these patients [9]. However, this conclusion is not unequivocally accepted, as other reports did not find higher rates of bacteremia in diabetic patients with pneumococcal pneumonia [11]. In addition, a recent report from the Community-Acquired Pneumonia Organization international cohort study not only disclosed that pneumococcal bacteremia did not impact the outcome, they moreover reported that people

with diabetes mellitus were more likely to achieve clinical stability and that diabetes was not a risk factor for death when suffering from bacteremic pneumococcal infection [12]. These data add to the general uncertainties regarding whether diabetes mellitus is indeed a major risk factor for such important infections as pneumonia and fuels the discussion of whether cardiovascular and renal comorbidities that are frequently associated with diabetes might cause susceptibilities and impact outcomes from infections rather than the metabolic alterations found in diabetic subjects.

Diabetes and the Immune Response

Epidemiologic data do not provide clear evidence for an altered adaptive immune response in diabetic patients, and respective investigations revealed that the overall response to vaccination was found to be preserved. To be more precise, while the primary antibody response to T cell-dependent and T cell-independent vaccines was found to be unaffected in type II diabetes, subjects with type I diabetes showed an impaired antibody response to hepatitis A and diphtheria [13]. Two other studies tested the response to influenza vaccination and did not find an impaired antibody response in diabetic subjects (type I and type II) [14]. In summary, adaptive immune responses, at least based on these studies, seem to be fairly unaffected by diabetes.

In order to comprehend the potentially altered antibacterial response in patients with diabetes, numerous groups investigated the cellular response pattern of innate immune cells using either material from diabetic patients or supplementing cells with glucose and/or insulin to mimic the hyperglycemic and/or hyperinsulinemic state characteristic for these patients. More recently, some groups also focused on the potential impact of adipokines, which are known to be altered in diabetic patients, and investigated their contribution to immunity.

The concept that diabetes might impact the inflammatory response to pathogens is based on a number of – mostly older – publications that investigated various aspects of predominantly innate immunity. As such it was shown that hyperglycemia, which was induced by either preincubating endothelial cells with serum from hyperglycemic patients or addition of 30 mM glucose, induced the upregulation of intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin on endothelial cells, which resulted in an increased adherence of neutrophils [15]. Likewise, increased expression of ad-

hesion molecules like CD11b on neutrophils from diabetic patients together with enhanced spontaneous adhesion was reported [16]. Despite this ‘adhesive’ phenotype, these studies demonstrated that neutrophil chemotaxis as such was impaired in the presence of diabetes [16]. Furthermore, evidence exists that the antibacterial activities of neutrophils are impaired in diabetic patients, as illustrated by decreased bactericidal activities following stimulation as well as reduced bacterial phagocytosis and killing mechanisms [16]. Extending these findings to monocytes from patients with type I diabetes, Chang and Shaio [17] demonstrated that the respiratory burst by monocytes from patients with poorly controlled disease with fasting glucose levels above 11 mmol/l was severely impaired when compared to patients with well-controlled disease and healthy people. These data not only extended the knowledge on functional alterations to monocytes but also illustrated that glucose levels impacted the cellular response pattern.

Preclinical Diabetes Models

Extending these in vitro investigations, several groups studied the immune response in experimental diabetes models in rodents. One such group focused on the inflammatory response within the pulmonary compartment of rats with type I diabetes induced by alloxan and discovered that both neutrophils and alveolar macrophages showed an impaired reaction in terms of cytokine release and phagocytosis that was partially restorable by insulin administration [18]. While these authors suggest that the lack of insulin is at least partially responsible for the impaired inflammatory response within the lungs of these rats, another report studied alveolar macrophages from alloxan-treated rabbits challenged ex vivo with particulate matter and found the opposite phenotype, i.e. an exaggerated inflammatory response when compared to cells from nondiabetic animals [19]. Using a model of streptozotocin-induced type I diabetes, Vallerskog et al. [20] explored mechanisms of altered immune responses to *M. tuberculosis*. Their main finding was that chronic diabetes impacts the immune response to mycobacteria by delaying the innate immune cell-mediated induction of a productive interferon- γ response [20]. This effect was suggested to depend on an impaired immediate inflammatory response by infected alveolar macrophages, since the migration of dendritic cells from lungs to local lymph nodes was not altered in diabetic mice. These studies collectively add to the confusion as to whether and to which

degree type I diabetes indeed influences the inflammatory response to infection.

It is important to differentiate between hyperglycemia – found in both type I and type II diabetes – and hyperinsulinism, which is characteristic for type II diabetes only. Mouse models of type II diabetes, such as leptin receptor mutant db/db mice, were used to explore the effects of diabetes on the host response during infectious diseases. As such, one group studied a *S. aureus* hind paw infection model in these animals and revealed db/db mice to be less able to kill bacteria and to therefore develop a chronic infection [21]. Likewise, db/db mice were more susceptible to *Burkholderia pseudomallei* [22] and *M. tuberculosis* infections [23]. Of interest though, Lemos et al. [23] demonstrated that bone marrow-derived cells were not responsible for the increased susceptibility and impaired inflammatory response during tuberculosis in db/db animals. Collectively, these data reflect and confirm the impaired immune defense against commonly found pathogens such as *S. aureus*, *B. pseudomallei* and *M. tuberculosis* in patients with type II diabetes. Nevertheless, the precise underlying molecular mechanisms that could explain this phenotype remain unknown.

Clamp Experiments

In order to better differentiate between the potential effects of hyperglycemia versus hyperinsulinemia, several investigators performed clamp experiments in which they studied immune responses while maintaining defined glucose and insulin levels. Neutrophil functions in healthy volunteers were tested under euglycemic/hyperinsulinemic conditions, and insulin was demonstrated to increase the chemotactic and phagocytic properties of these cells [24]. Interestingly, this effect was less pronounced when neutrophils of elderly people (approx. 69 years of age) were tested, while monocytes generally did not respond to insulin, despite the presence of insulin receptors on these cells [24]. Age-related differences in insulin and glucose effects on tumor necrosis factor (TNF) release by lipopolysaccharide (LPS)-stimulated blood was also discovered in a hyperinsulinemic-hyperglycemic clamp study of nondiabetic people, where TNF responses were only suppressed in younger volunteers (age approx. 22 years) but not in the elderly volunteers (age approx. 67 years) [25], thus suggesting that older people are less sensitive to changes in glucose and/or insulin. Another group studied the LPS-induced inflammatory response and neutrophil functions following 6 h of

low-insulinemic/euglycemic and hyperinsulinemic/euglycemic as well as low-insulinemic/hyperglycemic and hyperinsulinemic/hyperglycemic conditions [26]. These data show that any hyperinsulinemic condition enhanced the LPS-induced inflammatory response, since interleukin (IL)-1, IL-6 and IL-8 responses were significantly higher than in their respective low-insulinemic controls. TNF responses were only enhanced in the hyperinsulinemic/euglycemic group, but not in the presence of hyperglycemia. Moreover, the authors did not discover any differences in phagocytosis by neutrophils, and the migratory behavior of these cells was only enhanced under hyperinsulinemic/hyperglycemic conditions in response to platelet-activating factor, but not to C5a or phorbol 12-myristate 13-acetate [26]. Collectively, these data again illustrate that the impact of glucose and/or insulin on inflammatory responses and neutrophil functions varies greatly between different investigations, which renders it difficult to draw any consistent conclusions.

Since diabetes is not simply characterized by changes in glucose and insulin levels but is also associated with numerous alterations in metabolic mediators but also adipokines, more recent investigations tried to incorporate these factors into their experiments. As such, neutrophil function was assessed in the presence of resistin, which is elevated in diabetic patients [27]. Cohen et al. [27] found that resistin itself was sufficient to impair neutrophil functions in terms of chemotaxis, oxidative burst and phagocytosis, possibly via interference with phosphatidylinositol-3-kinase-dependent downstream pathways. Leptin is another adipokine that is secreted by adipocytes and considered an important link between metabolic disorders and immune functions. As such, leptin was initially thought to possibly play a role in the dampened immune response in overweight and diabetic people. However, animal studies using leptin-deficient mice (so-called ob/ob mice) yielded conflicting data. While one group found ob/ob mice to be more prone to succumb to *Klebsiella* infection [28], another group could not identify any significant differences when studying *S. pneumoniae* and *Klebsiella pneumoniae* models [29].

In vivo Effects of Glucose/Insulin in Humans

While most investigations were performed using cells from healthy people or diabetic patients without infection, only a few studies examined the immune response of patients with diabetes mellitus suffering from an actual infection. One such examination was published in

2010 and focused on inflammation, coagulation, fibrinolysis and cell surface markers in diabetic and nondiabetic patients diagnosed with community-acquired pneumonia [4]. Although this specific study identified diabetes as a risk factor for poor outcome from pneumonia, the authors did not discover any consistent differences in the early inflammatory response (IL-6, TNF, IL-10 release), coagulation parameters or cell surface expression of Toll-like receptors or human leukocyte antigen DR [4]. In line with this, another report studied the inflammatory and hemostatic response in diabetic patients with severe sepsis and again found no difference in inflammatory markers such as IL-6 or TNF and only very modest but transient differences in some anticoagulant proteins (antithrombin III, proteins S and C) when compared to the nondiabetic group [6]. In a more controlled setting, the same group applied clamp techniques in healthy volunteers and increased either glucose, insulin, both or none and administered a defined dose of LPS to induce a systemic inflammatory response [30]. After various time points, the inflammatory response and activation of coagulation/fibrinolysis was evaluated. The results demonstrate that hyperglycemia led to more pronounced activation of coagulation while at the same time neutrophil degranulation was diminished. Hyperinsulinemia in turn attenuated fibrinolysis, whereas inflammatory cytokines like TNF or IL-6 did not differ between the groups. The advantage of this latter study is the clear design and low interindividual variability, which possibly gives the best insight into the biological role of glucose and insulin levels during systemic inflammation in humans in vivo. Other investigations concentrated on the role of hyperglycemia in various infectious diseases in both diabetic and nondiabetic patients. One such study found hyper-

glycemia (plasma glucose concentration >11.1 mmol/l or 200 mg/dl) in patients with severe sepsis at admission to be associated with poorer outcome in nondiabetic patients, but interestingly, not in subjects with diabetes [6]. Similar results were independently reported from the German CAPNetz study group [31], which identified hyperglycemia at admission to dose-dependently worsen survival exclusively in nondiabetic patients with community-acquired pneumonia.

Conclusion

Although the presence of diabetes seems to predispose to some infectious diseases and possibly a worse outcome thereof, several lines of evidence suggest that diabetes-associated comorbidities importantly contribute to this phenotype. A number of investigations attempted to identify an altered immune response to explain the supposed susceptibility to infections, many focusing on the possibly impaired neutrophil function. Collectively, the data show that there seems to be a tendency for hyperglycemia itself to impair the antibacterial function of neutrophils, while insulin was shown to restore and even enhance the inflammatory response in other trials. However, almost every finding of an altered immune response is followed by another study that shows an unimpaired inflammatory response. This makes it difficult to comprehend the underlying problem and explains why epidemiologic studies yielded conflicting results as well. Considering that diabetes is a complex disease, associated with numerous metabolic disturbances, it is obviously impossible to pin the enhanced susceptibility to infections to a single pathway or cell type.

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