

# Immune dysfunction in patients with diabetes mellitus (DM)

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## Abstract

Patients with diabetes mellitus (DM) have infections more often than those without DM. The course of the infections is also more complicated in this patient group. One of the possible causes of this increased prevalence of infections is defects in immunity. Besides some decreased cellular responses *in vitro*, no disturbances in adaptive immunity in diabetic patients have been described. Different disturbances (low complement factor 4, decreased cytokine response after stimulation) in humoral innate immunity have been described in diabetic patients. However, the clinical relevance of these findings is not clear. Concerning cellular innate immunity most studies show decreased functions (chemotaxis, phagocytosis, killing) of diabetic polymorphonuclear cells and diabetic monocytes/macrophages compared to cells of controls. In general, a better regulation of the DM leads to an improvement of these cellular functions. Furthermore, some microorganisms become more virulent in a high glucose environment. Another mechanism which can lead to the increased prevalence of infections in diabetic patients is an increased adherence of microorganisms to diabetic compared to nondiabetic cells. This has been described for *Candida albicans*. Possibly the carbohydrate composition of the receptor plays a role in this phenomenon. © 1999 Federation of European Microbiological Societies. Published by Elsevier Science B.V. All rights reserved.

*Keywords:* Diabetes mellitus; Immune dysfunction; Infection

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## 1. Introduction

The incidence of infections is increased in patients with diabetes mellitus (DM) [1]. Some of these infections are also more likely to have a complicated course in diabetic than in nondiabetic patients [1]. Diabetic ketoacidosis, for example, is precipitated or complicated by an infection in 75% of the cases.

The mortality rate of patients with an infection and ketoacidosis is 43% [1]. In a prospective study of 101 293 adult hospitalized patients, 1640 episodes of bacteremia were diagnosed. Of 1000 hospitalized patients studied, 2/3 of the bacteremias were found in patients with DM compared to 1/3 in patients without DM ( $P < 0.001$ ) [2]. The question then arises as to which pathogenetic mechanisms are responsible for this high infection rate in patients with DM. Possible causes include defects in immunity, an increased adherence of microorganisms to diabetic cells, the presence of micro- and macroangiopathy or neuropathy, and the high number of medical interventions in this group of patients.

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The immune system can be divided into the innate and adaptive-humoral or cellular immune systems. Concerning the humoral adaptive immunity, serum antibody concentrations in patients with DM are normal and they respond to vaccination with pneumococcal vaccine as well as nondiabetic controls [3,4]. Furthermore, no differences have been shown in the immune response to intramuscular hepatitis B vaccine between children with DM type 1 and controls [5]. Concerning the adaptive cellular immunity, inhibition of the proliferative response to different stimuli has been observed in the lymphocytes of diabetics with poorly controlled disease [6]. An abnormal delayed type hypersensitivity reaction (cell-mediated immunity) has also been described in DM type 1 and type 2 patients [7–9]. Nevertheless, patients with DM do not have *Pneumocystis carinii* pneumonia or mycobacterial infections (as seen in patients with adaptive-cellular immunity dysfunctions like patients infected with the human immunodeficiency virus) more frequently than patients without DM. So, the question remains how important these in vitro disturbances are in vivo.

Considering the above, it seems that differences in innate immunity between diabetic and nondiabetic patients and in adherence of microorganisms to diabetic and nondiabetic cells are more important in the pathogenesis of the increased prevalence of infections in these patients. Studies about these two subjects are reviewed in this article.

## 2. Defects in innate immunity

### 2.1. Humoral innate immunity

#### 2.1.1. Complement function

In a study of 86 DM type 1 patients, 22 (26%) had a serum complement factor 4 concentration (C4) below the normal range [10]. The low C4 values did not appear to be the result of consumption. Since nondiabetic identical twins also had a C4 concentration below normal, and the genes encoding C4 are linked with the antigens DR3 and DR4 (which are expressed in 95% of the Caucasian diabetic patients in contrast to 40% of the general population [6]), the authors suggest that this reduced C4 may be an inherited phenomenon [10]. However, an isolated C4

deficiency is not a known risk factor for infections in nondiabetic patients and therefore seems not to play an important role in the increased risk of infections in patients with DM.

#### 2.1.2. Cytokines

Studies with whole blood, peripheral blood mononuclear cells (PBMCs), and isolated monocytes of diabetics have to be divided into studies with and without stimulation. Without stimulation tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) concentrations in patients with DM type 1 [11], interleukin (IL) 6 concentrations in patients with DM type 2 [12], and IL-8 concentrations in DM type 1 and 2 patients [13] have been studied. Elevated resting values of TNF- $\alpha$ , IL-6 and IL-8 were found in diabetic patients compared to nondiabetic controls.

Studies with PBMCs and isolated monocytes of diabetic patients after stimulation show the following results: in one study [14] the IL-1 secretion of PBMCs in response to lipopolysaccharide (LPS) was reduced in diabetic (type 1 and 2) PBMCs, while the TNF- $\alpha$  response was the same as in the control cells. In another study monocytes of DM type 1 patients showed a significantly lower production of IL-1 and IL-6, but again no differences in TNF- $\alpha$  concentrations were measured, after stimulation with LPS, compared with monocytes of DM type 2 patients and nondiabetic controls [15]. Possibly most of the TNF- $\alpha$  already disappeared after the incubation period of 24 h [15]. Neither glucose nor insulin showed any effect on the production of IL-1 or IL-6 in isolated monocytes, so the decreased production after stimulation with LPS seemed an intrinsic cellular defect of diabetic cells. It is possible that the elevated resting value of diabetic cells leads to the induction of tolerance to stimulation, which results in lower cytokine secretions after stimulation. This phenomenon has already been described in nondiabetic cells [16].

Studies of cytokine excretion by PBMCs of nondiabetic patients after the addition of different glucose concentrations have shown comparable results as studies with diabetic cells. One study [17] showed that after the addition of different glucose concentrations, unstimulated monocytes of nondiabetics showed an increased TNF- $\alpha$  and IL-6 response. Another study [18] showed that after pokeweed mitogen

stimulation lower IL-2, IL-6 and IL-10 concentrations were found after the addition of glucose (with a dose-response effect). Possibly, the induction of tolerance, described above, can also explain these results. In other words, the presence of glucose leads to a higher resting cytokine production; after stimulation, however, this cytokine production is impaired compared to the situation without glucose. Another substance which may play a role in the increased basal cytokine secretion is the advanced glycation end products (AGEs, which are products of glucose and lysine or arginine residues). An increased formation of AGEs takes place in poorly regulated diabetic patients [19]. Different studies have shown that binding of these AGEs to nondiabetic cells, without stimulation, leads to an increased cytokine production [17,20,21], so it seemed that the increased formation of these AGEs in diabetics may be responsible for the increased basal cytokine secretion.

### 2.1.3. Hyperglycemia/glucosuria

Following the 1985 WHO criteria DM is defined as a fasting glucose concentration of at least  $7.8 \text{ mmol l}^{-1}$  or a 2-h glucose concentration of  $11.1 \text{ mmol l}^{-1}$  or higher [22]. As a result of this patients with DM (also with medication) very often have hyperglycemia. This hyperglycemic environment can enhance the virulence of certain microorganisms. An example is *Candida albicans*, which expresses a surface protein that has great homology with the receptor for complement factor 3b (CR3). Normally, opsonization of microorganisms takes place by attachment of complement factor 3b (C3b). Receptors on phagocytizing cells recognize this bound C3b and attach, thereby initiating ingestion and killing. In a hyperglycemic environment, the expression of the receptor-like protein of *C. albicans* is increased, which results in competitive binding and inhibition of the complement-mediated phagocytosis [23]. Another example is the presence of glucosuria, as found in poorly regulated patients. We showed [24] that glucosuria enhances bacterial growth of different *Escherichia coli* strains, which probably plays a role in the increased incidence of urinary tract infections in diabetic patients.

So it seemed that an optimal diabetes regulation can decrease the virulence of some pathogenic microorganisms.

### 2.1.4. Other serum factors

In vitro tests analyzing the functions of nondiabetic polymorphonuclear cells (PMNs) are carried out by incubating these cells with plasma derived from patients with DM. These defects are not correlated with the amount of glucose present in plasma [6,25,26]. An example is the increased adherence of PMNs of nondiabetic patients to bovine aortic endothelium in the presence of diabetic plasma [27]. This increased adherence probably leads to a decrease in diapedesis and exudate formation of PMNs [27]. The question arises which factor in diabetic serum is responsible for the difference mentioned above. It has been suggested [28] that AGEs play a role. Since the formation of AGEs is increased in poorly regulated patients, it seemed that an optimal diabetes regulation possibly can improve the host response.

Another frequently mentioned substance in the pathogenesis of infections in diabetic patients is zinc. Low plasma zinc levels have been reported in DM type 1 and type 2 patients [6]. Nevertheless, in another study no differences in zinc levels between diabetic and nondiabetic subjects were found [29]. In vitro studies described a disturbed lymphocyte response and depression of chemotaxis in diabetic PMNs when zinc deficiency was present [1,6,28]. Other in vitro studies with PBMCs of nondiabetic patients showed an enhanced LPS-induced excretion of pro-inflammatory cytokines after the addition of zinc [30]. Considering the contradictory epidemiological data about zinc deficiency in DM patients, the clinical relevance of the above mentioned in vitro results in the pathogenesis of infections in diabetic patients remains unclear.

In conclusion, some innate (cytokines, complement) humoral immune functions are decreased and some remain the same in patients with DM compared to those without DM.

## 2.2. Cellular innate immunity – PMNs

### 2.2.1. Chemotaxis

A significantly lower chemotaxis has been found in PMNs of diabetic patients (type 1 and type 2) than in those of controls [25,31,32]. We, however, could not demonstrate this difference in our study in which we studied PMN function in women with DM and asymptomatic bacteriuria compared to nonbacteriuria.

ric diabetic women and healthy controls [33]. All studies used serum from healthy controls. It is possible that the different stimuli (zymosan, complement) of the PMNs and the differences in patient characteristics (duration, regulation and complications of DM, DM type 1 or DM type 2) in the above mentioned studies may explain these contradictory results. No correlation was found between glucose concentration [25,32] or hemoglobin A1c (HbA1c, which is a serum marker for the regulation of the DM) level and the chemotactic responses, although one study did show a further reduction in chemotaxis in patients with hyperglycemia [31]. Interestingly, one of the other studies showed that the chemotactic responses of the PMNs did not alter after the incubation of either glucose or insulin, but returned to normal values after the incubation with glucose and insulin together [32]. Since most PMN functions are energy-dependent processes [34], an adequate energy production is necessary for an optimal PMN function. Glucose needs insulin to enter the PMNs to generate this energy, which may explain the improvement of the chemotactic response after the addition of these two substances.

#### 2.2.2. Adherence

Conflicting data have been reported about the *in vitro* adherence of diabetic PMNs without stimulation [25,27,31,34,35]. In contrast, no differences have been found between diabetic and control PMNs after stimulation [27,31]. No correlation was found between plasma glucose or HbA1c and adherence [25,27,31]. However, in a small number of DM type 1 and DM type 2 patients with untreated hyperglycemia, the decreased adherence of PMNs to nylon fiber columns increased after the hyperglycemia was corrected [34,35]. Of course adherence to nylon fiber columns is not the same as to endothelial cells as a first step in the inflammation reaction. However, again a better regulation of the DM seemed to increase the host response.

#### 2.2.3. Phagocytosis

PMNs of diabetic patients have shown the same [25,33] and a lower [31,36] phagocytotic capacity compared to PMNs of controls. The mean HbA1c concentration was lower (better regulation) in patients without impaired phagocytosis [33] than in

those with impaired phagocytosis [31,36]. One study [36] showed an inverse relationship between the HbA1c levels and the phagocytotic rate. Another study [37] showed that the decreased phagocytosis improved, but did not become normal after 36 h of normoglycemia. Therefore, it seems that impairment of phagocytosis is found in PMNs isolated from poorly regulated patients and that better regulation of the DM leads to an improved phagocytotic function.

#### 2.2.4. Oxidative burst

Chemiluminescence (CL) corresponds to the emission of light directly or indirectly produced in the course of a chemical reaction. This phenomenon is often used to evaluate the oxidative potential of PMNs, a process during which free radicals are synthesized early in the phagocytotic process [31,38]. CL correlates well with antimicrobial activity [39] and may be used as a measure of phagocytotic capacity [38]. Compared to controls, CL at baseline was higher [31] or the same [36,39] in PMNs of diabetic patients. These studies [31,36,39] also showed that, after stimulation, the CL of diabetic PMNs was lower than that of control PMNs. It is possible that the reaction of diabetic PMNs to stimuli is quenched as a result of the higher resting CL. In our study [33], we did not find any differences in CL after stimulation between diabetic patients and controls. In general, however, the patients in our study were better regulated than those in the earlier studies, which may probably explain these different results.

#### 2.2.5. Killing

Data about the bactericidal activity of diabetic PMNs have yielded conflicting results [25,26,33,37]. In general, however, the killing capacity of diabetic PMNs is lower than that of control PMNs. Again, differences in either the patient characteristics (see Section 2.2.1) or the microorganisms used may explain these different results. An impaired killing function of diabetic PMNs was found in all studies using *Staphylococcus aureus* as the microorganism [25,26,37], but not in the studies in which the killing of *C. albicans* [33] was used as the measure. Killing was impaired in one study that used nondiabetic serum for opsonization [37], but not in another [33]. Thus, based on these studies we cannot draw any

conclusions about the effect of nondiabetic serum on the killing of diabetic cells. No correlation was found with glycemic level [25,26,37], although some studies have shown that bactericidal activity improved, but did not normalize after achieving normoglycemia [6,37].

#### 2.2.6. Influence of infections

In a study in our hospital [33], we were unable to demonstrate any differences in chemotaxis, phagocytosis, CL, and killing between PMNs of diabetic women with bacteriuria, diabetic women without bacteriuria, and nondiabetic controls. Furthermore, an earlier study showed no differences in phagocytosis and killing between diabetic patients with and without recurrent infections [26]. So, these studies do not indicate that the presence of infections influences PMN functions.

In conclusion, besides some of the conflicting results in studies mentioned above, different disturbances in diabetic compared to control PMN functions are described. However, the clinical relevance of these in vitro studies remains uncertain, mainly because of the differences in the tests performed. It is possible that only a combination of defects in PMN functions plays a role in vivo. Most studies show an improvement of PMN functions after a better metabolic regulation of DM.

#### 2.3. Cellular innate immunity – monocytes/macrophages

Both impaired chemotaxis and phagocytosis of the monocytes of diabetic patients have been described [1,40]. Since plasma from healthy controls does not cause any significant change in the phagocytotic ca-

capacity of diabetic monocytes [40], it seems that this impaired function is caused by an intrinsic defect in the monocytes themselves.

A lower immune response in children with DM type 1 compared to controls was found after intradermal (instead of intramuscular) administration of the hepatitis B vaccine [5]. It has been suggested that this lower response is probably partly the result of an impaired macrophage function in this patient group [5].

In combination with the earlier mentioned decreased production of pro-inflammatory cytokines after LPS stimulation in DM type 1 patients, it seemed that monocyte/macrophage functions are impaired in DM type 1 patients. The pathogenic mechanism remains unclear. Further research has to be done to explain this interesting phenomenon.

### 3. Adherence

Adherence of a microorganism to mucosal or epithelial cells is an important step in the pathogenesis of infections. Host-related factors may influence this adherence. For example, women with recurrent urinary tract infections have a greater adherence of *E. coli* to their vaginal and buccal cells compared to controls [41].

*C. albicans* infection is frequently found in diabetic patients. Since infection mostly is preceded by colonization Aly et al. investigated which risk factors increased the risk of *Candida* carriage in diabetic patients [42]. Risk factors for oral *Candida* carriage in patients with DM type 1 were a lower age and a higher HbA1c level (poor regulation of DM). Continuous wearing of dentures and the presence of glu-

Table 1  
Summary of the different immune dysfunctions found in diabetic patients

	Humoral		Cellular	
Innate	Complement	↓	PMNs	↓ =
	Cytokines without stimulation	↑	Monocytes/macrophages	↓
	Cytokines after stimulation	↓ =		
Adaptive	Immunoglobulins	=	T lymphocytes	↓
Adherence		↑		

↓ means that this function is decreased, = means that this function is the same and ↑ means that this function is increased in diabetic patients compared with nondiabetic controls.

cosuria (also an indication of a poor DM regulation) increased the risk of *Candida* carriage in DM type 2 patients, the mean number of cigarettes smoked per day was correlated with *Candida* carriage in DM type 1 and type 2 grouped together [42]. Cameron et al. extracted lipids from human buccal epithelial cells and found, using chromatogram overlay assays, that some *C. albicans* strains bind to fucose-containing and other *C. albicans* strains to *N*-acetylgalactosamine-containing lipids extracted from human buccal cells. The authors conclude that the existence of several adhesin-receptor systems contributes to the virulence of *C. albicans* [43]. The carbohydrate composition of receptors probably plays an important role in the susceptibility to infections. It has been shown that severely ill patients have a decreased amount of galactose and sialic acid on their buccal cells, compared with minimally ill patients and healthy controls. The investigators mentioned that these receptor changes possibly lead to an increased adherence of microorganisms and play a role in the high prevalence of Gram-negative bacterial colonization in the respiratory tract of these patients [44]. This mechanism of increased adherence, due to an altered receptor carbohydrate composition, is possibly also present in diabetic patients. Buccal cells from 50 diabetic patients (DM type 1 and type 2) showed an increased in vitro adherence of *C. albicans* compared to buccal cells from controls [45]. A significantly higher incidence of *Candida* infection, but not *Candida* carriage, was also found in this patient group (12% versus 0%) [45]. No relationships, however, were found between the frequency or quantity of *Candida* and age, duration, regulation, or type of DM [45]. This increased adherence to diabetic cells might also play a role for other microorganisms, for example the adherence of *E. coli* to uroepithelial cells, which would explain the increased prevalence of infections in patients with DM.

In conclusion, disturbances in cellular innate immunity play a role in the pathogenesis of the increased prevalence of infections in DM patients (Table 1). In general, a better regulation of the DM leads to an improvement of cellular function. A second important mechanism is the increased adherence of the microorganism to diabetic cells. Furthermore, some microorganisms become more virulent in a high glucose environment.

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