

The impact of diabetes on the pathogenesis of sepsis

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Abstract Diabetes is associated with an increased susceptibility to infection and sepsis. Conflicting data exist on whether the mortality of patients with sepsis is influenced by the presence of diabetes, fuelling the ongoing debate on the benefit of tight glucose regulation in patients with sepsis. The main reason for which diabetes predisposes to infection appears to be abnormalities of the host response, particularly in neutrophil chemotaxis, adhesion and intracellular killing, defects that have been attributed to the effect of hyperglycaemia. There is also evidence for defects in humoral immunity, and this may play a larger role than previously recognised. We review the literature on the immune response in diabetes and its potential contribution to the pathogenesis of sepsis. In addition, the effect of

diabetes treatment on the immune response is discussed, with specific reference to insulin, metformin, sulphonylureas and thiazolidinediones.

Abbreviations

<i>E. coli</i>	<i>Escherichia coli</i>
C3	Complement component 3
C5	Complement component 5
C8	Complement component 8
CAP	Community-acquired pneumonia
CD	Cluster of differentiation, a systematic classification of cell surface antigens
CR3	Complement receptor 3, also known as CD11b/CD18
CRP	C-reactive protein
HbA1c	Glycated hemoglobin, a measure of glycaemic control in diabetes
ICU	Intensive care unit
IL	Interleukin
LPS	Lipopolysaccharide
Mac-1	Macrophage 1 antigen, also known as CD11b/CD18
MODY	Maturity-onset diabetes of the young
NET	Neutrophil extracellular traps
OR	Odds ratio
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
<i>S. epidermidis</i>	<i>Staphylococcus epidermidis</i>
sFLT-1	Soluble fms-like tyrosine kinase-1
TNF- α	Tumour necrosis factor alpha
USAN	United States adopted name
WHO	World Health Organization, Geneva, Switzerland

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Introduction

Patients with diabetes mellitus have an increased risk of developing infections and sepsis [1, 2], and constitute 20.1–22.7% of all sepsis patients [3, 4]. This association was first observed a thousand years ago by Avicenna (980–1027), who noted that diabetes was frequently complicated by tuberculosis [5]. In the pre-insulin era, Joslin noted, in a series of 1,000 cases, that diabetic coma was usually precipitated by infection [6], and infection remains an important cause of death in diabetics [7]. Much of the literature does not distinguish between types of diabetes and regards all complications as secondary to hyperglycaemia and independent of diabetes aetiology.

We review the pathogenesis of infection in the diabetic patient and the altered host response, focusing on data from human studies.

Risk of infection and clinical considerations

A small number of conditions are strongly associated with diabetes, including malignant otitis externa [8–10], emphysematous pyelonephritis [11–14], emphysematous cholecystitis [15, 16], *Klebsiella* liver abscesses [17], rhinocerebral mucormycosis [18, 19] and melioidosis [20]. However, these are rare, and most infections in diabetics are those that occur also in the general population. Two population-based studies have proved pivotal to our understanding of the susceptibilities of patients with diabetes [1, 2]: a study of 523,749 Canadians with diabetes and an equal number of matched controls [2] found that diabetes increased the risk for cystitis (risk ratio 1.39–1.43), pneumonia (1.46–1.48), cellulitis (1.81–1.85) and tuberculosis (1.12–1.21). A study of 7,417 Dutch patients with diabetes found a higher incidence of lower respiratory tract infection (adjusted odds ratios [ORs] 1.42 for type 1 diabetes and 1.32 for type 2), urinary tract infection (1.96 and 1.24), and skin and mucous membrane infection (1.59 and 1.33) [1]. The association between diabetes and tuberculosis was re-confirmed by a recent meta-analysis [21].

Although diabetes mellitus is implicated in susceptibility to infection, its influence on the subsequent clinical course and outcome is less clear. Some studies have shown an association with increased mortality [22–25], others found no effect [4, 26–34], while still others found improved survival [15, 16, 35]. The largest of these (12.5 million sepsis cases) [15] found that diabetics were less likely to develop acute respiratory failure and linked this to two previous studies which found that diabetics seem to be protected from acute lung injury [36, 37]. The largest single study to show an adverse effect of diabetes on mortality in sepsis was conducted in 29,900 Danish

patients with community-acquired pneumonia and found that patients with diabetes had a higher risk of mortality (OR 1.2) [24].

The reasons for the different outcomes between these studies are unclear, but may relate to differences in the study population, varying outcome measures and differences in statistical analysis and in diabetes drug prescription habits between countries [38]. Population-based studies are less prone to selection bias compared to hospital-based studies, but more detailed clinical information is usually available in hospital-based studies. In terms of outcome measures, studies with outcomes at longer time points (e.g. 6 months versus 28-day mortality) are more likely to find informative differences, but are much more difficult to conduct [39]. Observational studies often make use of multi-variable regression techniques to correct for confounders (a common, but incorrect, approach to model-building is to include all measured parameters and then remove parameters on the basis of their *p*-value). Over-adjustment or unnecessary adjustment for variables that are not confounders can produce biased or spurious results [40]. Patients with diabetes also have multiple co-morbidities that may worsen outcomes: it is debatable whether these co-morbidities should be adjusted for, since many are caused by diabetes and, therefore, cannot be regarded as confounders [41]. Nevertheless, a number of studies have attempted to adjust for these comorbidities [23, 24, 26]. The possible influences of drug treatment are described below.

Diabetes and the immune system

In 1904, Lassar suggested that high levels of glucose may drive infection by serving as a nutrient source for bacteria [42], but in 1911, Handmann showed that glucose supplementation did not enhance bacterial growth [43], and proposed, instead, a defect in immune function. Da Costa and Beardsley first demonstrated the existence of an immune defect in 1907 [44]. The subsequent literature on this topic is complicated by the fact that different techniques have been used over the years, and gaps of a decade or more may separate experiments, making it difficult to compare results. Most studies have shown defects in neutrophil function, with good evidence for abnormalities in adhesion, chemotaxis and intracellular killing, but evidence for a phagocytosis defect are contradictory. The evidence that neutrophil defects are solely responsible for the increases in the susceptibility of diabetics to infection is equivocal [45]; there is good evidence that humoral responses in diabetics are poorer and may play a larger role than previously recognised.

General markers of inflammation

Diabetes is associated with elevations in C-reactive protein (CRP) [46], tumour necrosis factor alpha (TNF- α) [47], interleukin (IL)-6 [46] and IL-8 [48], but no differences are seen in circulating cell surface markers or coagulation markers between patients with and without diabetes in the context of sepsis. In a cohort of 1,799 patients with community-acquired pneumonia (CAP) [49], concentrations of pro-inflammatory cytokines (TNF- α , IL-6 and IL-10), coagulation (anti-thrombin, Factor IX and thrombin–anti-thrombin complexes) and fibrinolysis (PAI-1 and D-dimer) biomarkers were similar in subjects with and without diabetes at presentation and in the first week of hospitalisation [49]. In addition, monocyte expression of CD120a, CD120b, HLA-DR, TLR4 and TLR2 on monocytes was not different between the groups [49]. These results are consistent with a cohort study of 830 sepsis patients, in whom plasma concentrations of IL-6 and TNF- α were elevated to the same extent in patients with and without diabetes, both at admission and at follow-up [4]. In this second study, diabetes was not found to exacerbate the known pro-coagulant response seen in sepsis [4]. Since sepsis and diabetes both induce a pro-inflammatory and pro-coagulant state, and since both interfere with the host response, the lack of a strong influence of diabetes on the pro-inflammatory and coagulation pathways during sepsis is remarkable. Preclinical studies in healthy volunteers have shown that acute hyperglycaemia and insulin resistance may both directly influence inflammation and coagulation [50, 51], but these changes may not be detectable on the background of the much larger abnormalities attributable to sepsis. There is also evidence that local responses may be impaired in diabetes, e.g. levels of urinary IL-6 and IL-8 are lower in diabetic women with bacteriuria [52]. Endothelial activation has been implicated in the pathogenesis of sepsis [53] and diabetes is itself known to activate endothelium. A recent study of 207 sepsis patients (of whom 30% had diabetes) showed that markers of endothelial cell activation (plasma E-selectin and soluble fms-like tyrosine kinase-1 [sFLT-1]) were higher in diabetes [54].

Neutrophils

Adhesion

The recruitment of neutrophils to a site of inflammation requires endothelial adhesion followed by transmigration and exit from the circulation, a process requiring the expression by neutrophils of integrins (e.g. CD11a/CD18 and CD11b/CB18) [55, 56], which then bind to endothelial cell adhesion molecules (e.g. ICAM-1 [57–59]). A study in which neutrophils were harvested from 26 patients with

diabetes and an equal number of controls demonstrated that adhesion to bovine aortic endothelium was increased for neutrophils from diabetics, but only if the endothelium was also incubated with plasma from patients with diabetes [60]. Increased adhesion appears to be due to both an increase in the expression of integrins by diabetic neutrophils and of adhesion molecules by endothelium. Diabetic neutrophils have increased the expression of CD11b and CD11c [61], and glucose itself appears to be able to stimulate the expression of ICAM-1 by endothelial cells [57–59, 62–64], possibly via an osmotic effect [63, 64].

Chemotaxis

Chemotaxis is the ability of neutrophils to detect and move towards a chemical inflammatory stimulus. Studies may be divided by technique: those using the two-chamber Boyden technique [65] have produced conflicting results [66, 67], but those using the subagarose technique [68] (which includes a negative control, which Boyden's technique lacks) have reproducibly shown a defect in diabetes [61, 69].

Phagocytosis

Phagocytosis is the engulfment and ingestion of foreign bodies by a cell, allowing neutrophils to remove and destroy pathogens. The evidence for a defect in phagocytosis in diabetes is contradictory, with some reporting a defect [70–73], but others not [61, 74]. These inconsistencies may be attributed to differences in methodology: neutrophils will not phagocytose unopsonised particles, so bacteria and cells need first to be incubated with serum containing C3b or IgG. Many studies have used autologous serum [70–73], but those that have used a standard serum or opsonin have found no defect [61, 74]. In 1976, Bagdade found that phagocytosis of *Streptococcus pneumoniae* was reduced in neutrophils recovered from eight patients with poorly controlled diabetes, but this defect improved with diabetes treatment [70]. Notably, control neutrophils incubated with serum taken from patients with diabetes also demonstrated a defect in phagocytosis, implying that the defect was, in fact, due to defective opsonisation and not to a deficit in neutrophil function per se: in other words, the defect is humoral. In 1984, Davidson et al. studied the ingestion of *Candida guilliermondii* by neutrophils from 11 patients with diabetes and found that phagocytosis was reduced. However, if pre-opsonised yeast cells were used, then phagocytosis was no different from controls, again suggesting that a humoral defect must exist [72]. Delamaire et al. used a single control serum for all samples to remove the possibility of a difference in opsonisation [61], convincingly demonstrating that no phagocytosis defect exists.

Killing

Neutrophils have two distinct mechanisms for killing bacteria, intracellular and extracellular. Phagocytosed bacteria are killed by superoxide anions and other oxygen-derived species. Culture-based methods have demonstrated a defect in the intracellular killing of *Staphylococcus aureus* [69, 75, 76], *Streptococcus pneumoniae* [71, 77] and *Candida albicans* [78]. More recent studies have confirmed this finding used chemiluminescence methods [79–82], a superior method compared to culture, because it separates the effect of phagocytosis from that of intracellular killing. The killing defect cannot be corrected by incubation with normal serum [76], suggesting that it is cellular in origin, but improves with glycaemic control [81].

Neutrophils are also able to kill bacteria extracellularly by expelling chromatin, which combines with granule proteins to form neutrophil extracellular traps (NETs) [83]. Interestingly, β -hydroxybutyrate (a ketone body present in diabetic ketoacidosis) has been shown to inhibit the formation of NETs [84], but the relevance of this finding to patients remains to be demonstrated.

Monocytes

Monocytes in diabetes have been less well studied than neutrophils, but also appear to have defects of chemotaxis [85] and phagocytosis [86, 87]. Adhesion to endothelium is also enhanced [88, 89]. In contrast to neutrophils, intracellular killing seems to be enhanced [90]. Monocytes obtained from 24 diabetic patients produced similar amounts of TNF- α when compared to healthy controls when stimulated with lipopolysaccharide (LPS), but the IL-6 levels were higher in patients with type 1 diabetes [91].

Lymphocytes

Few studies have investigated the effect of diabetes on lymphocyte function. One measure of lymphocyte function is transformation in response to a mitogen or bacterial antigen. Studies containing acidotic patients appear to find that responses are diminished [92, 93] and that correction of the acidosis leads to prompt resolution of the defect [93], but more recent studies have found deficient proliferative T-cell responses, even in treated patients [82, 94]. Diabetic T-cells express higher levels of CD152, a downregulator of the immune response [95]. Three other studies failed to find a defect [67, 96, 97].

Humoral defects

In 1907, Da Costa and Beardsley [44, 98] found that sera from diabetes patients were less able to opsonise *S. aureus*

compared to sera from controls. In 1973, Farid and Anderson surveyed 46 patients and found that IgG levels were lower in insulin-treated diabetics, but not patients on oral treatments or diet alone. More recently, a study of 66 patients with type 1 diabetes demonstrated that total IgG levels were lower in uncontrolled diabetics as measured by HbA1c [99]. Also, the apparent defect in neutrophil phagocytosis appear to be humoral and not cellular in origin (see above).

The best evidence for a humoral defect in diabetic patients comes from vaccine studies. It was described as early as 1930 that deficient agglutinin responses are seen in the diabetic patients after subcutaneous typhoid vaccination [100, 101]. Multiple studies have shown that patients with diabetes are less likely to mount a protective antibody response to hepatitis B vaccination [102–105], leading some authorities to recommend routinely adding a booster dose to the standard regimen for patients with diabetes [102, 106]. The literature on influenza vaccination is more mixed (reviewed by Brydak and Machala [107]). Pozzilli et al. looked at 52 diabetic patients and found fewer activated lymphocytes in patients with type 2 diabetes following influenza vaccination, but no differences in antibody responses [108]. Muszkat et al., studying a more elderly population, found lower antibody responses in patients with type 2 diabetes [109]. Diabetes is also associated with a waning in the duration of protection afforded by tetanus vaccination, although the initial response appears to be normal [110, 111]. Diabetics appear to respond well to pneumococcal polysaccharide vaccine [112], although there are no studies studying the duration of protection in diabetic patients. There are no studies specifically linking humoral responses in sepsis to diabetes.

Complement abnormalities

Inherited deficiencies of component 4 (C4) have been implicated in the pathogenesis of type 1 diabetes [113–115], but whether this contributes to susceptibility to infection in type 1 diabetics is not known. By contrast, obesity and elevated insulin levels (as which occurs in type 2 diabetes) appear to be associated with elevations in C3 [116]. Karlsson et al., looking for biomarkers for maturity-onset diabetes of the young (MODY), found that complement C5 and C8 are both elevated in diabetes, regardless of aetiology [117], a possible mechanism for these abnormalities being that complement activation can be driven by glycated immunoglobulins [118]. One explanation for why diabetic sera are less able to opsonise bacteria may be that glucose attacks the thioester bond of complement C3 and prevents it from binding to the bacterial surface [119].

The role of hyperglycaemia

Warren noted in 1930 that the risk of infection in diabetic patients was inversely proportional to the degree of diabetes control [120], a finding replicated in 1982 by Rayfield [121]. The strongest evidence for the role of glycaemic control in preventing infection comes from the surgical literature. In a single-centre study of 8,910 cardiac surgery patients, glycaemic control in the immediate post-operative period was associated with a reduction in the risk of deep wound infection. In a multi-centre observational study of 55,408 diabetic post-surgical patients, the risk of post-operative infection was increased if serum glucose concentrations exceeded 8.3 mM [122]. Not all studies from the last 10 years have been able to replicate this finding: most notably, a carefully designed Australian study of 68 patients in the community failed to find a relationship between glycaemic control and infection risk [123], but the median HbA1c in that study was only 7.4%.

Diabetes medications and the immune response during sepsis

Insulin

Stegenga et al. dissected out the separate roles of insulin and glucose in infectious disease pathogenesis by studying healthy volunteers in whom insulin and glucose levels were maintained at preset levels for 6–8 h using tightly controlled infusions of insulin, glucose, somatostatin and glucagon, and intravenous *E. coli* LPS given to simulate sepsis [124]. Hyperglycaemia reduced neutrophil degranulation following LPS administration (independent of insulin concentration). Neither hyperinsulinaemia nor hyperglycaemia affected plasma cytokine levels (TNF- α , IL-6, IL-8 or IL-10) [125]. A second study using a similar design found intranuclear NF- κ B downregulation following insulin infusion [126]. In an intensive care unit (ICU) setting, high-dose insulin therapy was associated with the more rapid resolution of CRP levels and white blood cell counts, suggesting that an anti-inflammatory effect of insulin might be beneficial in sepsis [127].

Diabetic leukocytes display a reduced rate of glycolysis in vitro [128], which can be corrected by insulin supplementation [129]. The energy required for chemotaxis is supplied almost entirely by glycolysis [130], as their mitochondria are metabolically inactive [131] and insulin supplementation is able to reverse the chemotaxis defect seen in diabetes [66].

Clinical evidence for a benefit of intensive insulin therapy in sepsis [3, 132, 133] is contradictory. A single-centre study demonstrated a reduction in cardiothoracic

ICU mortality with intensive intravenous insulin [132], a second single-centre study at the same centre, but on the medical ICU, found no effect on mortality [133], and a subsequent multi-centre trial concluded that intensive insulin therapy increased mortality [3]. A recent meta-analysis concluded that, in critically ill patients, tight glucose control does not reduce mortality, but does increase the risk of severe hypoglycaemia [134].

Metformin

Metformin is prescribed as the first line treatment in Europe because it is associated with a 36% reduction in the all-cause mortality compared with diet alone [135]. There is little evidence for an immunomodulatory effect of metformin, although one study reported an association with reduced pro-inflammatory cytokine macrophage migration inhibitory factor (MIF) levels in obesity [136]. The main complication of metformin treatment in the context of sepsis is the risk of lactic acidosis [137], due to the metformin-mediated inhibition of pyruvate dehydrogenase promoting anaerobic respiration. This has prompted some authorities to recommend withdrawing metformin in sepsis [138].

Sulphonylureas

The best studied sulphonylurea in the context of sepsis is glibenclamide (= glyburide, United States adopted name [USAN]). Glibenclamide inhibits monocyte IL-1 secretion and has been used for over ten years in the laboratory specifically for that purpose [139]. The mechanism for this is the inhibition of inflammasome assembly [140], although the exact protein target has not been identified. Other sulphonylureas may not share this property [140]. Glibenclamide was associated with reduced inflammation and a halving in mortality in melioidosis, an infection strongly associated with diabetes [38]. Glibenclamide also has a direct pressor effect on vascular smooth muscle in vitro [141], and it has been proposed that glibenclamide therapy might find use as a vasopressor in septic shock [142]. Two small clinical studies in septic shock failed to find any effect on blood pressure [143, 144], although neither study was designed to look for an effect on mortality.

Thiazolidinediones

Observational studies of diabetic patients on the thiazolidinediones have demonstrated the suppression of nuclear factor- κ B [145, 146]. Rosiglitazone reduced renal injury [147] and improved other markers of end-organ damage [148] in murine sepsis models, while ciglitazone reduced bacterial burdens and local inflammation in a murine model of pneumococcal pneumonia [149], suggesting that thiazo-

lidinediones may find use as an adjunctive treatment for sepsis [150].

Conclusions

Infection remains an important cause of morbidity and mortality in diabetics, probably due to abnormalities of the host response, particularly in neutrophil chemotaxis, adhesion and intracellular killing. Humoral defects exist (both in antibody responses and complement opsonisation) and may explain earlier reports of a defect in phagocytosis, but are poorly studied in the pathogenesis of sepsis. Very little is known about the molecular mechanisms by which diabetes produces these effects, but the functional modification of host proteins and osmotic effects have both been proposed. For newly recognised phenomena such as neutrophil extracellular traps (NETs), we know almost nothing of the effect of diabetes, although preliminary evidence is that they may be important. Epidemiological studies of diabetes have produced conflicting results, and some of this difference may be explained by differences in the study design and epidemiological techniques used. Many studies have, so far, ignored the effects of drugs on the host response, and this omission may also explain the conflicting results in the literature.

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