

# Diabetes and Sepsis: Preclinical Findings and Clinical Relevance

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**B**ecause of its high prevalence and potential to alter critical elements of sepsis pathophysiology, diabetes is likely an important comorbid condition in this disease; yet the exact influence of diabetes on infection and the development of sepsis remain undefined. The aim of this article is to review evidence from preclinical and clinical trials to discuss the influence of diabetes on sepsis pathophysiology, susceptibility, and clinical outcomes.

## Evidence from animal and in vitro studies

**Diabetes has reduced bacterial clearance in animal models.** A series of studies investigated whether diabetic mice responded differently to sepsis compared with mice without diabetes. Thereby, 1–2 weeks prior to the experiment, diabetic conditions were induced with streptozotocin, a cytotoxic antibiotic substance isolated from *Streptomyces achromogenes*, which produces irreversible damage to pancreatic  $\beta$ -cells resulting in hyperglycemia. When mice were experimentally infected with group B streptococcal bacteria, diabetic mice had reduced clearance of bacteria and higher mortality rates (1). Remarkably, the increased mortality in diabetic animals occurred later in the course of the disease (after 72 h) and was associated with persistent bacteremia and prolonged sequestration of viable microorganisms in the hepatic and splenic reticuloendothelial system. Similar findings were reported after infecting diabetic mice with *Pseudomonas*

*aeruginosa*, where there was a direct association between increased numbers of microorganisms in liver, kidney, and spleen, and mortality (2). A more recent study investigated the host defense against tuberculosis (3). Diabetic mice had a significantly higher bacterial burden and increased inflammation in the lung. Production of  $\gamma$ -interferon (IFN- $\gamma$ ) was reduced by the presence of fewer antigen-responsive T-cells. Interestingly, Yamashiro et al. (4) expanded upon these findings by demonstrating increased numbers of live mycobacteria in lung, liver, and spleen, and lower IFN- $\gamma$  and interleukin (IL)-12 cytokine levels in diabetic mice. Importantly, the control of blood glucose levels by insulin therapy in this study resulted in improvement of the impaired host protection and T helper type 1-related cytokine synthesis.

**Hyperglycemia impairs polymorphonuclear neutrophil cell function and cytokine production.** Compelling evidence that diabetes impairs host defense is derived from in vitro studies demonstrating that important functions of the innate immunity are deficient in diabetic patients (Table 1). In vitro studies demonstrate that polymorphonuclear neutrophil (PMN) cells—the cornerstone of innate immunity—have impaired performance in the presence of hyperglycemia (5,6). In a series of experiments using blood from diabetic patients, Delamaire et al. (5) demonstrated a reduction of PMN cell function, including reduced endothelial adherence, chemotaxis, phagocytosis, and bacterial killing. Notably,

hyperglycemia was identified as the main mechanism responsible for the alteration in immune function, while type of diabetes, patient age, A1C level, and disease duration were not found to affect immune function. Another study (6) found that hyperglycemia induces an increase in intracellular calcium concentrations and thereby reduces ATP (adenosine triphosphate) levels, which in turn leads to reduced phagocytic ability of PMN cells. Correction of hyperglycemia led to a significant reduction in intracellular calcium levels, an increase in ATP content, and improved phagocytosis.

There is additional evidence that hyperglycemia interacts with different immune and hemostatic responses during experimental human endotoxemia (7,8). Stegenga et al. (7) found reduced neutrophil degranulation and exaggerated coagulation during human hyperglycemia, with a reversal of these effects when glucose was controlled with insulin therapy. In another study by Stegenga et al. (8), investigators found direct effects of hyperglycemia and insulin on gene expression during human endotoxemia. Hyperglycemia led to decreased lipopolysaccharides-stimulated mRNA levels of different proinflammatory cytokines (nuclear factor of  $\kappa$  light polypeptide gene enhancer in B-cells inhibitor  $\alpha$  [NF $\kappa$ B $\alpha$ ], interleukin-1 $\alpha$  [IL-1 $\alpha$ ], and chemokine [C-C motif] ligand 3 [CCL3]) compared with the euglycemic state, whereas insulin therapy influenced the expression of these inflammatory genes in the opposite direction.

Hyperglycemia has been shown to increase the duration of the cytokine response. A study (9) investigated the cytokine response to inoculation of bacteria in hyperglycemic mice 14 days after streptozotocin treatment. The initial cytokine response was similar, but diabetic mice showed a prolonged cytokine response over 3–5 days. The results were subsequently validated in a type 2 diabetes mouse model (*db/db*), where a prolonged production of the inflammatory cytokine tumor necrosis factor (TNF)- $\alpha$  was found. Other research has found that hyperglycemia may impair cytokine production locally, apart from the

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Table 1—Influence of diabetes/hyperglycemia on innate and adaptive immunity and other factors

System	Impaired organ/cell	Main effects	Selected references
Innate immunity			
Cellular	Neutrophils, monocytes, and macrophages	Dysfunction in adhesion, transmigration, chemotaxis, phagocytosis, microbial killing, apoptosis, and capability of antigen presentation	(5–8,11)
Humoral	Complement	Low or high levels of several complement components	(14)
	Cytokines	Baseline increased levels of TNF- $\alpha$ , IL-6	(8)
		Impaired cellular (in vitro) cytokine production of TNF- $\alpha$ , IL-1 $\beta$ , IL-8, IL-6, IFN- $\gamma$ at baseline and under LPS stimulation (increased or decreased)	(9)
		Impaired sequential patterns of cytokine production	(10)
		Impaired local cytokine production	(10)
Adaptive immunity			
Cellular	T-cells	Impaired response against different antigens	(12,13)
Humoral	Immunoglobulins	Quantitative defects: decrease in amount of global and specific antibodies	(14,53)
		Qualitative defects: glycosylation of antibodies, impaired humoral responses	(13,15)
Endothelium		Reduction in vasodilatation response; inflammatory endothelial activation: increased levels of adhesion molecules (VCAM-1, ICAM-1, E-Selectin)	(5,8,22–24, 54,55)
Coagulation		Induction of a procoagulant state: increased levels of TFP activity, FVIIa, FVIII, thrombin-antithrombin complexes, von Willebrand factor, TFPI activity, and a decrease in PAI-1 activity	(7,23,56)
Miscellaneous	Microbial colonization	Increased rate of colonization by pathogenic bacteria (nasal <i>Staphylococcus aureus</i> , pharyngeal gram negative bacteria, yeast)	
	Other organ systems	Diabetic gastropathy, urinary bladder dysfunction, reduced bronchial reactivity, and diminished bronchodilation	

Dysfunctions presented are obtained from literature based on diabetic patient and diabetic animal models. References regarding effect of hyperglycemia on healthy cells (in vitro) or healthy individuals (in vivo) have not been included. ICAM, intercellular adhesion molecule; LPS, lipopolysaccharide; PAI, plasminogen activator inhibitor; TFP, tissue factor procoagulant; TFPI, tissue factor procoagulant inhibitor; VCAM, vascular cell adhesion molecule.

systemic response. For example, diabetic women with bacteriuria present lower urinary levels of IL-6 and IL-8 (10). Production of macrophage-specific proteins

was also impaired in alveolar macrophages in diabetic mice challenged with intratracheal lipopolysaccharides (11).

**Diabetes has direct effects on the adaptive immune system.** In addition to PMN cell function and cytokine expression, diabetes has a direct inhibitory effect on the adaptive immune system. Spatz et al. (12) demonstrated a decreased proliferative response and delayed hypersensitivity reaction of T-cell function in diabetic patients. This was also true in animal models of diabetes, especially when the duration of diabetes was prolonged (13). Dysfunction of T-cells within these studies has been attributed to both a dysregulation between anti-inflammatory and proinflammatory cytokines as well as defects at the level of antigen-presenting cells (12,13). Diabetic mice display a lower production of IgM and IgG antibodies against a T-cell-dependent or -independent antigen (13). Additionally, a direct effect of high glucose concentration on lymphoid cell growth leading to early cell death was observed. Diabetic patients with poor long-term glucose control (elevated A1C levels) were found to have lower concentrations of circulating IgG antibodies (14). Other researchers found not only quantitative effects, but also qualitative defects. Lower functionality of IgG antibodies and impairment of antigen binding as a result of direct nonenzymatic glycation were displayed in diabetic patients (15). Still, an impact because of these antibody alterations has not yet been demonstrated, and diabetic patients seem to respond similarly to vaccinations compared with nondiabetic patients (16).

**Insulin may be protective to the host response.** The effect of insulin on the host response may be explained by two different mechanisms. First, insulin may prevent secondary adverse effects of high blood glucose on the immune function by correcting hyperglycemia as outlined above. Second, there may be other direct and indirect effects of insulin on the immune system. Indeed, previous studies have shown that insulin has strong anti-inflammatory properties and suppresses the production of a range of early proinflammatory substances including TNF- $\alpha$ , macrophage migration inhibitory factor, superoxide anions, and intranuclear NF- $\kappa$ B (17,18). In rat hepatoma cells, insulin was shown to directly inhibit cytokine-induced transcription of different acute phase proteins (19). Another study investigated possible anti-inflammatory effects of insulin in healthy subjects (17). Glucose concentrations were maintained stable at baseline values with dextrose and

insulin infusions (clamp), and this treatment was compared with saline infusions to study the direct effects of glucose. The investigators found a significant downregulation of intranuclear NF- $\kappa$ B and reactive oxygen species upon insulin infusion. Furthermore, soluble intercellular adhesion molecule-1, monocyte chemoattractant protein-1, and plasminogen activator inhibitor-1 levels dropped significantly following insulin infusion, while glucose or saline infusions showed no alterations. Another *in vitro* study found that insulin induces a shift in T-cell differentiation toward T helper type 2 cells. This resulted in a decrease in the interferon- $\gamma$ -to-IL-4 ratio by 33% (20). In addition, there was a significantly faster decrease in the levels of inflammatory mediators (i.e., C-reactive protein, white blood count) and resolution of hyperthermia in patients treated with high-dose intensive insulin therapy as compared with conventional-treated patients (21). Within this study, a multivariate-adjusted analysis suggested that the anti-inflammatory action on overall inflammation (as measured by C-reactive protein concentrations) largely explained the beneficial effects of intensive insulin therapy on morbidity and mortality.

**Diabetes induces endothelial dysfunction and a procoagulant state.** Diabetes and sepsis are both associated with activation of the vascular endothelium. In sepsis, activation of the endothelium occurs through a cascade of inflammatory mediators, which is crucial for the immune response. However, widespread excessive endothelial activation contributes to organ dysfunction as observed in severe sepsis and septic shock. Several of the endothelial pathways that are activated during sepsis are also found to be upregulated in diabetic patients without infection. Thus, for example, increased concentrations of plasma adhesion molecules (vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-Selectin) have been detected in patients and animal models with type 1 and type 2 diabetes (22). Obesity-related increases in proinflammatory cytokines induce an inflammatory cascade at the level of the endothelium in diabetic mice (23). Hyperglycemia and oxidative stress are other factors that directly activate cell adhesion molecules, pro- and anti-inflammatory molecules, and vascular endothelial growth factor signaling in human endothelial cells (24). Moreover, some studies have linked the extent of insulin resistance, as estimated with short insulin

tolerance tests, to increased levels of adhesion molecules (24). However, whether endothelial dysfunction is exacerbated in diabetic subjects compared with nondiabetic subjects during sepsis remains unclear. Emerging evidence suggests that insulin therapy has direct effects on the endothelium beyond the correction of hyperglycemia. A recent study including hyperglycemic patients with prolonged critical illness found that correction of hyperglycemia with intensive insulin therapy resulted in reduced endothelial cell activation demonstrated by a decrease in concentrations of circulating adhesion molecules (25). The main mechanism identified in this study was a direct suppression of the inducible nitric oxide synthase gene expression and lower circulating nitric oxide levels by insulin therapy. Similarly, insulin therapy increased arterial blood flow in the forearm (as measured by strain-gauge plethysmography) at 24 and 72 h after initiation of therapy in diabetic patients (26).

### Clinical evidence regarding infection susceptibility and outcomes

**Diabetic patients have increased susceptibility to infection.** Contrary to common belief, the association between diabetes and increased susceptibility to infection was not clear for a long time. Recent clinical reports, however, provide reasonably solid evidence that susceptibility to a variety of infections is increased in diabetic patients (Table 2A). In addition, several unusual infections such as malignant external otitis, rhinocerebral mucormycosis, emphysematous pyelonephritis, and emphysematous cholecystitis occur almost exclusively in diabetic patients (reviewed in [27] and [28]). Diabetes-related complications such as microvascular damage and neuropathy are important causes of skin ulceration, which likely predisposes patients to secondary skin infections. In a database study using patient data from 8,655 diabetic patients and demographically matched control subjects across the U.S., diabetes was identified as an important risk factor for skin infections including abscess and cellulitis (adjusted odds ratio [OR] 2.8) (29). Other infections such as urinary tract infections (UTIs) are also more common in diabetic subjects. A prospective case-control study in 218 diabetic patients and 799 sex-matched control subjects found a twofold increase in the relative risk of UTIs in diabetic women compared with control subjects

(30). Different potential mechanisms contributing to the increased susceptibility for UTIs in diabetic subjects were postulated. Higher glucose concentrations in urine may promote the growth of pathogenic bacteria and act as a culture medium. Genitourinary neurologic damage due to diabetes may result in dysfunctional bladder voiding and relative urinary retention, resulting in conditions conducive to UTI. Bacteriuria in patients with diabetes may result in severe infections such as emphysematous pyelonephritis, papillary necrosis, perinephric abscess, and candida pyelonephritis (reviewed in [27]).

In addition, there is evidence at a population level for increased incidence of infection in diabetic patients compared with nondiabetic subjects. A large cohort study using a Canadian database with >1 million patients found that nearly half of all people with diabetes had at least one hospitalization or physician claim for an infectious disease. In comparison with nondiabetic subjects, the risk ratio (RR) for acquiring an infection was 1.21 (99% CI 1.20–1.22) and the RR for an infectious disease-related hospitalization was 2.17 (2.10–2.23) (31). The in-hospital mortality in these hospitalized patients with diabetes, however, was not increased (RR 0.95 [95% CI 0.89–1.01] and 0.94 [0.87–1.01] for the 1999 and 1996 cohorts). A population-based longitudinal study from Europe with 10,063 patients also found an increased risk of infection-related hospitalization among diabetic subjects (32). Within this study, hyperglycemia carried an increased risk of infection as each 1 mmol/L increase in plasma glucose at baseline was associated with a 6–10% increased relative risk of pneumonia, UTI, and skin infection, after adjustment for other possible confounders. In addition, diabetic patients are at higher risk for the spread of tuberculosis (33) and systemic fungal infections such as peritonitis caused by back spread from vulvovaginal candidiasis or intracranial manifestations due to the spread from mucormycosis (reviewed in [27]). Diabetes also was previously found to be the single most important predisposing factor in true community-acquired candidemia (34).

Some methodological issues require consideration. Most studies did not have a detailed characterization of patients and the influence of diabetes-related factors such as type of diabetes, degree of obesity and insulin resistance, long-term glycemic

Table 2—Clinical studies investigating association between diabetes and susceptibility and outcome of infections

A. Studies investigating susceptibility of diabetic subjects to acquire infections						
Author	Year	Infection type	n	Study design	Main outcome measures	Main findings
Zhao (29)	2009	Skin infection	8,655	Longitudinal matched control	Incidence of skin infections	Higher risk for skin infections (adjusted OR 2.8)
Kornum (57)	2008	CAP	34,329	Population-based matched control	Pneumonia-related hospitalization	Increased risk for CAP-related hospitalization (RR 1.26 [95% CI 1.21–1.31])
Benfield (32)	2007	Infectious diseases	10,063	Prospective	Hospitalization, 28-day mortality	Higher risk for infection-related hospitalizations and UTI-related mortality (HR 3.9 [95% CI 1.2–12.7]); no difference in mortality because of sepsis, CAP, skin infection, and other infections
Boyko (30)	2005	UTI	1,017	Longitudinal matched control	Incidence of UTI	Higher risk of UTI (RR 1.8 [95% CI 1.2–2.7]) and antibiotic treatment (RR 2.3 [95% CI 1.3–3.9])
Thomsen (58)	2004	Pneumococcal bacteremia	598	Matched control	Bacteremia	Higher risk for pneumococcal pneumonia (OR 1.9 [95% CI 1.4–2.6])
Shah (31)	2003	Infectious diseases	513,749	Matched control	Hospitalization, mortality	Higher risk for hospitalization (RR 2.17 [95% CI 2.10–2.23]) and infection-related mortality (1.92 [1.79–2.05]); no difference in in-hospital mortality (1.05 [0.89–1.01] and 0.84 [0.87–1.01])
B. Studies showing an adverse association between diabetes and outcome						
Author	Year	Infection type	n	Study design	Main outcome measures	Main findings
Kornum (37)	2007	CAP	29,900	Population-based cohort	Complications, bacteremia, mortality	Higher mortality rates (1.2 [95% CI 1.1–1.3]), but similar rates of complications and bacteremia; mortality within patients with diabetes increased when initial glucose levels >14 mmol/L in multivariate analysis (adjusted MMR 1.46 [95% CI 1.01–2.12] compared with patients with glucose <6.1 mmol)
Thomsen (36)	2005	Enterobacteria bacteremia	1,317	National registry	Bacteremia, 30-day mortality	Higher risk for bacteremia (OR 2.9 [95% CI 2.4–3.4]) and a trend toward higher 30-day mortality (1.4 [1.0–2.0])
Fine (35)	1996	CAP	33,148	Meta-analysis	30-day mortality	Higher risk for mortality (OR 1.3 [95% CI 1.1–1.5])
C. Studies showing no or a protective effect of diabetes on outcome						
Author	Year	Infection type	n	Study design	Main outcome measures	Main findings
Stegenga (42)	2010	Septic shock within the ICU	830	Prospective study	28-day mortality	Equal mortality rate (DM 31.4%, non-DM 30.5%)

Table 2—Continued

C. Studies showing no or a protective effect of diabetes on outcome						
Author	Year	Infection type	n	Study design	Main outcome measures	Main findings
Vincent (41)	2010	Sepsis within the ICU	3,147	Prospective study	28-day mortality	Similar mortality after adjustment for severity of illness (HR 0.78 [95% CI 0.58–1.07])
Graham (46)	2010	Infectious diseases	1,509,890	Retrospective and prospective cohort	In-hospital mortality	Lower adjusted OR for mortality in both cohorts (0.75 [95% CI 0.74–0.76] and 0.88 [0.79–0.98])
Michalia (59)	2009	Blood stream infection	343	Prospective	In-hospital mortality	Similar mortality rates (25.8 vs. 23.0%, $P = 0.751$ )
Esper (43)	2009	Infectious diseases	12,500,000	National registry	Respiratory failure, in-hospital mortality	Lower risk for respiratory failure (9 vs. 14%, $P < 0.05$ ) and mortality (18.5 vs. 20.6%, $P < 0.05$ )
Tsai (40)	2007	Blood stream infection	839	Prospective	30-day mortality	No difference in mortality rates (HR 0.82 [95% CI 0.53–1.26])
McAlister (39)	2005	CAP	2,471	Prospective	Mortality, infection-related complications	No difference in mortality, but hyperglycemia had higher risk for both complications and mortality
Thomsen (45)	2004	<i>Pneumococcal</i> bacteremia	628	Population-based cohort study	30- and 90-day mortality	Lower 30- and 90-day mortality (11.1 vs. 16.5%, $P < 0.01$ and 16.0 vs. 19.5%, $P < 0.01$ )
Kaplan (38)	2002	CAP	623,718	National registry	In-hospital mortality	No difference in mortality rates, but hyperglycemia carried a higher risk for complications and mortality

Citations are in descending order of publication date. DM, diabetes; HR, hazard ratio.

control, and/or the presence of secondary micro- and macrovascular complications, making the independent relationship between diabetes and susceptibility a bit unclear. Moreover, epidemiologic studies carry the risk of selection bias as physicians caring for patients with diabetes may have had a lower threshold for hospital admission, leading to an overestimation of the risk for infection and infection-related hospitalizations.

**Influence of diabetes on sepsis outcomes.** A series of studies has investigated the influence of diabetes on outcome in patients with infections and sepsis. However, the findings are somewhat conflicting. While some studies show harm from diabetes (Table 2B) (31,32,35–37), other studies show no influence of diabetes on mortality rate (38–42), and yet a third group of studies show a protective effect (Table 2C) (43–46).

**Studies reporting increased mortality rates in diabetic patients with infection.** In 1995, a large meta-analysis including a total of 33,148 patients with community-acquired pneumonia (CAP) found an

increased mortality rate in patients with diabetes (summary OR 1.3 [95% CI 1.1–1.5]), which was comparable to the risk of male sex in this analysis (summary OR 1.3 [95% CI 1.2–1.4]) (35). However, this analysis did not adjust for confounding within the individual trials, and misclassification of hyperglycemic patients may have biased the results. Based on the results of a large prospective study, blood glucose level, but not diabetes, was later incorporated into the Pneumonia Severity Index, a prognostic score for 30-day mortality.

A retrospective matched case-control study using a large database of administrative data from Canada ( $n = 513,749$  in each group) reported a higher risk for infection-related mortality in diabetic patients (RR 1.9 [95% CI 1.8–2.1]) (31). Higher mortality rates in diabetic patients were also reported in several different European studies. Thomsen et al. (36) reported an increased risk for enterobacterial bacteremia for diabetic patients (adjusted OR 2.9 [95% CI 2.4–3.4]) using data of 1,317 case patients from Denmark

and a trend toward adverse prognosis for diabetic patients (adjusted OR for mortality 1.4 [95% CI 1.0–2.0]). Kornum et al. (37) examined whether diabetes increased the risk of death and complications following CAP in a population-based cohort of 29,900 patients in Denmark. He found adjusted 30- and 90-day mortality rate ratios of 1.2 (95% CI 1.1–1.3) and 1.10 (1.02–1.18) for diabetic patients, with no difference in terms of pulmonary complications or bacteremia. In addition, high glucose levels on admission were associated with death (adjusted 30-day mortality rate ratio for glucose level  $\geq 14$  mmol/L was 1.46 [1.01–2.12]). Importantly, after controlling for admission glucose level, diabetes was no longer associated with increased mortality (mortality rate ratio of diabetic patients with blood glucose levels of 6.1–11.0 mmol/L: 0.96 [0.69–1.35]). However, because hyperglycemia is such a prominent feature of diabetes, it is conceptually difficult to separate blood glucose levels from diabetes. In addition, for other infections such as tuberculosis, studies suggest that diabetic

patients have a higher risk for treatment failure and death (reviewed in [33]). Importantly, due to changes in oral absorption, decreased protein binding of drugs, and renal insufficiency with impaired drug clearance, it has been speculated that diabetes might alter the pharmacokinetics of antimicrobial drugs, which could lead to treatment failure or resistance (33).

**Studies reporting a lack of association between diabetes and mortality.** Other trials found no influence of diabetes on infection/sepsis outcomes (Table 2C) (38–46). For CAP, a large cross-sectional study of 623,718 Medicare recipients >65 years of age with a mortality rate of 10.6% found a harmful association between crude in-hospital mortality and diabetes (unadjusted OR 1.27 [1.23–1.31]). However, after adjusting for important confounders, diabetes was found to be mildly protective (adjusted OR 0.96 [0.93–0.99]) (38). The study does have limitations in its observational nature and that patients with diabetes were identified from hospital records, thus excluding diabetic patients who were never hospitalized. Similarly, a prospective Canadian study of 2,471 CAP patients found that hyperglycemia on admission was associated with a poor prognosis for both diabetic and nondiabetic patients, but overall a diabetes history did not predict in-hospital mortality (39). No significant influence on outcomes was also reported in a broader infectious disease population of consecutive patients with different types of community-acquired bacteremia in Taiwan (adjusted hazard ratio 0.82 [95% CI 0.53–1.26]) (40). Regarding the impact of diabetes on outcomes in higher severities of sepsis, namely critically ill patients with severe sepsis or septic shock, two very recent secondary analyses of prospective studies reported no difference in mortality rates (41,42).

#### Is diabetes protective during infection?

Some other reports suggest that diabetes may in fact have a protective effect during systemic infections. Postulated mechanisms for this include beneficial effects of exogenously administered insulin, prevention of acute lung injury (44), adaptation to previous oxidant stress, and an improved nutritional substrate in obese patients with diabetes (47).

In a large epidemiological study including 12,500,000 patients with sepsis from the U.S. National Hospital Discharge Survey, diabetic patients were less likely to develop acute respiratory failure (9 vs. 14%,  $P < 0.05$ ) and had a

significantly lower mortality rate (18.5 vs. 20.6%,  $P < 0.05$ ) (43). The same research group reported previously from an intensive care unit (ICU) cohort of septic shock patients that diabetes was associated with lower risk for acute respiratory distress syndrome (relative risk of diabetic subjects 0.53 [95% CI 0.28–0.98]) (44). The authors speculated that perhaps a blunted inflammatory response, an impaired neutrophil function, and altered neutrophil-endothelial interaction in diabetic subjects could protect against development of acute respiratory distress syndrome. A protective effect of diabetes on outcomes of critically ill patients was also suggested in a recent study (46) including data from parallel retrospective and prospective ICU patient cohorts. In both datasets, diabetes had a significantly lower adjusted OR for mortality (0.75 [95% CI 0.74–0.76] and 0.88 [0.79–0.98]). Finally, a population-based cohort study in Denmark (45) with 598 community-acquired pneumococcal bacteremia patients found a trend toward lower mortality rates in diabetic subjects (adjusted mortality rate ratio 0.6 [0.3–1.2]).

The discrepancies among these different diabetes outcome studies are possibly the results of a variety of methodological issues including selection bias, limited sample size, incomplete gathering of information concerning type of diabetes, metabolic control, secondary diabetes-related complications (i.e., chronic renal failure), and other diabetes-related factors. Unmeasured confounding may lead to an overestimation of diabetes-related risks. Another important confounding factor may be the change in paradigm concerning insulin therapy for hyperglycemia in all critically ill patients within the last decade based on randomized-controlled trials (48).

**Influence of hyperglycemia in diabetic and nondiabetic patients.** Hyperglycemia during critical illness and sepsis was previously proposed to be a beneficial, adaptive response to provide additional energy to organs that predominantly rely on glucose (48). However, clinical trials have demonstrated an association between hyperglycemia and adverse outcomes in septic patients with a U-shaped curve (49)—patients with low and high glucose levels have worse outcomes compared with those in the normal/moderate range. Notably, some studies demonstrated an association between hyperglycemia and increased mortality in nondiabetic patients, but not in diabetic

patients (37,46). These findings suggest that relatively acute hyperglycemia may have a different pathophysiologic effect in nondiabetic patients compared with patients with pre-existing diabetes. However, it remains unproven whether the association of hyperglycemia and mortality in nondiabetic patients is entirely because of the toxic effects of hyperglycemia or if hyperglycemia is simply a marker of stress and severity of disease.

**Influence of insulin therapy on outcomes.** To establish a causal relationship between tight glucose control with intensive insulin therapy and mortality, randomized controlled trials were performed in the critical care setting to assess the impact of preventing and/or treating hyperglycemia as compared with tolerating hyperglycemia. van den Berghe et al. (48) published the results from a large surgical ICU trial from Leuven, Belgium, where a lower overall mortality rate was found among patients treated with tight glucose control. Specifically, the greatest reduction in death was observed in patients with multiple-organ failure because of a proven septic focus. A reduced risk of secondary infection was also found in the insulin therapy group, with a 46% reduction in the risk of developing sepsis and a 35% reduction in the need for prolonged (>10 days) antibiotic therapy. van den Berghe et al. then conducted a subsequent trial in medical ICU patients that found a mortality reduction only in patients treated for three or more days (50). Here, the proportion of patients who had secondary bacteremia or received prolonged antibiotic therapy was not significantly reduced. Two more recent large-scale trials could not replicate the initial promising findings from Belgium and reported higher complication rates within the tight glucose control group (51,52). Brunkhorst et al. (51) included 537 patients with severe sepsis and found no difference in mortality but higher rates of hypoglycemia in intensively treated patients. In the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, Finfer et al. (52) included 6,104 medical ICU patients from 42 centers and reported higher mortality rates for patients in the intensive insulin treatment arm. Of note, patients with severe sepsis also tended to do worse when treated with intensive insulin therapy (OR 1.13 [95% CI 0.89–1.44]).

However, these trials differed substantially in terms of patient population,

nutritional support, and, most importantly, the level of glycemic control within the control arm: while the Leuven studies treated control patients at the renal threshold of 11 mmol/L, the subsequent trials targeted an intermediate blood glucose level of 8–10 mmol/L. Therefore, there is no definite answer of whether intensive glucose control has a long-term beneficial effect on the survival of septic patients, and the effect of insulin therapy in sepsis is not clearly delineated.

### Conclusions and future directions

It is relatively clear from preclinical studies that several features associated with diabetes influence host response to infection. Hyperglycemia impacts different components of the host response including function of immune cells and regulation of cytokines. Increased endothelial cell activation and procoagulant changes are found in diabetic subjects, but whether these changes alter endothelial function during sepsis remains unclear. Insulin therapy seems to have protective effects by both correcting hyperglycemia as well as through direct effects on cells. Clinical studies find a higher susceptibility for diabetic patients to acquire infections. However, whether diabetic subjects with infection have a worse prognosis is less clear. Clinical data show both extremes with some studies showing a harmful association between diabetes and mortality, while others show no association or a protective effect. In addition, the role for intensive insulin treatment in severely ill septic patients remains controversial.

The interpretation of preclinical and clinical data is challenging. Many basic science researchers use a hyperglycemia model where diabetes is induced in animals by destroying the pancreatic  $\beta$ -cells, similar to a type 1 diabetic patient with recent onset of disease. These models, however, may not unconditionally apply to type 2 diabetic patients. Other researchers reproduce type 2 diabetes by using models with leptin-deficient obese mice. These models may not accurately account for long-term complications of hyperglycemia such as arteriosclerosis and chronic renal failure. The clinical studies are often hampered by incomplete characterization of type and duration of diabetes, long-term metabolic control, degree of obesity and insulin resistance, and secondary micro- and macrovascular complications. It would also be interesting to investigate whether genetic

polymorphisms account for differences in susceptibility and outcomes as demonstrated for other diseases. Moreover, patients with diabetes may have a lower threshold for hospital admission, which could lead to a selection bias when reporting susceptibility rates and expected risks and outcomes.

Future research should focus on diabetes as a syndrome, taking into consideration important confounding factors such as hyperglycemia, obesity, secondary micro- and macrovascular complications, insulin therapy, endothelial dysfunction, and others to better understand the complex interplay of diabetes and sepsis in humans.

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