

# HbA1c is outcome predictor in diabetic patients with sepsis

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## Abstract

We have investigated predictive value of HbA1c for hospital mortality and length of stay (LOS) in patients with type 2 diabetes admitted because of sepsis. A prospective observational study was implemented in a university hospital, 286 patients with type 2 diabetes admitted with sepsis were included. Leukocyte count, CRP, admission plasma glucose, APACHE II and SOFA score were noted at admission, HbA1c was measured on the first day following admission. Hospital mortality and hospital length of stay (LOS) were the outcome measures. Admission HbA1c was significantly lower in surviving patients than in non-survivors (median 8.2% versus 9.75%, respectively;  $P < 0.001$ ). There was a significant correlation between admission HbA1c and hospital LOS of surviving patients ( $r = 0.29$ ;  $P < 0.001$ ). Logistic regression showed that HbA1c is an independent predictor of hospital mortality (odds ratio 1.36), together with female sex (OR 2.24), APACHE II score (OR 1.08) and SOFA score (OR 1.28). Multiple regression showed that HbA1c and APACHE II score are independently related to hospital LOS. According to our results, HbA1c is an independent predictive factor for hospital mortality and hospital LOS of diabetic patients with sepsis.

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## 1. Introduction

It is an accepted opinion that diabetes worsens prognosis of infection, particularly sepsis, although there is not much data published on this subject [1–3]. Reduced functional capacity of organ systems in diabetes and impaired immune mechanisms are probably most important causes.

Strict glucose control during critical illness improves outcome [4], supposedly by reducing acute glucose toxicity [5], and is now recommended treatment in sepsis [6]. However, influence of glycoregulation before sepsis occurs has not been investigated in relationship to outcome.

The most widely used marker of long-term glycoregulation is glycated haemoglobin (HbA1c) which reflects glucose levels 120 days before measurement [7]. It is formed in the process of non-enzymatic glycation, also responsible for the formation of advanced glycation end products (AGEs) found in elevated amounts in diabetes [8]. AGEs are associated with pathogenesis of diabetic complications through

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interaction with their receptors (RAGE) which can induce numerous changes linked to inflammation [9].

Our hypothesis was that HbA1c, since it reflects long-term regulation of blood glucose, might also represent changes in inflammatory response induced by hyperglycaemia and thus be associated with course and outcome of sepsis in diabetic patients.

## 2. Patients and methods

This was a prospective observational study set up in a university hospital that lasted 2 years (November 2003–December 2005). All adult patients with previously established diagnosis of type 2 diabetes mellitus (DM) admitted to medical wards or medical intensive care unit (ICU) because of sepsis were eligible for inclusion. Diagnosis of diabetes had to be established at least 6 months before the admission according to ADA criteria [10,11] by fasting plasma glucose ( $\geq 7.0$  mmol/l) or oral glucose tolerance test (2 h plasma glucose level  $\geq 11.1$  mmol/l). Sepsis was defined according to usual criteria: suspected or proven microbial aetiology of systemic inflammatory response syndrome defined by two or more of the following: (1) fever ( $>38$  °C) or hypothermia ( $<36$  °C); (2) tachypnea ( $>24$  breaths/min); (3) tachycardia ( $>90$ /min); (4) leukocytosis ( $>12,000/\mu\text{l}$ ) or leucopenia ( $<4000/\mu\text{l}$ ) or  $>10\%$  bands [12]. Exclusion criteria were: chronic renal failure (creatinine clearance lower than 30 ml/min), end-stage malignant disease and immunosuppressive therapy. Patients presenting with severe sepsis (sepsis with signs of organ dysfunction) and septic shock (arterial blood pressure  $<90$  or 40 mmHg lower than patient's normal blood pressure unresponsive to fluid resuscitation along with organ failure) at admission were also excluded.

Following parameters were noted at admission: leukocyte count, CRP and plasma glucose. To estimate severity of illness, sequential organ failure assessment (SOFA) score [13] and acute physiology and chronic health evaluation (APACHE II) score [14] were calculated for all patients at admission. HbA1c was measured on the first day following admission. Hospital mortality and hospital length of stay (LOS) were the outcome measures. Result of HbA1c measurement did not influence treatment in any way. All patients, regardless of previous hypoglycaemic therapy were treated

with insulin during the hospitalization when the plasma glucose exceeded 11.1 mmol/l.

Statistical analyses were performed using the MedCalc software. Results are presented as median with interquartile range (IQR). Wilcoxon and Kruskal–Wallis tests were used for group comparisons of continuous variables, Chi-square test for discrete variables. Multivariate analyses were performed to analyze predictors of hospital mortality and hospital LOS using logistic regression and multiple regression, respectively.  $P < 0.05$  was considered significant.

## 3. Results

During the study period 380 patients were considered for inclusion; 94 were excluded because they met one or more exclusion criteria and 286 patients were included. Basic characteristics of included patients are summarized in Table 1. Majority of patients ( $N = 251$ ; 87.8%) were initially admitted to medical wards. Overall hospital mortality was 21.6%, median LOS for surviving patients was 9 (IQR 7–13) days. The most common source of infection was the urinary tract (27.3%), followed by respiratory tract (25.2%), biliary tract (16.8%) and skin and soft tissue (13.6%). All other sources of infection combined were rare (8.4%) and for 25 patients (8.7%), the source of infection remained unknown. Majority of patients were treated with oral hypoglycaemic drugs (44.4%) prior to admission, least were treated with diet only (21.3%) before admission.

Patients who survived had significantly lower admission HbA1c values than those who died (median 8.2% versus 9.75%;  $P < 0.001$ ). HbA1c was not in correlation with admission plasma glucose, CRP, leukocyte count, age, APACHE II or SOFA score. HbA1c values did not differ significantly when comparing patients with different kinds of anti-diabetic treatment before admission ( $P = 0.222$ ).

Both APACHE II and SOFA score at admission were shown to be predictive of hospital mortality in univariate analysis. There was a strong correlation between admission APACHE II and SOFA scores

Table 1  
Biological and clinical characteristics of patients

	All patients	Survivors	Non-survivors	<i>P</i> -value
<i>N</i>	286	224 (78.3%)	62 (21.6%)	
Age (years)	61 (42–73)	61 (38–72)	66 (48–76)	0.008
Sex (females/males)	121/165	89/135	32/30	0.090
APACHE II	14 (8–20)	12 (8–17)	24 (16–29)	0.001
SOFA	4 (1–6)	3 (1–5)	7 (4–12)	0.001
CRP (mg/l)	150 (123–201)	152 (120–204)	145 (123–197)	0.582
HbA1c (%)	8.5 (7.0–10.3)	8.2 (6.75–9.9)	9.75 (7.7–11.6)	0.001
Plasma glucose (mmol/l)	10.5 (6.5–28.1)	11.3 (7.1–26.4)	13.2 (6.3–29.2)	0.278

**Table 2**  
Logistic regression for the risk of hospital mortality of sepsis in patients with diabetes

	Adjusted odds ratio	95% CI	P-value
Sex (female)	2.238	1.072–4.672	0.031
APACHE II (for each increase of 1 point)	1.076	1.014–1.143	0.016
SOFA (for each increase of 1 point)	1.276	1.115–1.459	<0.001
HbA1c (for each increase of 1%)	1.358	1.171–1.574	<0.001
Age (for each increase of 1 year)	1.019	0.999–1.041	0.679
Admission glucose (for each increase of 1 mmol/l)	1.031	0.833–1.282	0.768
Admission CRP (for each increase of 1 mg/l)	0.998	0.991–1.004	0.447

( $r = 0.77$ ;  $P < 0.001$ ). Age was also related with higher hospital mortality ( $P = 0.008$ ). Female patients had perceptibly higher mortality than males (26.4% versus 18.1%), but not significant ( $P = 0.090$ ) in univariate analysis.

In multivariate analysis by logistic regression, HbA1c was shown to be independent predictive factor of hospital mortality (Table 2). Female sex, APACHE II and SOFA scores were also shown to be independent predictors of mortality in the same analysis. Age, admission plasma glucose and CRP were not shown to be mortality predictors in the model.

Receiver operating curves (ROC) for HbA1c and APACHE II score as predictors of mortality are presented in Fig. 1. Area under ROC curve for HbA1c was 0.725 with sensitivity of 72.6% and specificity of 70.5% for 9% as the cut-off value. APACHE II score

**Table 3**  
Multiple regression for hospital LOS of diabetic patients with sepsis

	Coefficient	STD error	P-value
APACHE II score	0.179	0.047	<0.001
SOFA score	0.182	0.097	0.109
HbA1c	0.577	0.149	<0.001
Age	0.003	0.017	0.984
Admission glucose	−0.004	0.012	0.358
CRP	0.009	0.006	0.115

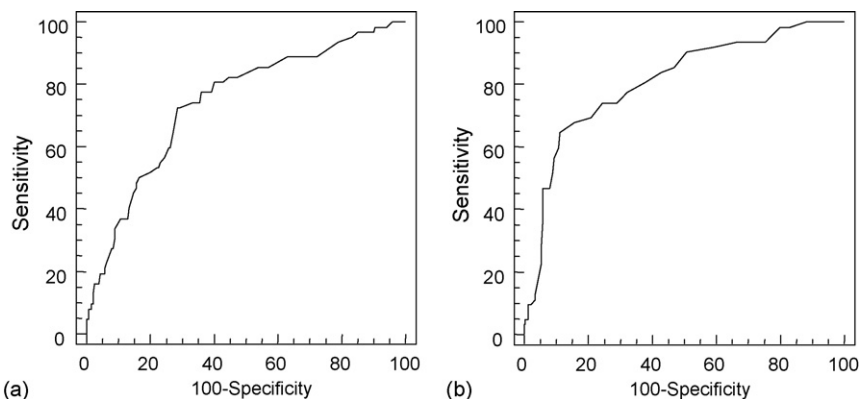
had better predictive values with area under ROC curve 0.809, sensitivity of 69.4% and specificity of 79% for 18 as the cut-off value.

A positive correlation was found between HbA1c levels at admission and hospital LOS of surviving patients ( $r = 0.29$ ;  $P < 0.001$ ). Hospital LOS was also in correlation with admission APACHE II score ( $r = 0.22$ ;  $P < 0.001$ ) and SOFA score ( $r = 0.19$ ;  $P < 0.001$ ).

Age, admission plasma glucose and CRP were not in correlation with hospital LOS. Univariate analysis also showed that there was no significant influence of sex ( $P = 0.326$ ) and source of infection ( $P = 0.632$ ) on length of hospitalization.

A multivariate analysis for hospital LOS has shown that HbA1c was independently associated with longer hospitalization ( $r = 0.577$ ;  $P < 0.001$ ). The model included other potential predictors of LOS (age, admission CRP, APACHE II and SOFA scores), but only APACHE II was shown to be independently correlated (Table 3). If APACHE II score was excluded from the model, SOFA score was shown to be associated with LOS ( $r = 0.182$ ;  $P < 0.001$ ).

There was no significant difference in hospital mortality or hospitalization length between patients



**Fig. 1.** (a) Receiver operating curve of HbA1c as predictor of hospital mortality for patients with diabetes. (b) Receiver operating curve of APACHE II score as predictor of hospital mortality.

with different sources of infection ( $P = 0.486$ ). No significant difference was found in mortality or length of hospitalization between patients with different kinds of anti-diabetic treatment previous to occurrence of sepsis. The three subgroups of patients did not differ in admission SOFA or APACHE II scores, age or sex distribution either.

#### 4. Discussion

Our results demonstrated that HbA1c is an independent prognostic factor for hospital mortality and hospital LOS for diabetic patients with sepsis. This was apparent for patients with diabetes regardless of source of infection or anti-diabetic treatment prior to admission. Plasma glucose levels at admission did not have prognostic value for mortality or LOS.

The two scores used in the study were both predictive of mortality and LOS in univariate analyses. In multivariate analyses, they were predictive of mortality independently of HbA1c, while only APACHE II score was independently predictive of LOS. A reason for that is probably strong correlation between the two scores, since SOFA was also predictive of LOS when APACHE II score was not in the model.

When evaluating severity of illness and prognosis of patients with sepsis, scoring systems such as APACHE II and SOFA scores are commonly used, but our results suggest that they do not differentiate patients with poorly regulated diabetes as those with increased risk. Even though APACHE II score evaluates chronic health, diabetes is not one of the chronic illnesses contributing to the score [14]. SOFA score evaluates only concurrent functional status of organ systems [13]. Neither of the scores was in correlation with HbA1c which supports thesis that poorly regulated glycaemia in diabetes as a risk factor is omitted in scoring.

A graphic illustration of HbA1c as a predictor of mortality, compared to APACHE II score (Fig. 1) demonstrates its potential value. Although comparison of the two is methodically not completely justifiable, since HbA1c is not meant to replace APACHE II score which is an established measure of severity of illness, it gives us an idea about the value of new parameter. Even though APACHE II score was shown to be slightly better predictor of mortality than HbA1c, usefulness of this parameter as an additional prognostic factor is obvious. Its most valuable use could be recognition of diabetic patients with increased mortality risk among those with similar severity scores.

Our study did not include non-diabetic patients with sepsis, so we can only discuss the importance of long-

term glucose control as a risk factor, not the disease itself. Previously published data however show increased risk for diabetics with sepsis, but with no regard to glucose regulation prior to infection.

The pathophysiological role of HbA1c molecules in sepsis is doubtful, given that HbA1c molecules are not themselves pathogenic. Reasons for increased mortality and longer hospitalization are probably in metabolic and inflammatory imbalance caused by prolonged hyperglycaemia which can be measured by HbA1c.

Hyperglycaemia influences numerous physiological processes important in systemic inflammatory response and sepsis. Changes in function of immune system [15,16], neutrophils [17,18], platelets [19,20] and coagulation [21,22] have been associated with hyperglycaemia.

One of the ways in which hyperglycaemia is associated with changes in inflammatory response is AGE formation, dependent of glucose levels similarly as the formation HbA1c [8]. AGE receptors (RAGEs) are involved in regulation of NF- $\kappa$ B transcription factor which is involved in initiation but also termination of inflammation [23]. Elevation of inflammatory markers was shown to be in correlation with HbA1c and AGE concentrations in diabetic patients without actual infection [24,25]. RAGE dependent modulation of inflammatory response has also been shown to negatively influence outcome of sepsis in animal model [26].

The correlation between HbA1c and AGE is not firmly established, although it would be logical to expect it considering their synthetic pathways. There are differing reports on such correlation [27–30], but relatively small numbers of patients were included in those studies. Since methods for determining levels of AGE are not widely available, it would be practical to use HbA1c as a rough estimate of overall glycation status, but definite evidence of correlation between HbA1c and AGE should exist before that.

Hyperglycaemia and consequent non-enzymatic glycation can affect soluble and cellular proteins [31,32] and change their function independently of AGE formation. All processes involved in the alterations of inflammatory and immune response have to be established in the future.

Influence of long-term control of glycaemia on chronic diabetic complications and consequent quality of life is beyond question. There is a large amount of evidence, notably from two major long-term multicentre studies, the diabetes control and complications trial (DCCT) and the United Kingdom prospective diabetes study (UKPDS), confirming the importance of

effective control of glycaemia, assessed by HbA1c in reducing chronic diabetic complications.

Influence of long-term glycoregulation to outcome of acute diseases has not been studied to a great extent. In acute myocardial infarction (AMI), HbA1c was not found to have prognostic value, whereas admission plasma glucose, as an indicator of sympathetic stimulation was shown to be associated with outcome [33]. Importance of acute inflammatory response in AMI is less significant, hence the changes in inflammatory response due to prolonged hyperglycaemia mentioned above play a minor role in influencing the outcome.

Our results emphasize the importance of long-term control of glycaemia in patients with diabetes who are inherently susceptible to infection. Proper glycoregulation could considerably contribute to reduction of mortality and length of hospitalization if sepsis occurs. Since sepsis is one of the leading causes of death, such reduction of mortality could have important influence on overall mortality of patients with diabetes.

There is no additional treatment that can be offered to patients with diabetes and sepsis in whom high HbA1c levels have been determined. Strict glucose control should be applied to all patients with diabetes and sepsis. However, those patients could be recognized as patients with increased risk and as such receive more consideration which could lead to earlier detection and dealing with complications.

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