Effect of hyperglycaemia on inflammatory and stress responses and clinical outcome of pneumonia in non-critical-care inpatients: results from an observational cohort study

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Abstract

Aims/hypothesis Despite the condition's high prevalence, the influence of hyperglycaemia on clinical outcomes in non-critical-care inpatients with infections remains ill defined. In this study, we analysed associations of glucose levels at admission and during initial inpatient treatment with the

inflammatory response and clinical outcome in community-acquired pneumonia (CAP) patients.

Methods This secondary observational analysis included 880 confirmed CAP patients. We used severity-adjusted multivariate regression models to investigate associations of initial and 96 h mean glucose levels with serially measured biomarker levels over 7 days (C-reactive protein [CRP], procalcitonin, white blood cell count [WBC], pro-adrenomedullin [ProADM]) and adverse clinical course (death and intensive-care unit admission).

Results In the 724 non-diabetic patients (82.3% of the study population), moderate or severe hyperglycaemia (glucose 6–11 mmol/l and >11 mmol/l, respectively) was associated with increased risk for adverse clinical course (adjusted OR [95% CI] 1.4 [0.8, 2.4] and 3.0 [1.1, 8.0], respectively) and with higher CRP, WBC and ProADM levels over 7 days ($p < 0.05$, ANOVA, all days). In diabetic patients ($n = 156$), no similar associations were found for initial hyperglycaemia, although mean 96 h glucose levels ≥ 9 mmol/l were associated with adverse clinical course (adjusted OR 5.4 [1.1, 25.8]; $p = 0.03$). No effect modification by insulin treatment was detected (interaction terms $p > 0.2$ for all analyses).

Conclusions/interpretation Initial hyperglycaemia in non-diabetic CAP patients, and prolonged hyperglycaemia in diabetic or non-diabetic CAP patients, are associated with a more pronounced inflammatory response and CAP-related adverse clinical outcome. Optimal glucose targets for insulin treatment of hyperglycaemia in non-critical-care settings should be defined.

Philipp Schuetz and Natalie Friedli contributed equally to this work

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Keywords Biomarker response · Diabetes · Glucose · Hyperglycaemia · Outcome · Pneumonia

Abbreviations

CAP	Community-acquired pneumonia
CRP	C-reactive protein
CURB65	Confusion, blood urea nitrogen, respiratory rate, blood pressure, age ≥ 65 years
ED	Emergency department
ICU	Intensive-care unit
PCT	Procalcitonin
ProADM	Pro-adrenomedullin
ProHOSP	Procalcitonin Guided Antibiotic Therapy and Hospitalisation in Patients with Lower Respiratory Tract Infections
WBC	White blood cell count

Introduction

Preclinical data suggest that hyperglycaemia has a profound influence on immune function. Hyperglycaemia interacts with components of the innate immune system *in vitro*, such as chemotaxis, phagocytosis and macrophage activation [1–3]. It also interacts with the adaptive immune system and directly inhibits T-lymphocyte, immunoglobulin and complement functions [4, 5]. In animal models of diabetes, hyperglycaemia was associated with decreased bacterial clearance and higher infection-related mortality [6].

Yet, results from studies of clinical outcomes in hyperglycaemic patients with severe bacterial infections outside critical care remain ambiguous. Some studies reported higher mortality rates among those with hyperglycaemia, while others found no influence of glucose homeostasis on outcomes (reviewed in [3]). For patients with community-acquired pneumonia (CAP), a recent large observational study found a step-wise increase in mortality with higher initial blood glucose levels [7]. Interestingly, certain investigators reported a protective effect of diabetes when examining infection outcomes [8–11]. Although the underlying mechanisms have not been well understood, it has been speculated that diabetic individuals with chronic hyperglycaemia are protected from toxic effects exerted by acute (stress) hyperglycaemia [3]. Trials regarding the prevention and treatment of hyperglycaemia have investigated the effects of tight glycaemic control on patient outcomes. While initial trials favoured tight, near euglycaemic, glucose control, more recent research found that prevention of hypoglycaemia and high glucose variability with more supraphysiological glucose target ranges (i.e. 6–10 mmol/l) ultimately may be the preferred strategy [12–14].

Importantly, the latter trials, as well as most research into the influence of glycaemia on the clinical outcome of bacterial infection, have been conducted in the critical-care setting, where insulin is given via infusion and patients are closely monitored. Few published studies have focused on inpatients with systemic infections in the non-critical-care setting, where

insulin is given subcutaneously and is less closely monitored. The influence of hyperglycaemia on clinical outcomes in this latter population therefore remains ill defined. A recent large study including patients with sepsis of varying infectious aetiology hospitalised in a non-critical-care ward found that higher glucose concentrations within the first 72 inpatient hours were associated with worse hospital outcomes in the non-diabetic population [15]. Although this association remained significant after adjustment for severity of illness, residual confounding could not be excluded. Interestingly, diabetic patients did not show the same association, which led us to hypothesise that because of chronic hyperglycaemic states, diabetic patients may have an altered response to glucose.

We therefore performed a secondary analysis of a completed prospective multicentre observational trial [16, 17] to study the association of initial or 96 h mean glucose levels with inflammatory and stress responses—reflected by serial measurement of four blood biomarkers—as well as with clinical outcomes in a large, well-characterised cohort of diabetic and non-diabetic patients with CAP.

Methods

Setting and study design This observational analysis included all patients with radiologically confirmed CAP participating in an investigator-initiated, prospective, randomised, controlled, multicentre antibiotic stewardship trial (Procalcitonin Guided Antibiotic Therapy and Hospitalisation in Patients With Lower Respiratory Tract Infections [ProHOSP] study) [17]. Details of the study design were published previously [16]. Briefly, of 1,825 screened patients with respiratory symptoms, this trial enrolled 1,359 consecutive patients with presumed lower respiratory tract infection presenting to emergency departments (EDs) in any of six tertiary care hospitals in Switzerland. A total of 237 patients were ineligible (included during earlier hospitalisations, not fluent in German, refused participation) and a total of 207 patients were excluded because of severe immunosuppression ($n=51$), concomitant infection ($n=29$), active drug abuse ($n=25$), hospital-acquired pneumonia ($n=45$), expected imminently terminal comorbidity ($n=45$) or other reasons ($n=12$). In all, 925 patients had a final diagnosis of CAP with an infiltrate in the initial chest x-ray, of whom 880 (95.1%) had an initial glucose measurement at ED admission and were thus eligible for this analysis.

The trial's main objective was to assess the effect of procalcitonin (PCT) monitoring on antibiotic consumption during the hospital stay and on clinical outcomes during the 30 days post admission. Patients were randomised 1:1 to use or non-use of serial PCT measurements as an input into the attending physicians' decision making regarding whether to start and how long to continue antibiotic therapy. Otherwise, patients with CAP in both study arms similarly received treatment for

pneumonia according to state-of-the-art clinical guidelines and local best practice. In both groups, hypoglycaemia was treated based on local insulin protocols. Oral glucose-lowering treatment was stopped and insulin treatment, mostly sliding-scale insulin with or without basal insulin, was started to keep glucose in the near-normal range (i.e. 5–10 mmol/l).

The study protocol was approved by all local ethical committees and written informed consent was obtained to collect blood on admission and during follow-up to measure biomarkers [17]. An independent monitoring committee assessed safety and adverse events during the trial. The study was registered in the ‘Current Controlled Trials Database’ (www.controlled-trials.com/ISRCTN95122877; identifier ISRCTN 95122877).

Hypothesis and general approach of this secondary analysis

We hypothesised that hyperglycaemia on admission and during inpatient treatment would be associated with a more severe (i.e. stressful) infectious course of CAP, as demonstrated by a more pronounced inflammatory and stress response and worse clinical outcome. To test this hypothesis, we first investigated the association of initial blood glucose concentrations with blood biomarker levels over 7 days, as well as with 30 day clinical outcomes. Based on the initial glucose concentration, patients were a priori classified as having normal levels (reference group, blood glucose <6 mmol/l), moderate hyperglycaemia (blood glucose 6–11 mmol/l) or severe hyperglycaemia (blood glucose >11 mmol/l), based on the classification in a recent publication [7]. We used blood levels of C-reactive protein (CRP), PCT, white blood cell count (WBC) and pro-adrenomedullin (ProADM) from the day of admission and days 3, 5 and 7 to reflect the inflammatory response. These markers are upregulated during systemic infections and correlate with inflammation (CRP, WBC), bacterial aetiology (PCT) and disease severity/mortality and other adverse outcome risk (ProADM) [18–22]. For the purpose of this study, we defined ‘adverse clinical course’ as all-cause mortality, intensive-care unit (ICU) admission, or both, during a 30 day follow-up.

In a second step, we assessed the association of mean glucose levels over the first 96 h of the hospital stay with biomarker levels and clinical outcomes as defined above. For this latter analysis, we focused on patients treated in the non-critical-care hospital ward with increased initial glucose levels (>7.5 mmol/l) ($n = 161$). Due to this elevation, all such patients had repeated preprandial glucose measurements over the hospital course. Based on the mean glucose levels over 96 h, we classified patients as having normal glucose levels (reference group, blood glucose <9 mmol/l) or hyperglycaemic levels (blood glucose ≥ 9 mmol/l). This a priori classification corresponds to guidelines by the Endocrine Society recommending that in-hospital glucose values outside critical care should be maintained in the range of 7.8–10 mmol/l [23].

Selection of participants, data collection and processing

Patients eligible for this analysis were aged 18 years or older and were admitted from the community or a nursing home with CAP of less than 28 days’ duration. CAP was defined by the presence of at least one respiratory symptom plus at least one finding during auscultation, or one sign of infection independent of antibiotic pretreatment, and a new infiltrate on chest radiograph [24–27]. Exclusion criteria were applied: inability to give written informed consent because of language restriction or severe dementia; active intravenous drug use; severe immunosuppression other than corticosteroid use; imminently life-threatening medical comorbidities; patients with hospital-acquired pneumonia (pneumonia onset >48 h after the study hospital admission or hospitalisation within 14 days before ED presentation in ProHOSP) and patients with chronic infections necessitating long-term antibiotic treatment.

We classified patients as having pre-existing diabetes based on self-report or medical record documentation, or both. We recorded initial blood glucose values in the ED in all patients. We also recorded subsequent preprandial glucose measurements during the first 96 h of the hospital stay. For the time course, we calculated the mean glucose concentration (mean glucose) assuming a linear trend between measurements and using all available measured preprandial blood glucose concentrations within the first 96 h.

Statistical analysis To describe the populations, values are expressed as means with SDs and frequencies as percentages or counts, as appropriate. We investigated the association of admission glucose and 96 h mean glucose values and outcomes in patients with or without diabetes. We stratified our analysis by presence of diabetes because previous studies suggested a differential impact of glycaemic states on clinical outcomes of severe bacterial infection in patients with or without that diagnosis. Admission glucose levels were analysed as categorical variables based on the following blood glucose ranges: <6 mmol/l (reference group), 6–11 mmol/l (mild hyperglycaemia) and >11 mmol/l (severe hyperglycaemia). These cut-offs were predefined based on a recent large CAP study [7]. For mean 96 h glucose levels, we used only one cut-off (i.e. 9 mmol/l, the median level) due to the low number of patients included. To assess whether insulin treatment interacts with the association of blood glucose and outcome (effect modification), we also included interaction terms in the statistical models.

The inflammatory response was graphically demonstrated by mean blood levels of four predefined biomarkers on the day of admission, and on days 3, 5 and 7. Association of glucose ranges and adverse outcomes was analysed using logistical regression with report of ORs and 95% CIs. We adjusted the analysis for CAP severity at presentation using the initial confusion, blood urea nitrogen, respiratory rate, blood pressure, age ≥ 65 years (CURB65) score, which is

well-validated for such classification [28]. All analyses were performed with Stata12 (StataCorp, College Station, USA).

Results

Baseline characteristics Of 880 patients with a definitive diagnosis of CAP and initial blood glucose measurements, 156 (17.7%) had a history of diabetes according to self-report, medical records, or both, overwhelmingly type 2 (98.1%). Baseline characteristics of the study cohort according to diabetes history are presented in Table 1. Compared with non-diabetic patients, diabetic patients were older, had more frequent cardiovascular comorbidities, a higher BMI and higher mean ($\pm$ SD) glucose levels at admission (11.1 ± 5.3 mmol/l vs 7.1 ± 2.0 mmol/l, $p < 0.0001$). On admission, the markers of inflammation/infection CRP, WBC and PCT were similar in diabetic and non-diabetic patients and ProADM was significantly higher in the diabetic population.

Association of initial glucose category with outcome In total, 112 patients (12.7%, 95% CI 11.9%, 17.8%) had a complicated course, including death ($n=46$), ICU admission ($n=80$), or both ($n=14$), during the 30 day follow-up. Overall, there was no difference in mortality or adverse clinical course between diabetic and non-diabetic patients (respectively, 5.7% vs 5.1%, $p=0.74$ and 16.3% vs 12.0%, $p=0.17$) (Table 1).

In non-diabetic patients, there was a stepwise increase in the adverse clinical course rate in patients with moderate or severe admission hyperglycaemia compared with the reference group (Fig. 1a). This pattern was also true for the endpoints of ICU admission or mortality (Table 2). Logistical regression confirmed the increased risk associated with severe admission hyperglycaemia, with respective ORs of 4.0, 4.4 and 4.1 for ICU admission, mortality and the combined endpoint of adverse clinical course within 30 days in non-diabetic patients. These associations also held true in a regression analysis adjusted for initial CAP severity using the CURB65 score, with respective ORs of 3.0, 2.9 and 3.0.

In contrast, in diabetic patients risks were similar in the different admission glucose range groups and logistical regression analysis did not show significant associations for any of mortality, ICU admission or adverse clinical course (Table 2).

Association of initial glucose category with course of biomarker levels Figure 2 shows levels of the inflammation/infection biomarkers WBC, CRP, PCT and ProADM on admission and on days 3, 5 and 7. In non-diabetic patients, higher admission glucose ranges were associated with higher initial and follow-up CRP, WBC and ProADM levels for all days ($p < 0.05$, ANOVA), but not with PCT levels at these measurement points ($p \geq 0.05$, ANOVA). In the diabetic

subgroup, no significant differences were found, except for CRP on the day of admission ($p < 0.05$).

Association of 96 h mean glucose levels with outcome and inflammatory response We also investigated the association of mean blood glucose levels over the first 96 inpatient hours with clinical outcomes as well as biomarker levels. Patients had preprandial glucose measurements taken routinely with a mean ($\pm$ SD) of 2.8 (± 0.80), 2.7 (± 1.2), 2.5 (± 1.3) and 2.2 (± 1.4) measurements taken, respectively, on days 1, 2, 3 and 4. A total of 70% of these patients were treated with subcutaneous sliding-scale insulin regimens, with a mean ($\pm$ SD) dose of 21 (± 22), 22 (± 23), 22 (± 24) and 23 (± 23) U, respectively, on days 1, 2, 3 and 4.

The risk for adverse outcome increased with increasing glucose levels, which, however, was more pronounced in the diabetic patient population ($p=0.015$) and non-significant ($p=0.204$) in the non-diabetic population (Fig. 1c, d). These observations held true in logistical regression analysis, where a mean glucose level of ≥ 9 mmol/l during the first 96 h of hospitalisation was found to be associated with increased risk of adverse clinical course in diabetic patients (adjusted OR 5.4, 95% CI 1.1, 25.8; $p=0.03$) (Table 3). Again, this association was non-significant in patients without diabetes (adjusted OR 1.8, 95% CI 0.4, 7.2; $p=0.43$). We did not find evidence for effect modification by insulin treatment ($p > 0.2$ for interaction in diabetic and non-diabetic patients).

Figure 3 shows the kinetics of the four blood biomarkers in patients stratified by mean 96 h glucose range (≤ 9.0 vs ≥ 9.0 mmol/l) and diabetes status. In diabetic patients, significant differences were found for CRP, with consistently higher levels in hyperglycaemic patients ($p < 0.05$, ANOVA, for all measurements), and for WBC on days 5 and 7 ($p < 0.05$, ANOVA, for both measurements). For non-diabetic patients, no significant differences were found ($p > 0.05$, ANOVA). Again, there was no evidence for effect modification of insulin treatment on the association of glucose range and biomarker level on any of the days ($p > 0.2$ for all interactions in diabetic and non-diabetic individuals).

Discussion

The key findings of this study are threefold. First, in non-diabetic patients with CAP in the non-critical-care setting, initial hyperglycaemia was associated with a more pronounced inflammatory response as demonstrated by the evolution of biomarker levels over 7 days and adverse 30 day outcomes. These findings were independent of severity of illness, arguing against an exclusive stress-dependent hyperglycaemia, and in favour of the potential toxic effect of glucose elevation. Second, the same association of admission hyperglycaemia and outcome was not found in the diabetic

Table 1 Patient characteristics by diabetes status

Characteristic	Non-diabetic patients (<i>n</i> = 724)	Diabetic patients (<i>n</i> = 156)	<i>p</i> value
Demographic characteristics			
Age, years, mean $\pm$ SD	67 $\pm$ 19.1	74 $\pm$ 10.4	<0.0001
Male sex, % (<i>n</i>)	57.2 (414)	66.7 (104)	0.029
Serum glucose level on admission, mean $\pm$ SD			
Initial mean glucose level, mmol/l	7.1 $\pm$ 2.0	11.1 $\pm$ 5.3	<0.0001
Initial glucose range, % (<i>n</i>)			<0.001
Euglycaemia, <6.0 mmol/l	27.6 (200)	10.3 (16)	
Moderate hyperglycaemia, 6–11 mmol/l	68.4 (495)	48.7 (76)	
Severe hyperglycaemia, >11 mmol/l	4.0 (29)	41.0 (64)	
Coexisting illnesses, % (<i>n</i>)			
Chronic heart failure	16.3 (118)	20.5 (32)	0.204
Coronary arterial disease	17.3 (125)	33.3 (52)	<0.0001
Cerebrovascular disease	8.4 (61)	11.5 (18)	0.217
Chronic renal failure	18.1 (131)	40.4 (63)	<0.0001
Peripheral arterial disease	4.3 (31)	9.0 (14)	0.016
Cardiovascular risk factors			
Current or former nicotine use, % (<i>n</i>) ^a	27.5 (193)	17.8 (27)	0.013
Pack years, mean $\pm$ SD	38.6 $\pm$ 27.6	42.8 $\pm$ 30.5	0.3193
BMI, kg/m ² , mean $\pm$ SD	25.2 $\pm$ 5.1	28.5 $\pm$ 5.9	<0.0001
BMI >25 kg/m ² , % (<i>n</i>)	56.2 (407)	76.3 (119)	<0.0001
Clinical history, % (<i>n</i>) ^a			
Antibiotic pretreatment on presentation	26.3 (189)	19.4 (30)	0.072
Cough	86.2 (598)	82.8 (125)	0.283
Dyspnoea	77.9 (538)	83.0 (122)	0.167
Fever or chills	68.6 (493)	60.7 (94)	0.057
Clinical findings			
Systolic blood pressure, mmHg, mean $\pm$ SD	133 $\pm$ 22.8	135 $\pm$ 24.4	0.292
Diastolic blood pressure, mmHg, mean $\pm$ SD	74 $\pm$ 14.8	73 $\pm$ 14.5	0.3116
Heart rate, beats/min, mean $\pm$ SD	96 $\pm$ 19.3	96 $\pm$ 18.5	0.9638
Treatment site, % (<i>n</i>)			
Inpatient	90.1 (652)	96.2 (150)	0.015
30 day outcome, % (<i>n</i>)			
Adverse clinical course: all-cause death + ICU admission ^a	12.0 (87)	16.3 (25)	0.173
All-cause death ^a	5.1 (37)	5.7 (9)	0.737
ICU admission	8.4 (61)	12.2 (19)	0.139
Initial laboratory findings, mean $\pm$ SD			
PCT, μ g/l	4.3 $\pm$ 15.3	4.2 $\pm$ 8.2	0.9462
CRP, nmol/l	1,714 $\pm$ 1,247	1,647 $\pm$ 1,190	0.5609
WBC, 10 ⁹ /l	13.6 $\pm$ 7.2	13.8 $\pm$ 8.8	0.8293
ProADM, nmol/l	1.5 $\pm$ 1.5	2.1 $\pm$ 1.6	<0.001

^a Data not available for some patients

population. Third, persistent hyperglycaemia over the first 96 h of inpatient treatment was associated with adverse clinical outcome and a more pronounced CRP response mainly in the diabetic population and independent of severity of illness.

Optimal glucose targets in the non-critical-care hospital setting have not been well defined. Still, guidelines of the

Endocrine Society and other organisations recommend maintaining in-hospital glucose values in the range of 7.8–10 mmol/l [23]. This recommendation is mainly based on several large studies, principally from the critical-care setting, reporting associations of elevated initial blood glucose levels and increased adverse outcome risk in postoperative patients and patients with sepsis [3, 15, 29–32]. Aligned with these

Fig. 1 Risk for 30 day adverse clinical course according to glucose level on admission (**a**) without diabetes ($p=0.014$) and (**b**) with diabetes ($p=0.895$), and 96 h mean glucose level (**c**) without diabetes ($p=0.204$) and (**d**) with diabetes ($p=0.015$)

observations, our study expands the evidence to patients with CAP. Our data show a strong association between

increased glucose levels and adverse outcome, which is largely independent of pneumonia severity as measured by the CURB65 score.

In a previous study [15] involving sepsis patients hospitalised in medical wards, an association between increased blood glucose values over 72 h and higher mortality was found in non-diabetic patients. In the current report (using 96 h rather than 72 h values), this association was not significant. This lack of significance may be explained by the relatively low number of non-diabetic patients with increased initial blood glucose levels who were included in this analysis (i.e. by low statistical power). Still, prolonged hyperglycaemia over 96 h was associated with adverse outcomes in the diabetic population. This suggests that diabetic patients may tolerate sporadic hyperglycaemia better than non-diabetic patients, whereas prolonged hyperglycaemia increases the risk for treatment failure in the diabetic population.

Preclinical studies have linked hyperglycaemia to different physiological defects such as platelet malfunction, endothelial dysfunction, impaired chemotaxis, diminished granulocyte adherence, decreased phagocytosis and reduced microbicidal capacity (reviewed in [3]). In vitro studies have shown that

Table 2 Association between glucose range on admission and 30 day outcomes by diabetes status

Diabetes status/outcome	Univariate		Multivariate ^a	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Non-diabetic patients				
Adverse clinical course (ICU admission, all-cause death or both)				
Euglycaemia (<6.0 mmol/l)	Reference		Reference	
Moderate hyperglycaemia (6–11 mmol/l)	1.5 (0.9, 2.7)	0.133	1.4 (0.8, 2.4)	0.283
Severe hyperglycaemia (>11 mmol/l)	4.1 (1.6, 10.6)	0.004	3.0 (1.1, 8.0)	0.032
ICU admission				
Euglycaemia (<6.0 mmol/l)	Reference		Reference	
Moderate hyperglycaemia (6–11 mmol/l)	1.9 (1.0, 3.9)	0.064	1.8 (0.9, 3.6)	0.116
Severe hyperglycaemia (>11 mmol/l)	4.0 (1.2, 12.6)	0.019	3.0 (0.9, 9.6)	0.072
Death				
Euglycaemia (<6.0 mmol/l)	Reference		Reference	
Moderate hyperglycaemia (6–11 mmol/l)	1.0 (0.5, 2.3)	0.934	0.9 (0.4, 2.0)	0.745
Severe hyperglycaemia (>11 mmol/l)	4.4 (1.4, 14.3)	0.013	2.9 (0.8, 9.9)	0.090
Diabetic patients				
Adverse clinical course (ICU admission, all-cause death or both)				
Euglycaemia (<6.0 mmol/l)	Reference		Reference	
Moderate hyperglycaemia (6–11 mmol/l)	1.4 (0.3, 7.1)	0.45	1.6 (0.3, 8.0)	0.55
Severe hyperglycaemia (>11 mmol/l)	1.3 (0.3, 6.6)	0.31	1.6 (0.3, 8.4)	0.56
ICU admission				
Euglycaemia (<6.0 mmol/l)	Reference		Reference	
Moderate hyperglycaemia (6–11 mmol/l)	1.0 (0.2, 5.4)	0.943	1.1 (0.2, 5.7)	0.888
Severe hyperglycaemia (>11 mmol/l)	0.9 (0.2, 4.6)	0.860	1.0 (0.2, 5.5)	0.996
Death				
Euglycaemia (<6.0 mmol/l)	Reference		Reference	
Moderate hyperglycaemia (6–11 mmol/l)	1.1 (0.1, 9.7)	0.961	1.1 (0.1, 10.9)	0.906
Severe hyperglycaemia (>11 mmol/l)	0.7 (0.1, 7.6)	0.798	0.9 (0.1, 9.9)	0.951

^a Adjusted for CURB65

Fig. 2 Association between serum glucose level on admission and selected inflammation/infection biomarkers during hospitalisation: CRP (**a**), WBC (**c**), PCT (**e**) and ProADM (**g**) in non-diabetic patients and CRP (**b**), WBC (**d**), PCT (**f**) and ProADM (**h**) in diabetic patients. Black lines, euglycaemia; grey lines, moderate hyperglycaemia; dashed lines, severe hyperglycaemia. In non-diabetic patients, higher admission glucose ranges were significantly associated with higher initial and follow-up levels of CRP, WBC and ProADM for all days ($p < 0.05$, ANOVA). No differences were found for PCT on any day ($p \geq 0.05$, ANOVA). In the diabetic population, no significant differences were found for any marker on any day ($p \geq 0.05$, ANOVA), except for CRP on the day of admission ($p < 0.05$, ANOVA)

these effects are at least partly reversible when glucose is lowered to normal values. Within our analysis, we investigated the effects of hyperglycaemia on the kinetics of different

blood biomarkers of inflammation and infection. Specifically, we investigated levels of CRP and WBC, two markers of inflammation and stress, and of PCT and ProADM, two

Table 3 Association of mean glucose during the first 96 inpatient hours and adverse clinical course (ICU admission, all-cause death or both) by diabetes status

Risk for adverse clinical course	Univariate		Multivariate ^a	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Non-diabetic patients				
Risk per 10% increase in 96 h mean glucose level (decile)	1.1 (0.9, 1.4)	0.395	1.1 (0.9, 1.4)	0.514
Hyper- vs euglycaemia				
Euglycaemia (≤ 9.0 mmol/l)	Reference		Reference	
Hyperglycaemia (≥ 9.0 mmol/l)	2.0 (0.5, 7.3)	0.3	1.8 (0.4, 7.2)	0.431
Diabetic patients				
Risk per 10% increase in 96 h mean glucose level (decile)	1.4 (1.1, 1.8)	0.015	1.4 (1.1, 1.9)	0.014
Hyper- vs euglycaemia				
Euglycaemia (≤ 9.0 mmol/l)	Reference		Reference	
Hyperglycaemia (≥ 9.0 mmol/l)	5.7 (1.2, 27.1)	0.027	5.4 (1.1, 25.8)	0.033

^a Adjusted for CURB65

Fig. 3 Association between biomarkers and serum glucose during the first 96 inpatient hours. CRP (**a**), WBC (**c**), PCT (**e**) and ProADM (**g**) in non-diabetic patients and CRP (**b**), WBC (**d**), PCT (**f**) and ProADM (**h**) in diabetic patients. Black line, mean glucose <9 mmol/l; dashed line, mean glucose ≥ 9 mmol/l. In diabetic patients, significant differences were found for CRP on all days ($p < 0.05$, ANOVA), and for WBC on days 5 and 7 ($p < 0.05$, ANOVA). For non-diabetic patients, no significant differences were found for any marker on any day ($p > 0.05$, ANOVA)

circulating substances referred to as ‘hormokines’, since they normally follow hormonal behaviour (i.e. expression in neuroendocrine cells and systemic action) but in response to inflammation or other physiological stress follow cytokine behaviour (i.e. expression in numerous cell types throughout the body and local action) [33]. To our knowledge, this is the first report linking hyperglycaemia to a more pronounced inflammatory response in non-diabetic individuals, as demonstrated by increased levels of CRP, WBC and ProADM over the first 7 days of inpatient treatment.

From our analysis, the question of association vs causation cannot conclusively be answered. Severe illness and systemic infection are associated with an increase in pro-inflammatory cytokines, such as IL-1, IL-6 and TNF- α among others [34]. These cytokines trigger the expression of CRP, PCT, ProADM and WBC as part of the immune response [35–41]. Also, severe illness and systemic infection activate the sympatho-adrenal system and the hypothalamic–pituitary–adrenal axis

[42–45], which causes peripheral insulin resistance, ultimately leading to hyperglycaemia [42]. To study the effects of hyperglycaemia on outcomes, we adjusted the analysis for CAP severity. Still, residual confounding is possible, and only an interventional study can definitively prove causation, were such a study to observe lower biomarker levels in patients treated with insulin compared with a control group.

In diabetic patients, no association between initial blood glucose level or blood glucose level over the first 96 h of hospitalisation and inflammatory biomarkers was found. This may be explained by the fact that insulin use in diabetic patients suppresses the production of nuclear factor kappa-light-chain-enhancer of activated B cells, which modulates the expression of the pro-inflammatory cytokines, such as IL-1 and TNF- α , ultimately leading to reduced blood levels of CRP, PCT, ProADM and leucocytes [46–48]. In our analysis, however, we did not find any evidence for effect modification of insulin treatment and biomarker levels. Yet, this observation may be due to the

small sample and lack of standardisation regarding insulin treatment. Further, diabetic patients are frequently treated with statins, which have been associated with reduced inflammation [49]. Finally, it is possible that in diabetic individuals with chronic hyperglycaemia, acutely increased glucose levels do not cause the same toxic effects as in non-diabetic individuals.

The present study has several limitations. First, this is a secondary analysis of a prospective trial and is thus hypothesis-generating rather than definitive. There is a risk for selection bias because the most severely ill patients with possible imminent death may not have been included in ProHOSP, or may not have had initial blood glucose measurement due to their condition. There is also a risk for confounding by indication regarding the repeated glucose measurement, with more frequent measurements in patients with higher levels. We also assumed a linear trend between measurements, which may underestimate average glucose levels. Optimally, continuous glucose measurement would be used to assess the true glucose mean. Second, classification of diabetes status was based on self-report and information from medical charts. We were not able to gather data about diabetes severity, long-term glycaemic control (e.g. HbA_{1c} levels) or the time since diabetes diagnosis. Most importantly, our analysis shows associations but does not prove causation and thus it remains unclear whether correction of hyperglycaemia would reverse the observed effects on inflammatory response and clinical outcome. Finally, unlike other investigations, such as the RABBIT 2 surgery trial [50], we did not find any evidence for effect modification of insulin treatment on the association of glucose and clinical outcome, or biomarker levels. However, our sample may have been too small and lacked statistical power to detect such effects. Also, we were unable to compare the effect of different insulin regimens, as insulin regimens were up to the discretion of treating physicians and thus not standardised.

In conclusion, this analysis links initial hyperglycaemia in non-diabetic CAP patients, and prolonged hyperglycaemia in both diabetic and non-diabetic CAP patients, to a more pronounced inflammatory response and adverse CAP-related clinical outcome. We found no evidence that insulin treatment would affect these associations. Although critical-care trials have produced controversial data about optimal glucose-lowering strategies, our data lend support to correcting hyperglycaemia—at least to levels of 9–10 mmol/l or below. Yet, optimal glucose targets for insulin treatment of hyperglycaemia for diabetic and non-diabetic patients in the non-critical-care setting need to be better defined.

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Contribution statement PS, NF, EG, AK and SH had the idea for and initiated the substudy, performed the statistical analyses and developed the initial draft of the manuscript. MC-C, RT, CHo, CHe, WZ and BM made substantial contributions to the conception and design of the initial trial and the acquisition of clinical data. All authors amended and commented on the manuscript, revising it critically for important intellectual content. All authors read and approved the final manuscript.

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