OBSERVATIONAL STUDY

OPEN

The Association Between Dysglycemia and Endotheliopathy in ICU Patients With and Without Diabetes: A Cohort Study

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IMPORTANCE: Dysglycemia in critically ill patients is associated with endotheliopathy. This relationship may be altered in patients with diabetes.

OBJECTIVES: Dysglycemia is common in critically ill patients and associated with increased mortality. Endotheliopathy is thought to play a role in this relationship; however, evidence is scarce. The aim of this study was to investigate the associations between dysglycemia and endotheliopathy to inform future glycemic management.

DESIGN, SETTING, AND PARTICIPANTS: This prospective observational study included 577 acutely admitted adult ICU patients at Copenhagen University Hospital–North Zealand, Denmark.

MAIN OUTCOMES AND MEASURES: Up to twenty-four hours of patient glycemia was paired with same-day levels of endothelial biomarkers measured after each 24-hour period for three consecutive days. Endotheliopathy was assessed by measurement of Syndecan-1, Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1), and soluble thrombomodulin (sTM).

RESULTS: Of the included patients, a total 57.5% were males, median age was 71 yr (interquartile range [IQR], 63–79), and 24.6% had diabetes prior to admission. Median admission time was 5 d (IQR, 3–10). Time above range (TAR) greater than 13.9 mmol/L, but not TAR 10.0–13.9 mmol/L, was associated with increase in sTM (0.01 ng/mL per %-point increase in TAR, $p = 0.049$) and PECAM-1 (0.01 ng/mL per %-point increase, $p = 0.007$). Glycemic variability was associated with increases in sTM (0.24 ng/mL per mmol/L increase in SD, $p = 0.001$ and 0.03 ng/mL per %-point increase in coefficient of variation, $p < 0.001$). Hypoglycemia 3.0–3.9 mmol/L was associated with increases in sTM (3.0 ng/mL, $p < 0.001$) and PECAM-1 (1.54 ng/mL, $p < 0.001$).

CONCLUSIONS AND RELEVANCE: In acutely admitted adult ICU patients, hypoglycemia was associated with endotheliopathy regardless of preadmission diabetes status. Hyperglycemia and high glycemic variability were associated with endotheliopathy in patients without diabetes. This suggests different responses to acute dysglycemia in patients with and without diabetes and warrants further investigation in clinical trials.

KEYWORDS: dysglycemia; endotheliopathy; glucose management; ICU

Impaired glucose metabolism induced by acute critical illness and medical treatment may result in dysglycemia, that is, hyperglycemia, hypoglycemia, and high glycemic variability in patients with and without preexisting diabetes (1, 2). Dysglycemia is common in ICU patients and studies have demonstrated associations between dysglycemia and increased morbidity and mortality, especially for patients without preexisting diabetes (3–8). However, the mechanisms linking dysglycemia and adverse clinical outcomes are poorly understood.

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KEY POINTS

Question: Which glucose levels or changes are associated with endotheliopathy?

Findings: In acutely admitted adult ICU patients, hypoglycemia was associated with endotheliopathy for all patients with and without diabetes. Hyperglycemia and high glycemic variability were also associated with endotheliopathy in patients without diabetes.

Meaning: The changes in markers of endothelial cell damage or activation varied with different glucose levels and glycemic variability and were different in patients with diabetes. This may indicate different degrees of harm in response to acute dysglycemia and supports further investigation of treatment targets and strategies in critically ill patients with and without diabetes.

Knowledge hereof could potentially prompt interventions and improve patient outcomes.

Endotheliopathy—indicated by an increase in circulating endothelial and glycocalyx markers due to shedding of the protective structure—is seen in response to acute critical illness such as sepsis and trauma and predicts poor outcome (9–12). Studies in non-hospitalized adult patients with and without diabetes have shown that endotheliopathy may be present in response to dysglycemia (13–19). In addition, maintaining normoglycemia in critically ill patients may have protective effect on the endothelium (20, 21), thus, endotheliopathy in response to dysglycemia in critically ill patients could explain the associations with clinical outcome.

The aim of this study was to investigate the association between different glycemic parameters and endothelial biomarkers in critically ill patients to inform future glycemic management. Syndecan-1, Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1), and soluble thrombomodulin (sTM) were used as markers of endotheliopathy. We hypothesized that dysglycemia would be associated with an increase in markers of endotheliopathy.

MATERIALS AND METHODS

Study Design and Setting

All reporting was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (22). This observational study was based on the Metabolomics cohort, a prospective single-center cohort study, which has previously been described in details elsewhere (10, 23–25). Patients were recruited between November 2016 and June 2019 from the ICU at the Copenhagen University Hospital—North Zealand, Denmark, an approximately 600-bed emergency hospital with a 10-bed mixed medical and surgical ICU with approximately 600 annual admissions. Patient level data were extracted both automatically and manually from the electronic health record or entered directly into an electronic case report form in REDcap (26, 27). Patient participation was approved by a trial guardian. Relatives and/or patients were subsequently approached for informed consent.

Study Participants

Patient eligibility criteria were age above 18 yr, acute admission to the ICU, and expected stay greater than 24 hours. Patients were excluded if further active treatment was deemed futile or if informed consent could not be obtained.

Endothelial Biomarkers

Syndecan-1, a proteoglycan part of the protective endothelial glycocalyx (28), is a widely studied biomarker for glycocalyx shedding and levels in plasma are increased in many acute and chronic diseases (29). PECAM-1 forms part of the tight junctions between endothelial cells (30), and is important for maintaining endothelial structure (31). Smaller in vitro studies in retinal cells have demonstrated that Syndecan-1 and PECAM-1 may be affected during hyperglycemia and diabetes (32, 33); however, no previous studies have investigated their role in dysglycemia in critically ill patients. Thrombomodulin is an endothelial membrane protein pivotal for the protein C anticoagulation systems, and is cleaved into its soluble form (sTM) (34). Elevated plasma levels of sTM have been associated increased ICU mortality and hyperglycemia (35, 36) in ICU patients with and without diabetes (12, 37).

Plasma samples were analyzed according to manufacturer's specifications, specified in detail in previous publications (10, 23). EDTA plasma was used, and samples underwent one freeze-thaw cycle for each biomarker. Samples were analyzed in uniplicate using enzyme-linked immunosorbent assays (Syndecan-1

& sTM: Diaclone SAS, Besancon, France; PECAM-1: R&D System, Minneapolis, MN).

Glycemic Parameters

All glycemic variables were derived from point-of-care glucose testing obtained prior to and during the first 72 hours of ICU stay. Glucose levels were measured in either arterial, venous, or capillary blood, and samples were taken as a part of routine patient care. The following glycemic parameters were assessed: 1) mean glucose level; 2) glycemic variability assessed as the SD of the glucose distribution and the coefficient of variation (CV) (defined as SD divided by the mean times 100%); 3) hypoglycemia (yes/no) and number of hypoglycemic episodes (at least 30 min apart), both level 1 3.0–3.9 mmol/L (54–70 mg/dL) and level 2 less than 3.0 mmol/L (<54 mg/dL); and 4) time above range (TAR), both level 1 10.0–13.9 mmol/L and level 2 greater than 13.9 mmol/L (38).

To assess glycemic status at admission, we used the following parameters: 1) diabetes (yes/no), 2) hemoglobin A1c (HbA1c) as a continuous variable, 3) HbA1c ≥48 mmol/mol (yes/no), 4) admission glucose level, and 5) glycemic gap defined as the difference between admission glucose and HbA1c-derived average glucose.

Patients with diabetes having prescribed only insulin therapy prior to admission were classified as type 1 and otherwise as type 2. HbA1c was measured in baseline blood samples.

Outcomes

Primary outcomes were the association between three consecutive periods of 24-hour glycemia, as defined above, and the subsequent levels of PECAM-1, Syndecan-1, and sTM. Secondary outcomes were the associations between admission glycemia and admission level of endothelial markers.

Statistical Analysis

A statistical analysis plan was developed prior to final analysis and published on the website of Copenhagen University Hospital–North Zealand (39). Categorical variables were presented as exact numbers and percentages, continuous variables following normal distribution as means with SDs and otherwise, as median with interquartile range (IQR). For the primary analysis, linear mixed models were used to investigate the associations between glycemic variables and endothelial markers. We investigated the association between glycemia and endotheliopathy by pairing three consecutive periods of up to 24-hour glycemia with endothelial biomarkers measured after each 24-hour period (**Fig. 1**). A univariate and multivariate analysis (main model) with adjustment for prespecified confounders were performed. Prespecified confounders were identified using a directed acyclic graph (**Additional file 1**, http://links.lww.com/CCX/B476). We identified HbA1c, inflammation (daily maximum level of C-reactive protein [CRP]), daily glucocorticoid administration and Simplified Acute Physiology Score (SAPS) 3 as confounders. The multivariate model was also adjusted for baseline level of endothelial marker. In addition, a third model (fully adjusted) which adjusted for all hypothetical confounders (HbA1c, diabetes status, sex, age, chronic kidney disease, maximum daily CRP levels, daily norepinephrine dose, daily insulin dose, SAPS, ICU glucocorticoid administration, liver failure and baseline endothelial levels) was completed. Due to the exploratory nature of the study, multiple comparisons were not adjusted for. For the secondary outcomes a linear regression analysis was used, and likewise, both univariate and multivariate analysis results are reported. Post-hoc a subgroup analysis for the primary outcome was conducted on patients with diabetes or HbA1c ≥48

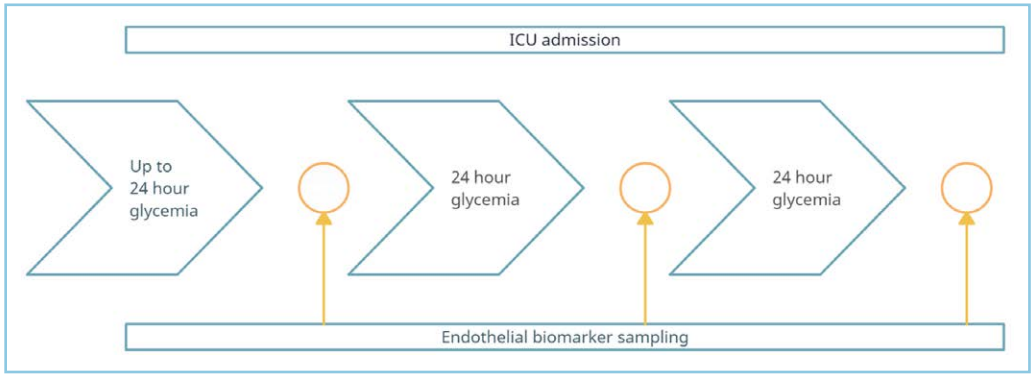

Figure 1. Overview of study flow and biomarker sampling.

mmol/mol vs. no diabetes and HbA1c <48 mmol/mol. Missing data were imputed using multiple imputation where predictive mean matching was used for numerical variables and logistical regression for categorical (40). Distribution and convergence of imputed data were inspected postimputation. Results were compared with a complete case analysis.

Results of study outcomes were presented as change in endothelial biomarkers (ng/mL) per change in glycemic unit. Level of statistical significance was defined as two-sided p value <0.05 and 95% CI. Analyses were conducted using R, Version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) (41).

Ethical Approval

The Metabolomics study was approved by the local research ethical committee (H-17027963) and the Danish Data Protection Agency (I-suite nrs. 04673 and 04674) (10). The use of biobank material to this study was also approved by the local research ethical committee (H-24010190).

RESULTS

Patient Characteristics

We included 577 acutely admitted, adult ICU patients (**Fig. 2**). Median age was 71 yr (IQR, 63–79), 332 (57.5%) were males, and median length of ICU admission was 5 d (IQR, 3–10). Median body mass index (BMI) was 26 kg/m^2 (IQR, 23–31). Diabetes prior to admission was registered in 142 patients (24.6%), of which 27 (19%) had type 1 diabetes and 115 (81%) had type 2 diabetes. Of patients with type 2 diabetes, 89 (77.4%) were treated with oral antidiabetics and 23 (20%) with insulin. In baseline blood samples, median HbA1c was 41.2 mmol/mol (IQR, 37.4–46.4) for all patients, 50 mmol/mol (IQR, 42.5–64.3), and 40 mmol/mol (IQR, 36.1–43.4) for patients with and without diabetes, respectively. A medical/nonsurgical condition was the primary reason for admission for 436 patients (75.6%), and 444 patients (77.0%) had sepsis at admission as defined by the Sepsis-3 criteria (42). All baseline characteristics are displayed in **Table 1**.

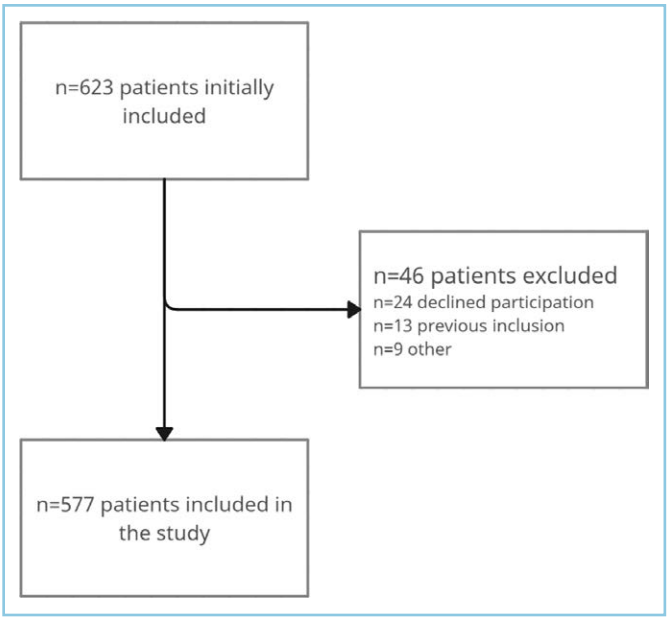

Figure 2. Patient inclusion flowchart.

Glucose Levels

A total of 15,869 glucose measurements were included in the analyses with a median of 7 (IQR, 5–10) measurements per day. Mean glucose level was 9.1 mmol/L (SD ±2.1; 168 mg/dL [SD ± 45]) for all patients, 10.8 mmol/L (SD ± 2.5; 194 mg/dL [SD ± 45]) for patients with diabetes, and 8.5 mmol/L (SD ± 1.6; 155 mg/dL [SD ± 29]) for patient without diabetes. Hyperglycemia was common with 222 patients (38.5%) having at least one glucose measurement 10.0–13.9 mmol/L (180–250 mg/dL) and 229 patients (39.6%) having at least one glucose measurement greater than 13.9 mmol/L (>250 mg/dL). Thirty-four patients (5.9%) had at least one episode of hypoglycemia 3.0–3.9 mmol/L (54–70 mg/dL), and 25 patients (4.3%) had at least one episode of hypoglycemia less than 3.0 mmol/L (54 mg/dL) (**Table 2**).

Dysglycemia and Endotheliopathy

Median levels of endothelial markers for the three consecutive periods of 24 hours are shown in **Figure 3**.

Hypoglycemia. Both occurrence of hypoglycemia (yes/no) and number of hypoglycemic episodes were associated with increase in sTM and PECAM-1. For sTM, we found a strong association for both level 1 hypoglycemia (yes/no) (3.0 ng/mL increase following hypoglycemia [95% CI, 2.1 to 3.9], $p < 0.001$) and level 2 hypoglycemia (yes/no) (2.7 ng/mL increase following hypoglycemia [95% CI, 1.3 to 4.2], $p < 0.001$). Only, level 1 hypoglycemia (yes/no) was significantly associated with Syndecan-1 (13.8 ng/mL increase following hypoglycemia [95% CI, 3.2–24.3], $p = 0.01$).

TABLE 1.
Baseline Characteristics

Patient Baseline Characteristics	Summary Statistics	All Patients (*n* = 577)
Male sex	*n* (%)	332 (57.5%)
Age, yr	Median (IQR)	71 (63–79)
Body mass index, median (IQR) kg/m^2	Median (IQR)	26 (23–31)
Length of stay, median (IQR) days	Median (IQR)	5 (3–10)
HbA1c all, mmol/mol[a]	Median (IQR)	41.2 (37.4–46.4)
HbA1c nondiabetes, mmol/mol[a]	Median (IQR)	40 (36.1–43.4)
HbA1c diabetes, mmol/mol[a]	Median (IQR)	50 (42.5–64.3)
Comorbidities[b]		
Diabetes	*n* (%)	142 (24.6%)
Diabetes type 1	*n* (%)	27 (19%)
Diabetes type 2	*n* (%)	115 (81%)
Ischemic heart disease	*n* (%)	63 (10.9%)
Hypertension	*n* (%)	272 (47%)
Heart failure	*n* (%)	52 (9%)
Stroke	*n* (%)	60 (10.4%)
Chronic obstructive pulmonary disease	*n* (%)	181 (31.4%)
Chronic kidney disease	*n* (%)	89 (15.4%)
Cancer (within 6 mo)	*n* (%)	27 (4.7%)
Chronic medications		
Insulin treated prior to admission (patients with diabetes)	*n* (%)	50 (35.2%)
Oral antidiabetic therapy, (patients with diabetes)	*n* (%)	89 (62.7%)
Antiplatelet therapy	*n* (%)	143 (24.8%)
Anticoagulant therapy	*n* (%)	107 (18.5%)
Overall admission type		
Medical, *n* (%)	*n* (%)	436 (75.6%)
Surgical, *n* (%)	*n* (%)	141 (24.4%)
ICU baseline parameters		
Glasgow Coma Scale	Median (IQR)	14 (9.5–15)
Sequential Organ Failure Assessment score	Median (IQR)	8 (5–10)
Simplified Acute Physiology Score	Median (IQR)	64 (56–73)
Sepsis	*n* (%)	444 (77.0%)
Shock	*n* (%)	132 (21.3%)
Baseline creatinine, mmol/L	Median (IQR)	75.4 (64.0–87.4)
Dialysis prior to admission	*n* (%)	17 (3.0%)
Mechanical ventilation[c]	*n* (%)	461 (79.9%)
Endothelial baseline biomarkers		
Platelet Endothelial Cell Adhesion Molecule-1, ng/mL	Median (IQR)	13.1 (11.2–14.5)

(*Continued*)

TABLE 1. (*Continued*)
Baseline Characteristics

Patient Baseline Characteristics	Summary Statistics	All Patients (*n* = 577)
Soluble thrombomodulin, ng/mL	Median (IQR)	10.2 (5.0–18.1)
Syndecan-1, ng/mL	Median (IQR)	45.8 (21.4–120.4)

HbA1c = hemoglobin A1c, IQR = interquartile range (Q1–Q3).
[a]Measured on baseline blood sample.
[b]Diagnosis prior to admission.
[c]Invasive and noninvasive mechanical ventilation.

TABLE 2.
ICU Glycemia

72-hr Glycemia and Mortality	Summary Statistics	Numbers
Total number of glucose measurements	*n*	15.869
Glucose measurements per patient	Median (IQR)	27 (19–36)
Glucose measurements per patient per day	Median (IQR)	7 (5–10)
Glucose level all, mmol/L	Mean (SD)	9.1 (2.1)
Glucose level diabetes, mean (SD) mmol/L	Mean (SD)	10.8 (2.5)
Glucose level non-diabetes, mean (SD) mmol/L	Mean (SD)	8.5 (1.6)
Coefficient of variation, %	Median (IQR)	24.7 (17.4–32.2)
Percentage of measurements in range, %	Median (IQR)	75 (48.5–92.9)
Time above range level 1, 10.0–13.9 mmol/L (180 mg/dL), %	Median (IQR)	17.1 (5.9–34.3)
Time above range level 2, >13.9 mmol/L (250 mg/dL), %	Median (IQR)	0 (0–10.6)
Number of patients with hypoglycemia level 1, <3.9 mmol/L (70 mg/dL) and ≥3.0 mmol/L (54 mg/dL)	*n* (%)	34 (5.9%)
Number of patients with hypoglycemia level 2, <3.0 mmol/L (54 mg/dL)	*n* (%)	25 (4.3%)
30-d all-cause mortality	*n* (%)	185 (32.1%)

IQR = interquartile range.

In subgroup analyses, hypoglycemia was associated with subsequent sTM increase in patients with diabetes or HbA1c ≥48 mmol/mol, and in patients with no diabetes and HbA1c <48 mmol/mol, hypoglycemia was associated with increase in all endothelial biomarkers (**Additional file 2**, http://links.lww.com/CCX/B476).

Glycemic Variability. We found a positive association between glycemic variability (SD and CV) and plasma sTM (0.2 ng/mL per mmol/L increase in SD [95% CI, 0.1–0.4], p = 0.001 and 0.03 ng/mL per %-point increase in CV [95% CI, 0.01 to 0.1], p < 0.001) (**Fig. 4**). No association was found between glycemic variability, Syndecan-1 (p = 0.10), and PECAM-1 (p = 0.58).

In a subgroup analysis, SD and CV were associated with increase in sTM in patients without diabetes and HbA1c <48mmol/mol but not in patients with diabetes or HbA1c ≥48 mmol/mol.

Hyperglycemia. We found a positive association between TAR >13.9 mmol/L (>250 mg/dL) and sTM (0.01 ng/mL per %-point increase in TAR [95% CI, 0.0 to 0.02], p = 0.049) and PECAM-1 (0.01 ng/mL per %-point increase [95% CI, 0.00 to 0.02], p=< 0.01) but not Syndecan-1 (p = 0.55). TAR >10.0–13.9 mmol/L was not associated with an increase in either sTM (p = 0.51), PECAM-1 (p = 0.49), nor Syndecan-1 (p = 0.29).

In a subgroup analysis, TAR >13.9 mmol/L was associated with sTM increase in patients without diabetes and HbA1c <48 mmol/mol but not in patients with diabetes or HbA1c ≥48 mmol/mol.

Mean Glucose. Mean glucose was positively associated with sTM (0.06 ng/mL per mmol/L increase [95%

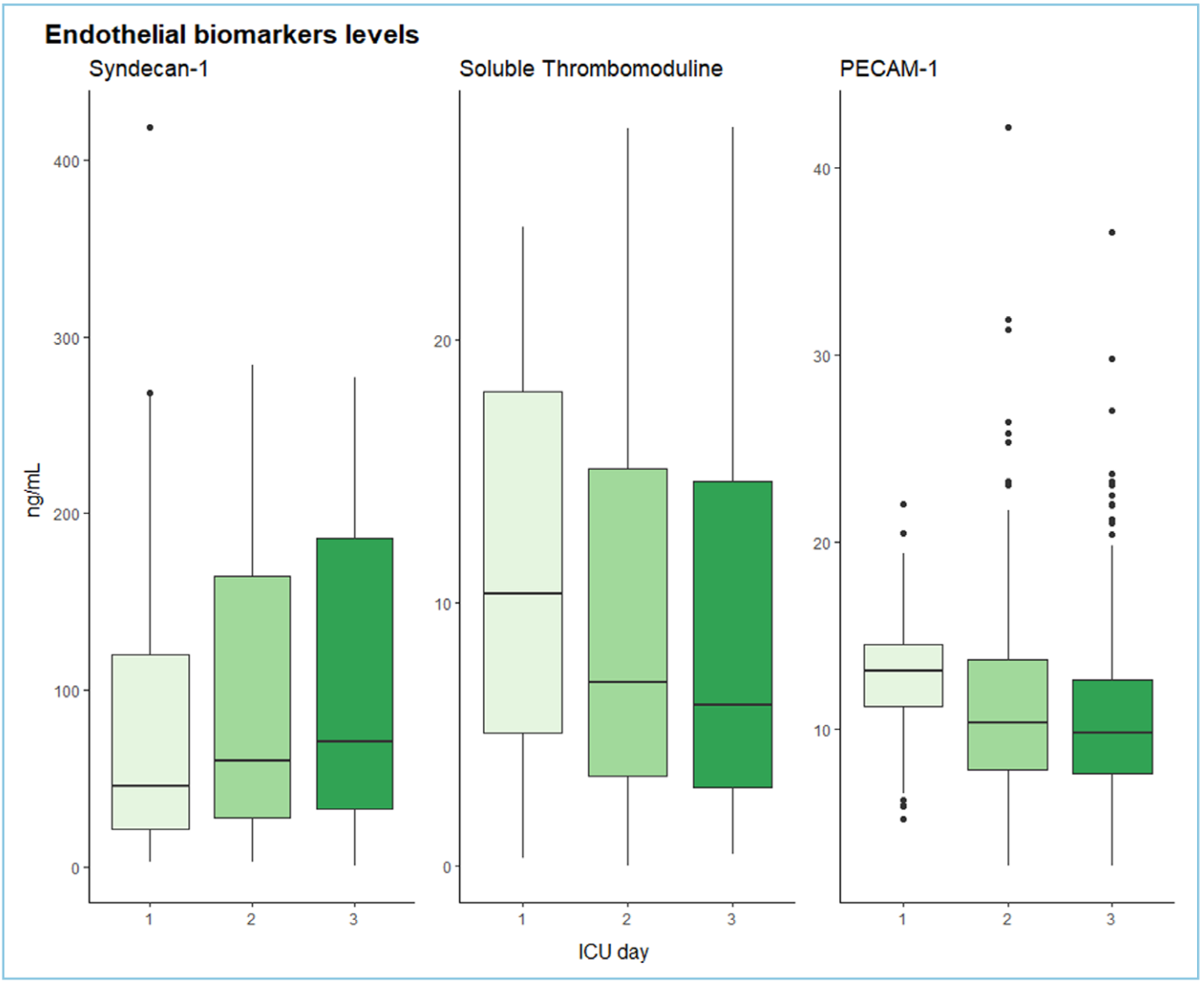

Figure 3. Levels of endothelial biomarkers on the three study days.

CI, 0.00 to 0.12], $p = 0.038$) but not Syndecan-1 ($p = 0.17$) and PECAM-1 ($p = 0.08$).

Admission Glycemia. In patients with diabetes, there was a positive association with admission levels of sTM (4.0 ng/mL higher compared with no diabetes [95% CI, 2.6 to 5.4], $p < 0.001$) and PECAM-1 (1.0 ng/mL [95% CI, 0.5 to 1.6], $p < 0.001$), but not with Syndecan-1 (**Additional file 3**, http://links.lww.com/CCX/B476). Likewise, admission HbA1c ≥48 mmol/L was also significantly associated with admission sTM levels (1.7 ng/mL [0.4 to 3.0], $p = 0.01$), irrespective of diabetes status. Admission glucose level and glycemic gap were not associated with admission endotheliopathy.

Model Comparison. Overall, comparing the adjusted and fully adjusted models, estimates were only affected marginally, and significance levels rarely impacted (Fig. 4). In the complete case analysis, the direction of associations generally remained unchanged, though the associations were weaker, and the estimates less precise (**Additional file 4**, http://links.lww.com/CCX/B476).

DISCUSSION

In this observational study, based on a prospective cohort including 577 acutely admitted adult ICU patients, we found that a range of glycemic parameters including hypoglycemia, glycemic variability, and hyperglycemia were all associated with increased circulating levels of markers of endotheliopathy. The largest increase was observed in hypoglycemia, where the association was sustained when subgrouping for pre-admission

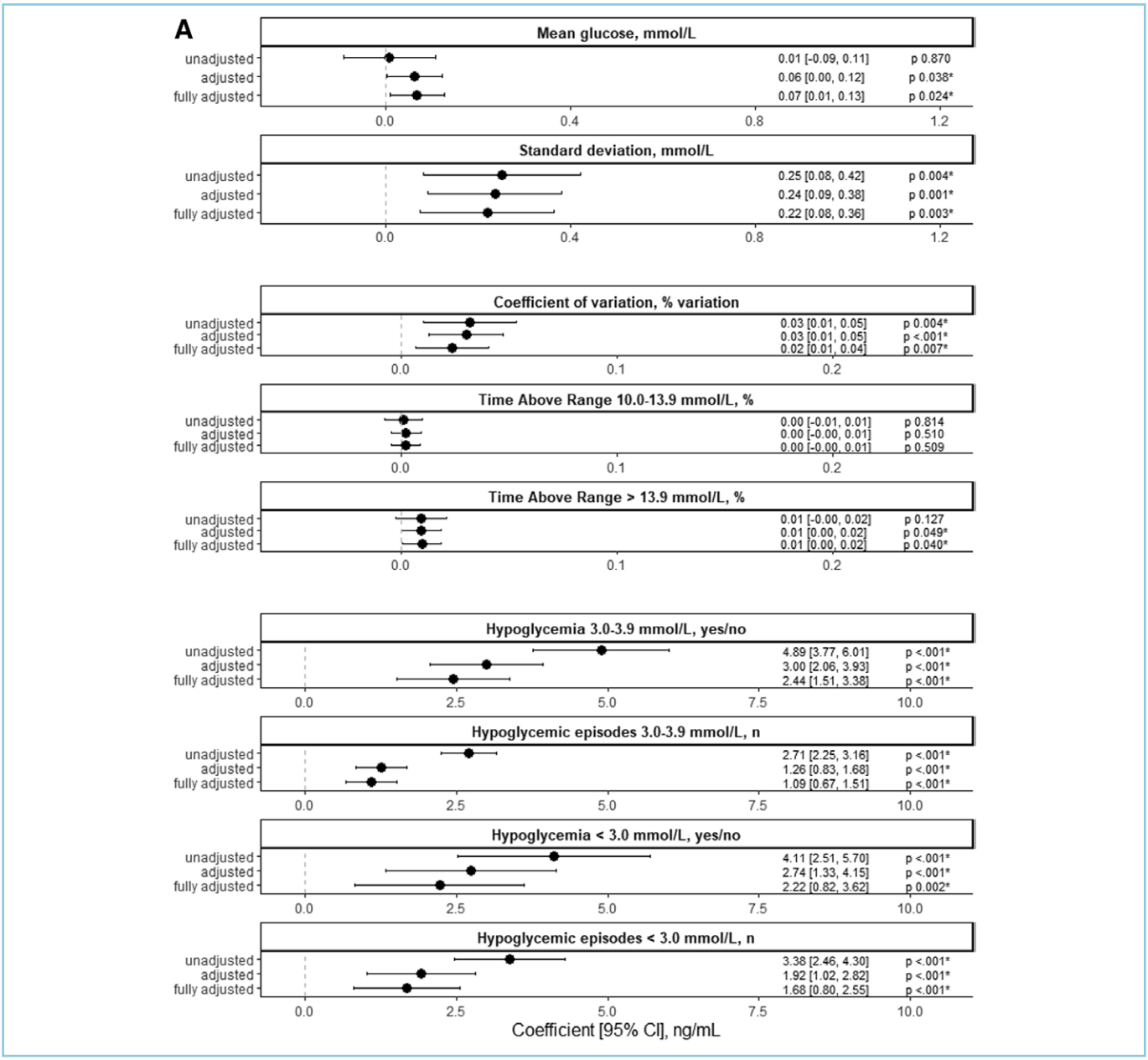

Figure 4. Associations between glycemic parameters and endothelial biomarkers. **A–C**, Associations between glycemic parameters and endothelial biomarkers. Adjusted model was adjusted for hemoglobin A1c (HbA1c), maximum daily C-reactive protein (CRP) levels, Simplified Acute Physiology Score (SAPS), ICU glucocorticoid administration, and baseline endothelial levels. Fully adjusted model was adjusted for HbA1c, diabetes status, sex, age, chronic kidney disease, maximum daily CRP levels, daily norepinephrine dose, daily insulin dose, SAPS, ICU glucocorticoid administration, liver failure, and baseline endothelial levels. Estimates are displayed as changes in absolute numbers per glycemic unit.

diabetes. Of the investigated endothelial biomarkers, sTM was most commonly associated dysglycemia.

Hypoglycemia

We identified associations between hypoglycemia and endotheliopathy for both patients with and without diabetes; however, the increase in markers of endotheliopathy was greater in patients without diabetes. These findings suggest that hypoglycemia could cause endotheliopathy by direct cell damage and tight junction disruption, thus supporting the current strong recommendations to prevent hypoglycemia (43) and providing a potential link between hypoglycemia and poor outcomes. As endogenous catecholamine causes endotheliopathy (9), our results could be explained

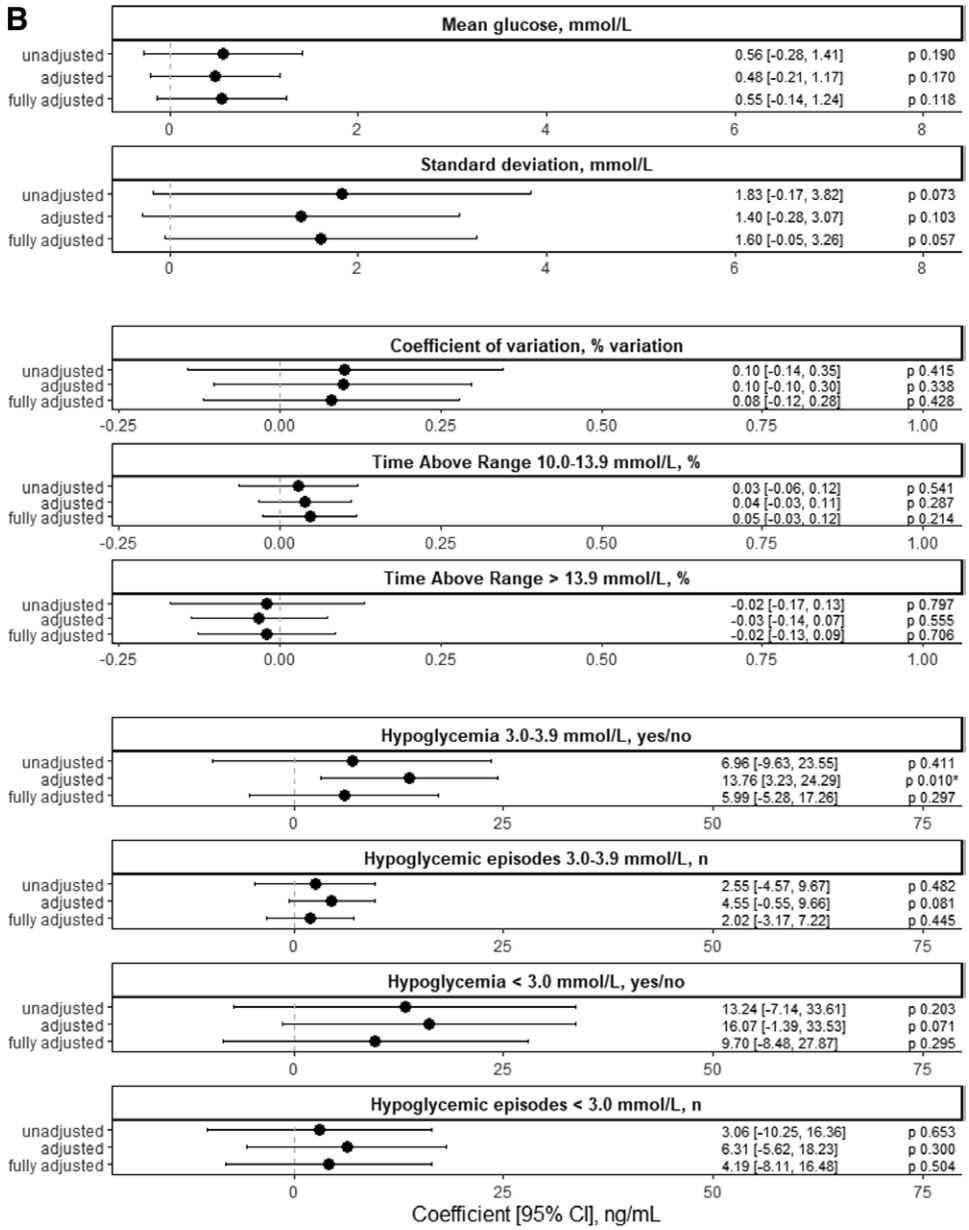

Figure 4. *(Continued)*

by an endogenous catecholamine spike released in response to hypoglycemia. This aligns with earlier observations, where a study by Tanaka et al (44) found that hypoglycemia induced endothelial dysfunction in persons without diabetes. However, we did not measure catecholamine levels consecutively following hypoglycemia. Increased endothelial permeability, could also be explained by release of vascular endothelial growth factor in the relation to hypoglycemia (45). For all endothelial biomarkers, the increase in serum levels were slightly higher when looking at the number of hypoglycemic events less than 3.0 mmol/L compared with 3.0–3.9 mmol/L, indicating a potential dose response relationship.

Glycemic Variability

We found that both CV and SD were associated with sTM increase. In a subgroup analysis however, associations were only significant for patients without diabetes and HbA1c <48 mmol/mol and a trend toward significance in patients with diabetes was observed. As the sample size was smaller and the baseline levels of both sTM and PECAM-1 were significantly higher in

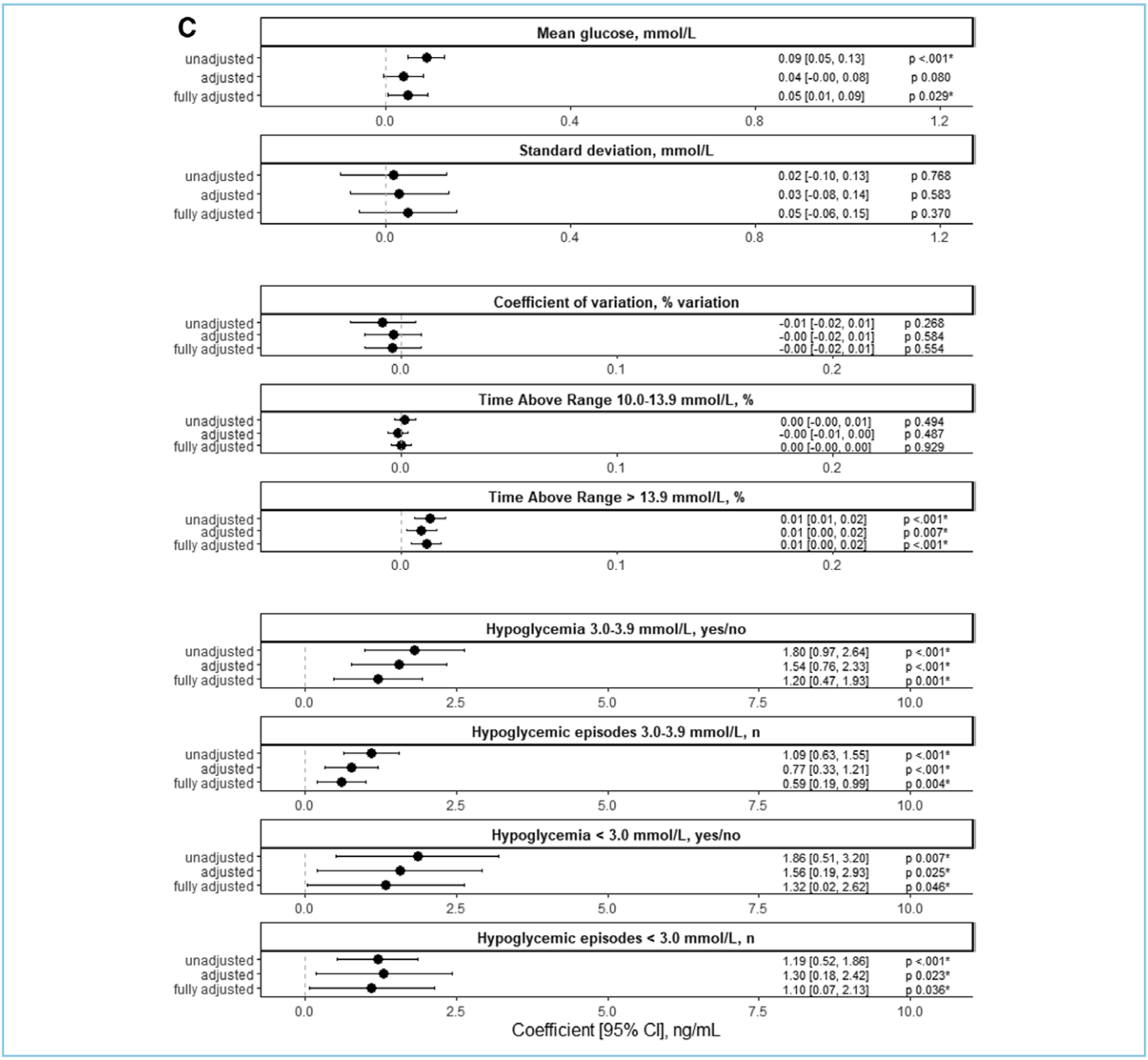

Figure 4. *(Continued)*

the group with diabetes, changes caused by dysglycemia induced by acute illness may have been more difficult to detect.

Ceriello et al (46) also found that glycemic variability was associated with an increase in oxidative stress and endothelial dysfunction compared with constant high glucose levels in both persons with and without diabetes, which supports our findings. Considering this and that glycemic variability in a recent 2024 metanalysis was consistently associated with increased mortality (47), it might be relevant to consider whether reducing glycemic variability should be a therapeutic target in addition to avoiding hyper—and hypoglycemia.

Hyperglycemia

Numerous observational studies have described the association between hyperglycemia and increased mortality in critically ill patients, and a recent study found that glucose levels above 10.5 mmol/L (190 mg/dL) were associated with a higher risk of in-hospital mortality (48). In the present study, we found that percentage of glucose measurements >13.9 mmol/L (250

mg/dL) was associated with endotheliopathy, but hyperglycemia 10–13.9 mmol/L (180–250 mg/dL) was not. This was reproduced only in patients without diabetes and HbA1c <48 mmol/mol. This may suggest a higher threshold for harmful hyperglycemia—especially for patients with known diabetes. The observed endotheliopathy could be explained by increased production of reactive oxygen species, advanced glycation end-products, and inflammation during severe hyperglycemia (49), though the latter was partly adjusted for via CRP in our analyses. This is supported by the findings by Ceriello et al (46), who concluded that maintaining a plasma glucose level of 15 mmol/L compared with 10 mmol/L over a 24-hour period was associated with increased endothelial dysfunction and oxidative stress in persons both with and without diabetes. Van Vught et al (50) found no increase in markers for endothelial cell activation in septic patients with hyperglycemia at admission, and, comparably, admission glucose was not associated with corresponding endotheliopathy in our study.

We found no significant associations between neither hyperglycemia nor glycemic variability and Syndecan-1, and thus no association with glycocalyx shedding, which has otherwise been described in non-ICU settings (18). The reasons for this could be several. As the patients in this cohort were severely ill, glycocalyx shedding will likely already be ongoing (Fig. 3) why adding the potential effect of dysglycemia may not affect the circulating Syndecan-1 levels significantly. Also, the 24-hour period for assessing glycemia may be too long and thereby failing to capture immediate Syndecan-1 fluctuations which may occur acutely upon exposure.

Clinical Implications

Several randomized clinical trials (RCTs) in the past 2 decades have investigated the clinical effect of maintaining strict glycemic targets compared with a more liberal approach (51, 52), and a 2024 metanalysis found no survival benefit with strict glycemic control, but rather an increased risk of hypoglycemia (53). As only glucose greater than 13.9 mmol/L (250 mg/dL) was associated with endotheliopathy in our study, this supports the use of a less strict glucose target during admission. Conversely, two previous RCTs found that intensive insulin therapy may decrease AGE and sTM and have a protective effect on the endothelium (20, 21). Optimized insulin therapy—for example, through the use of optimized insulin protocols, staff training, and continuous glucose monitoring systems—may play an important role in improving glycemic control and minimizing glycemic variability. Future RCTs should investigate whether this can be achieved and may improve patient important outcomes.

Finally, our findings in relation to hyperglycemia support the concept of differentiated treatment strategies for patients with and without diabetes (54), and importantly, our findings strongly support avoiding hypoglycemia in all patients.

Strengths and Limitations

In this large prospective cohort study, a high level of detailed in-hospital and baseline data was available allowing for detailed analyses and confounder adjustment. However, a number of limitations remain. We did not have continuous glucose monitoring; thus, the number of glucose measurements was not the same for all patients, and samples may have been taken more frequently in different clinical situations, for example, fluctuating glucose levels. Also, type of diabetes was designated based on antidiabetic medications at admission. The single-center design and overweight of medical patients (and not surgical) might reduce generalizability of our findings.

CONCLUSIONS

In acutely admitted adult ICU patients, hypoglycemia was associated with endotheliopathy regardless of preadmission diabetes status. Hyperglycemia and high glycemic variability were associated with endotheliopathy in patients without diabetes. This suggests different responses to acute dysglycemia in patients with and without diabetes and supports further investigation of treatment targets and strategies.

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