Plasma Glycated Hemoglobin A1c Could Predict 30-Day All-cause Mortality of Intensive Care Unit Patients with Hyperglycemia

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ABSTRACT

Background: An increased serum glucose level is a common finding among patients admitted to hospital with acute illness, including the intensive care unit (ICU), even without a history of previous diabetes mellitus (DM). Glycated hemoglobin (HbA1c) is not only a diagnostic tool for DM but may also has prognostic value for diabetic and non-diabetic populations.

Objectives: To assess the relationship between HbA1c level on admission and clinical outcome among patients admitted to the ICU due to cardiopulmonary disorders with hyperglycemia.

Methods: Patients consecutively admitted to the ICU due to cardiopulmonary disorders who presented with hyperglycemia at admission were evaluated during a 6-month period. HbA1c and serum glucose levels were tested on admission and during the first 24–48 hours of hospitalization. Patients were divided according to HbA1c and compared in term of demographics. We evaluated the effect of HbA1c levels at admission on the clinical outcomes.

Results: Of patients with cardiopulmonary disorders who presented with hyperglycemia at admission to the ICU, 73 had HbA1c levels ≥ 6%, 92 had HbA1c levels < 6%; 63/165 (38.2%) known as diabetic patients. The 30-day all-cause mortality was higher in the group with high HbA1c levels; 38/73 vs. 32/98 (P = 0.02). Increased length of stay in the ICU and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were associated with HbA1c ≥ 6% (P < 0.022 and P < 0.026), respectively.

Conclusions: HbA1c ≥ 6% has an important clinical prognostic value among diabetic and non-diabetic patients with cardiopulmonary disorders and hyperglycemia.

KEY WORDS: diabetes mellitus (DM), hyperglycemia, glycated hemoglobin (HbA1c), intensive care unit (ICU), length of stay (LOS)

Diabetes mellitus (DM) is a well-documented risk factor for poor prognosis in the intensive care unit (ICU). The diagnosis is probably related to the degree of glycemic control in diabetic patients before hospitalization [1]. Hyperglycemia is a common condition involving more than 30% of hospitalized patients with severe illness in general, not just those in the ICU. New onset hyperglycemia in hospitalized patients without a history of DM is known to account for approximately 12% of patients with high blood glucose levels [2].

Elevation of blood glucose due to acute illness is called "stress hyperglycemia." In the contemporary medical literature, there is still no quantitative universal definition for this condition. Moreover, an increase in glucose levels in distress status is sometimes caused by a latent and continuous disruption in sugar metabolism, and sometimes even unknown DM [3].

Glycated hemoglobin (HbA1c) is a reliable prognostic parameter in a diabetic and non-diabetic population [4,5], especially in elderly patients who are older than 65 years [6]. It is likely that controlling blood glucose by providing insulin improves prognosis and reduces morbidity and mortality in ICU patients with prolonged hyperglycemia. Recent studies have shown improved outcomes (fewer cases of sepsis and shorter stays in the ICU) after insulin administration [7,8].

According to recent studies, HbA1c is also a good prognostic measure in a diabetic population presenting with severe cardiac failure [9]. Although a link between hyperglycemia and poor ICU prognosis has been described, the association between HbA1c and ICU prognosis is less clear [1].

The aim of this study was to examine whether there is any association between initial HbA1c level and clinical outcomes including 30-day all-cause mortality in diabetic and non-diabetic patients with cardiopulmonary disorders and hyperglycemia who were admitted to the ICU.
PATIENTS AND METHODS

All patients over the age of 18 years who were hospitalized in the ICU at the Galilee Medical Center in northern Israel because cardiopulmonary disorders who presented with hyperglycemia at admission between October 2014 and March 2015 were included in the study. We included non-traumatic patients who were admitted because cardiopulmonary causes and hyperglycemia such as acute respiratory failure, chronic obstructive pulmonary disease, congestive heart failure, severe lung infections, and pneumonia. Their stay in the ICU was less than 48 hours. We excluded patient with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score lower than 12, diabetic ketoacidosis, hyperosmolar hyperglycemic state, or HbA1c > 8.5%.

For each patient, the following variables were collected: sex, age, APACHE II score on admission to ICU, cause of hospitalization (trauma, surgery, infection, or other), presence of systemic failure (kidney failure, heart failure), known/unknown DM at admission, blood glucose levels, and HbA1c values in the first 24-48 hours of hospitalization and during hospitalization.

Study patients with acute new onset hyperglycemia and undiagnosed diabetic patients with prolonged hyperglycemia were treated by intravenous insulin according to the standard protocol in the unit to maintain sugar values between 140 and 180 mg/dl. We began enteral or parenteral feeding after the first 24-48 hours.

The clinical outcomes of this study were: the length of stay (LOS) in the ICU, APACHE II score severity, and 30-day all-cause mortality. We divided our study patients into two groups according to HbA1c, using 6% as a cutoff according to previous studies that showed that HbA1c level < 6% was associated with lower risk of mortality among patients with symptomatic chronic heart failure [6] or in older diabetic patients [7].

DEFINITIONS

- **Hyperglycemia**: According to the American Diabetes Association, hyperglycemia is defined as a blood glucose level above 100 mg/dl in fasting and above 140 mg/dl in hospitalized patients [10].

- **APACHE score**: The score provides an initial risk classification of severely ill hospitalized patients in defined groups. It is applied within 24 hours of admission to the ICU. An integer score from 0 to 71 is computed based on several measurements. Higher scores correspond to more severe disease and a higher risk of death. The point score is calculated from 12 admission physiologic variables comprising the Acute Physiology Score, the patient's age, and chronic health status: APACHE II scores are composed of AaPO2 or PaO2 (for FiO2 ≥ 0.5 or < 0.5, respectively), body temperature (rectal), mean arterial pressure, blood pH, heart rate, respiratory rate, serum sodium, serum potassium, creatinine (double point score for acute renal failure), hematocrit level, white blood cell count, Glasgow Coma Scale [11].

- **30-day all-cause mortality**: Death within 30 days from the date of hospitalization is defined as 30-day mortality. We retrieved data of 30-day mortality / survival from the hospital registry.

STATISTICAL ANALYSIS

Continuous data were described using means and standard deviations. Categorical data were described using frequencies and percentages. Comparison of numeric data between groups was performed by an independent sample t-test.

Relationships between categorical variables and sample groups were examined using chi-square test or Fisher's exact test depending on the sample size. A multivariable logistic regression model was calculated to show the correlation between different variables and the risk of 30-day all-cause mortality with adjustment for potential confounders. P-value lower than 5% was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

Between October 2014 and March 2015, 570 patients with cardiopulmonary disorders who presented with hyperglycemia were admitted to the ICU. We included 165 patients (28.9%) who responded to our study criteria. The prominent reasons for ICU admission of our patients were congestive heart failure exacerbation (43 patients, 26%), pulmonary infections (38 patients, 23%), and COPD exacerbations (25 patients, 15%). Patients were divided into two groups according to HbA1c level, using 6% as a cutoff.

DEMOGRAPHIC CHARACTERISTICS AND MORTALITY INDICES

Compared to patients with HbA1c < 6%, those with HbA1c ≥ 6% were more likely to be older, female, and diabetic [Table 1]. We did not find any significant differences between the groups in term of co-morbidities such as liver, renal, and cardiac, COPD, malignancy, or neurological diseases. Compared to patients with normal HbA1c, those with high HbA1c had significantly longer LOS, higher APACHE II scores, and higher 30-day all-cause mortality. The 30-day all-cause mortality of the elevated HbA1c group (52.1%) was significantly higher than that of the normal HbA1c (34.8%) (P = 0.026).

Of 73 patients with elevated HbA1c, 12 had HbA1c between 6% and 6.5%. Of 61 patients with HbA1c > 6.5% (subgroup of high HbA1c), 18 (29.5%) presented with new onset high HbA1c. When we compared within the subgroup of high HbA1c (n=61), those with a new onset high HbA1c (n=18) and those with previous high HbA1c (n=43), we did not find any significant dif-
Table 1. Demographic and clinical characteristics of the study participants according to their HbA1c values (≤6% vs. >6%)

<table>
<thead>
<tr>
<th>Variables</th>
<th>All participants (n=165)</th>
<th>HbA1c &lt; 6% (n=92)</th>
<th>HbA1c ≥ 6% (n=73)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>89 (53.9)</td>
<td>56 (60.9)</td>
<td>33 (52.2)</td>
<td>0.045</td>
</tr>
<tr>
<td>Female</td>
<td>76 (46.1)</td>
<td>36 (9.1)</td>
<td>40 (56.8)</td>
<td></td>
</tr>
<tr>
<td>Age, year (mean ± SD)</td>
<td>69.7 ± 17.9</td>
<td>67.1 ± 21.0</td>
<td>72.9 ± 12.3</td>
<td>0.040</td>
</tr>
<tr>
<td>Disease presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>63 (38.2)</td>
<td>17 (18.5)</td>
<td>46 (63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1 (1.8)</td>
<td>3 (3.3)</td>
<td>0 (0)</td>
<td>0.255</td>
</tr>
<tr>
<td>Renal failure</td>
<td>44 (29.1)</td>
<td>22 (23.9)</td>
<td>26 (35.6)</td>
<td>0.100</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68 (41.2)</td>
<td>34 (37.0)</td>
<td>34 (46.6)</td>
<td>0.212</td>
</tr>
<tr>
<td>COPD</td>
<td>25 (15.2)</td>
<td>12 (13.0)</td>
<td>13 (17.8)</td>
<td>0.397</td>
</tr>
<tr>
<td>Malignancy</td>
<td>14 (8.5)</td>
<td>7 (7.6)</td>
<td>7 (9.6)</td>
<td>0.450</td>
</tr>
<tr>
<td>Neurological diseases</td>
<td>14 (8.5)</td>
<td>6 (6.5)</td>
<td>8 (11.0)</td>
<td>0.310</td>
</tr>
<tr>
<td>CVA</td>
<td>8 (4.8)</td>
<td>2 (2.2)</td>
<td>6 (8.2)</td>
<td>0.140</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>29 (17.6)</td>
<td>17 (18.5)</td>
<td>12 (16.4)</td>
<td>0.732</td>
</tr>
<tr>
<td>Hypthyroidism</td>
<td>5 (3.0)</td>
<td>2 (2.2)</td>
<td>3 (4.1)</td>
<td>0.656</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (2.4)</td>
<td>2 (2.2)</td>
<td>2 (2.7)</td>
<td>0.814</td>
</tr>
<tr>
<td>Mental disorder</td>
<td>3 (1.8)</td>
<td>2 (2.2)</td>
<td>1 (1.4)</td>
<td>0.701</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>50 (30.3)</td>
<td>24 (26.1)</td>
<td>26 (35.6)</td>
<td>0.184</td>
</tr>
<tr>
<td>LOS in ICU in days, (mean ± SD)</td>
<td>10.9 ± 22.3</td>
<td>7.0 ± 10.2</td>
<td>15.8 ± 30.9</td>
<td>0.202</td>
</tr>
<tr>
<td>APACHE II score (mean ± SD)</td>
<td>17.9 ± 7.2</td>
<td>16.8 ± 7.4</td>
<td>19.3 ± 6.8</td>
<td>0.026</td>
</tr>
<tr>
<td>30-day all-cause mortality, n (%)</td>
<td>70 (42.6%)</td>
<td>32 (36.8%)</td>
<td>38 (52.1%)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

APACHE II = Acute Physiology and Chronic Health Evaluation II, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease including atrial fibrillation and heart failure, HbA1c = glycated hemoglobin, ICU = intensive care unit, LOS = length of stay, SD = standard deviation.

Discussions

Inferences in terms of LOS in ICU and APACHE II score, but we found a significant difference in 30-day all-cause mortality, 8 vs. 30 deaths, P < 0.001, respectively. The major cause of mortality in both groups was cardiovascular. Causes of death in the group of patients with new onset HbA1c > 6.5% in which arrhythmias such as atrial fibrillation and ventricular tachycardia were recorded. One had asystole and two died of severe sepsis.

Table 2 shows the multivariate regression analysis for predictors of 30-day all-cause mortality in patients with cardiopulmonary disorders and hyperglycemia who were admitted to the ICU: age ≥ 70 years odds ratio (OR) 4.13, 95% confidence interval (95% CI) 1.98–8.61, P < 0.001, DM OR 3.1, 95% CI 1.43–6.74, P = 0.004, and HbA1c ≥ 6% at admission OR 1.25, 95% CI 0.6–2.5, P = 0.05 were associated with 30-day all-cause mortality.

Discussion

The main finding of this prospective study was that HbA1c ≥ 6% at admission is an important clinical prognostic value among diabetic and non-diabetic. The score was associated with increased LOS in the ICU, APACHE II score, and 30-day all-cause mortality in patients admitted to the ICU due to cardiopulmonary disorder and hyperglycemia. Moreover, we found that age ≥ 70 years and DM were independent predictors of 30-day all-cause mortality of hyperglycemic ICU patients.

A previous study, which aimed to determine the prevalence of in-hospital hyperglycemia and the survival and functional outcome of patients with hyperglycemia with and without a history of DM, showed that in-hospital hyperglycemia was a
common finding and represented an important marker of poor clinical outcome and mortality in patients with and without a history of DM [11]. Hyperglycemia was present in 38% of patients admitted to the hospital, of whom 26% had a known history of DM, and 12% had no history of DM before the admission.

In our study, the prevalence of hyperglycemia was 165/570 (28.9%) at admission, 63/165 (38.2%) had a known DM. The prevalence of hyperglycemia in our study is similar to previous studies, about 30% of hospital admission so-called admission hyperglycemia, which is associated with increased hospital mortality in critically ill patients [12].

The results of our study demonstrated a direct and statistically significant relationship between HbA1c ≥ 6% (in diabetic and non-diabetic patients) and increased LOS of ICU, APACHE II score, and 30-day all-cause mortality. A prospective observational study on 286 patients with type 2 DM admitted with sepsis showed that admission HbA1c of median 9.75% is an independent predictor of hospital mortality, and hospital LOS of diabetic patients with sepsis [13]. In another study on a community-based population of non-diabetic adults, glycated hemoglobin was associated with a risk of diabetes and more strongly associated with risks of cardiovascular disease and death from any cause as compared with fasting glucose [14]. To the best of our knowledge, this study is the first to show that levels of admission HbA1c ≥ 6 is predictor of increased LOS of ICU, APACHE II score, and 30-day all-cause mortality.

DM is a known risk factor for increased mortality in ICUs in various groups, especially in patients after cardiovascular surgery [15]. The study showed that diabetic patients (known or unknown) had a higher mortality rate than non-diabetic patients or patients with a pre-diabetic condition. A multicenter observational cohort study on the prospective outcome, including adult patients with a hospital stay < 48 hours before ICU admission and a documented invasive pneumococcal infection (IPI) within the first 72 hours of ICU admission, showed that DM was the only co-morbid condition that independently influenced mortality in patients with IPI [16].

When we compared patients with new onset HbA1c ≥ 6.5% and those with known DM, we did not find any significant differences regarding the LOS in ICU and APACHE II score. However, we found a lower mortality rate among patients with new onset HbA1c ≥ 6.5% compared to those with previous HbA1c ≥ 6.5% (previous DM). A similar finding was also observed in a previous study, which showed that hyperglycemia in patients who underwent cardiac catheterization was a strong predictor of adverse outcome and was mainly related to dysglycemic background and to a lesser extent to the acute stress accompanying acute coronary syndrome [17].

LIMITATIONS

Our study has some limitations. First, our study included a relatively small number of patients. Second, our patients were all from a single center. Third, with regard to the increased age of our sample, the mean age of our participants was 70 ± 18 years. Last, we only included a short follow-up period.

CONCLUSIONS

HbA1c ≥ 6% has an important clinical prognostic value among diabetic and non-diabetic patients with cardiopulmonary disorders and hyperglycemia. The level was associated with increased LOS of ICU, higher APACHE II score, and 30-day all-cause mortality. Further prospective studies are needed to assess these findings evaluate the usefulness of admission HbA1c as predictor of several clinical outcomes. Hyperglycemia at the time of admission to the ICU is a common condition, with approximately one-third of admitted patients. In concordance with other studies, we found prognostic clinical importance of the HbA1c index and mortality among diabetic and non-diabetic patients admitted to the ICU. There is a direct relationship between the level of HbA1c and hyperglycemia and the length of hospitalization in the ICU.
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References

**Capsule**

**Regulatory T cells (Tregs) in visceral-adipose tissue**

Regulatory T cells (Tregs) in visceral-adipose tissue (VAT) are key to regulating local and systemic metabolism. Circadian rhythm pathways are up-regulated in tissue Tregs, but it is unclear how they affect VAT Tregs. Xiao et al. determined the transcriptomic and metabolic profiles of VAT Tregs at various circadian time points that expressed or were deficient in genes that control circadian rhythms.

**VAT Tregs had altered phenotypes at various times during the circadian cycle. Ablation of a core clock gene led to VAT Treg constitutive activation, resulting in altered metabolism, fitness loss, and greater suppression of adipocyte lipolysis.**

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**Capsule**

**Memory CD8+ T cell diversity and B cell responses correlate with protection against SARS-CoV-2 following mRNA vaccination**

Understanding immune responses to SARS-CoV-2 messenger RNA (mRNA) vaccines is of great interest, principally because of the poor knowledge about the mechanisms of protection. Bravu and colleagues analyzed longitudinally B cell and T cell memory programs against the spike (S) protein derived from ancestral SARS-CoV-2 (Wuhan-1), B.1.351 (Beta), B.1.617.2 (Delta), and B.1.1.529 (Omicron) variants of concern (VOCs) after immunization with an mRNA-based vaccine (Pfizer). According to the magnitude of humoral responses 3 months after the first dose, the authors identified high and low responders. In contrast to low responders, high responders were characterized by enhanced antibody-neutralizing activity, increased frequency of central memory T cells and durable S-specific CD8+ T cell responses. Reduced binding antibodies titers combined with long-term specific memory T cells that had distinct polyclonal properties were found associated with subsequent breakthrough with VOCs in low responders. These results have important implications for the design of new vaccines and new strategies for booster follow-up.

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