Risk determinants of hyperglycaemia among critically ill inpatients without diabetes

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The aim of this study was to identify risk determinants of hyperglycaemia among critically ill inpatients without diabetes. A sample of 450 intensive care inpatients were categorised according to whether they had hyperglycaemia and diabetes, hyperglycaemia without diabetes or no hyperglycaemia. The majority of patients (71.6%) had hyperglycaemia despite no history of diabetes. Significant risk factors for hyperglycaemia were found to include age 46–60 years, neurological disorders, more severe illness, enteral nutrition and mechanical ventilation. Intensive care units should consider the importance of protocols related to the monitoring of glucose levels in patients with these risk factors, in order to manage hyperglycaemia early and improve outcomes.

Stress-induced hyperglycaemia is defined as the transient elevation of plasma glucose to more than 11.1 mmol/L as a natural response to metabolic stress in critically ill people (Gupta et al, 2020). As a result of elevated stress hormones, 90% of critically ill patients may develop decreased glucose tolerance, insulin resistance or both (Davidson et al, 2015). Hyperglycaemia has adverse direct and indirect effects on the whole body (including the renal, visual, neurological and cardiovascular systems), worsens outcomes and may risk multiple organ system failure. It is correlated with elevated morbidity and mortality in critically ill patients with various conditions (such as acute myocardial infarction, stroke, congestive heart failure and chronic obstructive pulmonary disease), following a coronary artery bypass graft, trauma or cerebral endarterectomy, and in elderly patients (Baker et al, 2006; Barsheshet et al, 2006; Szerszen et al, 2009; Meizoso et al, 2016; Lim et al, 2018).

Patients with hyperglycaemia have higher rates of extended intensive care unit (ICU) stay, hospitalisation and death compared to those without hyperglycaemia (Pourmand et al, 2018; Silva et al, 2019). Temel and Yuksel (2018) found a clear correlation between hyperglycaemia and poor clinical outcomes, with critically ill patients with hyperglycaemia having a higher incidence of newly acquired infection, increased length of ICU stay and higher mortality rates than those without hyperglycaemia. In seriously ill mechanically ventilated patients with poor prognoses, hyperglycaemia may contribute to ventilator-associated pneumonia and longer ICU stay.

The American Diabetes Association has suggested that hyperglycaemia is an independent risk factor for death in critically ill patients (Lheureux et al, 2019). Cheung et al (2019) also showed that hyperglycaemia is associated with a higher mortality rate in patients without diabetes than in those with diabetes. Determinants of hyperglycaemia are well understood among people with diabetes but are more ambiugous among those without the condition.

The average age of ICU patients is increasing (Davis et al, 2020), and ageing is linked to

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Article points

1. Hyperglycaemia in critically ill inpatients is associated with worse outcomes, increased length of hospital stay and mortality.
2. A high proportion of critically ill patients will have hyperglycaemia even in the absence of diabetes.
3. Age 46–60 years, neurological disorders, more severe disease, enteral nutrition and mechanical ventilation were found to be risk factors for hyperglycaemia.
4. Inpatients with these risk factors should be carefully monitored in order to detect hyperglycaemia and to treat it early.

Key words

- Critical care
- Hyperglycaemia
- Inpatient care

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Audit of the identification and management of steroid-induced hyperglycaemia and steroid-induced diabetes

An audit to evaluate the incidence and management of steroid-induced hyperglycaemia on medical wards and to assess adherence to a newly introduced steroid pathway by ward staff.

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augmented insulin resistance in peripheral tissues and reduced glucose-induced insulin release. Elderly patients are more vulnerable to stroke and mortality, with hyperglycaemia exacerbating the risk (Katan and Luft, 2018; Teh et al, 2018). Hyperglycaemia may exaggerate endothelial cell damage during the acute stage of stroke and lead to worse outcomes (Lim et al, 2018).

Retrospective studies in critically ill patients have shown a clear correlation between hyperglycaemia and poor clinical outcomes in all groups, including the elderly, but the overall incidence of hyperglycaemia in elderly patients without diabetes in the ICU is uncertain (Nukui et al, 2019; Zhao et al, 2019).

Nutritional support is a further challenge that can compromise the state of glucose regulation in critically ill patients. The addition of glucose components through nutritional support can further exacerbate hyperglycaemia (Davidson et al, 2015). Enteral and parenteral nutrition can be used to maintain nutritional status, but overnutrition and inappropriate use can lead to hyperglycaemia (Yang et al, 2017). Parenteral nutrition is known to be a risk determinant of hyperglycaemia in critically ill patients, but other determinants need to be investigated (Davidson et al, 2015; Nguyen and Ha, 2016). Hospitalised patients' nutritional status correlates with morbidity, mortality and greater length of stay in hospital (Kyle et al, 2004). Length of ICU stay is affected by a patient's diagnosis, age and nutritional intervention (Tucker, 2002), so it is important to identify the association of these factors with hyperglycaemia.

Critically ill inpatients with associated hyperglycaemia have poorer outcomes and increased mortality rates. However, limited data are available about the risk of hyperglycaemia in critically ill patients without previously diagnosed diabetes.

Study aim

To identify risk determinants of hyperglycaemia among critically ill inpatients without diabetes.

Materials and methods

Design

A descriptive research design was used to conduct this study.

Setting

The study was conducted in four general ICUs at Teaching University Main Hospital in Egypt. Unit I has eight beds, unit II eight beds, unit III 15 beds and unit IV 10 beds.

Sample

A convenience sample of 450 newly admitted, male and female, critically ill patients aged >18 years was involved in the study. Haemodynamically unstable patients (systolic blood pressure <90 mmHg) and those whose medication might interfere with blood glucose levels (such as vasopressor agents) were excluded from the study. The sample size was calculated based on the power analysis with the following information: population size=300 over six months; expected frequency=50%; acceptable error=5%; and confidence coefficient=95%.

Assessment tool

After reviewing the relevant literature (Davidson et al, 2015; Nguyen and Ha, 2016; Krinsley et al, 2017), the researcher developed a tool, "Risk determinants of hyperglycemia assessment", to assess the determinants contributing to hyperglycaemia in critically ill patients. It consisted of three parts:

1. Demographic and clinical data: Demographic data included age and gender; clinical data included admission date, medical history, current diagnosis, blood glucose level, consciousness level, steroid therapy, nutritional route and Acute Physiology and Chronic Health Evaluation II (APACHE-II) score. APACHE-II is one of the scoring systems used in ICUs to measure the severity of disease for adult patients. It is performed within 24 hours of the patient's admission to the ICU. It is calculated based on several measurements and scored from 0 to 71, with higher scores indicating more severe disease and a higher risk of death (VijayGanapathy et al, 2017).
2. Perfusion data: Heart rate, mean arterial blood pressure, administration of intravenous glucose fluids, and fluid balance/24 hours.
3. Ventilation data: Whether patients were mechanically ventilated and partial pressure of arterial oxygen.

Validity and reliability of the assessment tool

The tool was examined for content validity by

five experts in the fields of critical care nursing and critical care medicine. Content reliability of the tool was assessed using Cronbach's alpha coefficient, and was deemed to be acceptable (α=0.88).

Ethical and administrative considerations

Before collecting data, the approval of the Faculty of Nursing's Ethics Committee and the responsible university hospital authority was obtained. Informed written consent was obtained from each participant (or family member for unconscious patients).

Pilot study

A pilot study was carried out in 40 patients recruited from the study sample to test the feasibility and applicability of the assessment tool. No changes were required for the final version of the tool.

Data collection

Data were collected from January 2015 to June 2016. Clinical, perfusion and ventilation data were collected within the first 24 hours of the patient's admission to ICU using the assessment tool. The blood glucose level of each patient was measured once on the day of admission using a random venous sample, as it was likely to be at its highest during this period owing to stress (Yang et al, 2017). The patients were assigned to three groups based on history of diabetes and hyperglycaemia:

- Group 1: no hyperglycaemia.
- Group 2: no diabetes but hyperglycaemia.
- Group 3: diabetes and hyperglycaemia.

A comparison of the groups' demographic, clinical, ventilation and perfusion data was made to assess determinants contributing to hyperglycaemia among critically ill patients.

Data analysis

Data were entered into a computer and analysed using SPSS Statistics 20 (IBM Corp., Armonk, NY, USA). Reliability statistics were assessed using Cronbach's alpha test, with data described using numbers and percentages. Comparisons were done using the chi-squared test, with a significance value of $P \leq 0.05$.

Results

Table 1 shows the distribution of the studied groups' demographic data. Group 1 comprised 22.0% of the sample, Group 2 comprised 71.6% and Group 3 comprised 6.4%. Compared with the other groups, Group 2 had a higher proportion of patients aged 46–60 years, with a significant relationship between age and hyperglycaemia occurrence ($P \leq 0.05$).

Table 2 presents the groups' clinical data. Compared with the other groups, Group 2 had a higher percentage of patients with no history of diabetes, no liver or pancreatic disease, a neurological disorder, enteral nutrition and mean APACHE-II score (indicating more severe disease). Hyperglycaemia occurrence was significantly associated with absence of diabetes, absence of liver or pancreatic disease, current diagnosis, enteral nutrition and more severe disease ($P \leq 0.05$ for all comparisons).

Table 1. Distribution of the studied groups' demographic data (*n*=450).

Demographics	Overall (*n*=450; 100%)	Group 1* (*n*=99; 22.0%)	Group 2* (*n*=322; 71.6%)	Group 3* (*n*=29; 6.4%)	Significance test
Gender					
Male	242 (53.8%)	58 (12.9%)	172 (38.2%)	12 (2.7%)	χ^2=3.1
Female	208 (46.2%)	41 (9.1%)	150 (33.3%)	17 (3.8%)	*P*=0.38
Age (years)					
≤30	131 (29.1%)	35 (7.7%)	92 (20.4%)	4 (0.9%)	
31–45	127 (28.2%)	25 (5.6%)	99 (22.0%)	3 (0.7%)	χ^2=25.1
46–60	192 (42.7%)	39 (8.7%)	131 (29.1%)	22 (4.9%)	***P*<0.001**†

*Group 1: no hyperglycaemia; Group 2: hyperglycaemia and no diabetes; Group 3: diabetes and hyperglycaemia.
†Statistically significant at $P \leq 0.05$.

Table 2. Comparison among the studied groups according to clinical data (*n*=450)

Clinical data	Group 1* (*n*=99; 22.0%)	Group 2* (*n*=322; 71.6%)	Group 3* (*n*=29; 6.4%)	Significance test
History of diabetes				
Yes	19 (4.2%)	0 (0%)	29 (6.4%)	χ^2=450
No	80 (17.8%)	322 (71.6%)	0 (0%)	***P*<0.001**†
History of liver or pancreatic disease				
Yes	9 (2.0%)	17 (3.8%)	2 (0.4%)	χ^2=7.68
No	90 (20.0%)	305 (67.8%)	27 (6.0%)	***P*=0.05**†
Diagnosis				
Cardiovascular disease	20 (4.4%)	41 (9.1%)	4 (0.9%)	
Respiratory disease	14 (3.1%)	40 (8.9%)	4 (0.9%)	
Renal disease	3 (0.6%)	6 (1.3%)	7 (1.6%)	
Neurological disease	43 (9.5%)	140 (31.1%)	13 (2.9%)	
Gastrointestinal disease	4 (0.9%)	12 (2.7%)	0 (0.0%)	χ^2=68.7
Poisoning	15 (3.4%)	83 (18.4%)	1 (0.2%)	***P*<0.001**†
APACHE-II score (mean±SD)	19.5±8.1	22.1±6.7	18.5±7.8	*F*=2.99 ***P*=0.03**†
Consciousness level				
Conscious	21 (4.6%)	62 (13.8%)	5 (1.1%)	χ^2=1.9
Unconscious	78 (17.3%)	260 (57.8%)	24 (5.3%)	*P*=0.60
Steroids administered				
Yes	11 (2.4%)	47 (10.4%)	6 (1.3%)	χ^2=1.8
No	88 (19.55%)	275 (61.1%)	23 (5.1%)	*P*=0.61
Route of nutrition				
Nil by mouth	1 (0.2%)	29 (6.4%)	4 (0.9%)	
Oral	11 (2.4%)	20 (4.4%)	2 (0.4%)	
Enteral	79 (17.6%)	234 (52.0%)	23 (5.1%)	χ^2=17.3
Parenteral	8 (1.8%)	39 (8.7%)	0 (0%)	***P*=0.04**†
Intravenous glucose administered				
Yes	19 (4.3%)	88 (19.6%)	11 (2.4%)	χ^2=4.9
No	80 (17.8)	234 (52.0%)	18 (4.0%)	*P*=0.18

*Group 1: no hyperglycaemia; Group 2: hyperglycaemia and no diabetes; Group 3: diabetes and hyperglycaemia.
†Statistically significant at $P \leq 0.05$.
APACHE-II: Acute Physiology and Chronic Health Evaluation II.

Table 3 compares the groups according to ventilation and perfusion parameters. Group 2 had a higher percentage of patients who were mechanically ventilated and those with an increased heart rate. Hyperglycaemia occurrence was significantly associated with these factors ($P \leq 0.05$ for both comparisons).

Discussion

This study revealed that a high proportion of inpatients were hyperglycaemic despite the absence of diabetes. This is consistent with the findings of Ertorer et al (2010), who found that hyperglycemia was present in almost half (48.4%) of of inpatients without diabetes. Davidson et al (2015) also indicated that 90% of the most critically ill patients had impaired glucose tolerance. In addition, Temel and Yuksel (2018) observed stress hyperglycemia in 64% of patients in the ICU.

Table 3. Comparison among the studied groups according to ventilation and perfusion parameters (n=450).

Parameter	Group 1* (*n*=99; 22.0%)	Group 2* (*n*=322; 71.6%)	Group 3* (*n*=29; 6.4%)	Significance test
Mechanical ventilation				
Yes	81 (18.0%)	291 (64.7%)	25 (5.6%)	χ^2=7.78
No	18 (4.0%)	31 (6.9%)	4 (0.9%)	***P*=0.05**†
Partial pressure of arterial oxygen				
Normal	59 (13.11%)	220 (48.9%)	21 (4.7%)	χ^2=3.75
Decreased	40 (8.9%)	102 (22.7%)	8 (1.8%)	*P*=0.31
Heart rate				
Normal	40 (8.9%)	141 (31.3%)	9 (2.0%)	
Increased	52 (11.6%)	170 (37.8%)	19 (4.2%)	χ^2=12.6
Decreased	39 (8.7%)	142 (31.6%)	9 (2.0%)	***P*=0.05**†
Mean arterial blood pressure				
Normal	60 (13.3%)	218 (48.4%)	21 (4.7%)	
Increased	26 (5.8%)	55 (12.2%)	5 (1.1%)	χ^2=6.1
Decreased	13 (2.9%)	49 (10.9%)	3 (0.7%)	*P*=0.41
Fluid balance/24 hours				
Zero balance	0 (0%)	2 (0.4%)	0 (0%)	
Positive	52 (11.6%)	145 (32.2%)	14 (3.1%)	χ^2=3.47
Negative	48 (10.7%)	170 (37.8%)	19 (4.2%)	*P*=0.75

*Group 1: no hyperglycaemia; Group 2: hyperglycaemia and no diabetes; Group 3: diabetes and hyperglycaemia.
†Statistically significant at $P \leq 0.05$.
APACHE-II: Acute Physiology and Chronic Health Evaluation II.

In this study, a higher percentage of older patients without diabetes had hyperglycaemia, with a significant age-to-hyperglycaemia relationship. This may be due to physiological changes in older adults that lead to an increase in the prevalence of hyperglycaemia. In addition, such individuals may need to take drugs such as beta-blockers, glucocorticoids and diuretics, based on diagnosis. These drugs have side effects on the metabolism of carbohydrates, which exacerbate hyperglycaemia. Koyfman et al (2018) revealed that older age and hyperglycaemia were independent risk determinants of ICU mortality.

There was a significant relationship between hyperglycaemia and the absence of diabetes, liver disease and pancreatic disease. This suggests that hyperglycaemia will likely occur in critically ill patients regardless of the presence of these comorbidities. Acute hyperglycaemia can be a reaction to physiological stress in patients with acute illness, even in the absence of pre-existing diabetes. Yang et al (2017) noted that there was a relationship between hyperglycaemia and high mortality rates in people with and without diabetes.

A higher percentage of patients without diabetes who had neurological disorders had hyperglycaemia. Zhu et al (2019) revealed that, among inpatients without diabetes, stroke patients had a higher incidence of hyperglycaemia compared with non-stroke patients; the hyperglycaemia was observed to be stress-related. Mi et al (2018) have shown that hyperglycaemia in stroke patients is associated with worse prognosis and higher mortality. Yao et al (2016) found that hyperglycaemia was associated with reduced functional potential in stroke patients without diabetes.

There was a significant relationship between hyperglycaemia and higher APACHE-II score. This indicates that hyperglycaemia can be associated with

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This article discusses the implications of artificial nutrition in people with diabetes and offers recommendations on the management of the hyperglycaemia that can result.

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more severe disease, possibly due to a rise in stress hormones in seriously ill patients. This is consistent with Ertorer et al (2010), who found that patients with hyperglycaemia in the absence of diabetes had a higher APACHE-II score. In addition, Bosarge et al (2013) have shown that the more sick or seriously injured patients are, the higher the glucose level. Carmona et al (2018) observed a significant relationship between glycaemic variability and more serious illness.

There was a significant relationship between hyperglycaemia and enteral nutrition in patients without diabetes. This suggests that hyperglycaemia can be amplified by the dietary intake. This was ascertained by Deane et al (2019), who found that enteral nutrition including high levels of carbohydrate could exacerbate hyperglycaemia. Conversely, Batista et al (2016) showed that blood glucose could be lowered by administering enteral nutrition with low-carbohydrate formulations. López-Gómez et al (2019) also showed that hyperglycaemia was associated with enteral nutrition and was an independent risk factor for mortality. Marik and Preiser (2010) observed that, at equivalent degrees of glycaemic regulation, patients receiving enteral nutrition had a higher mortality rate than those receiving parenteral nutrition. On the other hand, Koyfman et al (2018) and Yébenes et al (2019) have shown that parenteral nutrition is the main source of hyperglycaemia in critically ill patients. Ma et al (2018) showed that parenteral nutrition resulted in hyperglycaemia among critically and non-critically ill patients, regardless of history of diabetes.

There was also a significant relationship between hyperglycaemia and mechanical ventilation. This means that mechanical ventilation, as a source of stress, may increase the risk of hyperglycaemia in critically ill patients. Pierre et al (2005) have shown that hyperglycaemia can extend the duration of mechanical ventilation support and that normalising blood glucose levels can accelerate weaning from ventilation. Mukherjee et al (2014) indicated that hyperglycaemia increases the risk of polyneuropathy, which could lead to prolonged mechanical ventilation. Marik (2016) revealed that hyperglycaemia was followed by a diagnosis of new ventilator-associated pneumonia in patients without diabetes.

Study limitations

This study was limited by the convenience nature of the sample. Furthermore, data were collected from a single hospital, which can hinder the generalisability of the study results.

Conclusion and recommendations

Based on the current results, it can be concluded that age 46–60 years, neurological disorders, more severe disease, enteral nutrition and mechanical ventilation are risk factors for hyperglycaemia in critically ill inpatients without diabetes.

Intensive care units should consider the importance of protocols related to the monitoring of glucose levels in those patients identified as high-risk in this study, in order to manage hyperglycaemia early. Further assessments should be made in those needing enteral nutrition. ■

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