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# Prognostic Factors of Concomitant Hyperglycemia and Hypocalcemia in Pediatric Intensive Care Units

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## Abstract

**Background:** Hyperglycemia and hypocalcemia have separately been attributed to adverse outcomes in critically ill patients. This study aimed to investigate the simultaneous effects of the two conditions on mortality and morbidity in a pediatric intensive care unit.

**Methods:** All children aged 1 month to 18 years, admitted for at least 24 hours to medical pediatric intensive care unit (PICU), Nemazee Hospital, Shiraz, Iran were reviewed over one year period. Those with a history of diabetes mellitus and any calcium disorders were excluded.

**Results:** Data on blood glucose and calcium during the first 6 hours of admission, in-PICU length of stay, need for mechanical ventilation, vassopressor drugs administration, and mortality were assessed. The incidence of hyperglycemia [≥150 mg/dl (8.3mmol/L)] and hypocalcemia [serum calcium < 8.5 mg/dl (2.12mmol/L)] were 26.5% and 43.9%, respectively. Hyperglycemia and hypocalcemia were associated with increased mortality. Among the survivors, hyperglycemia and hypocalcemia had no significant effect on PICU length of stay. The interaction of hyperglycemia and hypocalcemia did not intensify their separate effects on mortality, the need for mechanical ventilation and vasopressor infusion.

**Conclusions:** Although hyperglycemia and hypocalcemia separately increase the mortality rate, their simultaneous presence is not associated with poorer outcomes in critically ill patients.

**Keywords:** Hyperglycemia; Hypocalcemia; Mortality; Pediatrics

## Introduction

Critical illnesses caused by any severe medical or surgical diseases may trigger an acute phase response which is associated with several metabolic derangements.[1,2] These include hypo- and hyperglycemia, hypo-and hypercalcemia, hypo-and hyperphosphatemia, hypo-and hypermagnesaemia.[3]

In the most recent studies, hyperglycemia and hypocalcemia have separately been attributed to adverse outcomes including higher mortality and longer length of hospitalization in critically ill patients.[4-11] However, such studies suffer from some shortcomings. First, most of them have been conducted on critically ill adult patients and there are few studies of this type on pediatric age groups. Secondly, most authors have evaluated the effects of hyperglycemia and hypocalcemia on the outcomes separately. To the best of our knowledge, there is no study evaluating their interactions with mortality and length of stay (LOS) in pediatric intensive care units (PICU).

The objective of this study was to determine whether hyperglycemia and hypocalcemia together adversely affect the outcome of the critically ill children admitted to PICU. The Pediatrics Risk of Mortality III Score (PRISM-III) was used as a measure of patient acuity to control the confounding effects of disease severity.

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## Materials and Methods

The setting for the study was a 5-bed medical PICU which is a tertiary care center affiliated with Shiraz University of Medical Sciences, Shiraz, south of Iran. All patients admitted to PICU from September 2006 to September 2007 were eligible to be included in the study. Patients with pre-existing or new diagnosis of diabetes mellitus and those with known calcium disorders including hypo-and hyperparathyroidism were excluded. In addition, all patients older than 18 years and those with PICU stay of shorter than 24 hours were excluded.

The independent variables were initial blood sugar (BS) and serum calcium (Ca) within the first 6 hours of admission to PICU. Primary outcome was in-hospital mortality while secondary outcome was in-PICU LOS. Demographic data, diagnosis at admission to PICU, PRISM-III, outcomes and information about mechanical ventilation and vasoactive infusion (dopamine, dobutamine, epinephrine and norepinephrine) were recorded. Vasoactive agents were administered routinely as per hospital PICU's protocol. The approval of the institutional review board was obtained. The study was approved by the ethics committee of the university.

The patients were classified into two groups based on their blood sugar levels. Group 1 with BS<150 mg/dl (8.3 mmol/L) and group 2 with BS≥150 mg/dl (8.3 mmol/L).[12] During the study, no particular protocol was adapted for monitoring blood glucose or maintaining euglycemia in patients, and all the staff in the intensive care unit unanimously treated glucose>180 mg/dl. The cut-off point for hypocalcemia was defined as serum Ca<8.5 mg/dl (2.12 mmol/L).[13] The Ca level was corrected, using albumin level following the formula: " corrected Ca (mg/dl)=measured total Ca [(mg/dl)+0.8 (4-serum albumin g/dl)], where 4 represents the average albumin level in children. The data were stated in terms of mean±standard deviation (SD) or mean and interquartile.

The data were compared, using student's t-test for continuous, normal distributed variables, and the Mann-Whitney test for non-normally distributed variables. Categorical variables were compared, using the Chi-Square or Fisher Exact test. Logistic regression analysis was used to analyze the interaction of the two variables. *p* value less than 0.05 was considered significant. Statistical analysis was performed using SPSS software (version 15, Chicago, IL, USA). Analysis of covariance (ANCOVA) was used to eliminate the confounding effects of disease severity on the outcomes reflected by PRISM-III.

## Results

There were a total of 290 admissions to PICU during the study period, of which 196 patients were enrolled. Ninety four patients were excluded from the study because of exclusion criteria as aforementioned. The diagnosis included respiratory illnesses (18.98%), cardiac medical illnesses (9.20%), central nervous system disorders (22.96%), sepsis (17.86%), liver failure (5.60%), hematology and oncology problems (7.65%), poisoning and drug overdose (9.69%), renal failure (4.08%), and metabolic disorders (4.08%). Male subjects accounted for 56% of the studied population. The mean age of the patients was 18 months (first quartile: 8 and 3rd quartile: 72 months of old). A total of 67 out of 196 patients (34.2%) died during their hospital admission. Among the survivors, mean±SD in-PICU LOS was 4.68±4.83 days which ranged from one to 30 days (Table 1).

**Table 1:** Demographic characteristics of the studied population

| Age | No. (%) |
|---|---|
| 1 m- 6 m | 61 (31) |
| 7m-24 m | 55 (28) |
| 25-216 m | 80 (41) |
| Sex | |
| Male | 110 (56.1) |
| Female | 86 (42.9) |
| Survival | |
| Yes | 129 (65.8) |
| No | 67 (34.2) |
| Use of Mechanical ventilation | |
| Yes | 110 (56.1) |
| No | 86 (43.9) |
| Vasopressor infusion | |
| Yes | 60 (30.6) |
| No | 136 (69.4) |

The initial BS ranged from 14 mg/dl (0.77mmol/L) to 635 mg/dl (35.27 mmol/L) with a mean±SD of 140.63±89.94 mg/dl. The incidence of hyperglycemia [i.e. BS≥150 mg/dl (8.3 mmol/L)] was 26.5%. During admission to the PICU, 75.5% of the patients had their total serum Ca checked with a range of 5.3-11.7 mg/dl (1.32-2.91 mmol/L) [8.52±0.98 mg/dl (mean±SD)]. The incidence of hypocalcemia [i.e. Ca<8.5 mg/dl (2.12 mmol/L)] was 43.9%.

Among the survivors, BS and Ca values caused no significant effects on PICU LOS ($p$=0.867 and 0.218, respectively) (Table 2).

The mortality rate was 51.9% in patients with BS≥150 mg/dl and 27.8% in patients with BS<150 mg/dl. BS≥150 mg/dl was associated with 2.8 fold increase in the risk of death (95% confidence interval 1.45-5.41, $p$=0.002). Also, the frequency of patients with BS≥150 mg/dl who needed mechanical ventilation (69.2%) or vasoactive drugs administration (46.2%) was significantly higher than that in patients with BS<150 mg/dl (52.8% and 25.01%, respectively) ($p$=0.04 and 0.005, respectively) (Table3).

ANCOVA test was used to test the contribution of hyperglycemia and survival when disease severity was assessed as a covariate. Upon controlling the disease severity by ANCOVA test, hyperglycemia was still more prevalent among the non-survivors compared with that in the surviving group ($p$=0.046). Considering the indicators of morbidity including mechanical ventilation use and vasoactive drugs administration, there was no statistically significant difference between the mean glucose values of the paired groups, i.e. mechanically ventilated vs. non-mechanically ventilated ($p$=0.059) and vasoactive administration vs. non-vasoactive use group ($p$=0.073).

Regarding the total serum Ca levels, the mean serum calcium was significantly lower in non-survivors than that in survivors, i.e. 8.19±0.94 versus 8.70±0.97mg/dl, $p$<0.001 (odds ratio: 3.5, 95% CI=1.71-7.14). The death rate was 49.2% in the hypocalcemia group versus 21.7% in the normocalcaemic group ($p$<0.0001). Those with hypocalcemia during the PICU admission needed more supportive treatment with vasopressor drugs compared to the normocalcemic patients ($p$<0.001), but the use of mechanical ventilation was not significantly different in both groups ($p$=0.105) (Table 3). Mann-Whitney test was used, revealing that PRISM-III is not a confounding variable regarding the total serum Ca level ($p$=0.069), so there was no need to control its effects.

Finally, we analyzed the interaction of BS and Ca with mortality, use of mechanical ventilation and vasopressor drugs adjusted for PRISM-III effects, but to our surprise, their interactions did not synergize their separate effects on mortality or morbidity (Table 4).

**Table 2:** Blood sugar, calcium levels and their corresponding length of stay at PICU

| | No. | LOS (d) (Mean±SD) | *P* value |
|---|---|---|---|
| BS | | | |
| < 150 mg/dl (8.3 mmol/L) | 144 | 4.68±5.05 | 0.87 |
| ≥ 150 mg/dl (8.3 mmol/L) | 52 | 4.54±4.1 | |
| Ca | | | |
| < 8.5 mg/dl (2.12 mmol/L) | 64 | 4.75±4.14 | 0.22 |
| ≥ 8.5 mg/dl (2.12 mmol/L) | 83 | 5.82±5.87 | |

BS: Blood sugar, Ca: Calcium, LOS: Length of stay

**Table 3:** Blood glucose, calcium levels and their corresponding mortality, use of mechanical ventilator and vasopressin infusion

| | | Survival | | *P* value | Mechanical ventilation | | *P* value | Vasopressor infusion | | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| **All patients** | | **Yes** | **No** | | **Yes** | **No** | | **Yes** | **No** | |
| Bs (mg/dl) | ≥150 | 25 (48.1%) | 27 (51.9%) | 0.002 | 36 (69.2%) | 16 (30.8%) | 0.04 | 24 (46.2%) | 28 (53.8%) | 0.005 |
| | <150 | 104 (72.2%) | 40 (27.8%) | | 76 (52.8%) | 68 (47.2%) | | 36 (25.0%) | 108 (75.0%) | |
| Ca (mg/dl) | <8.5 | 33 (50.8%) | 32 (49.2%) | <0.001 | 46 (70.8%) | 19 (29.2%) | 0.105 | 31 (47.7%) | 34 (52.3%) | <0.001 |
| | ≥8.5 | 65 (78.3%) | 18 (21.7%) | | 48 (57.8%) | 35 (42.2%) | | 14 (16.9%) | 69 (83.1%) | |

BS: Blood sugar, Ca: Calcium

**Table 4:** Simultaneous effects of blood sugar and calcium on mortality rate, use of mechanical ventilation and vasopressor infusion (PRISM-III effect adjusted)

| | Survival | | *P* value | Mechanical ventilation | | *P* value | Vasopressor infusion | | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| **All patients** | **Yes** | **No** | | **Yes** | **No** | | **Yes** | **No** | |
| Sub group 1 (BS<150 mg/dl PRISM-III≥5) | | | | | | | | | |
| Ca (mg/dl) (mean±SD) | 8.49±0.88 (n=40) | 8.51±0.97 (n=14) | 0.944 | 8.6±0.81 (n=32) | 8.33±0.99 (n=22) | 0.276 | 8.06±0.97 (n=12) | 8.62±0.84 (n=42) | 0.055 |
| Sub group 2 (BS≥150 mg/dl PRISM-III≥5) | | | | | | | | | |
| Ca (mg/dl) (mean±SD) | 8.5±0.87 (n=13 ) | 8.31±1.03 (n=13) | 0.612 | 8.39±0.94 (n=20) | 8.47±1.04 (n=6) | 0.856 | 8.34±0.92 (n=14) | 8.48±0.99 (n=12) | 0.698 |

BS: Blood sugar, Ca: Calcium, PRISM-III: Pediatric Risk of Mortality-III Score

## Discussion

The present study demonstrated that hyperglycemia and hypocalcemia together did not affect the mortality and outcome of the critically ill children admitted to PICU. To the best of our knowledge, there has been no reported study on this issue. Meanwhile, the results of the present study revealed that hyperglycemia and hypocalcemia were significantly more prevalent among non-survivors in comparison to those who survived PICU admission. These findings have been revealed in previous studies as well,[14-22] particularly among critically ill surgical patients.[4-6] It has also been demonstrated that even moderate degree hyperglycemia [BS>110 mg/dl (6.11 mmol/L)] was associated with an increase in hospital mortality.[15,16] Of interest, it has been observed that the intensity and duration of hyperglycemia are independently associated with mortality in PICU.[18] Hirshberg and her colleagues also showed that hyperglycemia and glucose variability are associated with increased prevalence of nosocomial infection in pediatric critically ill patients.[23]

Although Klein and his colleagues in a recent study claimed that hyperglycemia was not independently associated with increased mortality and LOS,[24] our study revealed that even upon controlling the disease severity, hyperglycemia was independently associated with increased mortality. However, PICU morbidity including LOS, use of mechanical ventilation and vasopressor drugs infusion were not affected by blood glucose level at admission time when confounding effects of disease severity reflected by PRISM-III were eliminated.

In contrast to previous studies,[4-11,23] we could not find any association between hyperglycemia and longer length of PICU admission. This might be due to the use of In-PICU LOS in the present study instead of In-hospital LOS parameter used in other studies. It seems that it is somehow the reflections of the disease severity and not simply the deleterious effects of hyperglycemia as it was asserted by Srinivasan and his Co-workers.[18]

Moreover**,** like previous studies,[18,19] the present study investigated the traditional approach of permissive hyperglycemia with blood glucose just below the renal threshold (180-200 mg/dl) (10-11.11 mmol/L) in critically ill patients. It seems that tight glucose control might have favorable effects on the outcomes of patients admitted to intensive care units,[24] although this approach has been recently questioned by Klein and his colleagues in their large retrospective study.[23]

Another finding of the present study was the lower mean Ca level among non-survivors compared with that in the survivors (8.19±0.94 versus 8.7±0.97 mg/dl, $p$=0.003). Also, the death rate was significantly higher in hypocalcemic critically ill patients than normocalcemic groups ($p$<0.002). The same findings have been reported in some previous studies.[19-21]

The present study revealed that although hypocalcemia was associated with increased risk of vasopressin usage, it could not be shown in terms of using mechanical ventilator and in-PICU LOS. Similarly, higher mortality and in-hospital LOS has been reported in PICU.[11] Also, it has been suggested that hypocalcemia should be considered in hypotensive patients refractory to fluid and vasopressors.[11]

Whether hypocalcaemia has a direct impact on survival or is a marker of serious illness is not clear.

However, it has been observed in other studies that using ionized Ca is more accurate than using the total serum Ca.[11,21] Ca correction, based on the used formula, does not always correlate with ionized Ca particularly if hypocalcaemia is considered to be clinically significant in critically ill patients.

The present study has surely some limitations. In addition to the limitations imposed by the retrospective nature of our study, the causality between BS, Ca and mortality or morbidity can not be implied based on statistical analysis alone. Considering the retrospective design of the present study, the methods of BS and Ca collection and analysis were not standardized. The timing of blood glucose and calcium estimation was also not standardized. Also, we used PRISM-III to describe the disease severity and to eliminate the confounding effects of disease severity on the outcomes. PRISM is more likely to be biased by the quality of treatment during the first 24 hours of PICU admission in response to bad or good intensive care. This bias could be avoided by using an alternative approach such as Pediatric Risk of Mortality (PIM) score. Moreover, due to the lack of facilities required to check ionized calcium in the studied center, we had to check total serum Ca which is less accurate than ionized Ca. In addition, serum Ca was not checked in all of the studied population. Another limitation was that we did not follow serial Ca and BS in hypocalcaemic and hypoglycemic patients. So we do not have any information regarding the intensity and duration of the abnormalities. More prospective randomized studies on this aspect are recommended.

Taking into account the above findings, we can conclude that although hyperglycemia and hypocalcemia separately increase the risk of mortality and to some extent morbidity, the concomitant presence of both is not associated with poorer outcome in critically ill patients.

As demonstrated, the prevalence of hyperglycemia and hypocalcemia in critically ill patients is considerable. Also, a clear negative correlation of both disturbances with survival has been shown. However, considering the disease severity, the association of hyperglycemia and hypocalcemia with PICU indicators of morbidity could not be verified. In addition, the interaction of both disturbances did not have any synergistic effect on mortality and morbidity. It seems that more prospective, randomized multi-center trials are needed to consolidate the findings and help make more proper judgment.

**Conflict of interest:** None declared.

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