Original Research Article

Study of glycemic gap in hyperglycemic emergencies of type 2 diabetes mellitus

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Received: 19 February 2018
Accepted: 26 February 2018

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is associated with two serious hyperglycemic emergencies namely Diabetic ketoacidosis (DKA) and Hyperosmolar hyperglycemic state (HHS). The aim of the study was to determine the usefulness of glycemic gap in T2DM patients with DKA and HHS.

Methods: T2DM cases above 20 years of age were included in this study. The study population was divided into three broad groups as T2DM without hyperglycemic emergencies, T2DM with DKA, T2DM with HHS, with 50 subjects in each group. Glycemic gap was calculated in the study population and compared between the three groups. The relationship between glycemic gap and the conventional indicators of severity in hyperglycemic emergencies of T2DM were determined.

Results: Of the three study groups, T2DM cases with HHS presented with substantial alterations in the baseline biochemical parameters. The glycemic gap was also highly elevated in the HHS cases than the others. Glycemic gap showed significant correlation only with plasma osmolality of the HHS cases.

Conclusions: Elevated glycemic gap indicating stress induced hyperglycemia (SIH) occur in hyperglycemic emergencies of T2DM, especially HHS.

Keywords: Diabetic ketoacidosis, Glycemic gap, Hyperglycemic emergencies, Hyperosmolar hyperglycemic state, Type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic progressive metabolic disorder with hyperglycemia due to insulin resistance and relative insulin deficiency. The diabetic burden of India is rapidly increasing with a prevalence rate of 8.7%, while the estimated global prevalence was 8.8% as on 2015.¹ Chronic T2DM patients develop many of the long term diabetic complications, with microvascular and macrovascular pathologies resulting from prolonged hyperglycemia. When hyperglycemia is grossly uncontrolled, T2DM patients go for hyperglycemic emergencies. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the two common hyperglycemic emergencies occurring in T2DM patients. Of these, although HHS is seen commonly in T2DM and DKA presents commonly in type 1 diabetes mellitus (T1DM), a third of the DKA cases occur in T2DM cases also.² The estimated incidence rates were 4 to 8 per 1000 diabetic patients for DKA and 1 per 1000 diabetic patients for HHS. The hyperglycemic emergencies cause sudden mortality in many T2DM cases; DKA has a mortality rate of 1-5 %, while HHS has a mortality of 5-20%.³
Insulin deficiency, along with increased counter-regulatory hormones forms the pathogenic basis of the diabetic hyperglycemic emergencies. Similar variations in the levels of glucose regulatory hormones also occur in most acute severe illnesses of diabetics, which therefore result in Stress Induced Hyperglycemia (SIH), associated with increased mortality in these patients. Glycemic gap, a measure of SIH in diabetic critically patients, predicted the adverse outcomes in these patients. It is the gap between admission plasma glucose and the HbA1C derived estimated average glucose (eAG) levels. Glycemic gap has also been useful in predicting the unfavorable outcomes in diabetics with trauma and other diseases like pyogenic liver abscess, community acquired pneumonia.

The diagnosis and severity staging of diabetic hyperglycemic emergencies involve plasma glucose, serum osmolality, serum bicarbonate, arterial pH, anion gap, urine ketones, mental status. The objective of this study is to determine the usefulness of glycemic gap as a prognostic indicator in acute hyperglycemic emergencies of T2DM.

METHODS

This was a descriptive study involving T2DM cases above 20 years of age. The study was approved by the Institute Ethics Committee and exempted from obtaining informed consent. The study population was divided into three broad groups as T2DM cases without hyperglycemic emergencies, T2DM cases with DKA, T2DM cases with HHS, with 50 subjects in each group.

The clinical diagnosis of T2DM, DKA and HHS were based on the American Diabetes Association (ADA) criteria. Clinical and demographic data were retrieved from the medical case records of the study population, during the period of May 2017 to October 2017. Cases with incomplete clinical data, as well as cases of prolonged starvation, chronic alcoholics, hemoglobinopathies, aspirin poisoning and autoimmune disorders were excluded from the study.

The routine biochemical investigations were done in Roche Cobas C311 autoanalyser, electrolytes were assayed in Roche 9180 electrolyte analyzer, and arterial blood gas (ABG) analyses were done in Roche Cobas b121 analyzer. Estimated average glucose (eAG) was calculated as follows from the HbA1C values: eAG = (28.7 × HbA1C)−46.7.9 Anion gap was calculated from the formula: Anion gap = [Serum Sodium (mEq/L)]−[Serum Chloride (mEq/L)]+ Serum Bicarbonate (mEq/L).10 Delta anion gap is the difference between calculated anion gap and mean normal anion gap. Plasma osmolality was calculated from the following formula:

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\text{Plasma osmolality} = 1.86 \times (\text{Serum Sodium} \ (\text{mEq/L})) + \text{Plasma Glucose} \ (\text{mg/dL})/18 + \text{Plasma Urea} \ (\text{mg/dL})/2.8 + 9.11 \times \text{eGFR was calculated from the CKD-EPI creatinine (2009) formula using the National Kidney Foundation tool.12}
\]

Glycemic gap is the difference between admission plasma glucose and eAG derived from HbA1C levels. Glycemic gap was calculated in the study population and compared between the three groups. The relationship between glycerimic gap and the conventional indicators of severity in hyperglycemic emergencies of T2DM were determined.

Statistical analysis

The data were expressed as mean, median, standard deviation (SD) and interquartile range. One-way ANOVA test and Kruskal Wallis test were used to compare the glycemic gap and other baseline biochemical parameters across the study groups. Spearman correlation test was used to correlate the glycemic gap with the indicators of severity in DKA and HHS. SPSS 16 software was used for statistical analysis. p-value <0.05 was considered statistically significant.

RESULTS

Demographic data was compared across the three study groups, and there was not any significant variation in gender distribution among the three groups (Table 1). But there was a significant difference in the age of the study groups, with HHS cases having highest mean age.

Majority of the baseline biochemical parameters also showed marked deviations across the study groups. The biochemical measures of glycemic control like admission plasma glucose, HbA1C and eAG presented notable changes between the groups, as the T2DM cases with HHS had highest levels. Likewise, glycemic gap was also significantly higher in the HHS group than the remaining study groups.

Renal function tests like serum urea and creatinine were increased, with a substantial decline in eGFR levels in T2DM cases with HHS than the other two groups. Serum electrolyte and ABG analyses showed significant reduction in sodium and bicarbonate levels, with simultaneous rise in anion gap and delta anion gap levels.

Glycemic gap was correlated with the biochemical indicators of severity in the hyperglycemic emergencies. In T2DM cases with DKA, there was not any appreciable correlation between glycemic gap and the severity indices like arterial pH, bicarbonate and anion gap levels (Table 2). Whereas in the HHS group, glycemic gap had significant positive correlation only with plasma osmolality levels (Table 3).
### Table 1: Comparison of demographic data and baseline biochemical parameters across the study groups.

| Parameter                              | T2DM without hyperglycemic emergencies | T2DM with DKA       | T2DM with HHS       | Table value | p value |
|----------------------------------------|----------------------------------------|---------------------|---------------------|-------------|---------|
| Males (%)                              | 32 (64%)                               | 29 (58%)            | 31 (62%)            | 0.39        | 0.821²  |
| Age (years)                            | 52.06±10.32                           | 51.60±13.42         | 56.72±9.98          | 3.12        | 0.047²  |
| Admission Plasma Glucose (mg/dL)       | 262 (223,322)                          | 351.50 (293,480.25) | 630.50 (609.75,683.75) | 104.63      | <0.001³  |
| Serum urea (mg/dL)                     | 18 (15,24.25)                          | 30 (21,54)          | 55.58 (33.50,73.50) | 55.41       | <0.001³  |
| Serum creatinine (mg/dL)               | 0.70 (0.60,0.80)                       | 0.90 (0.70,1.20)    | 1.15 (0.90,1.60)    | 39.59       | <0.001³  |
| eGFR (mL/min)                          | 106 (91.75,112.50)                     | 89 (61,110.50)      | 59 (43.75,83.75)    | 38.68       | <0.001³  |
| HbA₁C (%)                              | 8.03±1.37                              | 8.45±1.78           | 9.95±1.59           | 19.99       | <0.001²  |
| eAG (mg/dL)                            | 183.94±39.38                           | 195.70±50.98        | 238.86±45.86        | 20.06       | <0.001²  |
| Glycemic gap (mg/dL)                   | 90.50 (29.50,144)                      | 159 (112.50,259.50) | 419 (376.50,462)    | 99.00       | <0.001³  |
| Serum Na⁺ (mEq/L)                      | 136.10±3.38                            | 132.12±6.41         | 132.56±5.62         | 8.49        | <0.001²  |
| Serum K⁺ (mEq/L)                       | 4.24±0.42                              | 4.38±0.87           | 4.27±0.85           | 0.52        | 0.59²   |
| Serum Cl⁻ (mEq/L)                      | 100.62±4.70                            | 99.34±6.69          | 97.19±14.93         | 1.55        | 0.22²   |
| Serum HCO₃⁻ (mEq/L)                    | 23.9±2.41                              | 17.88±4.24          | 18.58±4.34          | 38.16       | <0.001²  |
| Anion gap (mEq/L)                      | 15.5 (10.75,20)                        | 19 (16,22.25)       | 18 (14,23)          | 9.69        | 0.008²  |
| Delta anion gap (mEq/L)                | 3.5 (1.25,8)                           | 7 (4,10.25)         | 6 (2,11)            | 9.68        | 0.008²  |
| Plasma osmolality (mOsm/kg)            | 294.30±0.87                            | 299.46±17.85        | 321.36±12.29        | 56.60       | <0.001²  |

1-Chi square test, 2- One-way Anova test, 3-Kruskal Wallis test, * Significant p value <0.05

### Table 2: Correlation of glycemic gap levels with severity indices in T2DM patients with DKA.

| Correlation coefficient | p value |
|-------------------------|---------|
| Arterial pH              | 0.182   | 0.21¹  |
| Serum HCO₃⁻ (mEq/L)      | 0.107   | 0.46¹  |
| Anion gap (mEq/L)        | 0.05    | 0.73¹  |

1-Spearman correlation test, *Significant p value <0.05

### Table 3: Correlation of glycemic gap levels with severity indices in T2DM patients with HHS.

| Correlation coefficient | p value |
|-------------------------|---------|
| Admission Plasma Glucose (mg/dL) | 0.70    | 0.63¹  |
| Plasma osmolality (mOsm/kg)     | 0.007   | 0.03¹  |
| Serum urea (mg/dL)             | 0.028   | 0.85¹  |
| Serum creatinine (mg/dL)       | 0.2     | 0.16¹  |
| eGFR (mL/min)                  | 0.19    | 0.18¹  |

1-Spearman correlation test, *Significant p value <0.05
DISCUSSION

The demographic data findings in this study show that the groups were gender matched, while the increased mean age of HHS group can be attributed to the fact that elderly T2DM patients are at a high risk to develop HHS.3 The baseline biochemical changes observed here are in conformance with the diagnostic criteria for hyperglycemic emergencies; DKA is characterized by hyperglycemia (>250 mg/dL) along with high anion gap metabolic acidosis and ketosis, while HHS is diagnosed by extreme hyperglycemia (>600 mg/dL) together with a coexisting hyperosmolar state (plasma osmolality >320 mOsm/Kg).2 The variations in the HbA1C and eAG levels suggest poor glycemic control in the T2DM cases with hyperglycemic emergencies. The concurrent prerenal azotemia is due to the acute hyperglycemia, hyperosmolarity, dehydration and hypotension seen in the hyperglycemic emergencies, more so in the cases of HHS. This is in agreement with the results of Bai F et al, that is elevated serum creatinine and decreased eGFR occur in hyperglycemic emergencies.13 Hyponatremia in hyperglycemic emergencies is the effect of dehydration, while bicarbonate depletion is caused by the metabolic acidosis. The accumulation of unmeasured anions such as ketone bodies cause high anion gap and delta gap levels seen in the ABG reports of the hyperglycemic emergencies, particularly DKA.

Glycemic gap was elevated in the hyperglycemic emergencies, with HHS group having maximum levels, subsequent to the severe hyperglycemia occurring in these cases. These findings are similar to many of the available literatures, that acute severe illnesses are associated with Stress induced hyperglycemia (SIH).14 The SIH is caused by elevated anti-insulin hormones (cortisol, catecholamines, growth hormone) ensuing the accelerated functioning of hypothalamic-pituitary-adrenal (HPA) axis, sympathoadrenal system and inflammatory cytokines.15 Moreover, the inflammatory mediators like cytokines, interleukins (IL-1, IL-6, IL-10, TNF-α) and C-reactive protein (CRP) decrease insulin sensitivity in peripheral tissues.16 Thus, increased gluconeogenesis and decreased glucose uptake by tissues lead to hyperglycemia of SIH.

SIH is an adaptive response of acute illnesses, so mild to moderate SIH is found to be beneficial, while the severe form is deleterious.15 The predicted mechanisms of SIH induced damage are osmolar and acidic changes and superoxide generation, affecting the immune, coagulation and other vital functions.17 SIH can be clinically determined by the elevated levels of admission plasma glucose, mean plasma glucose and plasma glucose variability.18 Several studies deduced the association of SIH with adverse outcomes in critically ill patients with diseases like acute myocardial infarction, trauma, acute ischemic stroke, pulmonary embolism, arrhythmias, unstable angina, sepsis, community acquired pneumonia.16,19,22

The results were discordant between diabetic and non-diabetic ICU patients, with Egi M et al stating that SIH did not have a definitive predictive role in diabetic critically ill patients; the reason could be the pre-existing diabetic hyperglycemia adding up to the hyperglycemia due to SIH during any acute illness.23 Hence in diabetics, the chronic hyperglycemia is viewed as a confounder in interpreting SIH using the conventional variables like admission plasma glucose, thereby proposing the usage of glycemic gap which removes the confounding effect of chronic diabetic hyperglycemia by subtracting eAG from admission plasma glucose.24

The correlations of glycemic gap with severity indices of hyperglycemic emergencies were not significant except for the plasma osmolality levels in HHS group. This linear relationship between glycemic gap and plasma osmolality could be due to that the plasma glucose is a component of the calculated plasma osmolality.13 HHS cases with major increase in plasma glucose, therefore had consecutively raised in plasma osmolality levels. Glycemic gap had insignificant positive correlations with the other severity indices of hyperglycemic emergencies. Although glycemic gap had paramount elevations in hyperglycemic emergencies especially HHS, its role in predicting the severity and prognosis of the hyperglycemic emergencies is not substantiated by the present findings. This is in contrary to most previous results confirming the definitive negative prognostic role of glycemic gap and other SIH indices under varied disease setting like ICU, pyogenic liver abscess, community acquired pneumonia, trauma; such studies were lacking in diabetic hyperglycemic emergencies.6,7 Nevertheless, the role of elevated glycemic gap and SIH in critically ill diabetics as well as hyperglycemic emergencies could not be entirely ruled out, as the current guidelines laid by the American College of Critical Care Medicine suggested intensive insulin therapy to maintain a tight glycemic control, thereby improving the clinical outcome of critically ill diabetics.25

CONCLUSION

 Elevated glycemic gap indicating stress induced hyperglycemia (SIH) occur in hyperglycemic emergencies of T2DM, especially HHS; but its role in predicting the severity of the hyperglycemic emergencies is not warranted.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Sivakumar P, Moonishaa TM, George N. Study of glycemic gap in hyperglycemic emergencies of type 2 diabetes mellitus. Int J Res Med Sci 2018;6:1151-5.