Acid-base and electrolyte disturbances in patients with diabetic ketoacidosis

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Abstract

We undertook the present study to examine the acid-base and electrolyte disturbances in relation to hydration status in patients with diabetic ketoacidosis (DKA). A total of 40 insulin-dependent diabetes mellitus patients (22 male, 18 female), aged 18–61 years with DKA admitted to our hospital during the last 2 years, were studied. The duration of diabetes averaged 9 ± 2 years. In all cases a detailed investigation of the acid-base status and electrolyte parameters was performed. Twenty-one patients had a pure metabolic acidosis with an increased serum anion gap, seven had DKA combined with hyperchloremic metabolic acidosis, nine had DKA coexisting with metabolic alkalosis, while three had DKA with a concurrent respiratory alkalosis. Hydration status as evidenced by the ratio of urea/creatinine seems to play an important role in the development of mixed acid-base disorders (detected by changes in the ratios Δ anion gap/Δ bicarbonate (ΔAAG/ΔHCO₃⁻) and sodium/chloride (Na/Cl)). In fact, hyperchloremic acidosis developed in the patients with the better hydration status. However, contradictorily, the severely dehydrated patients who experienced recurrent episodes of vomiting developed DKA with a concurrent metabolic alkalosis. Finally, patients with pneumonia or gram-negative septicemia exhibited DKA combined with a primary respiratory alkalosis. We conclude that patients with DKA commonly develop mixed acid-base disorders, which are partly dependent on patients' hydration status.

Keywords: Δ anion gap/Δ bicarbonate (ΔAAG/ΔHCO₃⁻) ratio; Diabetic ketoacidosis; Serum anion gap; Sodium/Chloride concentration ratio (Na/Cl)

1. Introduction

Patients with diabetic ketoacidosis (DKA) commonly develop mixed acid-base disorders which are possible to be diagnosed only when a careful...
search of acid-base balance and electrolyte parameters is performed [1–6]. It has been stated that hydration status can modify the appearance of mixed acid-base disorders as well as the values of these parameters [4,6,7]. In the present paper, a careful approach of the acid-base and electrolyte abnormalities in relation to hydration status is attempted in patients with DKA.

2. Material and methods

We studied a total of 40 insulin-dependent diabetes mellitus patients (22 male, 18 female) aged 18–61 years with DKA, who were hospitalized during the last 2 years in our University Hospital (600 beds). This hospital is one of the two tertiary hospitals which care for the whole region of Northwestern Greece (0.5 million people). The duration of diabetes averaged 9 ± 2 years (range 1–17 years). The diagnosis of DKA was based on the presence of a high (> 20 mmol/l) serum anion gap (SAG) metabolic acidosis with hyperglycemia (serum glucose more than 250 mg/dl) and was confirmed by the demonstration of ketonemia, defined as serum acetate reaction of 4+ in a dilution greater than 1:2. In 24 patients, insufficient insulin was the primary cause of ketoacidosis, while in the remaining 16 patients DKA was ascribed to a superimposed infection of the urinary tract or the lungs (11 patients), to acute primary trauma (2 patients), to severe emotional stress (2 patients), and to acute myocardial infarction (1 patient). Patients with chronic renal failure (serum creatinine > 1.6 mg/dl after rehydration), liver failure, hypoalbuminemia of any cause, chronic obstructive lung disease, lactic acidosis, as well as alcoholic patients, or patients consuming drugs affecting acid-base status and electrolyte parameters, were excluded from the study. Fifty-one randomly selected patients aged 19–62 years who had no conditions that could cause acid-base disorders and were admitted for elective procedures were used as controls. In all cases admission serum was available before treatment for the determination of serum glucose, urea, creatinine, total proteins and electrolytes (potassium, sodium, chloride, and bicarbonate). Arterial blood was also obtained for blood gases measurement. SAG was computed as: SAG = Na+ − (Cl− + HCO3−) [8]. A decrease in serum bicarbonate (ΔHCO3) was calculated as the normal serum bicarbonate (24 mmol/l) minus the measured serum bicarbonate. The excess anion gap (ΔAG) was estimated as the calculated anion gap minus the normal anion gap (12 mmol/l).

The diagnosis of pure DKA was established when no conditions that could have caused mixed acid-base disorders were present and the decrease in serum bicarbonate was approximately equal to the increase in serum anion gap (ΔAG/ΔHCO3 ratio between 0.8 and 1.2). The presence of mixed acid-base disorders was defined as follows: a hyperchloremic acidosis component was diagnosed when the reduction in serum bicarbonate was significantly greater than the increase in anion gap in the absence of respiratory alkalosis, resulting in a ΔAG/ΔHCO3 ratio less than 0.8. The coexistence of DKA with a primary metabolic alkalosis was present when the decrease in serum bicarbonate was significantly less than the increase in anion gap resulting in a ΔAG/ΔHCO3 ratio more than 1.2. Finally, the combination of DKA with a primary respiratory alkalosis was diagnosed when the measured PCO2 was less than that predicted by the formula of Albert et al [9] (expected arterial carbon dioxide tension = 1.5 (serum bicarbonate) + 8 + 2).

Hydration status was evaluated by the serum urea/creatinine ratio, which has been suggested to be especially helpful in the evaluation of hypovolemic states, even though it is affected to some degree by the rate of urea production.

The results were expressed as means ± SD. Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by student’s t-test to assess differences between groups. Linear regression analysis was performed for the correlation between parameters. Comparisons with P values less than 0.05 were considered statistically significant.

3. Results

Laboratory parameters based on the type of acid-base disturbances are shown in Table 1.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control population (n = 51)</th>
<th>Pure DKA (n = 21)</th>
<th>DKA + hyperchloremic acidosis (n = 7)</th>
<th>DKA + metabolic alkalosis (n = 9)</th>
<th>DKA + respiratory alkalosis (n = 3)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum glucose (mg/dl)</td>
<td>90 ± 9</td>
<td>385 ± 49</td>
<td>340 ± 44</td>
<td>408 ± 62</td>
<td>376 ± 44</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum urea (mg/dl)</td>
<td>25 ± 5</td>
<td>68 ± 16</td>
<td>43 ± 12</td>
<td>88 ± 11</td>
<td>66 ± 12</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.1 ± 0.3</td>
<td>1.9 ± 0.5</td>
<td>1.6 ± 0.4</td>
<td>2.1 ± 0.2</td>
<td>1.8 ± 0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum urea/creatinine</td>
<td>21 ± 6</td>
<td>36 ± 7</td>
<td>27 ± 6</td>
<td>42 ± 8</td>
<td>35 ± 6</td>
<td>0.005</td>
</tr>
<tr>
<td>Total serum proteins (g/dl)</td>
<td>7.9 ± 0.5</td>
<td>8.6 ± 0.5</td>
<td>7.6 ± 0.5</td>
<td>9.5 ± 0.5</td>
<td>8.5 ± 0.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>4.2 ± 0.1</td>
<td>4.2 ± 0.5</td>
<td>4.1 ± 0.6</td>
<td>3.5 ± 0.6</td>
<td>4 ± 0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>140 ± 4</td>
<td>141 ± 9</td>
<td>141 ± 8</td>
<td>137 ± 7</td>
<td>139 ± 9</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum chloride (mmol/L)</td>
<td>101 ± 3</td>
<td>101 ± 5</td>
<td>109 ± 4</td>
<td>95 ± 6</td>
<td>105 ± 5</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum Na/Cl</td>
<td>1.4 ± 0.02</td>
<td>1.4 ± 0.03</td>
<td>1.29 ± 0.07</td>
<td>1.5 ± 0.06</td>
<td>1.34 ± 0.03</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum bicarbonate (mmol/L)</td>
<td>23.5 ± 2</td>
<td>8 ± 5</td>
<td>8 ± 4</td>
<td>16 ± 4</td>
<td>8 ± 5</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum anion gap (mmol/L)</td>
<td>12 ± 2.4</td>
<td>30 ± 6</td>
<td>24 ± 4</td>
<td>25 ± 4</td>
<td>26 ± 4</td>
<td>0.01</td>
</tr>
<tr>
<td>ΔAG/ΔHCO₃</td>
<td>...</td>
<td>1.01 ± 0.06</td>
<td>0.76 ± 0.03</td>
<td>1.7 ± 0.2</td>
<td>0.82 ± 0.06</td>
<td>0.001</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.39 ± 0.02</td>
<td>7.22 ± 0.08</td>
<td>7.20 ± 0.06</td>
<td>7.28 ± 0.05</td>
<td>7.30 ± 0.06</td>
<td>0.01</td>
</tr>
<tr>
<td>PCO₂ (mmHg)</td>
<td>39.5 ± 2</td>
<td>23.5 ± 6</td>
<td>22.5 ± 5</td>
<td>26.5 ± 4</td>
<td>16 ± 8</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data: means ± SD
DKA: diabetic ketoacidosis
* ANOVA
In 21 cases no evidence of mixed acid-base disorders was found. In these patients, the sodium/chloride concentration ratio (Na/Cl) was found to be within the range obtained in the control population (1.37–1.44). Seven patients had DKA combined with hyperchloremic metabolic acidosis. In these cases the ratio Na/Cl was found to be lower than 1.37 (the lowest value observed in the normal controls). Compared with patients developing pure DKA, the group of patients demonstrating DKA combined with hyperchloremic metabolic acidosis had significantly decreased serum glucose, urea, creatinine, urea/creatinine, total proteins, and anion gap levels, as well as significantly increased serum chloride levels. In two out of these patients a chronic diarrheal syndrome was present, while another patient had increased serum potassium levels. In this patient laboratory investigation after treatment of acidemia confirmed the diagnosis of hyporeninemic hypoaldosteronism. Nine patients had DKA coexisting with metabolic alkalosis. These patients exhibited an increased Na/Cl ratio higher than the upper normal limit (1.44). They also had significantly increased serum glucose, urea, creatinine, urea/creatinine, total proteins, bicarbonate, anion gap, arterial pH and PCO₂ levels, as well as decreased serum potassium, sodium and chloride levels compared to patients with pure DKA or DKA combined with hyperchloremic metabolic acidosis. These patients experienced recurrent bouts of vomiting due to DKA. Finally, three patients had DKA coexisting with respiratory alkalosis. This small group of patients had significantly decreased serum Na/Cl, anion gap, ΔAG/ΔHCO₃ and PCO₂ levels, as well as increased serum chloride and arterial pH levels compared with patients exhibiting pure DKA. Primary hyperventilation was due to gram-negative septicemia (two patients) or to pneumonia (one patient). The last patient, who also exhibited chronic obstructive lung disease, had a PCO₂ of 27 mmHg, a value which is relatively high, possibly owing to a concomitant respiratory acidosis component.

It should be mentioned that no difference in the frequency of the various forms of DKA was found between younger (< 40 years) and older (> 40 years) patients.

No correlation was found between SAG and serum urea or the ratio of urea/creatinine in the whole group of patients. However, a very good correlation was found between the ratio urea/creatinine and both the ratios ΔAG/ΔHCO₃ (r = 0.72, P < 0.001) and Na/Cl (r = 0.68, P < 0.001). Moreover, serum glucose levels were well correlated with serum urea (r = 0.31, P < 0.01), as well as with the ratio of urea/creatinine (r = 0.61, P < 0.001).

In all patients the restoration of intravascular volume, the appropriate electrolyte management, the insulin administration, and the treatment of the precipitating conditions leading to DKA was followed by the reversal of acid-base abnormalities irrespective of the type of DKA.

4. Discussion

In our study the positive correlation between the ratio of urea/creatinine and both the ratios of ΔAG/ΔHCO₃ and Na/Cl in the whole group of patients suggests that the hydration status plays a prominent role in the development of mixed acid-base disorders, evidenced by changes in the ratios ΔAG/ΔHCO₃ and Na/Cl. In fact, hyperchloremic acidosis occurred in patients with the better hydration status. These patients can excrete ketones in the urine so efficiently that the anion gap is relatively normal before any therapy has been instituted resulting in a low (< 0.8) ΔAG/ΔHCO₃ ratio [2,4,6,10]. This ketoacid loss, which tends to lower the anion gap, is responsible for the concomitant hyperchloremic metabolic acidosis, as these ketoacid anions, if retained, could have been converted back into bicarbonate. In this setting, hyperchloremia is due to the retention of sodium chloride by the kidneys in an effort to preserve the extracellular volume. Moreover, the loss of the sodium salt of β-hydroxybutyrate and acetoacetate, together with water, leaves a fixed quantity of chloride to be distributed in a smaller volume, thereby increasing its concentration [2,4,6]. Furthermore, diarrhea as well as hyporeninemic hypoaldosteronism observed in some of these patients could have contributed to the development of hyperchloremic acidosis [11]. On the
other hand, patients with DKA combined with a metabolic alkalosis had the most severe degree of hypovolemia. The coexistent metabolic alkalosis was due to vomiting, frequently complicating ketoacidosis, which raised the serum bicarbonate concentration (and therefore the arterial pH) without significantly affecting the anion gap, thus leading to an increase in the ΔAG/ΔHCO₃ ratio [11]. Moreover, hypovolemia resulted from both vomiting and osmotic diuresis and contributed to the pathogenesis of metabolic alkalosis (contraction alkalosis) [12]. Additionally, this group of patients had lower serum levels of potassium, sodium and chloride compared with the other groups of DKA patients reflecting the greater volume and electrolytes losses observed. Finally, few patients had DKA coexisting with a primary respiratory alkalosis due to primary hyperventilation. In these patients, the ratio ΔAG/ΔHCO₃ was decreased because the degree of reduction in serum bicarbonate was exaggerated by the additive effects of accumulated acid (as reflected by the ΔAG) and the metabolic compensation for respiratory alkalosis [11]. The observed worsening of hypocarbonatremia in the face of virtual normalization of arterial pH emphasizes the fact that the serum bicarbonate concentration by itself does not give enough information to appropriately evaluate acid-base disorders. Furthermore, a decrease of the ratio Na/Cl was evident, due to respiratory alkalosis-induced hyperchloremia [13].

Interestingly, a positive correlation between serum glucose levels and the urea/creatinine ratio was noticed in the whole group of patients implying that the hydration status can influence glucose control, since volume depletion tends to increase hyperglycemia [7,14].

In conclusion, patients with DKA commonly develop mixed acid-base disorders, which are partly dependent on patients' hydration status.

Acknowledgements

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References