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ORIGINAL ARTICLE

Clinical Analysis of Electrolyte Disorders in Patients with Diabetic Ketoacidosis

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SUMMARY

Background: **The changes in the electrolyte profiles in patients with diabetic ketoacidosis (DKA) have rarely been reported. This study reports the abnormalities in the electrolyte profile, such as serum potassium, sodium, chloride, calcium, magnesium, and phosphorus.**
Methods: **Forty individuals in each of the DKA, diabetic ketosis (DK), nonketotic diabetes mellitus, and healthy control groups were included in this study to evaluate their clinical indicators, such as blood glucose, glycated hemoglobin (HbA1c), renal function, electrolytes, and arterial blood gas concentrations.**
Results: **Compared with the other three groups, patients in the DKA group had a longer course of diabetes; significantly higher levels of blood glucose, HbA1c, and serum creatinine ($p < 0.05$ or $p < 0.001$); lower estimated glomerular filtration rate (eGFR) ($p < 0.001$); and higher levels of serum potassium, sodium, phosphorus, magnesium, and effective osmotic pressure ($p < 0.05$). In the DKA patients, the incidences of hyperkalemia and hypokalemia were 32.5% ($p < 0.05$ or $p < 0.001$ vs. the other groups) and 7.5%, respectively. In the DKA patients, type 1 diabetes patients were younger and had higher blood glucose than type 2 patients ($p < 0.05$), but the electrolyte profiles were not significantly different. There were no significant differences in the serum electrolyte profile between mild to moderate DKA patients and severe DKA patients. Serum potassium was negatively correlated with eGFR ($r = -0.378$, $p = 0.018$). Regression analysis showed that eGFR was an important factor affecting serum potassium ($\beta = -0.378$, $p = 0.018$).**
Conclusions: **When DKA occurs in diabetes patients, the renal function deteriorates significantly because the electrolytes are generally elevated due to hemoconcentration. Hyperkalemia is the main manifestation, and it is necessary to prevent the decrease in serum potassium during the treatment.**
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INTRODUCTION

Diabetic ketoacidosis (DKA) and diabetic ketosis (DK) are common and severe complications in diabetes patients. DKA is more common in type 1 diabetes (T1D) patients, and DKA and DK can also be found in T2D patients who are prone to ketosis. DKA also often oc-

curs in severe T2D patients, with more severe clinical manifestations and poor prognosis than in T1D. T2D patients with previous DKA have a higher risk of stroke, especially ischemic strokes [1].

When DKA occurs in either T2D or T1D patients, internal environmental disorders, acid-base imbalance, and electrolyte disorders occur, which require comprehensive diagnosis and timely treatment. Improper diagnosis and treatment of DKA may increase the risk of complications and mortality [2-4].

Previous studies have focused on pathological and physiological changes, such as inflammatory factors, in DKA patients [5,6]. We have reported the changes in several indicators in DKA patients, such as peripheral blood cell classification and liver and kidney functions [7,8]. Paying attention to the clinical parameters of these patients is conducive to appropriate diagnosis and timely and reasonable treatment. Clinicians often first pay attention to glycemic control in DKA patients and overlook the changes in acid-base balance and electrolytes with decreasing blood glucose. DKA patients have elevated serum creatinine, uric acid, and serum potassium [4], while changes in other electrolytes, such as sodium, chloride, calcium, magnesium, and phosphorus, have rarely been reported.

In this study, DKA and DK patients were studied to investigate the electrolyte abnormalities in both types of patients, which may make up for the limitations of previous studies.

MATERIALS AND METHODS

Inclusion and exclusion criteria of study subjects

Subjects in this study were selected from outpatients, inpatients, and those undergoing health check-ups in our hospital from July 2010 to March 2013. The study was approved by the hospital ethics committee, and all subjects signed informed consent forms. The clinical trial registration number is ChiCTR-OCH-12003077. Forty individuals were included in each of the DKA, DK, nonketotic diabetes mellitus (non-DK), and healthy control groups. The DKA group included 19 T1D patients and 21 T2D patients. The DK group included 18 T1D patients and 22 T2D patients. The non-DK group included 17 T1D patients and 23 T2D patients. In the DKA group, the plasma glucose was > 13.90 mmol/L, the urinary ketones were rated + to +++, and the arterial blood pH was < 7.30 at the time of enrollment. The DKA severity standard was as follows: $7.2 \leq pH < 7.3$ was mild, $7.1 \leq pH < 7.2$ was moderate, and $pH < 7.1$ was severe [4].

Subjects underwent routine physical examination before enrollment. The subjects with cardiac dysfunction, hematological diseases, or renal failure were excluded. Of the patients previously having renal dysfunction, the ones with a history of taking chemical, nephrotoxic, or other medications were also excluded.

Biochemical test

Peripheral venous blood samples were collected from patients in the fasting state or upon emergency department admission and submitted to the laboratory for timely testing. The laboratory test parameters included plasma glucose, glycated hemoglobin (HbA1c), serum creatinine, serum potassium, sodium, chloride, calcium, phosphorus, magnesium, and other electrolytes.

Statistical analysis

SPSS 18.0 software was used for statistical analysis. The normally distributed measurement data are expressed as the mean ± standard deviation, the skewed measurement data are expressed as the median (minimum - maximum), and count data are expressed as a percentage (%). Analysis of variance was used to compare the normally distributed data between the four groups. The Mann-Whitney U test was used to compare the nonparametric data between two groups. The chi-squared test was used to compare overall rates or proportions between two groups. The two-sided significance threshold was $\alpha = 0.05$, $p < 0.05$ was considered statistically significant, and $p < 0.01$ was considered extremely significant.

RESULTS

As shown in Table 1, 160 subjects were included in this study. There were no significant differences in age, gender, or diabetes type between groups. Compared with the DK, non-DK, and healthy control groups, the DKA group had a longer course of diabetes ($p < 0.05$); higher blood glucose (29.05 ± 7.98 mmol/L), HbA1c (12.48 ± 2.03 mmol/L), and serum creatinine (132.41 ± 66.76 mmol/L) ($p < 0.001$); and lower estimated glomerular filtration rate (eGFR) (57.99 ± 25.15 mL/min per 1.73 m^2) ($p < 0.001$). Serum potassium was significantly increased in DKA patients ($p < 0.001$), and there were 13 cases of hyperkalemia ($K^+ > 5.5$ mmol/L), for an incidence of 32.5% ($p < 0.001$ vs. other groups), and only 3 cases of hypokalemia ($K^+ < 3.5$ mmol/L), for an incidence of 7.5%.

The effective osmotic pressure in the DKA group (326.68 ± 15.79 mmol/L) was significantly higher than those of the other three groups (all $p < 0.001$). In the DKA patients with hyperglycemia compared with the other three groups, the serum sodium correction (143.67 ± 6.65 mmol/L), serum magnesium (2.25 ± 0.45), and serum phosphorus (1.61 ± 0.95 mmol/L) were higher ($p < 0.05$), but serum chlorine was not significantly different, and serum calcium (2.20 ± 0.27 mmol/L) was slightly lower ($p < 0.05$). Compared with the non-DK and healthy control groups, the DK group had higher blood glucose (16.94 ± 5.06 mmol/L) and HbA1c (13.11 ± 2.64 mmol/L) ($p < 0.001$) and lower serum sodium (142.99 ± 3.84 mmol/L), serum magnesium (2.23 ± 0.28 mmol/L), serum chlorine (99.14 ± 3.26 mmol/L)

Table 1. Comparison of clinical characteristics and serum electrolytes among the four groups.

Variables	Control group (n = 40)	Non-DK group (n = 40)	DK group (n = 40)	DKA group (n = 40)
Gender (female/male)	20/20	17/23	14/26	22/18
Age (years)	43 ± 8	50 ± 11	49 ± 16	43 ± 17
Diabetes types (1/2)	/	17/23	18/22	19/21
Course of diabetes (years)	/	4.0	0.5 §	5.5 †
		(0.0 - 20.0)	(0.0 - 12.0)	(0.0 - 26.0)
Blood glucose (mmol/L)	4.74 ± 0.33	10.40 ± 4.53 **	16.94 ± 5.06 $^{**, \S\S}$	29.05 ± 7.98 $^{**, \S\S, \dagger\dagger}$
HbA1c (%)	5.20 ± 0.24	10.40 ± 2.58 **	13.11 ± 2.64 $^{**, \S\S}$	12.48 ± 2.03 $^{**, \S\S}$
Serum creatinine (μmol/L)	93.59 ± 11.18	92.64 ± 17.12	88.84 ± 14.12	132.41 ± 66.76 $^{**, \S\S, \dagger\dagger}$
eGFR (mL/min per 1.73 m^2)	73.73 ± 10.15	74.66 ± 14.10	82.30 ± 19.13	57.99 ± 25.15 $^{*, \S\S, \dagger\dagger}$
Serum potassium (mmol/L)	4.06 ± 0.14	4.17 ± 0.37	4.06 ± 0.47	5.04 ± 1.11 $^{**, \S\S, \dagger\dagger}$
Hypokalemia (< 3.5 mmol/L) (n)	0	1	1	3
Hyperkalemia (> 5.5 mmol/L) (n)	0	0	1	13 $^{**, \S\S, \dagger\dagger}$
Serum sodium (mmol/L)	140.44 ± 1.38	142.14 ± 2.25	142.99 ± 3.84 *	143.67 ± 6.65 *
Serum calcium (mmol/L)	2.36 ± 0.12	2.34 ± 0.15	2.30 ± 0.14	2.20 ± 0.27 $^{*, \S}$
Serum magnesium (mmol/L)	/	1.95 ± 0.19	2.23 ± 0.28 §	2.25 ± 0.45 §§
Serum chlorine (mmol/L)	102.46 ± 1.92	100.86 ± 2.61	99.14 ± 3.26 *	100.28 ± 7.87
Serum phosphorus (mmol/L)	1.23 ± 0.24	1.19 ± 0.20	1.11 ± 0.24	1.61 ± 0.95 $^{*, \S, \dagger\dagger}$
Anion gap (mmol/L)	/	/	28.01 ± 7.88	43.23 ± 8.81
Effective osmotic pressure (mmol/L)	293.72 ± 2.99	303.01 ± 7.10 **	311.02 ± 10.22 $^{**, \S}$	326.68 ± 15.79 $^{**, \S\S, \dagger\dagger}$

Compared with the control group: (*) $p < 0.05$, (**) $p < 0.001$; compared with the non-DK group: (§) $p < 0.05$, (§§) $p < 0.001$; compared with the DK group: (†) $p < 0.05$, (††) $p < 0.001$; the course of diabetes had a skewed distribution and is expressed as the median and range (minimum-maximum).

Table 2. Comparison of clinical characteristics and electrolyte levels of T1D and T2D patients in the DKA group.

Variables	T1D (n = 19)	T2D (n = 21)	p-value
Gender (female/male)	13/6	9/12	0.105
Age (years)	35 ± 19	52 ± 10	0.001
Course of diabetes (years)	7.00	5.00	0.299
	(0.00 - 26.00)	(0.00 - 15.00)	
Blood glucose (mmol/L)	31.82 ± 8.53	26.54 ± 6.68	0.035
HbA1c (%)	12.97 ± 2.25	11.94 ± 1.71	0.214
Arterial blood pH	7.01 ± 0.16	7.04 ± 0.14	0.486
$HCO3^{-}$ (mmol/L)	4.76 ± 3.47	5.60 ± 3.40	0.446
Serum creatinine (μmol/L)	122.92 ± 47.87	141.01 ± 80.41	0.399
eGFR (mL/min per 1.73 m^2)	60.63 ± 25.29	55.60 ± 25.41	0.534
Serum potassium (mmol/L)	5.01 ± 1.06	5.07 ± 1.18	0.863
Hypokalemia (< 3.5 mmol/L) (n)	1	2	0.400
Hyperkalemia (> 5.5 mmol/L) (n)	7	6	0.230
Serum sodium (mmol/L)	143.55 ± 7.92	143.78 ± 5.39	0.914
Serum calcium (mmol/L)	2.19 ± 0.35	2.22 ± 0.17	0.758
Serum magnesium (mmol/L)	2.28 ± 0.42	2.22 ± 0.49	0.666
Serum chlorine (mmol/L)	99.58 ± 7.67	100.95 ± 8.20	0.595
Serum phosphorus (mmol/L)	1.80 ± 0.94	1.43 ± 0.95	0.224
Anion gap (mmol/L)	44.22 ± 8.74	42.29 ± 8.99	0.500
Effective osmotic pressure (mmol/L)	328.95 ± 17.14	324.53 ± 14.51	0.390

Table 3. Comparison of characteristics and electrolyte levels between mild-to-moderate DKA patients and the severe DKA patients.

Variables	Mild and moderate DKA patients (n = 15)	Severe DKA patients (n = 25)	p-value
Gender (female/male)	7/8	15/10	0.517
Age (years)	47 ± 20	41 ± 14	0.250
Course of diabetes (years)	8.00	5.00	0.134
	(0.00 - 26.00)	(0.00 - 15.00)	
Blood glucose (mmol/L)	29.23 ± 9.24	28.94 ± 7.32	0.914
HbA1c (%)	12.35 ± 2.72	12.54 ± 1.72	0.837
Arterial blood pH	7.18 ± 0.05	6.93 ± 0.10	< 0.001
$HCO3^-$ (mmol/L)	8.35 ± 3.17	3.30 ± 1.78	< 0.001
Serum creatinine (μmol/L)	139.33 ± 87.10	128.26 ± 52.63	0.618
eGFR (mL/min per 1.73 m^2)	59.89 ± 26.25	58.05 ± 25.02	0.985
Serum potassium (mmol/L)	5.31 ± 0.77	4.88 ± 1.26	0.248
Hypokalemia (< 3.5 mmol/L) (n)	0	2	0.380
Hyperkalemia (> 5.5 mmol/L) (n)	7	6	0.090
Serum sodium (mmol/L)	143.10 ± 6.37	144.02 ± 6.93	0.681
Serum calcium (mmol/L)	2.28 ± 0.21	2.17 ± 0.30	0.227
Serum magnesium (mmol/L)	2.19 ± 0.39	2.28 ± 0.49	0.572
Serum chlorine (mmol/L)	99.92 ± 5.10	100.50 ± 9.29	0.825
Serum phosphorus (mmol/L)	1.32 ± 0.43	1.79 ± 1.13	0.140
Anion gap (mmol/L)	40.14 ± 6.71	45.16 ± 9.52	0.083
Effective osmotic pressure (mmol/L)	326.05 ± 16.39	327.08 ± 15.75	0.846

($p < 0.05$ or $p < 0.001$).

The clinical characteristics and electrolyte levels of T1D and T2D patients in the DKA group are shown in Table 2. Compared to T2D patients, T1D patients were younger (35 ± 19 years) ($p = 0.001$) and had higher blood glucose at the time of disease onset (31.82 ± 8.53 mmol/L) ($p = 0.035$), but HbA1c, arterial blood pH, renal function, and electrolytes were not significantly different.

The clinical characteristics and electrolyte levels were compared between the mild to moderate DKA patients and the severe DKA patients (Table 3). In the severe DKA patients, the arterial blood pH (6.93 ± 0.10) and $HCO3^-$ (3.30 ± 1.78 mmol/L) were significantly lower than those of the mild to moderate DKA patients ($p < 0.001$), but the differences in renal function and electrolyte profile were not statistically significant. In addition, correlation analysis revealed that serum potassium was negatively correlated with eGFR ($r = -0.378$, $p = 0.018$) and was positively correlated with blood glucose ($r = 0.334$, $p = 0.038$), serum phosphorus ($r = 0.337$, $p = 0.036$), and serum creatinine ($r = 0.331$, $p = 0.033$). The regression analysis excluded the variables blood glucose, blood phosphorus, and blood creatinine, revealing that eGFR was an important factor affecting blood potassium ($\beta = - 0.378$, $p = 0.018$).

DISCUSSION

Electrolytes are indispensable substances in the human body, and stable electrolyte balance is the basis of cell metabolism, blood circulation, and normal physiological functioning. The results of this study showed that blood glucose was significantly increased and the electrolyte profile was imbalanced in DKA patients with diabetes. Hyperkalemia was the main clinical manifestation, and the eGFR was significantly reduced. The results of this study are conducive to a comprehensive understanding of the pathophysiology of DKA, which is conducive to rational clinical diagnosis and treatment. Diabetes patients have different electrolyte abnormalities under different metabolic states, and the specific mechanism of each patient is also different due to multiple factors.

DKA patients have a series of internal environmental disorders, and their clinical manifestations are more severe than those of DK patients. Significantly elevated blood glucose, metabolic acidosis, and significantly decreased eGFR are common manifestations, so the clinical characteristics and electrolyte levels of T1D and T2D patients in the DKA group were similar. Overall, serum potassium in the DKA group was significantly increased ($p < 0.001$), the incidence of hyperkalemia was as high as 32.5% ($p < 0.001$), and the incidence of hypokalemia was low. These findings contradict com-

mon knowledge, and it may have been taken for granted that DKA mainly causes hypokalemia rather than hyperkalemia.

In addition, the effective osmotic pressure significantly increased; serum sodium, magnesium, and phosphorus were also increased to varying degrees; and serum calcium was slightly decreased. Serum calcium is a negative indicator of critical illness, while C-reactive protein (CRP) is a positive indicator of critical illness. Serum potassium was negatively correlated with eGFR, and eGFR is an important factor affecting serum potassium. There are other factors affecting hyperkalemia, such as hemoconcentration due to dehydration, insufficient intake of potassium, excessive discharge of potassium, and hydrogen-potassium exchange in cells caused by metabolic acidosis.

The comparison between the mild to moderate DKA patients and the severe DKA patients showed that there were differences in pH and $HCO3^{-}$ but no significant differences in the electrolytes. This suggested that the changes in serum potassium were not only caused by acidosis but by multiple factors, such as hemoconcentration, insufficient intake, and excessive discharge. Due to the combined effects of multiple factors, the effect of acidosis was not significant, so serum potassium was not correlated with pH or level.

In DKA patients, metabolic acidosis, an important factor affecting serum potassium, increases the release of cytokines and inflammatory mediators and reduces blood volume, and these risk factors directly impair renal excretory function [9]. At the same time, the changes in serum potassium can predict the clinical severity to a certain extent. T1D and T2D are caused by completely different pathophysiological mechanisms, and the change trends of liver and kidney functions are significantly different between T1D and T2D patients [7]. Based on blood glucose, the metabolic state of the enrolled individuals in this study was divided into four groups, i.e., from normal to DKA. The progression of patients from stable state to DKA was elaborated in this single-center cross-sectional study, providing important complementary laboratory data for disease diagnosis and assessment.

Hyperketonemia with or without acidosis is an acute complication in diabetes patients. The severity of hyperketonemia is correlated with arterial blood pH. High H^{+} concentration may significantly reduce the synthesis and release of enzymes and proteins in the liver. Compared with mild to moderate DKA patients, severe DKA patients have significantly lower total protein, albumin, globulin, and prealbumin [7], which are the negative indicators of critical illness, like serum calcium. Elevated levels of ketones can cause oxidative damage in cells, accelerate cell apoptosis, and inhibit the growth of monocytes, thereby reducing the number of monocytes [10]. Further research should be devoted to this topic. The development of DKA is associated with severe insulin deficiency, systemic active inflammation, and oxidative stress. The clinical application of insulin and rehydration therapy could result in a decrease in serum potassium, the renal function of patients could gradually return to normal, and the levels of liver function-related proteins could also increase after insulin therapy. The differential diagnosis of prerenal insufficiency is clinically important. In both DK and DKA patients, water and electrolytes are consumed to varying degrees. To some extent, prerenal azotemia is closely related to the occurrence of hyperglycemic crisis, and dehydration can result in hypotension and hypertonicity [6,9]. The clinical manifestations and symptoms of patients depend on the duration and severity of DKA. The right treatment of hyperglycemia, the correction of metabolic acidosis, and the prevention of treatment-induced electrolyte disorders are key to disease recovery.

This study had limitations due to its single-center, cross-sectional nature. The small sample only provides preliminary evidence about patients with acute hyperglycemia. Large studies are still needed to accumulate more evidence about the risk factors for hyperkalemia and hypokalemia in DKA patients.

CONCLUSION

DKA and DK have adverse effects on the electrolyte profile. In particular, there were significant electrolyte abnormalities in DKA patients, and hyperkalemia is an important manifestation of this malady. Electrolyte imbalances that can lead to cardiovascular events should be avoided.

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Declaration of Interest:
The authors have declared no financial or other conflicts of interest.

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