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Original Article

Rhabdomyolysis; is it an overlooked DKA complication☆

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ABSTRACT

Background: Rhabdomyolysis is considered by some studies as a rare complication of a common disorder of diabetic ketoacidosis, while others consider it as not so uncommon. The mechanism is still not clear but can be attributed to a number of factors like acidosis, hyperglycemia and electrolyte disturbances especially hypophosphatemia and hypokalaemia. Missing it may lead to more serious complications and may prolong and/or complicate full recovery of diabetic ketoacidosis.
Aim: The aim of this study was to measure the incidence of rhabdomyolysis among patients presented with diabetic ketoacidosis in the emergency department of Baghdad Teaching hospital, its relation to the severity of diabetic ketoacidosis and the associated electrolytes disturbances.
Patients and methods: This is a cross sectional study carried out in the emergency department of Baghdad teaching hospital/Iraq; where 43 patients with type1 diabetes presenting with diabetic ketoacidosis were included. Diabetic ketoacidosis was classified into mild, moderate and severe, and the incidence of rhabdomyolysis was calculated accordingly. Full blood investigations, urinary ketones and arterial blood gasses were done.
Results: Rhabdomyolysis was found in 3 (6.98%) patients with more severe acidosis and urinary ketones in the setting of moderate and severe diabetic ketoacidosis. Statistically significant finding was observed with the duration of diabetes, higher serum creatinine, higher serum potassium, higher serum chloride, severe acidosis and urinary ketones.
Conclusions: Rhabdomyolysis incidence in this study was 6.98% of patients with more severe acidosis, urinary ketones in the setting of moderate to severe diabetic ketoacidosis and with longer duration of diabetes.

1. Introduction

1.1. Rhabdomyolysis

Rhabdomyolysis is a term that describes the rapid breakdown, rupture and necrosis of striated muscle fibers, which may be triggered by a variety of initiating events, resulting in the leakage of muscle contents, including electrolytes, myoglobin, enzymes such as creatine kinase (CK), and other sarcoplasmic proteins [1]. The final common pathway for injury is an increase in intracellular free ionized cytoplasmic and mitochondrial calcium. This may be caused by the depletion of adenosine triphosphate (ATP), and/or by direct injury and rupture of the plasma membrane [2,3], which also results in ATP depletion. A rapid introduction of calcium ions into the myocytes will result in a pathological interaction between actin and myosin, in addition to the activation of cell proteases. ATP depletion leads to myocyte injury and the release of intracellular muscle constituents, including muscle enzymes, myoglobin, various electrolytes and very large amounts of CK, in the bloodstream and extracellular space [4,5].

Rhabdomyolysis can cause acute renal failure, cardiac arrhythmias and significant electrolyte abnormalities, all of which could result in significant morbidity and mortality [2].

Creatine kinase levels are the most sensitive indicators of myocyte injury. Under normal condition, CK levels are 45–260 U/L.

☆ This work has been approved by the appropriate ethical committees related to the institution(s) in which it was performed.

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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In rhabdomyolysis, the levels of CK can rise up to 10.000–200.000 U/L or even to 3.000.000.000 U/L. This elevation occurs in the first 12 h, peaks during the first 3 days and normalizes at around 5 days after injury [6]. No other condition except rhabdomyolysis can cause such extreme CK elevation; therefore high serum CK levels makes a reliable and definitive diagnosis of rhabdomyolysis [7].

1.2. Rhabdomyolysis & diabetic ketoacidosis

Rhabdomyolysis is considered by some studies as a rare complication of a common disorder of diabetic ketoacidosis (DKA), while others consider it as not so uncommon in DKA [8,9]. Till now, it is not well studied or documented and is usually overlooked, because they either present in a subclinical mild form with no symptoms or present with a severe form with markedly elevated CK levels, also the CK levels is not routinely sent in patients with DKA [10,11]. The first case report of a patient with DKA and rhabdomyolysis was in 1962 [12], then after other reports had described the signs and symptoms of rhabdomyolysis in patients with DKA, as a rare complication of a common diseases [8]. Not many studies have reported the incidence of rhabdomyolysis in DKA, one study reported that the incidence of rhabdomyolysis was 10% in adult patients with DKA [13], while in another study rhabdomyolysis was reported to occur in as many as 50% of patients presenting with DKA or the hyperglycemic hyperosmolar nonketotic syndrome [11]. The exact mechanism of DKA mediated muscle injury is uncertain and has yet to be established [1]. Low PH, high serum sodium, blood urea, creatinine, osmolarity and blood glucose were the major determinants for rhabdomyolysis in adults with diabetes [2], in addition to other electrolyte abnormalities such as hypophosphatemia and hypokalemia [10]. Theories include insufficient energy delivery to muscle, hyperosmolar effects, and underlying metabolic defects, such as McArdle's myophosphorylase deficiency causing glycogen accumulation and reduced muscle ATP generation as the cause of rhabdomyolysis in DKA [11].

The aim of this study was to measure the incidence of rhabdomyolysis among patients presented with diabetic ketoacidosis in the emergency department of Baghdad Teaching hospital, its relation to the severity of diabetic ketoacidosis and the associated electrolytes disturbances.

2. Patients& methods

2.1. Study design and setting

This is a cross sectional study carried out in the emergency department (ED) of Baghdad Teaching Hospital/Iraq. Patients with type1 diabetes presented with DKA who accepted to take part in the study were included. DKA patients with acute myocardial infarction, stroke, end stage renal disease, severe trauma, alcoholics, history of drug abuse and those on statins were excluded. Data was collected from the patients using a specific questionnaire including; age, gender, type, duration and treatment of DM. Proper samples were sent for random blood sugar, blood urea & serum creatinine, serum electrolytes (Na^+, K^+, Ph and Cl^-), (Hb, WBC and platelets count), Arterial blood gas, serum creatine kinase (CK) and ketones in the urine. All were drawn at time of admission and then as recommended by the treatment protocol of DKA, Data from the first laboratory results were used in this study, except for the CK level. CK level was measured after 24 h.

2.2. Definitions

Diagnosis of DKA was done according to the American Diabetes Association guidelines [14] that is based on a glucose threshold of >250 mg/dL (13.9 mmol/L), presence of positive serum and/or urine ketones and a confirmation of an acidosis as bicarbonate < 15 mmol/L or pH < 7.3 PH of less than 7.3, or an anion gap >10. Also DKA patients were classified according to the severity of the DKA to mild, moderate and severe [14] (Table 1). Rhabdomyolysis was diagnosed depending on the CK levels. A CK level five times the upper limit of normal (≥1000 U/L), without apparent cardiac or brain injury, confirms the diagnosis [6].

2.3. Statistical analysis

Statistical Package for Social Sciences (SPSS) version 20 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Multiple contingency tables conducted and appropriate statistical tests performed, Fishers exact test was used for categorical variables and independent sample *t*-test was used to compare between two means. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs. Statistical analysis of the study was done by the community medicine specialist.

3. Results

The 43 patients with type1 diabetes, had a mean age of 29.2 ± 8.5 years; 25 (58.1%) of them were females and 18 (41.9) were males, the female to male ratio is 1.4:1. Mean duration of DM was 5 ± 4.5 years; 17 (39.5%) of them had DM duration of 5 years and more, (Table 2).

The mean value of random blood sugar (RBS) was 468.8 ± 99 mg/dl; All (100%) patients had high RBS, 36 (83.7%) of patients had high blood urea, and 13 (30.2%) of patients had high serum creatinine. Mean ketones in urine was 2.6 ± 1 +; 21 (48.8%) of the patients had 3-5 pluses. Mean serum sodium (Na) was 133.9 ± 6.4 mEq/L; 21 (48.8%) of the patients had low serum Na. Mean serum potassium (K) was 3.8 ± 0.9 mEq/L; 16 (37.2%) of the patients had low serum K. Mean serum phosphate (Ph) was 3.25 ± 1.1 mg/dL; 3 (6.9%) of the patients had low serum Ph. Mean serum chloride (Cl) was 104.4 ± 20.5 mEq/L; 17 (42.5%) of the patients had high serum Cl. Mean hemoglobin (Hb) was 12.3 ± 1.6 mg/dl; 30 (69.8%) of the patients had low hemoglobin. Mean white blood cell count (WBC) count was 11.7 ± 4.3 × 10^3; 24 (55.8%) of the patients had high WBC count. Mean platelets count was 307.2 ± 97.3 × 10^3; 9 (19%) of the patients had high platelets count, (Table 3).

All patients were acidotic, the mean PH was 7.16 ± 0.13 and mean bicarbonate level (HCO_3) was 14.5 ± 3.6 mEq/L; all patients had low PH and low HCO_3. Mean serum CK was 106.8 ± 91.5 U/L; 3 (6.98%) of the patients had very high serum CK and is considered of having rabdomyolysis. Mild, Moderate and severe DKA was observed in 18 (41.9%) 15 (34.9%) and 10 (23.2%), respectively, (Table 4 and Fig. 1).

No statistically significant difference was observed between the patients with rhabdomyolysis and those with no rhabdomyolysis regarding their age and gender. There was a significant association between increased mean DM duration and DKA patients with rhabdomyolysis (p < 0.05), (Table 5and Fig. 2).

No significant difference was observed between the patients with rhabdomyolysis and those with no rhabdomyolysis regarding random blood sugar (RBS), blood urea, serum NA and serum Ph levels. There was a significant association between increased urinary ketones in DKA patients with rhabdomyolysis (P = 0.01). Mean serum creatinine, serum K and serum Cl levels were significantly higher among DKA patients with rhabdomyolysis (P < 0.05) than those without, (Table 6 and Fig. 3).

There was no significant association between DKA patients with

Table 1
Classification of the severity of DKA.

Criterion	Mild Serum glucose >250 mg/dl	Moderate Serum glucose >250 mg/dl	Severe Serum glucose >250 mg/dl
pH	7.24 to 7.30	7.00 to <7.24	<7.00
Serum bicarbonate	15-18 mEq/L	10 to <15 mEq/L	<10 mEq/L
Urine or serum ketone	Positive	positive	positive

Table 2
Characteristics of DKA patients.

Variable	No.	%
Age/mean ± SD* (29.2 ± 8.5 years)		
Male	18	41.9
Female	25	58.1
Disease duration/mean ± SD (5 ± 4.5 years)		
<5 years	26	60.5
≥5 years	17	39.5

SD* Standard deviation.

Table 3
Laboratory results of study sample.

Variable	No.	%
Random blood sugar/mean ± SD* (468.8 ± 99 mg/dl)		
High	43	100.0
Blood urea/mean ± SD (55.3 ± 20.9 mg/dl)		
Normal	7	16.3
High	36	83.7
Serum creatinine/mean ± SD (1.24 ± 0.79 μg/dl)		
Normal	30	69.8
High	13	30.2
Ketones in urine/mean ± SD (2.6 ± 1 +)		
1-2 (+)	22	51.2
3-5 (+)	21	48.8
Serum NA/mean ± SD (133.9 ± 6.4 mEq/L)		
Low	21	48.8
Normal	19	44.2
High	3	7.0
Serum K/mean ± SD (3.8 ± 0.9 mEq/L)		
Low	16	37.2
Normal	25	58.1
High	2	4.7
Serum Ph/mean ± SD (3.25 ± 1.09 mg/dL)		
Low	3	6.9
Normal	36	83.7
High	4	9.4
Serum Cl/mean ± SD (104.4 ± 20.5 mEq/L)		
Low	9	22.5
Normal	14	35.0
High	17	42.5
Hb/mean ± SD (12.3 ± 1.6 mg/dl)		
Normal	13	30.2
Low	30	69.8
WBC count/mean ± SD (11.7 ± 4.3 × 10^3/mm^3)		
Normal	19	44.2
High	24	55.8
Platelets count/mean ± SD (307.2 ± 97.3 × 10^3/mm^3)		
Normal	34	81.0
High	9	19.0

* Standard deviation.

rhabdomyolysis and those without regarding the hemoglobin level, although all cases with rhabdomyolysis had low hemoglobin level. The WBC count and platelets count showed no statistically significant association, (Table 7).

There was statistically significant association between PH level and Hco_3, both were very low (in the setting of moderate and severe DKA) in cases with rhabdomyolysis. Mean serum Creatine kinase was 1164.33 ± 138.21U/L in cases with rhabdomyolysis while it was only 77 ± 27.6 U/L in patients without rhabdomyolysis.

Table 4
PH, bicarbonate and creatine kinase of all study patients.

Variable	No.	%
PH/mean ± SD* (7.16 ± 0.13 PH)		
Acidic	43	100.0
HCO_3^-/mean ± SD (14.5 ± 3.6 mEq/L)		
Low	43	100.0
Serum Creatine kinase/mean ± SD (106.8 ± 91.5 IU/L)		
Normal	40	93.02
High	3	6.98
Severity of DKA		
Mild	18	41.9
Moderate	15	34.9
Severe	10	23.2

* Standard deviation.

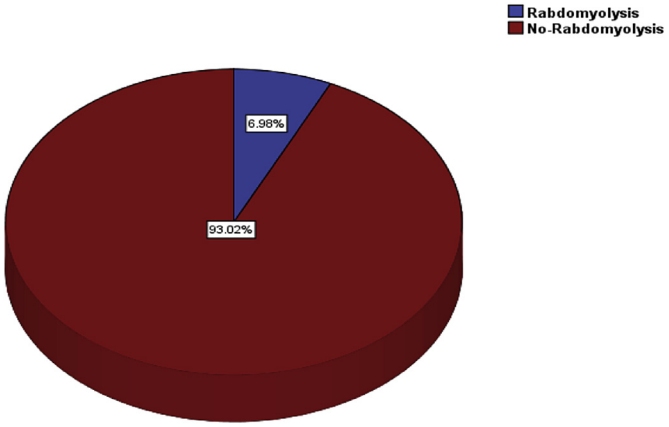

Fig. 1. Incidence of rhabdomyolysis among the study sample.

There was no statistically significant difference according to the severity of DKA and the incidence of rhbdomyolysis, although rhabdomyolysis was only present in moderate and severe DKA, (Table 8).

4. Discussion

DKA is an acute serious complication of diabetes mellitus (DM), accompanied by severe electrolyte and metabolic disturbances. The seriousness of the patient's medical condition at the ER obliges the caring medical team, to deal immediately with this emergency, by following the management guidelines. The most cited, downloaded and distributed guidelines are that of the American diabetes association and the Joint British Diabetes Societies, Inpatient Care Group [15,16]. When revising these guidelines, nothing is mentioned about rhabdomyolysis, whether its diagnosis, management and the possibility of being one of the DKA complication. Therefore it is not unusual to miss this lethal complication when it occurs in a patient with severe DKA. In fact both DKA and rhabdomyolysis may mimic each other in their morbidity and mortality, they both may cause acute renal failure, severe hyperkalemia and severe electrolyte disturbances [13].

Table 5
Distribution of sociodemographic characteristics according to rhabdomyolysis frequency.

Variable	Rhabdomyolysis		No rhabdomyolysis		P. Value
	No.	%	No.	%	
Age/year					
Mean ± SD∞ *Standard deviation,*	30.4 ± 2.6		29 ± 8.9		0.7*** NS
Gender					
Male	2	66.6	16	40.0	0.5** NS
Female	1	33.4	24	60.0	
Disease duration (years)					
<5 years	1	20.0	25	65.8	
≥5 years	2	80.0	15	34.2	
Mean ± SD	11.33 ± 6.35		4.1 ± 3.6		<**0.05**S

*Chi-square test **Fishers exact test, ** Independent sample *t*-test.
∞ Standard deviation, NS=Not significant, S=Significant.

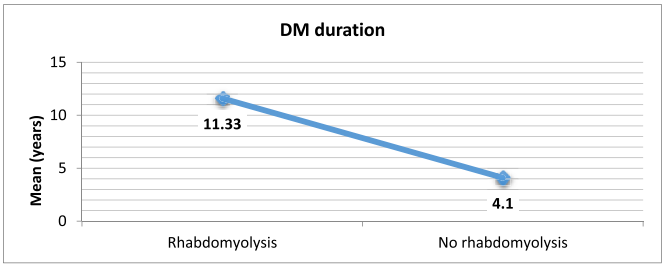

Fig. 2. Distribution of DM duration according to presence of rhabdomyolysis.

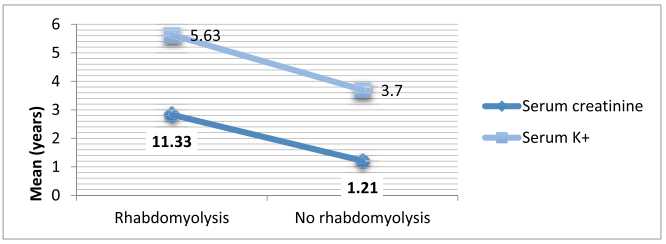

Fig. 3. Distribution of serum creatinine and serums K^+ level according to rhabdomyolysis.

Table 6
Biochemical laboratory results distribution according to presence of rhabdomyolysis.

Variable	Rhabdomyolysis		No rhabdomyolysis		P. value
	No.	%	No.	%	
RBS (mg/dL)					
Mean ± SD∞ (mg/dl)	420.33 ± 26.5		476.2 ± 102.2		0.35**NS
Blood urea (mg/dL)					
Normal	0	0	7	17.5	1.0* NS
High	3	100.0	33	82.5	
Mean ± SD	85.06 ± 4.8		46.6 ± 16.8		0.32**NS
Serum creatinine (μg/dL)					
Normal	0	0	29	72.5	<**0.05***S
High	3	100.0	11	27.5	
Mean ± SD	2.83 ± 0.30		1.21 ± 0.81		<**0.05****NS
Ketones in urine (+)					
1-2 (+)	0	0	22	55.0	**0.01***S
3-5 (+)	3	100.0	18	45.0	
Mean ± SD	3 ± 0.5		2.5 ± 1.7		0.6** NS
Serum NA (mEq/L)					
Low	1	33.4	20	50.0	0.6*** NS
Normal	2	66.6	17	42.5	
High	0	0	3	7.5	
Mean ± SD	133 ± 4.0		133.8 ± 6.6		0.8**NS
Serum K (mEq/L)					
Low	0	0	16	40.0	<**0.001***S
Normal	1	33.4	23	57.5	
High	2	66.6	1	2.5	
Mean ± SD	5.63 ± 0.64		3.7 ± 0.7		<**0.001****NS
Serum Ph (mg/dL)					
Low	0	0	3	7.5	
Normal	3	100.0	33	82.5	
High	0	0	4	10.0	
Mean ± SD	3.27 ± 0.76		3.45 ± 1.08		0.78*NS
Serum Cl (mEq/L)					
Low	0	0	9	30.0	0.11*S
Normal	0	0	14	35.0	
High	3	100.0	14	35.0	
Mean ± SD	134 ± 17.7		100.3 ± 17.1		<**0.05****S

* *Fishers exact test, ** Independent sample t-test ***Chi-square test.*
∞ *Standard deviation, NS = Not significant, S = Significant.*

Table 7
Blood count laboratory results distribution according to presence of rhabdomyolysis.

Variable	Rhabdomyolysis		No rhabdomyolysis		P. value
	No.	%	No.	%	
Hb (g/dL)					
Normal	0	0.0	17	42.5	<0.265* NS
Low	3	100	23	57.5	
Mean ± SD	12.3 ± 0.9		12.1 ± 1.82		0.054**NS
WBC count ($x10^3/mm^3$)					
Normal	2	66.6	17	42.5	0.5* NS
High	1	33.4	23	57.5	
Mean ± SD ($x10^3$)	9.83 ± 30.8		11.9 ± 4.4		0.66**NS
Platelets count ($x10^3/mm^3$)					
Normal	3	100.0	31	77.5	1.0* NS
High	0	–	8	22.5	
Mean ± SD	226.6 ± 68.0		321 ± 93.3		0.09** NS

* *Fishers exact test, ** Independent sample t-test ***Chi-square test.*
∞ *Standard deviation, NS = Not significant, S = Significant.*

Table 8
Acidosis, CK level and DKA severity, distribution according to rhabdomyolysis.

Variable	Rhabdomyolysis		No rhabdomyolysis		P. value
	No.	%	No.	%	
PH					
Mean PH± SD∞	6.9 ± 0.08		7.1 ± 0.13		**<0.05**^{**S}
No	**3**	**6.98**	**40**	**93.02**	
HCO3					
Mean ± SD (mEq/L)	9.2 ± 0.55		14.5 ± 3.5		**<0.05**^{**S}
No.	**3**	**6.98**	**40**	**93.02**	
Serum CK					
Mean ± SD	1164.33 ± 138.21		77 ± 27.6		**<0.001**^{**S}
No.	**3**	**6.98**	**40**	**93.02**	
Severity of DKA					
Mild	0	60.0	18	78.9	0.29* NS
Moderate	1		14		
Severe	2	40.0	8	21.1	

* Chi-square test, ** Independent sample *t*-test, ∞ Standard deviation, S= Significant, NS=Not significant.

Many studies consider rhabdomyolysis as a rare complication of DKA [8,13], but when revising its incidence a question mark can be drawn for these statements. The reported incidence ranges from 10-50% in different studies [11,13], therefore rhabdomyolysis should always be kept in mind and in fact to be honest the reported 3 (6.98%) cases in this study would have been missed if we were not conducting a study about the incidence of rhabdomyolysis, as their recovery was uneventful, they were well hydrated, and bicarbonate infusion was administered due to the severe acidosis.

The 6.98% incidence of rhabdomyolysis in this study was lower than that found in other studies mentioned before, and this can be attributed to the smaller sample size, and to the better management of DKA nowadays, as most of these reported incidence were reported in studies conducted during the 1980s [8], 1990s [11], and one have measured the incidence of rhabdomyolysis in both DKA and HHS together [11]. New management guidelines of DKA now recommended a fixed low dose insulin infusions (i.e. 0.1 units/Kg/hr) rather than a priming (bolus) dose of insulin, the use of crystalloid fluid rather than colloids, close monitoring and prompt correction of electrolytes, and the availability of bed side monitoring devices, all may have played a role in decreasing the incidence of rhabdomyolysis [16]. A study in 1955 by Zierler has shown that an alteration of electrolytes and glucose in the incubation medium in the presence of insulin can lead to leakage of intracellular enzymes from an isolated in vitro muscle preparation [17]. And after that many other studies [13] speculated that the cause of rhabdomyolysis is due to the accompanied metabolic, electrolyte disturbance and the insulin dose used [17], but the exact mechanism is still unclear.

In this study; there was a significant association of rhabdomyolysis with, the duration of DM, high Serum creatinine, high serum potassium, high serum chloride, more severe acidosis than their counterparts and high urinary ketones.

Longer duration of DM, especially those with bad control may put the patient at risk of malnutrition, chronic ill health, chronic electrolyte disturbances, and metabolic abnormalities [18] making the patient more susceptible for rhabdomyolysis.

High Serum creatinine significant association with rhabdomyolysis can be attributed to acute renal insult, either due to the DKA per se, as not all patients with high serum creatinine (11 patient (27.5%)) developed rhabdomyolysis, or rhabdomyolysis it self may have caused the acute renal impairment [13].

High serum potassium significant association can also be attributed to either DKA or rhabdomyolysis. In DKA it is not unusual for the patient to present with hyperkalemia which is usually is corrected after initiation of treatment by correction of dehydration and metabolic acidosis [14]. While in rhabdomyolysis the destruction of myocytes releases K^+ into the circulation, 60–70% of human cellular mass is made from skeletal muscles, and it's estimated that the necrosis of about 100 g of muscle tissue, could increase serum potassium by 1 mEq/L [19].

Hyperchloremia are present in approximately 10.0% of patients with DKA with or without rhabdomyolysis, and it actually increases with sodium chloride 0.09% infusion, then corrected usually spontaneously by the kidney as the renal function improves [16].

DKA patients with rhabdomyolysis had statistically significant

more severe acidosis than their counterparts with a PH of 6.9, and HCO_3 of 9.2 compared to 7.1, and 14.5, respectively. Also urinary ketones was more severe and statistically significant in DKA patients with rhabdomyolysis than in patients with DKA alone. Both the severity of acidosis and urinary ketones were in the setting of moderate and severe DKA, although the severity of DKA had no statistically significant relation to rhabdomyolysis incidence. Therefore the only possible explanation for the occurrence of rhabdomyolysis in this study was the severity of acidosis.

5. Conclusions

Rhabdomyolysis incidence in this study was 6.98% of patients with more severe acidosis, urinary ketones in the setting of moderate to severe diabetic ketoacidosis and with longer duration of diabetes. Screening for rhabdomyolysis in all patients with diabetic ketoacidosis should be considered.

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Conflicts of interest

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Author(s) agreement/declaration

We certify that all authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2018.07.005.

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