Nontraumatic rhabdomyolysis during diabetic ketoacidosis

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Summary. The frequency of nontraumatic rhabdomyolysis in diabetic ketoacidosis was investigated by serial measurements of the serum levels of myoglobin and the serum activity of creatine kinase isoenzyme MM in 12 consecutively admitted ketoacidotic patients. In 5 patients (Group 1) we found hypermyoglobinaemia and elevated activity of creatine kinase isoenzyme MM on admission to hospital, whereas these two variables were normal in 7 patients (Group 2). On admission significantly higher median blood glucose levels and higher median serum osmolality were found in Group 1 than in Group 2 (for blood glucose: 49.6 mmol/l versus 19.0 mmol/l, $p < 0.02$; for serum osmolality: 360 mosm/kg H₂O versus 315 mosm/kg H₂O, $p < 0.05$). Decreased renal function was found in Group 1 as reflected by significantly higher beta₂-microglobulin serum concentrations in Group 1 compared

with Group 2 on admission (median values 4.1 mg/l versus 1.7 mg/l, $p < 0.01$) and during the first 3 days of therapy. The serum concentration of hypoxanthine (an indicator of the cellular energy state) was elevated in all patients on admission, with no difference between patients with or without hypermyoglobinaemia. In conclusion, our findings suggest that nontraumatic rhabdomyolysis with hypermyoglobinaemia and elevated serum activity of creatine kinase isoenzyme MM may be a hitherto unrecognized common feature of diabetic ketoacidosis.

Key words: Rhabdomyolysis, diabetic ketoacidosis, myoglobin, creatine kinase isoenzyme MM, beta₂-microglobulin, hypoxanthine, renal function.

Nontraumatic rhabdomyolysis during diabetic ketoacidosis complicated with anuria or acute renal failure has been described earlier in only 4 case reports [1–4]. However, the findings by other investigators of elevated serum activity of creatine phosphokinase and the observation of a positive urine test for haemoglobin in the absence of haematuria may indicate that damage to striated muscle cells with hypermyoglobinaemia and myoglobinuria accompanying diabetic ketoacidosis may be more frequent than previously recognized [5–7]. In order to estimate the frequency and severity of rhabdomyolysis during diabetic ketoacidosis, we have serially measured the serum concentration of myoglobin by radioimmunoassay and the serum activity of creatine kinase isoenzyme MM in 12 patients with diabetic ketoacidosis on admission to hospital and during recovery.

Subjects and methods

Twelve patients (3 women, 9 men), consecutively admitted to hospital with diabetic ketoacidosis, were serially investigated from admission to full recovery. Diabetic ketoacidosis was diagnosed clinically and confirmed by excessive ketonuria, lowered plasma standard bicarbonate concentration (< 18 mmol/l) and an arterial pH below 7.35.

The treatment was immediately started with fluid replacement in the form of intravenous saline, isotonic potassium chloride and supplementary isotonic glucose infusion with approaching normoglycaemia, and by intravenous low-dose insulin treatment with 12 IU/h. No patient received sodium bicarbonate or phosphate supplement.

Blood samples were taken on admission and every 4 h for the first 24 h and thereafter at days 2, 3 and 7.

Electrocardiograms were taken daily for the first 3 days and at the seventh day. During hospitalization any muscular trauma, including intramuscular injections, were carefully avoided.

Plasma standard bicarbonate concentrations, arterialized capillary pH and serum phosphate concentrations were measured using routine laboratory methods. Capillary blood glucose was measured with an autoanalyzer [8]. Serum concentration of beta₂-microglobulin was determined by a double antibody radioimmunoassay (Pharmacia Beta₂-micro RIA*, Pharmacia Diagnostics AB, Uppsala, Sweden). Serum concentration of myoglobin was measured by a radioimmunoassay (MYOK, Cis-Sorin, St. Quentin Yvelines, France) [9]. Total creatine kinase activity in serum was determined spectrophotometrically [10], and creatine kinase isoenzyme MM was determined by separation of the isoenzymes by electrophoresis and the quantification of the MM isoenzyme by scanning fluorometry [11]. Serum osmolality was measured by freezing point depression with a membrane osmometer (Membran-Osmometer, Wissenschaftliche Geräte KG,

Table 1. Analytical performance with precision (coefficient of variation in %) and accuracy data for assays used in this investigation

	Precision		Accuracy
	Within-assay (%)	Between-assay (%)	Recovery (in %)
Glucose	4.2	6.9	98.5
Beta ₂ -microglobulin	2.7	7.4	102.4
Myoglobin	5.3	9.7	102.0
Creatine kinase (total)	2.0	5.0	99.5
Creatine kinase isoenzyme MM	5.0	10.0	99.5
Hypoxanthine	8.0	8.8	107.0
Osmolality	1.4	2.8	99.0
Urea	1.2	2.4	103.8

Table 2. Clinical data and some paraclinical variables on the 12 patients investigated

Patient number	2 ^a	3 ^a	5 ^a	6 ^a	11 ^a	1
Sex	Male	Male	Female	Male	Female	Male
Age (years)	76	39	56	50	77	70
Diabetes type	1	1	1	1	1	1
Duration of known diabetes (years)	40	7	27	11	13	15
Daily insulin dose (U)	60 (27/73) ^b	92 (13/87)	48 (50/50)	40 (0/100)	36 (0/100)	28 (0/100)
Microvascular complications	Retinopathy	None	None	None	None	None
Macrovascular complications	None	None	None	Claudication	Claudication	None
Creatinine clearance ^d (ml · min ⁻¹ · 1.73 m ² ⁻¹)	44	80	62	71	71	60
Cause of ketoacidosis	Gastroenteritis	Unknown	Unknown	Interruption of daily insulin therapy by the patient	Interruption of daily insulin therapy by the patient	Cystitis

Table 2. Continuation

Patient number	4	7	8	9	10	12
Sex	Male	Male	Male	Male	Male	Female
Age (years)	39	16	36	29	22	20
Diabetes type	1	1	1	1	1	1
Duration of known diabetes (years)	c	c	c	8	10	7
Daily insulin dose (U)	32 (0/100)	28 (0/100)	28 (0/100)	40 (0/100)	48 (25/75)	64 (0/100)
Microvascular complications	None	None	None	Retinopathy	None	None
Macrovascular complications	None	None	None	None	None	None
Creatinine clearance ^d (ml · min ⁻¹ · 1.73 m ² ⁻¹)	112	104	98	93	112	107
Cause of ketoacidosis	Unknown	Unknown	Unknown	Respiratory infection	Interruption of daily insulin therapy by the patient	Unknown

^a Patients with elevated serum myoglobin levels on admission to hospital; ^b values in parentheses are rapidly-acting versus intermediately-acting insulin in percentage of daily dose. In patients with first-appearance diabetes, daily dose is dose on discharge from hospital; ^c first appearance of diabetes mellitus; ^d estimated after treatment of metabolic decompensation using serum creatinine concentration, age, sex, body weight and height [17]

Table 3. Paraclinical data on admission to hospital in the 12 patients with diabetic ketoacidosis. Values in parentheses are reference ranges

Patient number	2 ^a	3 ^a	5 ^a	6 ^a	11 ^a	1
B-glucose (3.1–5.6 mmol/l)	51.20	42.80	31.00	50.50	49.60	23.20
Arterialized capillary pH (7.35–7.42)	7.15	7.00	7.20	7.11	7.17	7.29
P-standard bicarbonate (21.3–25.8 mmol/l)	10.50	6.00	15.10	7.30	9.60	16.30
S-potassium (3.5–5.0 mmol/l)	5.80	6.10	5.60	5.80	5.20	3.80
S-phosphate (0.80–1.55 mmol/l)	3.60	1.50	2.00	3.10	3.00	0.79
S-urea (3.0–7.5 mmol/l)	27.40	17.40	17.90	16.50	21.30	6.40
S-osmolality (280–290 mosm/kg H ₂ O)	382.00	360.00	332.00	392.00	365.00	315.00
S-Hypoxanthine (0–8 µmol/l)	21.00	15.00	23.00	18.00	45.00	10.00

Table 3. Continuation

Patient number	4	7	8	9	10	12
B-glucose (3.1–5.6 mmol/l)	19.00	33.00	33.90	15.20	18.00	18.70
Arterialized capillary pH (7.35–7.42)	7.18	7.15	7.13	7.25	7.26	7.06
P-standard bicarbonate (21.3–25.8 mmol/l)	9.00	10.50	7.80	15.40	12.20	8.00
S-potassium (3.5–5.0 mmol/l)	5.10	5.30	4.10	5.40	5.00	5.20
S-phosphate (0.80–1.55 mmol/l)	1.39	0.64	1.70	1.60	2.05	2.05
S-urea (3.0–7.5 mmol/l)	8.70	11.90	11.80	7.30	9.50	9.70
S-osmolality (280–290 mosm/kg H ₂ O)	309.00	310.00	364.00	302.00	325.00	340.00
S-Hypoxanthine (0–8 µmol/l)	24.00	22.00	22.00	11.00	22.00	15.00

B, blood; P, plasma; S, serum; ^a patients with elevated serum myoglobin levels on admission to hospital

Fig. 1. Semilogarithmic plot of the time-concentration curve of serum myoglobin. Solid and broken horizontal lines mark upper reference limit of non-ketotic Type 1 (insulin-dependent) diabetic patients and of healthy subjects respectively. $\square$ group 1, $\blacksquare$ group 2, — median values in the individual groups

Oberursel/Taunus, FRG). Serum concentration of hypoxanthine was measured by a xanthine oxidase method [12]. The reference range for serum hypoxanthine in both healthy and in non-ketotic Type 1 (insulin-dependent) diabetic subjects is 0–8.0 $\mu\text{mol/l}$ [13].

Serum concentration of urea was measured on a Technicon SMA 12/60 autoanalyzer system [14].

Analytical performances for each of the above mentioned analyses are given in Table 1.

Statistical analysis

Nonparametric methods [15, 16] were used. Comparison at a certain time between two groups was made by the Mann-Whitney test. The Spearman rank correlation coefficient was used to measure the association between two variables at a given time. Analysis of variance by time of a variable was made by the Friedmann test as modified by Conover [15] for pairwise comparison if an overall difference was found. A 5% level (two-tailed) of statistical significance was used.

Results

Clinical data for each of the 12 patients are shown in Table 2, and paraclinical data on admission in Table 3. Figure 1 shows the serum myoglobin concentrations in the 2 groups of patients during recovery from diabetic ketoacidosis. In 5 patients the serum myoglobin concentrations on admission to hospital were above the reference range of healthy subjects (Group 1). After a small initial increase following insulin administration, the myoglobin concentration decreased slowly and was within normal range at day 7 in all except 1 patient. In the remaining 7 patients the serum myoglobin concentration was normal during the entire observation period (Group 2). The difference in myoglobin concentration between the two groups remained statistically significant during the first 3 days ($p < 0.01$).

Fig. 2. Semilogarithmic plot of the time-activity curve of serum creatine kinase isoenzyme MM. Broken horizontal line marks upper reference limit of healthy subjects. $\square$ group 1, $\blacksquare$ group 2, — median values in the individual groups

Fig. 3. Time-concentration curve of serum β_2 -microglobulin. Broken horizontal line marks upper reference limit of healthy subjects. $\square$ group 1, $\blacksquare$ group 2, — median values in the individual groups

The serum creatine kinase isoenzyme MM activity on admission to the hospital and during recovery is given in Figure 2. The patients in Group 1 had a significantly higher creatine kinase isoenzyme MM activity than the patients in Group 2 during the first 3 days ($p < 0.01$). The time-activity curve of creatine kinase isoenzyme MM in Group 1 almost paralleled the time concentration curve of serum myoglobin.

β_2 -microglobulin concentration in serum (Fig. 3) was elevated above the reference range of healthy sub-

Table 4. Median value of serum osmolality, blood glucose and serum urea on admission to hospital (0 h) and during the first 12 h of treatment. Ranges are given in parentheses. Group 1: patients with elevated serum myoglobin on admission. Group 2: patients with normal serum myoglobin on admission

	0 h	4 h	8 h	12 h
Osmolality (mosm/kg H ₂ O)				
Group 1	360 (332–392)	339 (316–347)	325 (298–339)	316 (283–336)
Group 2	315 (302–364)	305 (302–325)	304 (276–312)	298 (282–310)
<i>p</i>	<0.05	<0.05	<0.05	NS
Glucose (mmol/l)				
Group 1	49.6 (31.0–51.2)	33.0 (23.2–40.8)	18.5 (9.7–27.0)	12.9 (2.7–14.9)
Group 2	19.0 (15.2–33.9)	13.0 (6.4–26.8)	8.1 (3.8–15.1)	9.5 (4.3–15.8)
<i>p</i>	<0.02	<0.02	<0.05	NS
Urea (mmol/l)				
Group 1	17.0 (16.5–27.4)	18.7 (13.2–27.0)	14.7 (9.5–27.1)	14.8 (7.7–26.4)
Group 2	9.5 (6.4–11.9)	8.2 (6.1–10.2)	6.5 (4.1–7.4)	5.3 (3.5–6.1)
<i>p</i>	<0.01	<0.01	<0.01	<i>p</i> < 0.01 ^a

^a The difference in serum urea between Group 1 and Group 2 continued (*p* < 0.01) at 16, 20, and 24 h as well as on day 2 and 3, but was lost on day 7

Table 5. Spearman's rank correlation coefficient for association in the 12 patients with diabetic ketoacidosis between serum myoglobin (MYO) and serum creatine kinase isoenzyme MM (CKMM) as well as between these two variables and blood glucose, serum osmolality, serum beta₂-microglobulin and serum urea

	0 h		4 h		8 h		12 h		16 h	
	MYO	CKMM	MYO	CKMM	MYO	CKMM	MYO	CKMM	MYO	CKMM
CKMM	0.64 ^a		0.78 ^b		0.87 ^c		0.81 ^b		0.88 ^c	
B-glucose	0.63 ^a	0.61 ^a	0.86 ^c	0.59 ^a	0.75 ^b	0.63 ^a	NS	NS	NS	NS
S-osmolality	0.69 ^a	0.64 ^a	0.80 ^b	0.59 ^a	0.75 ^b	0.59 ^a	NS	NS	NS	NS
S-beta ₂ -microglobulin	0.72 ^a	0.61 ^a	0.89 ^c	0.64 ^a	0.87 ^c	0.72 ^a	0.87 ^c	0.68 ^a	0.60 ^a	0.61 ^a
S-urea	0.64 ^a	0.61 ^a	0.81 ^b	0.63 ^a	0.78 ^b	0.76 ^b	0.81 ^b	0.87 ^c	0.60 ^a	0.77 ^b

Table 5. Continuation

	20 h		24 h		Day 2		Day 3		Day 7	
	MYO	CKMM	MYO	CKMM	MYO	CKMM	MYO	CKMM	MYO	CKMM
CKMM	0.82 ^b		0.85 ^b		0.78 ^b		0.75 ^b		NS	
B-glucose	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
S-osmolality	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
S-beta ₂ -microglobulin	0.62 ^a	0.61 ^a	0.88 ^c	0.74 ^a	0.60 ^a	0.59 ^a	0.67 ^a	0.60 ^a	NS	NS
S-urea	0.63 ^a	0.75 ^b	0.62 ^a	0.59 ^a	0.59 ^a	0.64 ^a	0.72 ^a	0.78 ^b	NS	NS

B, blood; S, serum; ^a *p* < 0.05; ^b *p* < 0.01; ^c *p* < 0.001

jects in Group 1 patients during the first 8 h after institution of treatment. A significant difference in median serum beta₂-microglobulin concentration in Group 1 and Group 2 was found during the first 3 days (*p* < 0.01 during first 24 h and *p* < 0.05 at days 2 and 3). One patient in Group 1 had elevated beta₂-microglobulin (and concomitantly elevated serum myoglobin) after 7 days. Otherwise, this parameter had normalized in all patients.

Blood glucose concentration and serum osmolality were significantly different in the two groups of patients during the first 8 h of treatment. In the group of patients with hypermyoglobinaemia, blood glucose and serum osmolality were significantly higher than in the group of patients with normal serum myoglobin concentration

(Table 4). Serum urea was also significantly higher in Group 1 than in Group 2 at admission and remained higher during the first 3 days of therapy (*p* < 0.01, Table 4).

Serum phosphate decreased significantly following insulin administration in both groups (*p* < 0.01). The lowest concentration was observed 8 h after the initiation of therapy. Thereafter the serum phosphate concentration slowly normalized without phosphate infusion. No statistically significant difference in phosphate concentration was found between the two groups during the observation period.

The concentration of hypoxanthine in serum was elevated in all patients on admission to the hospital and was gradually decreased during recovery, with normal

values in all patients at the seventh day ($p < 0.01$). There was no difference between Group 1 and Group 2 with respect to the serum hypoxanthine level.

In Table 5 are given values for the correlation between myoglobin and creatine kinase isoenzyme MM as well as between these 2 variables and blood glucose, serum osmolality, serum beta₂-microglobulin and serum urea for all 12 patients during recovery. We found that myoglobin and creatine kinase isoenzyme MM was significantly correlated from admission to day 3, and that both these variables were correlated to beta₂-microglobulin and urea during the first 3 days. Blood glucose and serum osmolality were correlated to both myoglobin and creatine kinase isoenzyme MM during the first 8 h.

We found no relationship between the presence of hypermyoglobinaemia and age of the patient, duration of diabetes, fluid deficit, pH of arterialized blood, plasma standard bicarbonate and insulin dose given during the first 48 h.

None of our patients suffered from frank symptomatic rhabdomyolysis with muscle pain and swelling.

Discussion

Rhabdomyolysis with resultant hypermyoglobinaemia and myoglobinuria may be caused by other diseases than diabetic ketoacidosis, as reviewed by Grossman [18]. However, none of these disorders were present in our patients. We have thus concluded that the hypermyoglobinaemia and the transient elevation of the MM fraction of serum creatine kinase found in 5 of our patients was in some way caused by the diabetic ketoacidotic state.

Earlier reports have suggested that rhabdomyolysis may be related to a state of cellular phosphate depletion [19–21]. During insulin treatment of diabetic ketoacidosis, a precipitous fall in serum phosphate often occurs due to the transfer of phosphate from the extracellular to the intracellular compartment [22]. Our patients also showed a marked decrease in serum concentration of phosphate during the first hours of therapy. However, no difference in serum phosphate was found between the group of patients with and without hypermyoglobinaemia. Thus, based on the serum levels of phosphate, no relationship was found between phosphate depletion and rhabdomyolysis.

On the other hand, we found that the patients with hypermyoglobinaemia had significantly higher blood glucose concentrations and serum osmolality than the patients with normal serum myoglobin levels, suggesting that these parameters could be of importance in the development of rhabdomyolysis. It has been proposed by Rainey et al. [1] that decreased cellular utilization of carbohydrates in diabetic ketoacidosis – reflected by elevated blood glucose concentration – may result in deprivation of an important source of energy for muscle

cells, leading to cellular damage. This hypothesis assumes that the muscles cannot preserve adequate metabolism by other metabolic pathways. Accordingly, it would be anticipated that the content of cellular high energy phosphates might decrease, leading to an increase in the serum concentration of hypoxanthine – a degradation product of intracellular nucleotides. The concentration of serum hypoxanthine is known to correlate inversely with the cellular energy state (the cellular high energy phosphate content) [23–25]. A similar ATP-depletion theory for the pathogenic mechanism of rhabdomyolysis in severely phosphate depleted patients has previously been proposed by Rowland [26]. However, we found no association between the concentration of hypoxanthine and the presence of hypermyoglobinaemia. Consequently, the increase in serum hypoxanthine seemed not to reflect metabolic changes directly associated with rhabdomyolysis.

Caplan [27] found that mouse skeletal muscle enzyme leakage in vitro was independent of osmolality. In our study, we found evidence of an association between hyperosmolality and the concentration of serum myoglobin and creatine kinase enzyme MM.

Serum urea levels is a result of several factors such as glomerular filtration rate, urine flow (i.e. the degree of dehydration), protein intake and protein metabolism. This makes use of serum urea levels as an indicator of renal function difficult in our patients, as one must necessarily know or control the influence of the other factors. However, the finding of significantly higher levels of serum urea in the patients with hypermyoglobinaemia may be of clinical importance, and may point to a more severe metabolic decompensation in these patients because blood urea has been shown to be an important prognostic factor in the outcome of diabetic coma [28]. Our observation of an association between hypermyoglobinaemia and elevated concentration of beta₂-microglobulin is not surprising, as the kidneys are known to play a central role in the myoglobin turnover [29]. Serum beta₂-microglobulin was used in this study as a measure of renal function instead of serum creatinine, as serum beta₂-microglobulin has been shown to be a sensitive indicator of the glomerular filtration rate [30], and because both creatine and creatinine can be released from muscles in rhabdomyolysis, leading to falsely high serum levels of creatinine [26]. Furthermore, if creatinine is measured in diabetic ketoacidosis with the common alkaline picrate method, interference by serum acetoacetate would give falsely high serum creatinine levels [31, 32].

We found that patients with elevated beta₂-microglobulin and hypermyoglobinaemia had concomitantly increased creatine kinase isoenzyme MM activity. The elimination of creatine kinase isoenzyme MM is mainly dependent on the function of the reticuloendothelial system, and is largely independent of renal function. Patients with chronic renal failure have normal serum creatine isoenzyme MM levels. In patients with acute

renal failure, only slightly elevated creatinine isoenzyme MM levels [33] have been found. The persistent increase in creatine kinase isoenzyme MM in our patients with hypermyoglobinaemia and elevated beta₂-microglobulin in serum (Group 1) thus seemed to be caused by a greater degradation of muscle tissue in this group than in the rest of the patients. Consequently, the decrease in glomerular filtration rate reflected by elevation of beta₂-microglobulin in serum may be the result of, rather than the cause of, hypermyoglobinaemia in this group of patients. A common mechanism associated with both renal impairment and rhabdomyolysis could also, however, be the underlying cause.

In conclusion, we have found rhabdomyolysis with hypermyoglobinaemia and elevated creatine kinase isoenzyme MM activity in 5 of 12 patients with diabetic ketoacidosis. In the same patients, a decrease in renal function was found. The pathogenic mechanism leading to rhabdomyolysis in diabetic ketoacidosis remains unsettled.

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