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Case Report

Markedly elevated troponin and NT-proBNP and myocardial dysfunction in an adolescent with severe diabetic ketoacidosis: A case report

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Highlights

- We report a marked elevation of troponin and NT-proBNP in an adolescent with severe DKA.
- Myocardial dysfunction developed after DKA resolution, suggesting the involvement of inflammatory immune responses.
- Long-term follow-up of the cardiovascular function indicated no underlying cardiac pathology in our case.

Abstract. Severe diabetic ketoacidosis (DKA), rarely, may be associated with elevated troponin and proBNP levels in adults with a history of diabetes. However, few cases have reported this association in children with severe and complicated DKA. We describe a case of severe DKA (pH: 6.89, HCO3: 6.5) in a 14-yr-old female adolescent in which the symptoms of DKA were presented days before the diagnosis. The patient was under the effect of acidosis (Kussmaul respiration) for 12 h before admission to our hospital, where she was admitted in a critical clinical condition. After successful treatment with DKA with intensive intravenous fluid and regular insulin, the patient presented with abnormal cardiac rhythm, disturbance of interventricular septum motility, a mild decrease in left ventricular systolic function, negative T waves in leads III and aVF, and a marked increase in troponin and brain natriuretic peptide (NT-proBNP) levels. All abnormal findings completely resolved within 8 days after the initiation of DKA treatment. The phenomenon in our case was transient, and the patient had a good long-term outcome. However, it represents a challenge for clinicians; therefore, emphasis should be given to cardiac monitoring during the course of severe and prolonged DKA in children and adolescents.

Key words: diabetic ketoacidosis, adolescent, troponin, NT-proBNP, myocardial dysfunction

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Introduction

Diabetic ketoacidosis (DKA) is an acute metabolic emergency that frequently occurs at the time of pediatric type 1 diabetes (T1D) diagnosis. Insulin deficiency and high concentrations of counter-regulatory hormones during DKA cause numerous acute complications, including hyperglycemia, high free fatty acids (FFA) levels, hyperketonemia, and metabolic acidosis, which may lead to dysfunction of body organs and systems (1).

Myocardial injury with increased troponin and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels is an uncommon manifestation of DKA. Elevated troponin levels reflect acute myocardial necrosis in severe cardiac and noncardiac clinical conditions, including DKA (2). This association has been previously described in adult patients with underlying prediabetes or type 1 and 2 diabetes without evidence of acute coronary syndrome (2–4). In addition, positive troponin levels during DKA in adults are associated with long-term adverse cardiac events (4). In children, only three reports have suggested an association between severe DKA and increased troponin levels (5–7).

NT-proBNP is another cardiac biomarker secreted by cardiomyocytes in response to myocardial stretching and fluid overload (8). Similar to troponin, increased levels are associated with many other conditions, including ventricular dysfunction and extracardiac pathologies such as sepsis, renal failure, and other severe diseases (8). However, to our knowledge, high NT-proBNP levels and their association with severe new-onset DKA have not been previously reported.

Herein, we describe a case of severe DKA associated with significantly elevated high-sensitivity troponin and NT-proBNP levels and some degree of myocardial dysfunction-injury in an adolescent with newly diagnosed T1D and the possible underlying mechanisms.

Patient and Methods

A 14-yr-old female presented to the emergency department of a tertiary pediatric care hospital with respiratory distress and impaired consciousness.

The patient had a 2-wk history of malaise, dizziness, foul taste perception, and subsequent irritability and fatigue. Twenty-four h prior to admission, the patient developed vomiting and abdominal pain in addition to Kussmaul breathing over the previous 12 h. A review of these systems revealed excessive polydipsia and polyuria, weight loss, and the aforementioned symptoms.

Upon admission, the patient was severely dehydrated, lethargic (Glasgow Coma Scale 13/15) with Kussmaul breathing (35 breaths/min), and an $SaO2^{blood}$ of 98%. Heart auscultation was unremarkable with no added sounds or murmurs, although the patient had tachycardia [heart rate 155 bpm beats/min], relatively high blood pressure (BP = 133/83 mmHg), delayed capillary refill time (> 3 sec), and no fever (36.7°C). Abdominal examination was unremarkable. The patient body mass index was 16.7 kg/m^2 (50 kg weight). At discharge, her weight increased to 52.7 kg (estimated weight loss upon admission of 5.12%). The patient had no previous medical problems and was not taking any medication. A family history of autoimmune disease was noted; her mother had Hashimoto's thyroiditis, and her maternal and paternal aunts had psoriasis.

The diagnosis of DKA was confirmed with high serum glucose level (775 mg/dL) and metabolic acidosis on venous blood gas (pH: 6.9, HCO_3: 6.5 mEq/ml, pCO_2: 22 mmHg). Urinalysis revealed severe ketonuria and glucosuria. Biochemistry revealed the following: urea 44 mg/dL, creatinine 1.4 mg/dL, Na+ 130 mEq/L (corrected Na+ 136.7 mEq/L), K+ 5.3 meq/L, Ca 9.3 mg/dL, P 4.4 mg/dL, Mg 2.3 mg/dL, CPK 120 U/L, SGOT 11 U/L, and SGPT 18 U/L. The ECG was normal without evidence of potassium abnormalities.

The patient was promptly administered an intravenous normal saline bolus (10 mL/kg) and the DKA treatment protocol. Insulin infusion (regular) was started at a rate of 0.1 Units/kg/h, and IV fluids composed of dextrose 5% with normal saline 0.45% at a total rate of 120 mL/h (including deficit replacement plus maintenance fluid requirements) were administered over 48 h. Potassium chloride was added at the maximum dose (40 mEq/L), and sodium bicarbonate (1 mEq/kg) was administered slowly over 1 h. Blood glucose levels, pH, electrolytes, and other biochemical parameters were closely monitored (**Table 1**). It is worth mentioning that the estimated glomerular filtration rate (eGFR) was moderately decreased (51 mL/min/1.73 m^2) upon admission, it increased to 89 mL/min/1.73 m^2 24 h after treatment and was normalized (136 mL/min/173 m^2) 48 h after treatment initiation. In addition, the anion gap decreased from 35 mEq/L upon admission to 13 mEq/L at 24 h after treatment (**Table 1**).

The patient's alertness improved a few hours after rehydration and recovered from DKA (pH: 7.33 and HCO_3: 18 mmol/L) 20 h after admission. However, excessive fatigue was noted over the following few days. The patient was administered an intensive insulin regimen (basal/bolus).

On the second day of hospitalization, the patient clinically felt fatigued, particularly while standing up. Cardiac auscultation revealed a non-specific gallop rhythm without vital sign abnormalities. The patient underwent a comprehensive cardiac evaluation. The electrocardiogram obtained by the cardiologist 48 h after admission showed normal sinus rhythm, HR 82 bpm, low voltage QRS, and flattened T-waves in the inferior leads (II, III, and aVF) (**Fig. 1**). Echocardiography revealed severe paradoxical motion of the interventricular septum and mildly reduced left ventricular ejection fraction (LVEF 50%). The apex of the right ventricle appeared excessively trabeculated, and a prominent moderator band was noted. However, RV systolic function was normal without regional ventricular dyskinesia or aneurysms.

Subsequently, cardiac enzyme levels that were first

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Table 1. Laboratory values during the patient's hospitalization

	Upon admission	6 h after	12 h after	18 h after	24 h after	48 h after	72 h after	96 h after
Blood glucose mg/dL	775	477	305	286	165	180		
pH	6.95	7.14	7.19	7.29	7.33	7.35		
HCO_3 mmol/L	6.5	4	12	14	18	22		
pCO_2 mmHg	22	11	37	29	36	34		
K mEq/L	5.3	4.5	4.8	4.1	4	4.4		
Nα mEq/L	130	140	139	137	142	139		
Cl mEq/L	88	107	110	108	111	106		
Ca/P/Mg mg/dL	9.3/4.4/2.3				9.7/2.8/1.7	9.8/3.0/1.4		
Urea mg/dL	44	42	37	32	30	22		
Creatinine mg/dL	1.4	1.3	1.1	0.9	0.8	0.6		
Anion Gap	35.5	29	17	17	13	11		
eGFR (mL/min/1.73 m^2)	51	55	65	79	89	136		
Estimated osmolality *2 × (sodium [Na]) + glucose in millimoles per L*	303	286	277					
Troponin pg/mL						147.9	134.2	29.55
pBNP pg/mL						748	632	157
HbA1C %								10.70%
Anti GAD								positive
Anti IA2								positive
C-peptide ng/mL (serum)								0.31

checked were found markedly increased: hs-troponin level was 147.9 pg/mL (normal: < 14), and NT-proBNP was 748 pg/mL (95th percentile, normal: < 242 according to age) (9), further suggesting myocardial involvement and injury. At the time of cardiological evaluation, blood glucose, pH, Na, K, Ca, and P levels were within normal values. However, regular measurements of NT-proBNP and hs-troponin levels showed a gradual decrease over the following days (**Table 1**).

To investigate possible myocarditis due to a recent or concurrent infection, serum antibody titers against influenza A and B, enteroviruses (Echo, Coxsackie), and *Mycoplasma pneumoniae* were measured based on the Sars-Cov 2 pre-pandemic protocol and were negative.

On the fifth day of hospitalization, follow-up ECG showed negative T waves in leads III and aVF (**Fig. 2**). Following the expected ECG pattern sequence after acute myocardial injury. Echocardiography revealed improved left ventricular systolic function (LVEF recovered to 55%–60%) with a mild paradoxical motion of the interventricular septum. The systolic and diastolic functional indicators of the RV were normal. In addition, NT-proBNP levels were within normal limits, and troponin T levels were reduced to near-normal levels (**Table 1**).

The patient was placed on a selective β receptor blocker (metoprolol), and an ACE inhibitor and was given instructions to avoid moderate and vigorous physical activity for the following 6 months. In addition, the patient was scheduled for 24 h Holter monitoring and cardiac magnetic resonance imaging (MRI). Diabetes management education was provided to the patient and her parents during hospitalization. Furthermore, 24-hour Holter monitoring conducted 4 days post-discharge showed a normal heart rate with an average of 73 bpm (range 43–135). Cardiac MRI 8 days post-discharge showed the normal systolic and diastolic function of both ventricles without signs of myocardial inflammation or fibrosis. Apical trabeculations of the right ventricle and a small amount of pericardial fluid were also observed. As a follow-up, Holter monitoring and echocardiographic examinations were normal at 1, 3, and 6-mo post-discharge, prophylactic antiarrhythmic therapy and restricted physical activity recommendations were discontinued. At 30 mo post-discharge, the follow-up did not reveal any abnormal cardiac findings.

Ethical consideration

The patient's parents provided informed consent for the publication of clinical data.

Discussion

The present study reports a newly diagnosed T1D in an adolescent, who presented with severe DKA complicated with myocardial dysfunction, significantly elevated troponin and NT-proBNP levels, and ECG and echocardiographic abnormalities, all of which gradually recovered completely. DKA was treated according to the current guidelines of the International Society for Pediatric and Adolescent Diabetes (10). Biochemically, DKA resolved within 20 h, as indicated by serum bicarbonate > 15 mmol/L and venous pH > 7.3. Ketones were absent in urinalysis, and no further electrolyte abnormalities were observed during the subsequent healing process when complications often developed as serum glucose levels normalized and the level of

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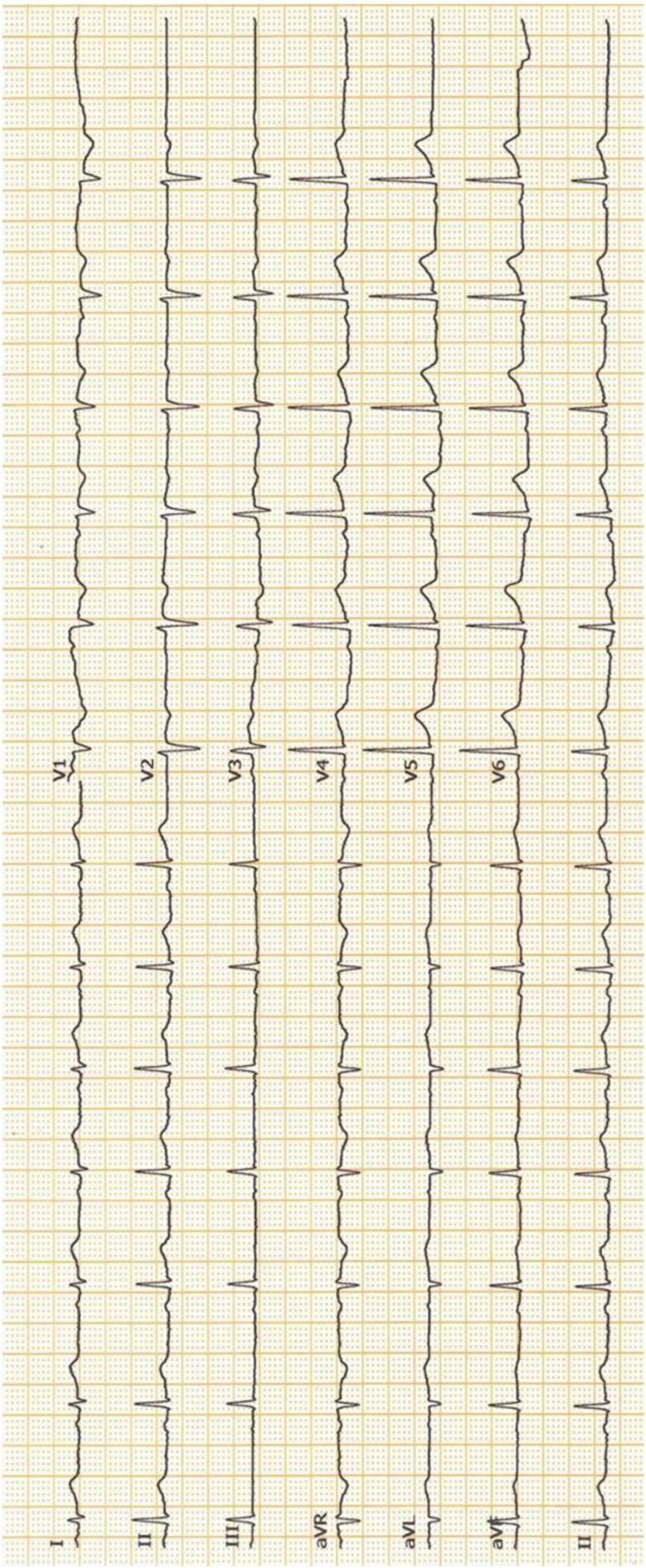

Fig. 1. ECG of patient showing flattened waves in inferior leads.

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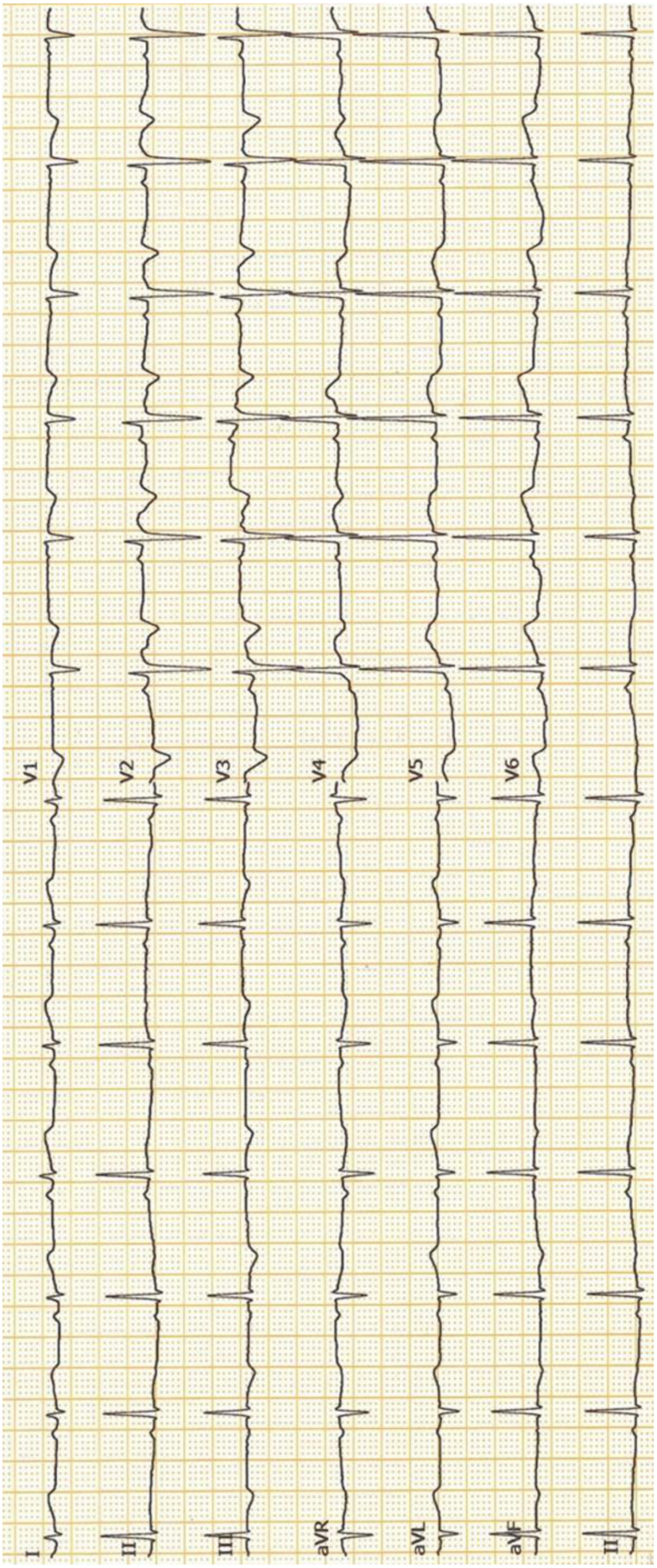

Fig. 2. ECG of patient showing negative waves in leads III and aVF.

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consciousness recovered. However, the 10-fold rise in troponin levels and other markers of myocardial damage presents a novel challenge in identifying potential underlying pathophysiological mechanisms.

The possibility of myocarditis seems unlikely in our case due to the lack of compatible symptoms, negative serology against common viruses associated with myocarditis, complete resolution of abnormal findings, and lack of evidence of inflammation on cardiac MRI.

Although significant troponin level elevation indicates myocardial necrosis or ischemia, the possibility of myocardial infarction is extremely rare in children. The only reported case of acute myocardial infarction was a 12-yr-old patient with severe hyperosmolarity secondary to DKA (11). Despite elevated estimated osmolality levels upon admission, as shown in **Table 1**, our patient had no respiratory symptoms or chest pain, most importantly, no specific ECG findings for coronary occlusion.

This is a novel case of severe DKA associated with mild myocardial dysfunction and disproportionately elevated NT-proBNP and troponin levels in a newly diagnosed T1D in an adolescent. As mentioned earlier, to the best of our knowledge, only three cases of myocardial injury have been observed in pediatric patients with severe new-onset DKA (5–7). In all of the above cases, patients experienced a fulminant clinical course of the disease with severe complications, while troponin levels were mildly elevated. Therefore, the myocardial injury was most likely the result of the accompanying DKA complications. In contrast to the above cases, our patient had considerably increased cardiac enzymes and a moderate clinical course without further DKA complications (such as cerebral or pulmonary edema, sepsis, or myocardial infarction), suggesting a direct effect of ketoacidosis on the myocardium. However, myocardial dysfunction was mild despite elevated troponin and NT-proBNP levels.

This pattern resembles previous reports of adults with acute uncontrolled diabetes and elevated troponin levels in the absence of acute coronary syndrome (2). In a retrospective study, Eubanks *et al*. demonstrated that approximately 10% of adult patients with acute metabolic derangement in the absence of clinically evident acute coronary disease had elevated troponin levels (12). Moreover, low pH (less than 7.1) upon admission has been suggested as an independent predictor of elevated serum troponin levels (12).

Interestingly, a recently published study reported a significant increase in troponin and NT-proBNP levels and QTs prolongation in a 12-yr-old patient with moderate DKA (pH 7.11; HCO_3 7.1 mEq/L). This patient was slightly younger than ours, had uncontrolled T1D (5 yr duration), and most importantly, had a fever and high inflammatory markers during DKA, all of which may contribute to myocardial injury (7).

The timing of the onset of myocardial damage in our case is not clear since troponin and NT-proBNP were not measured upon admission, as they are not part of the DKA ISPAD protocol (10). Indeed, clinically evident myocardial dysfunction in our case became evident 48 h after admission, while regular physical examination, including cardiac auscultation, vital signs, and electrolytes, were normal during the first 48 h. Indeed, the increase in troponin may have started earlier than noted and reached a maximum at a time following the resolution of acidosis, as has been shown by Kaefer *et al*. (2). Regarding the possibility of rhabdomyolysis, it is important to note that global markers of muscle damage, including ALT, AST, and CPK, and negative urinalysis results were not indicative of rhabdomyolysis upon admission.

Mechanisms probably involved in elevated troponin levels during DKA

Severe metabolic acidosis has been previously suggested to promote ***a rise in intracellular calcium levels*** leading to proteolysis and myocardial stunning (2, 12, 13). Nevertheless, the delayed increase in troponin levels associated with the resolution of acidosis has been previously reported, a finding suggestive of the implication of additional mechanisms associated with the duration and severity of ketoacidosis on the development of myocardial injury (2).

Immune inflammatory response

Notably, DKA is characterized by an immune-inflammatory response (14) with high levels of circulating cytokines, especially interleukin-6 (Il-6) recorded for up to 5 days after initiation of treatment in children (15). Given that IL-6 can damage the endothelium and enhance capillary permeability during DKA (14), it may also be implicated in the induction of myocardial injury and elevation of troponin levels, even after the resolution of acidosis.

Hypothesis of autoimmunity eliciting myocardial injury

Severe DKA and the accompanying inflammatory cytokines were found to trigger the production of autoantibodies to cardiac autoantigens (myosin and vimentin) involved in the early development of cardiomyopathy in children and adolescents with T1DM (16). However, the early toxic effects of autoantibodies on cardiomyocytes during DKA remain to be studied.

Free fatty acid and counter-regulatory hormones

Another mechanism involved in the increase of troponin levels during DKA could be excessive circulating FFA, which causes destabilization of the plasma membrane of cardiomyocytes (2, 3) and an increase in counter-regulatory hormones (adrenalin, cortisol, and glucagon) released during insulin deficiency (2, 3). These

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hormones may cause an imbalance between decreased myocardial oxygen supply or increased oxygen demand, inducing myonecrosis and the release of troponin (2, 12, 13).

Additionally, catecholamines, hypoxia, and inflammation stimulate the production and secretion of proBNP, in conjunction with a low glomerular filtration rate that reduces the excretion of proBNP, which may explain its high circulating levels (8, 17).

Conclusion

This case suggests that severe DKA in adolescents may be associated with myocardial dysfunction, ECG abnormalities, and elevated troponin and proBNP levels. Therefore, early screening and monitoring of cardiac function during severe DKA and long-term follow-up are necessary. In addition, future studies should investigate the frequency, and a complete understanding of this association should be investigated in pediatric patients.

Conflict of interests: The authors have nothing to disclose.

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