Acute coronary syndrome and diabetic keto acidosis: the chicken or the egg?

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Abstract: We sought to describe two cases of diabetic ketoacidosis (DKA) with elevated troponin. The association of DKA with myocardial infarction (MI) is very frequent. We therefore decide to look deeply in the potential mechanisms behind this strong relationship. We did review the potential role of severe acidosis, intracellular calcium, the counter-regulatory hormones and the potential of the free fatty acid release. Those two conditions can trigger each other and it is often difficult to know which condition appear first. Ultimately, it stands to reason that the message for the clinician should be that a troponin elevation in a DKA patient should always be considered as a coronary abnormality until proven otherwise.

Keywords: Acute coronary syndrome (ACS); acute metabolic acidosis; diabetic keto acidosis

Submitted Mar 15, 2019. Accepted for publication Jun 03, 2019.
doi: 10.21037/atm.2019.07.38
View this article at: http://dx.doi.org/10.21037/atm.2019.07.38

Introduction

Myocardial infarction (MI) is a rare but well-known cause of diabetic decompensation. The frequency is of the order of 1%. Conversely, congestive heart failure and MI account for 28% of deaths in diabetic ketoacidosis (DKA) (1). The increase of troponin is a marker of myocardial necrosis, However, it is not limited to MI but also occurs in a variety of other conditions in ICU such as sepsis, pulmonary embolism, stroke, or renal failure without acute coronary syndrome (ACS) (1). DKA is a reported cause of troponin increase without ACS (2,3). In addition, the elevated troponin level is a predictor of poor outcome in patients admitted to intensive care for clinical conditions other than ACS (4). The two clinical cases presented below, demonstrate the various aspects of troponin increase in patients in DKA and are an opportunity to review the different mechanisms by which this occurs (*Table 1*).

Table 1 Biological characteristics of both patients

Characteristics	Patient 1	Patient 2
Age (y)	44	49
Sex	Female	Male
HbA1C (%)	10.3	10.4
pH	6.98	6.93
PCO_2 (mm Hg)	12	14
HCO_3 (mEq/L)	7	7
Base excess (mEq/L)	–26.1	–28.2
Anion gap	25	29.6
Glucose level (mmol/L)	23.2	38.9
Lactate (mmol/L)	2	4.10
Peak troponin (ng/L)	209	142

Case presentation

Case 1

A 44-year-old female patient with type 1 diabetes was admitted to the ICU ward for DKA due to an inappropriate reduction of her insulin therapy. At 14 h post admission, a troponin elevation of 209 ng/L was observed without any chest pain (*Figure 1*). The electrocardiogram didn't show

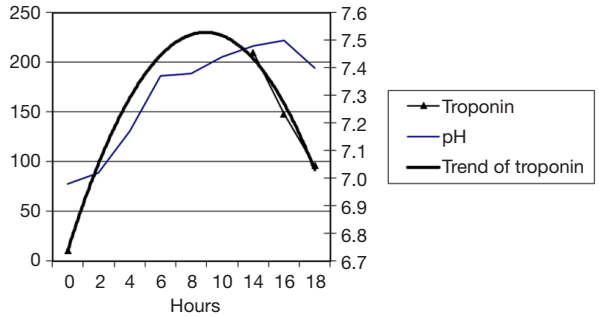

Figure 1 Delayed elevation of troponin compared with resolution of acidosis during troponin peak during the first 18 hours.

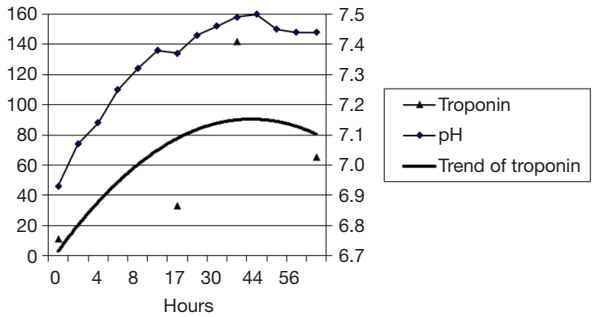

Figure 2 Delayed elevation of troponin compared with resolution of acidosis during troponin peak during the first 56 hours.

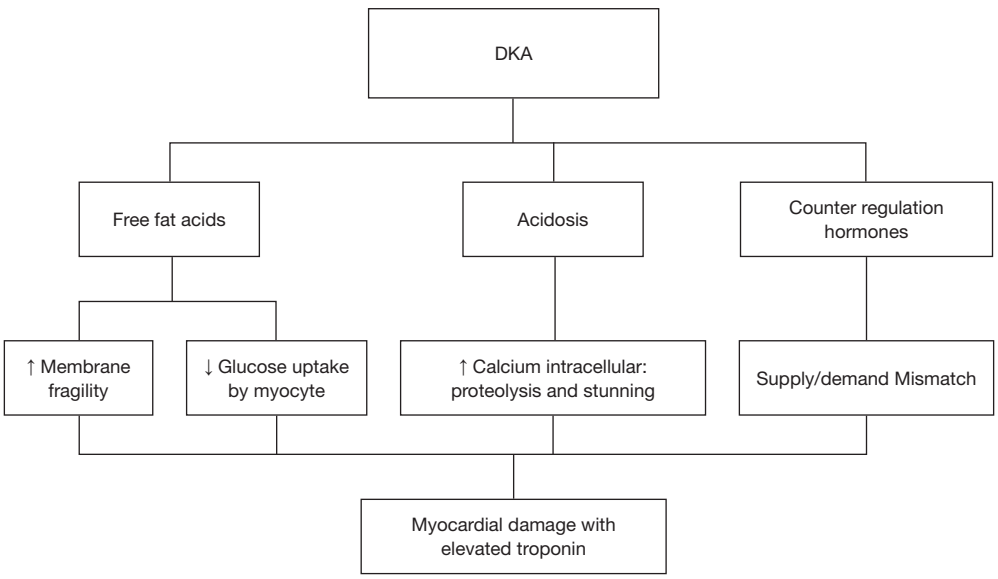

Figure 3 Simplified pathophysiological pattern of troponin elevation in diabetic ketoacidosis. DKA, diabetic ketoacidosis.

a rise of the ST segment. Cardiac ultrasound did not show segmental dyskinesia. A coronary angiography performed after resolution of the acidosis revealed a sub-occlusion of the right coronary artery. The patient was therefore treated with angioplasty with stenting.

Case 2

A 49-year-old male patient, suffering from type 1 diabetes, was admitted to ICU for DKA following an inappropriate insulin therapy justified by vomiting and abdominal pain. At 14 h post admission, the troponin level was at 33 ng/L and reached a maximum pic of 142 ng/L at 38 h post admission (*Figure 2*) without a history of chest pain. The electrocardiogram shows an elevation of the ST segment less than 2 mm from leads V1 to V3. An anterior apical dyskinesia was revealed by an ultrasound and the coronary angiography did not show any subsequently coronary anomaly.

Discussion

The interpretation of cardiac biomarkers is complex in DKA, which is due to the fact that the ACS can be the cause and also the consequence of the DKA. MI is the most common cause of death in DKA (5). Different hypotheses have been proposed to explain this phenomenon (*Figure 3*).

The interaction between acidosis and intracellular calcium

In a case report by Moller *et al.* two patients with elevated

troponin levels had no abnormalities at the angiography and had a pH of 6.9 (3). Eubanks *et al.* have shown that a pH below 7.10 is an independent pronostic factor for troponin (cTnI) elevation on admission in DKA (6).

PH and intracellular calcium interact in complex ways. Following severe acidemia, intracellular calcium is increased by changes in transmembrane ionic motion at the sarcoplasmic membrane and sarcoplasmic reticulum (6). The rise of active intracellular calcium stimulates different biochemical pathways leading to proteolysis. Severe acidosis inhibits the interaction between calcium and contractile proteins, leading to myocardial stunning. Proteolysis and stunning both increase the serum level of cTnI (7).

The counter-regulatory hormones

Acute decompensation of diabetes is associated by a rise in counter-regulating hormones such as adrenaline, cortisol and glucagon (8,9). These hormones increase the oxygen demand of the myocardium (10). In diabetic patients with a history of coronary heart disease, coronary blood flow is compromised with an increase in supply-demand mismatch, resulting in myonecrosis with elevated cTnI (6).

The free fatty acid release

The release of free fatty acids was also observed in the acute diabetic decompensation (8,9). Free fatty acids are the precursors for hepatic ketone body formation. A high circulating level of free fatty acid leads to the incorporation of fatty acids into the lipid structure of the myocyte membrane with the formation of micelle with destabilization and rupture of this membrane (3,11).

Circulating insulin governs the extraction rate of glucose by cardiomyocytes (11). In case of DKA, insulin deficiency is associated with a high level of free fatty acids and ketone bodies, which inhibits the glucose uptake by the cell and thus deprives the myocardium of its energy substrate (12). In addition, the above-mentioned excess of catecholamines decreases the insulin reserves and increases the free fatty acid uptake by the myocardium, which is toxic to the myocardium (12). This phenomenon of cellular toxicity induces the cTnI production (10).

Conclusions

The troponin increase is a phenomenon described in patients with DKA and corresponds either to a pre-existing coronary pathology unmasked by a metabolic stress or to the toxicity of acidosis, the insulin deficiency or the presence of free fatty acids on the myocyte. A troponin elevation in a diabetic patient should always be considered a coronary abnormality until proven otherwise. The troponin kinetics, even delayed, does not allow us to distinguish if the cause is coronary or not.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

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Cite this article as: Kaefer K, Botta I, Mugisha A, Berdaoui B, De Bels D, Attou R, Honoré PM, Redant S. Acute coronary syndrome and diabetic keto acidosis: the chicken or the egg? Ann Transl Med 2019;7(16):397. doi: 10.21037/atm.2019.07.38

