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Distinctive Characteristics and Specific Management of Diabetic Ketoacidosis in Patients with Acute Myocardial Infarction, Stroke and Renal Failure

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/52390>

1. Introduction

Diabetic ketoacidosis (DKA) is considered a predominantly acute type 1 diabetic complication, although it may occur in type 2 diabetes as well, particularly in patients who already have a decreased insulin secretion capacity. Stress –induced burst in catecholamine and ACTH secretion in acute myocardial infarction (AMI) promotes release of free fatty acids and their hepatic and muscular tissue utilization. The impairment in insulin-mediated intracellular glucose influx owing to the absent or insufficient pancreatic insulin secretion is the prerequisite for the occurrence of diabetic ketoacidosis.

The results of the analysis of acid – base disturbances from our previous study [26] performed in the intensive-care unit in diabetics and non-diabetics suffering acute myocardial infarction are shown in Fig. 1.

Cardiovascular accidents have a marked place among the possible causes of diabetic ketoacidosis. Cardiovascular morbidity influences the severity and duration of diabetic ketoacidosis and limits the first and most important step in its treatment- the fluid resuscitation. The resulting hyperosmolarity of body fluids precipitates a pro-thrombotic state, thus aggravating prognosis in patients with myocardial infarction. The clinical features of hyperglycemic/hyperosmolar state and diabetic ketoacidosis may overlap and are observed simultaneously (overlap cases) [44].

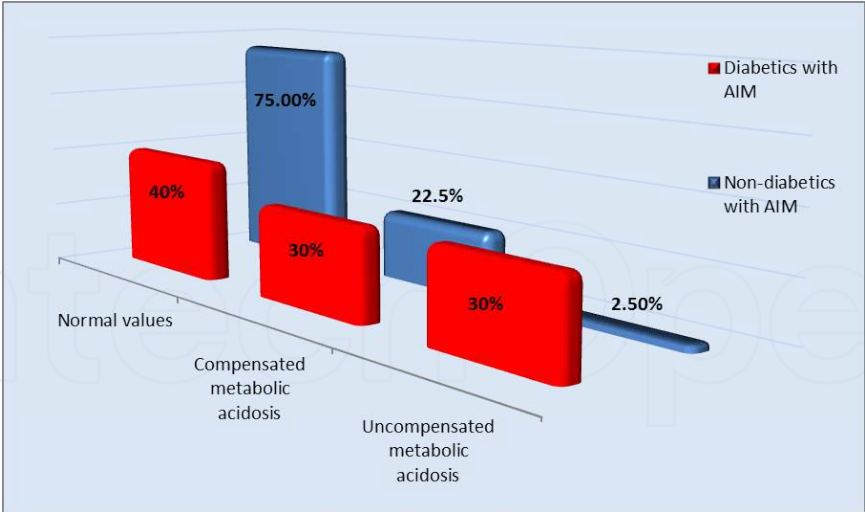


Figure 1. Acid-base disturbances in diabetics and non-diabetics suffering acute myocardial infarction: Almost one-third of diabetic patients with acute myocardial infarction had un-compensated metabolic acidosis defined as pH< 35, HCO₃⁻ < 22mmol/L. Although acidosis was mild in most of the cases at least third of these patients had criteria for true diabetic ketoacidosis (pH<30, HCO₃⁻ <15mmol/L). Additional 30% had a compensated metabolic acidosis with normal pH and mild to moderately decreased bicarbonate level. The pH was normalized at a price of the increased respiratory effort to lower the PaCO₂ which may lead to respiratory muscle fatigue.

Additional risk factors for development of hyperosmolarity include the presence of congestive heart failure, impaired thirst, limited access to water (especially in patients with dementia or who are bed bound), older age, and poor kidney function. Table 1 depicts the significant correlations of pH values and certain clinical and biochemical parameters in diabetics suffering AML.

Spearman's correlation coefficients p	
	pH
Blood glucose	-0.71
Blood ketones	-0.72
Anion gap	-0.77
Noradrenaline	-0.54
Heart failure	-0.41
Rhythm / Conduction disturbances	-0.5
SaO2	0.68
CK	-0.62
Serum lactate	-0.54

Table 1. Significant (p<0.05 and less) correlations between serum pH and clinical and biochemical parameters in diabetics suffering AMIAs expected, serum pH correlated with glycemic control, but also with clinical and biochemical parameters that were related to tissue hypo-perfusion (incidence of heart failure and rhythm/conduction disturbances, haemoglobin oxygen saturation, serum lactate) and to infarct size and stress-hormone release (e.g. serum creatinine – kinase and plasma noradrenaline values)

Hyperosmolar state and circulatory impairment with decreased oxygen tissue delivery may stimulate lactate production. Although true lactic acidosis occurs rarely, the increased lactate load may further contribute to the degree of acidosis. In our study, bicarbonate levels was lower ($p<0.05$) and base deficit were significantly ($p<0.01$) higher in patients with diabetes mellitus and acute myocardial infarction comparing to patients with acute myocardial infarction only. Serum lactate was moderately high (Fig.2), but true lactic acidosis defined as serum lactate > 5 mmol/l was registered only in one case with lethal outcome. Moreover, it seems that rise in the serum lactate level between diabetics and non-diabetics with AMI was not accounted for the differences in oxygen delivery, since hemoglobin saturation was much the same in both groups. Therefore, it seems that DKA itself caused further tissue hypo-perfusion and contributed to serum lactate rise. These findings are compatible with the results of the recent study performed by Cox et al. [14]

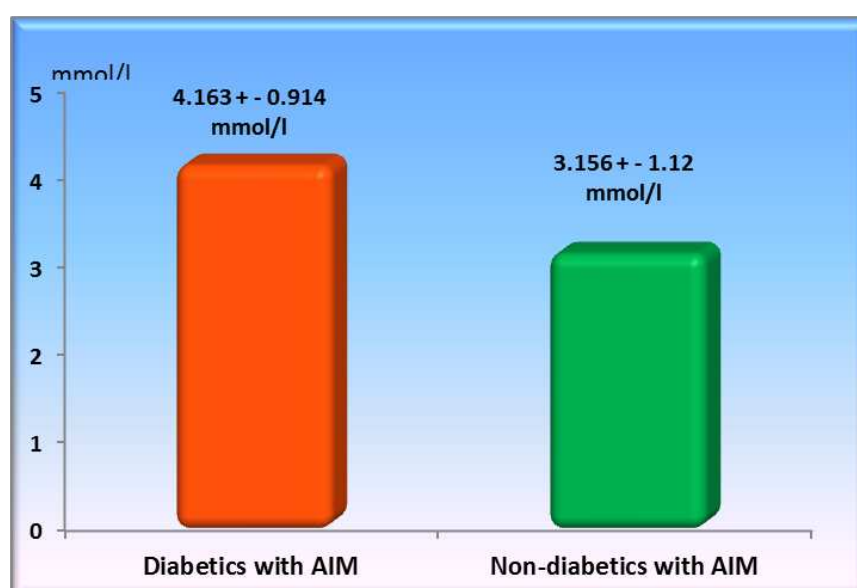


Figure 2. Serum lactate in diabetics and non-diabetics suffering AMI The lactate level in diabetic / AMI patients was higher (4.143 ± 0.914 vs. 3.156 ± 1.12 mmol/L, $p<0.01$) comparing to patients with acute myocardial infarction only

Finally, the intensive care unit mortality reached 15% among DM/AMI patients comparing to 5% in patients with AMI only.

The excess in-hospital mortality of diabetic patients results primarily from an increased incidence of congestive heart failure, severe coronary artery disease, decreased vasodilatory reserve of epicardial artery resistance, abnormal metabolism of myocardial substrate, diffuse nature of the atherosclerotic disease and hyper-coagulable state. Autonomic neuropathy predisposes patients to ventricular arrhythmia [5]. Also, inhibition of myocardial protective mechanisms against ischaemia / reperfusion injury may contribute to the increased mortality rate [46, 58]. The similar mechanisms are operative in developing cerebrovascular injury in diabetics [18].

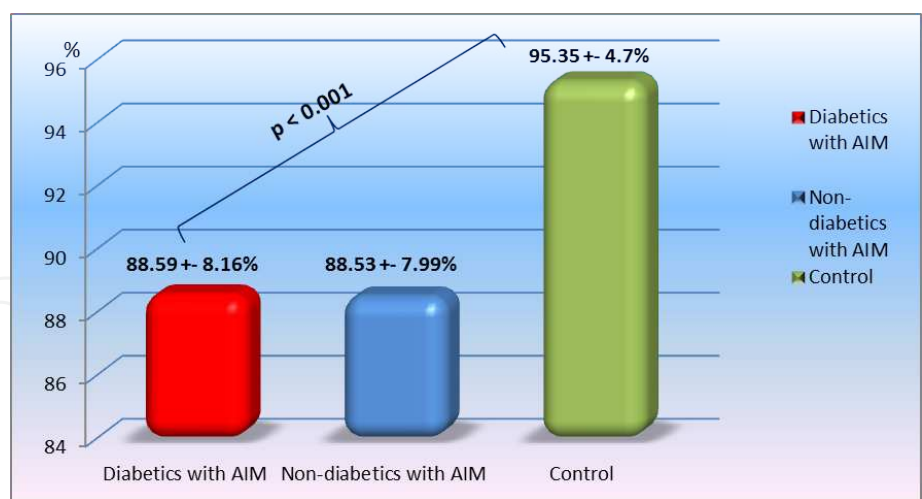


Figure 3. Haemoglobin saturation (SaO2) in diabetics and non-diabetics suffering AMI and in control group Although SaO2 was significantly depressed in all patients suffering AMI comparing to control group subjects, there was no significant difference between diabetics and non-diabetics with AMI.

Diabetic acidosis itself may be the precipitating event for the occurrence of serious arrhythmia, pulmonary edema or even acute myocardial infraction [22]. When acidosis is severe, i.e. pH is less than 7.2 the H⁺ ions have a direct cardiac depressant action. They cause negative inotropy, bradycardia, reduced cardiac output, peripheral vasodilatation and severe shock. Sometimes, a bio-marker elevation is also noted, without further evidence of a true myocardial infarction [42].

Potassium deficit is one of the most important of electrolyte imbalances seen in DKA, as it can lead to fatal arrhythmia, especially when the serum potassium level is < 3 mmol/L. On the other hand iatrogenic or spontaneously occurring hyperkalemia may lead to ventricular tachycardia or fibrillation, intra-ventricular conduction defects, sine wave, slow ventricular escape rhythm or ventricular stand. Hyperkalemia can also induce a current of injury called ‘dialyzable current of injury’, which can cause ST-segment elevation and thus be mistaken for acute infarction. [7, 6].

Pseudo-infarction presents a unique danger for the clinician treating these critically ill patients. While the mechanism of these and other temporary electrocardiographic changes in diabetic ketoacidosis remains unclear, appreciation of their transient nature is essential if misdiagnosis of myocardial infarction and possible inappropriate delay in intravenous fluid administration are to be avoided [21]. However a true myocardial necrosis was also reported with the DKA as the precipitating factor [50], which further complicates the management and the outcome of these patients.

A pulmonary edema in the absence of left ventricular failure has also been reported in DKA and may be a variant of adult respiratory distress syndrome (ARDS). The aetiology may be pulmonary vascular microangiopathy seen in diabetics. Vigorous fluid therapy can precipitate this condition.

Since volume repletion must be done cautiously and gradually, its therapeutic reach in diabetic ketoacidosis is limited. Intravenous insulin remains the keystone in treatment of diabetics with AMI, yet their recovery from ketoacidosis may be prolonged.

Potassium levels must be monitored continuously and corrected as need occurs. If the potassium level is less than 3.3 mEq per L (3.3 mmol per L), potassium replacement should be given immediately and insulin should be started only after the potassium level is above 3.3 mEq per L. Phosphate replacement is needed occasionally.

Bicarbonate therapy is not recommended unless pH falls to critically low levels (<7.0). Even then, positive effects of bicarbonate therapy remain questionable.

Phosphate replacement is done only if the patient's serum phosphate level is below normal. Excessive replacement can lead to hypocalcemia.

A serum deficit of about 1 mmol per L of magnesium usually exists. Severe magnesium deficiency may lead to cardiac dysrhythmias. Magnesium level should be monitored, especially in patients who receive diuretics and low levels should be corrected in order to avoid this and other complications of hypomagnesaemia.

In summary, acute myocardial infarction may precipitate diabetic ketoacidosis. Heart failure following infarction reduces patients' capacity for volume resuscitation, so clinical features of hyperglycemic hyperosmolar state and diabetic ketoacidosis may overlap and are observed simultaneously. Additional risk factors for development of hyperosmolarity include the presence of congestive heart failure, impaired thirst, limited access to water, older age, and poor kidney function.

When acidosis is severe, i.e. pH is less than 7.2, the H⁺ ions have a direct cardiac depressant action. Another consequence of tissue hypoperfusion resulting both from impaired myocardial output and increased osmolality as well as counter-regulatory hormone metabolic effects is increased lactate production. Increased lactate production may aggravate existing acidosis.

Diabetic acidosis itself may be the precipitating event for the occurrence of a true myocardial necrosis. Also, the ECG changes in hyperkalemia in DKA can mimic acute anteroseptal myocardial infarction. Moreover, a bio-marker elevation was also noted, without further evidence of a true myocardial infarction. Knowing that "silent" myocardial infarction occurs with higher incidence among diabetics, the differential diagnosis between myocardial necrosis and hypokalemic disturbances may be difficult.

Since volume repletion must be done cautiously and gradually, its therapeutic reach in diabetic ketoacidosis is limited. Intravenous insulin remains the keystone in treatment of diabetics with AMI, yet their recovery from ketoacidosis may be prolonged. Potassium levels must be monitored continuously and corrected as need occurs. Phosphate replacement is needed occasionally. Bicarbonate therapy is not recommended unless pH falls to critically low levels (<7.0).

2. Diabetic ketoacidosis and cerebrovascular accidents

Although cerebrovascular accidents represent a significant and well-known precipitating factor for DKA, the literature data on precise mechanisms, distinctive features or management guidelines for patients are quite few or missing. The prevalence of stroke as the precipitating factor for DKA was 0% in some studies [40] to as much as 7% in others [24]. Considering the data from the recent study in USA, most of the DKA patients (e.g. 80%) were in the age 18-65 years, with only 18% younger than 18; even 24% of all patients with DKA were in the age 45-65 years [32] Based on these data, it seems that the prevalence of DKA in patients with stroke may be underestimated and its importance under-appreciated in many cases.

Cerebrovascular accidents lead to increased release of counter-regulatory hormones (catecholamines, cortisol) which lead to hyperglycemia. Hyperglycemia develops as a result of three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues. Also these hormones increase the release of free fatty acids from peripheral tissues and their utilization as the energy source in hepatic and muscle mitochondria (beta-oxidation) with the increased ketone production as the direct consequence. This sequence is identical to the one seen in acute myocardial infarction [32], [19].

There is a significant overlapping of the symptoms in stroke and DKA (table 2). One can assume that an interference of symptoms of the two conditions during the clinical examination may be confusing and their interpretation difficult particularly in elder and less communicative patients.

DKA	STROKE	COMMENTS
Excessive thirst or drinking lots of fluid	Inability to swallow	
Frequent urination	Incontinence	Frequent urination and incontinence may be difficult to differentiate in a somnolent/ comatose patient
General weakness	General weakness, a feeling of weakness in one arm / leg	
Nausea and vomiting	Nausea and vomiting	
Loss of appetite	Loss of appetite	Loss of appetite in DKA results from predominantly catabolic pattern of metabolism, nausea and confusion
Confusion, somnolence, stupor, comma	Confusion, somnolence, stupor, comma	Mental status changes can be seen with mild-to-moderate DKA; more severe deterioration in mental status is typical with moderate-to-severe DKA.

DKA	STROKE	COMMENTS
Abdominal pain	Headache	
Shortness of breath, increased rate of breathing -Kusmaul's type	Increased or decreased breathing frequency , abnormal breathing patterns, Cheyne-Stokes type	Breathing patterns may be similar and interchangeably assigned to either of the diseases stroke the clinical examination
A generally ill appearance	A generally ill appearance	
Dry skin	Skin may be dry , or moisture	A dehydration may occur in case of not having access to water or fluids, or intensive use of osmotic diuretics
Dry mouth,	Often dry mouth	
Increased heart rate,	Increased heart rate	
Low blood pressure	Mainly high blood pressure, sometimes low	
A distinctive fruity odor on the breath, fruity-scented breath	Different kinds of breath odor not uncommon	Fruity scented breath may be hardly recognizable. Moreover, the odor appearing after ingestion of various sweet and fruits may imitate the characteristic odor of DKA
High blood sugar level	High sugar level in diabetics	Due to the effect of counter-regulatory hormones
High ketone level in serum and urine	Moderately high ketone level in urine in diabetics, alcohol abuse, starvation	
Low (<7.3) plasma pH	Plasma pH usually normal	
Low serum (<15 mmol/l) bicarbonate	Serum bicarbonate usually normal	
Increased (>12) anion gap	Anion gap usually >12	

Table 2. Symptoms and signs in diabetic ketoacidosis and stroke: the overlapping features

Blood glucose levels are high in the majority of diabetic patients suffering stroke. Moreover, pH, bicarbonate and anion gap are not routinely monitored in all diabetic patients suffering stroke, at least not in secondary level health institutions worldwide. In conclusion, some of the DKA cases in patients with stroke may easily be overlooked.

Furthermore, there is striking lack of literature data concerning management of adult diabetic patients with stroke. Although there are clear concerns about the volume overload, intensive use of osmotic and Henley's loop diuretics and the need for careful volume and monitoring in patients suffering cerebrovascular accident and DKA no clear guidelines were produced for intensive care units and intensive care neurologic units.

Some of the management guidelines may be defined here:

1. It is important that patients with stroke complicated by DKA avoid dehydration since both DKA and stroke correlate with the pro-thrombotic state and dehydration potentiates a tendency toward intravascular thromboembolism. Since the use of osmotic and sometimes also other kinds of diuretics is inevitable in patients with stroke a careful hydration is recommended in order to avoid further thrombotic complications.
2. Fluid resuscitation must be performed carefully, in small aliquots, and with constant monitoring of blood pressure, hematocrit and plasma sodium; novel minimal invasive procedures [39] should have advantages over central venous catheter since CVP itself was reported to be a risk factor for cerebrovascular thromboembolism [33]. Excessive use of diuretics may precipitate pro-thrombotic state.
3. Infused insulin is the principle therapeutic tool for fighting DKA in patients with cerebrovascular accidents. Since fluid resuscitation must be restricted, DKA itself is expected to have more prolonged clinical course. This may be of importance, since DKA itself may be a precipitating factor for stroke (see later)
4. Serum potassium must be carefully monitored in all cardiovascular patients with DKA (see earlier). Hyper or hypokalemia should be promptly corrected; thus said, insulin-induced intracellular shift of potassium must be taken in account when evaluating potassium levels or performing potassium substitution
5. Bicarbonate therapy is not recommended except in extreme acidosis.

Not only does stroke precipitate DKA, but the vice-versa is also true [20]: diabetic ketoacidosis itself was reported as a risk factor for the occurrence of stroke in children and youth. The risk of acute ischemic or hemorrhagic stroke during the acute DKA episode is perhaps under-appreciated.

Systemic inflammation is present in DKA, with resultant vascular endothelial perturbation that may result in coagulopathy and increased hemorrhagic risk. Hyperglycemia and acidosis may contribute to oxidative injury [25], as well as ischemic injury [34]. Thrombotic risk during DKA is also elevated by abnormalities in coagulation factors, platelet activation, blood volume and flow, and vascular reactivity.

Recent data demonstrate that DKA is associated with reduced cerebral blood flow and with brain cell swelling [23]. These data suggest that cerebral injury resulting from DKA may be similar to hypoxic/ischemic brain injury. A cerebral hypo-perfusion occurs in untreated DKA. [23] In analogy with ischemia/reperfusion injury, DKA could be associated with metabolic abnormalities similar to those of hypoxic/ischemic brain injury and that these abnormalities would worsen during initial DKA treatment as normal cerebral perfusion is reestablished [15, 4].

Although a small percentage of children have clinically apparent cerebral injury at presentation of DKA prior to treatment, neurological decline during DKA treatment is more common [16]. During initial DKA treatment with insulin and intravenous saline, key aspects of

the cerebral metabolic state worsen. After initiation of DKA therapy, abnormalities in Protein C, Protein S, plasma homo-cysteine, and von Willebrand Factor (vWF) were demonstrated [11, 9]. While protein C levels normalize with treatment, free protein S, the active anticoagulant of protein S, is reduced and does not return to baseline with treatment.

Arterial ischemic stroke [47], cerebral venous thrombosis [29], and hemorrhagic stroke [36] were noted in children following DKA. DKA-associated cerebral edema may also predispose to ischemic injury and hemorrhage, though cases of stroke without concomitant cerebral edema have been identified [49]. As stroke itself may cause cerebral edema, it becomes difficult to ascertain whether cerebral edema in DKA is the cause or an effect of acute cerebral infarction. A sub-arachnoid or intra-ventricular hemorrhage may occur without cerebral edema as was demonstrated using on CT scanning. Clinically, a transcranial Doppler ultrasound in children with DKA demonstrated significant vascular dysregulation with vasodilation, decreased cerebral blood flow velocity, and loss of normal cerebral blood flow regulation that only normalized after treatment. Another group of researchers found normal to increased cerebral blood flow with impaired cerebral auto-regulation during episodes of DKA not associated with overt CE in 6 children [20].

Treatment with bumetanide, [27] an inhibitor of Na-K-2Cl Co-transport, resulted in improvements in metabolic measures during untreated DKA and amelioration of the declines in metabolic measures during initial DKA treatment.

It is clear that at least some of these mechanisms may be operative in adult DKA. Abnormalities in coagulation during DKA or its treatment have been also noted in adults. Indeed, an endothelial injury, platelet activation, relative hypo-fibrinolysis, and activation of the coagulation system [20] even in the absence of clinical signs of thrombosis were all demonstrated in patients with DKA. However, the up-regulation was not to a degree expected for the increase in coagulation activity (thrombin-antithrombin III complex and prothrombin fragment 1 + 2 levels) at DKA presentation.

In summary, cerebrovascular accidents represent a significant and well-known precipitating factor for DKA. It seems that the prevalence of DKA in patients with stroke may be underestimated and its importance under-appreciated in many cases.

It is important that patients with stroke complicated by DKA avoid dehydration since both DKA and stroke correlate with the pro-thrombotic state and dehydration potentates a tendency toward intravascular thromboembolism. Unfortunately, like in acute myocardial infarction, the volume replenishment capacity in patients with stroke is often limited. Intravenous insulin and monitoring and correction of possible electrolyte imbalances are the mainstay of the treatment.

Not only does stroke precipitate DKA, but the vice-versa is also true: diabetic ketoacidosis itself was reported to be a risk factor for the occurrence of stroke in children and youth. A cerebral hypo-perfusion occurs in untreated DKA and may lead to cerebral injury. Arterial ischemic stroke, cerebral venous thrombosis and hemorrhagic stroke were noted following DKA episodes.

Treatment with bumetanide, an inhibitor of Na-K-2Cl co-transport, resulted in improvements in metabolic measures during untreated DKA and prevented cerebral metabolic aggravation during initial DKA treatment.

3. Diabetic ketoacidosis and renal failure

Renal failure occurs with increased frequency in patients with diabetes. Fortunately, the co-incidence of type 1 diabetes with DKA and acute renal failure is uncommon. Volume overload and hyperkalemia may complicate the condition. It has been reported that DKA in patients with acute renal failure may be sometimes associated with respiratory distress syndrome [17].

3.1. Diabetic ketoacidosis and acute renal failure

Although acute renal failure (ARF) rarely develops in patients with diabetic ketoacidosis (DKA), these serious complications can be life threatening in critically ill patients [43]. The estimated mortality with combined DKA and ARF still reaches around 50%. ARF pre-renal failure may occur as a result of the severe fluid depletion associated with diabetic ketoacidosis; underlying diabetic nephropathy as well as hypotension, sepsis, renal artery occlusion, serious urinary infections complicated by papillary necrosis and exposure to nephrotoxic agents. Of the latter, a certain antibiotics and radio-contrast agents, but also angiotensin converting enzyme inhibitors were mentioned. [51]. The increased incidence of cardiovascular disease may also lead to renal impairment.

The long-lasting ketoacidosis in combination with infused insulin can lead to severe hypophosphatemia. Patients with uncontrolled diabetes may already be predisposed to hypophosphatemia due to osmotic diuresis and often decreased muscle mass; however, the majority of the imbalance results from phosphate shift from extracellular to intracellular space[30]. In the presence of metabolic acidosis, proximal tubular reabsorption of phosphate is inhibited and their urinary excretion is initially increased, thereby critically reducing the overall level of the extracellular phosphate [10].

Hypophosphatemia, in turn, further contributes to the deepening of the metabolic acidosis. Acidosis cannot be compensated by renal production of ammonia, because later in the course of diabetic ketoacidosis, with a reduction in the total amount of phosphate in the body, a reduction in urinary excretion of phosphate ensues. Prolonged metabolic acidosis accompanied by hypophosphatemia may be the cause of transient rhabdomyolysis. Acidosis and rhabdomyolysis lead to renal injury. In addition, prolonged hypophosphatemia can lead to cardiomyopathy due to decreased concentration of intracellular adenosine - triphosphate and 2,3-diphosphoglycerate (DPG). [35]. It is, therefore important to detect changes in serum phosphate levels of order in early to prevent these complications.

Acute hypophosphatemia may be associated with respiratory problems, confusion, irritability, seizures, ataxia or coma, metabolic acidosis due to reduced phosphate reabsorption.

However, even the severe symptoms may be hardly recognizable for they can mimic those of the underlying disease – e.g. DKA itself. Hypophosphatemia may be the cause of rhabdomyolysis, which (though not often) can lead to occurrence of cardiomyopathy and acute renal failure.

Even after initiation of phosphate replacement, serum phosphate levels are often difficult to normalize, and a severe metabolic acidosis can last despite insulin-induced normalization of blood glucose.

In cases of severe acidosis, phosphate replacement is of paramount importance [31]. However, after initial-phase phosphate replacement, the re-institution of acid-base balance phosphate re-shifts from intra- to extracellular space; this can lead to the hyperphosphataemia later in the course of treatment [13]. Therefore, serum phosphate levels should be monitored continuously. With the occurrence of acute renal failure, indications for haemodialysis include oliguria, persistent metabolic acidosis resistant to standard therapy, fluid overload and hypertension. Early initiation of haemodialysis is not only effective against the direct consequences of acute renal failure - uremia and hypervolemia – but also contribute to rapid correction of metabolic acidosis and hypophosphatemia [28]. Indeed, the existing hypophosphataemia is easily corrected once a normal acid-base balance is established by haemodialysis. Prompt institution of dialysis is important as the diabetic patient may tolerate uraemia less well. Uncontrolled ketosis may worsen hyperkalemia and metabolic acidosis. Insulin requirements may be increased due to insulin resistance, or decreased due to impaired clearance of circulating insulin [38, 56].

The vast majority of patients require intermittent haemodialysis. Patients with cardiac dysfunction or autonomic neuropathy tend to develop hypotension during treatment. Also, anticoagulation with heparin may increase the risk of hemorrhage from proliferative retinopathy, therefore prostacyclin may be a safer alternative [52]. Peritoneal dialysis may be complicated by peritonitis and chest infections. Also, haemodialysis allows greater fluid removal and remove restrictions for administration of drugs and nutrition [56].

3.2. Diabetic ketoacidosis and chronic renal failure

Despite the strong prevalence of compromised immune status, constant state of protein malnutrition, frequent vascular accessing with a predisposition to significant infections, increased incidence of cardiovascular diseases, the occurrence of DKA in patients with chronic renal failure is quite rare. [41, 3]. Kidneys play a major role in insulin breakdown [38]; advanced chronic renal failure is associated with both insulin resistance and decreased insulin degradation. The latter may lead to a marked decrease in insulin requirement. Therefore, many patients see an improvement in glycemic control when they progress to haemodialysis. Furthermore, in hyperglycemic dialysis-dependent patients volume contraction due to osmotic diuresis is not encountered. Since glycosuria and osmotic diuresis account for most of the fluid and electrolyte losses seen in DKA, anuric patients may be somewhat protected from dehydration. However they may still be prone to development of hyperkalemia and metabolic acidosis [37]. In persistent and long-lasting DKA, a substantial volume loss can

still occur due to a prolonged decrease in oral intake or increased insensible water losses related to tachypnea and fever.

The uremic environment can affect methods used to assess glycemic control. Changes in dietary intake and exercise (ie, reduced intake due to anorexia prior to starting dialysis) can also affect the response to administered insulin). Renal inability to reabsorb/regenerate bicarbonate and excrete hydrogen ions may lead to metabolic acidosis even in the absence of DKA; in addition, patients often suffer from anorexia, nausea, vomiting, infections, and even acute coronary events predisposing them to catabolic pattern of metabolism. In patients treated with peritoneal dialysis, glucose contained in peritoneal dialysate will tend to increase the need for hypoglycemic therapy.

Therefore, the treatment of oliguric patient certainly differs from the wide accepted DKA treatment guidelines. [8]. First of all, end-stage-renal-disease patients with DKA may be less likely volume depleted; in most cases the extracellular volume is expanded from its baseline secondary to hyperglycemia. The volume expansion may cause dyspnea, nausea, vomiting, seizures and coma [54]. In oliguric patient, fluid hydration in amounts usually administered in the DKA treatment may precipitate severe pulmonary edema. Therefore, the need for fluid resuscitation in these patients must be justified clinically or by laboratory testing and potential volume resuscitation should be performed carefully, using central venous access for continuous monitoring. [2]. When volume overload is apparent, immediate haemodialysis is the therapy of choice.

Metabolic control can be difficult to achieve. Insulin is normally metabolized by kidneys and in chronic renal failure insulin degradation is much slower. Furthermore, insulin is not excreted either by haemodialysis or peritoneal dialysis. Hyperinsulinemia resulting from aggressive glucose – lowering therapies may easily lead to severe and prolonged hypoglycemia. One cannot readily predict insulin requirements in this setting and careful individualized therapy is essential.

As already emphasized, kidneys in end-stage renal disease are not able to contribute to the overall acid-base balance. Therefore, DKA in these patients may be both profound and prolonged. In addition, pulmonary dysfunction related to volume overload and sometimes underlying pulmonary infections can impair respiratory compensation to metabolic acidosis. Bicarbonate administration is rarely of value in DKA [55] and the associated volume, sodium and osmotic overload may be particularly problematic for anuric patients. In this situation, significant metabolic acidosis will only be correctable by haemodialysis [53].

Total body concentration of potassium is unchanged, and patients with DKA and end stage renal failure frequently have a high serum potassium level. Lack of insulin causes translocation of intracellular potassium to the extracellular compartment. Hyperglycemia causes hypertonicity of extracellular fluids, which also leads to shift of potassium from the cells to the extracellular compartment. The important potassium – lowering effect of osmotic diuresis is missing. DKA aggravates hyperkalemia in more than 50% of cases [48]. Even when testing reveals hypokalemia, total body potassium stores may be high, and these patients are unable to excrete a potassium load. Consequently, hypokalemia must be documented and

acidosis corrected before potassium supplementation is initiated. All dialysis patients presenting with significant symptoms should undergo immediate cardiac monitoring. If there is clinical suspicion or electrocardiographic evidence of hyperkalemia, they should receive immediate potassium lowering therapies, including emergent haemodialysis. [8].

In a study performed in USA in 2001 [1] the occurrence of diabetic ketoacidosis after renal transplantation was followed. A female sex, recipients of cadaver kidneys, patients age 33–44 (vs. >55), more recent year of transplant, and patients receiving tacrolimus vs. cyclosporine had significantly higher risk of diabetic ketoacidosis. However, the rate of diabetic ketoacidosis decreased more over time in tacrolimus users. Diabetic ketoacidosis was independently associated with increased mortality.

In summary, acute renal failure rarely develops in patients with diabetic ketoacidosis, but it can be life-threatening. Insulin requirements may be increased due to insulin resistance, or decreased due to impaired clearance of circulating insulin.

Patients with uncontrolled diabetes may already be predisposed to hypophosphatemia. In the presence of metabolic acidosis, proximal tubular reabsorption of phosphate is inhibited, and the overall level of the extracellular phosphate is further reduced. In cases of severe acidosis, phosphate replacement is of paramount importance.

Indications for haemodialysis in patients with acute renal failure and DKA include oliguria, persistent metabolic acidosis resistant to standard therapy, fluid overload and hypertension. Early initiation of haemodialysis is not only effective against uremia and hypervolemia but also contribute to rapid correction of metabolic acidosis and hypophosphatemia.

The occurrence of DKA in patients with advanced chronic renal failure is quite rare. Chronic renal failure is associated both with insulin resistance and decreased insulin degradation. The latter may lead to a marked decrease in insulin requirement. In patients treated with peritoneal dialysis, glucose contained in peritoneal dialysate will tend to increase the need for hypoglycemic therapy.

In oliguric patients, fluid hydration in amounts usually administered in DKA treatment may precipitate severe pulmonary edema. Sodium and osmotic overload may be particularly problematic for anuric patients. Pulmonary dysfunction due to frequent pulmonary infections can impair ventilatory compensation to metabolic acidosis. Bicarbonate administration is rarely of value in DKA. In this situation, significant metabolic acidosis will only be correctable by haemodialysis.

Most DKA patients on both peritoneal and haemodialysis are hyperkalemic and the potassium replacement in DKA is usually not necessary.

4. Conclusion

Diabetic ketoacidosis is serious metabolic complication in diabetic patients with acute myocardial infarction, stroke and renal insufficiency. Conversely, severe diabetic ketoacidosis is

an important risk factor for acute myocardial infarction, stroke and acute renal failure. The presence of DKA makes patients' management difficult and aggravates the outcome.

Acidosis in these patients is usually deeper, prolonged and resistant to therapy. In all of the three conditions a fluid resuscitation in quantities commonly used in the treatment of DKA can not be performed. In addition, in many cases there is more or less marked insulin resistance. In chronic renal insufficiency, on the contrary, intensive insulin therapy usual for the treatment of ketoacidosis may carry a risk of hyperinsulinemia and prolonged hypoglycemia. Electrolyte imbalance, especially potassium deficiency or excess can have serious consequences, especially in patients with myocardial infarction, and special care should be given to electrolyte monitoring.

Finally, we believe that more attention should be paid to the possible acid-base disorders in diabetic patients suffering cerebrovascular insults. Clinical assesment in these cases is not sufficient because the significant overlapping of the signs and symptoms, therefore DKA symptoms may be attributed to cerebrovascular pathology. The conclusions based on blood glucose levels would not be appropriate, since glycemia tends to be high in distressed patients. Acid-base status should be determined routinely, along with glycemia and HbA1c in all diabetics affected by stroke in order to prevent misdiagnosis.

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