Diabetic ketoacidosis: current aspects of evaluation and treatment

Pedro P. Ferreira,* Mariete Pires, ** José Filipe Guia, *** Ana Leitão,*** Clementina Rodrigues,**** A. Sales Luís*****

Abstract

Diabetic ketoacidosis is a clinical entity associated with high morbidity and mortality. The clinical and therapeutic approach to this problem has been modified throughout the years according to different schools of thought. High dose versus low dose insulin, vigorous or conservative rehydration, bicarbonate, potassium and phosphorus replacement have all been advocated. The authors try to focus on the recent aspects concerning clinical diagnosis and treatment of this condition.

Key words: diabetic ketoacidosis, pathogenesis, insulin therapy, hydration therapy, complications of therapy.Keywords: antibodies anti-GAD, type I diabetes, autoimmunity.

Introduction

iabetic ketoacidosis is a clinical syndrome defined by a triad of hyperglycaemia, ketonemia and metabolic acidosis.

The epidemiological analysis was for many years prejudiced due to a lack of uniformity on the diagnosis criteria. In order to carry out comparative studies among different sites, it was necessary to establish common diagnosis criteria. For such purpose, several authors advocate the diagnosis of ketoacidosis in patients presenting: glycaemia above 250 mg/dL , positivity for serial ketonic bodies in a dilution above 1:2,ketonuria, arterial pH below 7.3 and bicarbonatemia lower than 15 mEq/L. [1,2,3]

Epidemiologic studies are rare and rely on diagnostic criteria already established in the United States, the incidence mentioned in literature is 14 cases per 100.000 inhabitants and 46 cases per 10.000 diabetic patients.[1,4]

The mortality rate before insulin was discovered, by Banting and Best, in 1922 was almost 100%; however, since insulin was introduced it was reduced to 29%.[1] The knowledge of the pathophysiological mechanisms, and improvements on the treatment of triggering factors associated to the implementation of treatment in intensive care units was responsible for a new mortality decrease. In the last 10 years, such rate became stable, ranging from 2 to 5% in developed countries, in contrast with 6 to 24% in other countries.[3,5,6] In the elderly and in children, mortality is significantly higher, with values reported up to 20%.[3,7,8]

Two major groups of triggering factors can be found in diabetic ketoacidosis: situations of total lack of insulin and conditions of relative lack of insulin (*Table 1*). Infection, omission or inadequate use of insulin are triggering factors in already known diabetics. In teenagers, psychiatry changes and non-compliance with therapy are important factors.

The use of an infusion pump of subcutaneous insulin was associated to an increase of ketoacidosis incidence; however, as gadgets have improved, such trend was reduced.[9] At present, an incidence of 0.15 episodes – year in diabetic patients carrying subcutaneous pump, is reported in contrast with 0.04 episodes – year into those subject to conventional therapy.[10]

But the diabetic ketoacidosis is a common presentation of insulin dependent diabetes mellitus (IDDM). It occurs from 3 to 8 cases for each 100 IDDM inaugural cases, corresponding to around 20% of all ketoacidosis cases. [1,2,11,12]

Pathophysiology

Glucose uptake, glycogenolysis and gluconeogenesis are the main sources of blood glucose, while glycolysis, lipogenesis and glycogenesis are the mechanisms

*Resident to the Internal Medicine Supplementary Internship

**Internal Medicine Consultant

***Internal Medicine Interim Hospital Assistant

**** Internal Medicine Consultant

*****Head of Internal Medicine Service

Medicine Service of Sao Francisco Xavier Hospital

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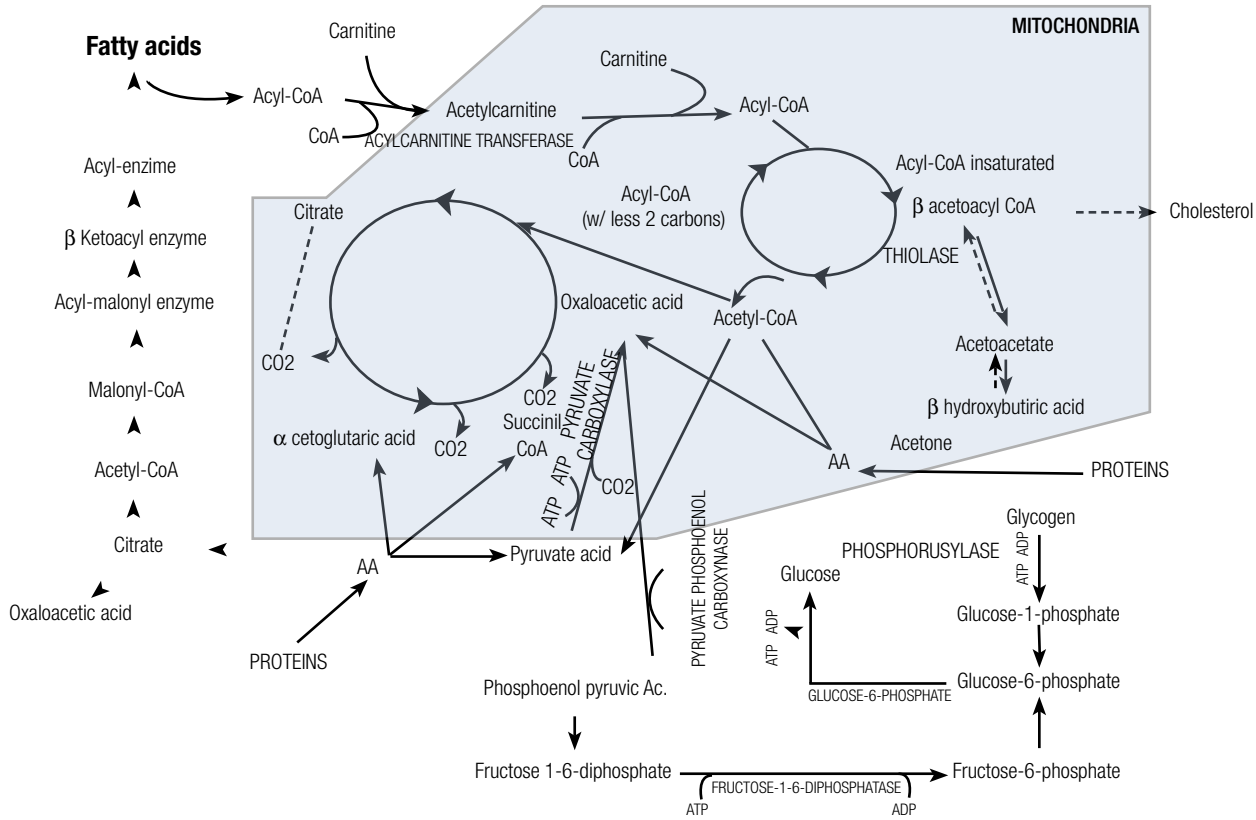


Metabolism in the hepatocyte, schematic and simplified representation. 1. Postprandial condition after insulin release. Glucose enters the cell being phosphorylated in glucose-6-phosphate. From this molecule onwards, two paths are possible: glycogenesis and glycolysis. On the second one, a succession of chemical reactions is verified, some of them irreversible, producing Acetyl-CoA and the entry in the Krebs cycle. Due to a citrate accumulation and under insulin influence, it is carried to the cytoplasm and metabolized, in successive reactions, in acyl-enzyme and subsequently in fatty acid. Aminoacids are used to form proteins and its catabolism inhibition.The key-enzymes of this metabolic process are referred. In the glycogenesis, glycogen synthase; glycolysis, glucokinase, phosphofructokinase and pyruvate kinase; and, in the lipogenesis, acetyl-CoA carboxylase. All these enzymes are unidirectional and activated by insulin.

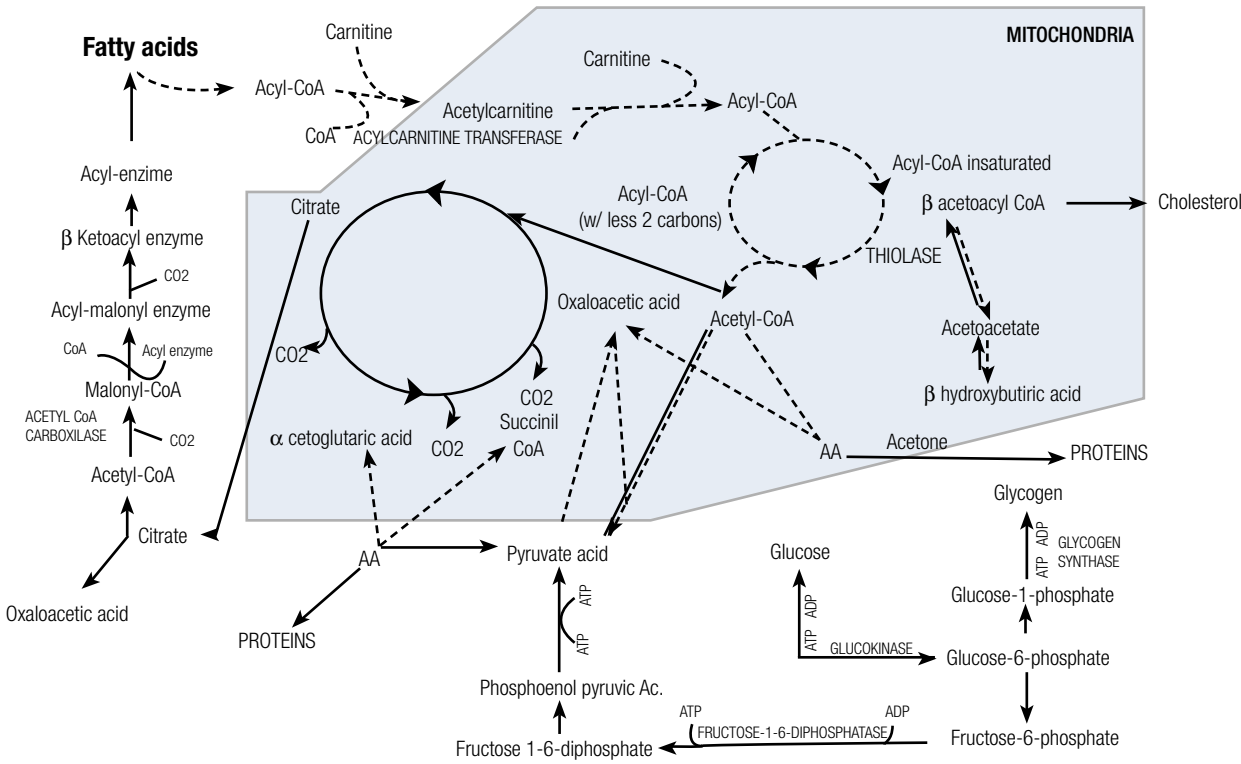
FIG. 1A

reducing serial glucose.

Ketoacidosis occurs in two situations: in the absolute deficiency or insulin relative, the latter in the presence of excessive secretion of counterregulatory hormones.[4]

Insulin is the main anabolic hormone responsible for numerous actions in the prandial period. It determines directly in the myocytes and adipocytes, the rate of glucose transport through the cell membrane and its subsequent metabolism. In the hepatocytes, its action is mediated by changes in the enzymatic activity favouring glucose absorption, inhibiting the intracellular processes related with production and glucose release and promoting glycolysis, lipogenesis and glycogenesis. Insulin stimulates fatty acid synthesis by the hepatocyte and its subsequent capture by the adipocyte. It promotes the intracellular esterification by increasing glycerol-3-phosphate availability . Regarding the protein metabolism, insulin increases the capture of most aminoacids by myocyte, increases the protein synthesis, reduces the protein catabolism decreasing aminoacid oxidation (*Fig 1.A*).

A less use of glucose by the tissues and the glucose super production by the liver characterize the insulin deficiency status. The increase on glucose production relates with an increase on the glucagon-insulin in the portal vein. Glucagon lowers the hepatic levels of fructose-2-6-diphosphate, speeding up gluconeogenesis and glycogen catabolism. These mechanisms explain the presence of high glycaemia values in



Ketoacidosis condition. In the ketoacidosis, a great number of fatty acids arrive into the hepatocyte being responsible for an increase of the cytoplasmic concentration of acyl-CoA. This molecule is carried into the mitochondria by the carnitine-acyltransferase enzyme. In the mitochondria, starts the oxidation process producing acetyl-CoA. The increase on the intramitochondrial concentration of acyl-CoA associated to a non-inhibition by the insulin of the hydroxymethylglutaryl-CoA, enzyme, responsible for producing ketonic bodies. In this situation, the gluconeogenesis is triggered using glycogen, aminoacids and acetyl-CoA. In gluconeogenesis, the pyruvic acid is first metabolized as oxaloacetic acid and only afterwards in phosphoenolpyruvic. This molecule goes through several chemical reactions until glucose is produced. Key-enzymes of this metabolic process are referred. In glycogenolysis, the glucokinase; in gluconeogenesis, glucose-phosphatase; fructose-1-6-diphosphatase, the phosphoenolpyruvate-carboxylase and pyruvate-carboxylase. Such enzymes are activated by counterregulatory hormones

FIG. 1B

the ketoacidosis, even in the presence of prolonged fasting. In patients with diabetes evolving for a few years, glucagon release is definitely affected, explaining a significantly lower glycaemia at the time of the diagnosis. Glycogen reserves are quickly used and due to changes on the lipid metabolism, the aminoacids are the only available precursors for gluconeogenesis. From this process it results a consumption of protein body reserves (*Fig. 1.B*).

Insulin deficiency is responsible for a lipolysis increase in the adipocyte, for the non-inhibition of hormone sensitive lipase. It should be added the adipocyte does not have the glucokinase necessary to reuse the glycerol released through lipolysis, depending on the re-esterification of glucophosphate bioavailability, a metabolite of carbohydrate metabolism, which is reduced.

From this process it results the release of huge amounts of free fatty acids circulating which will be used by the cells, mainly hepatocytes and myocytes, as source of energy.

In the hepatocyte, fatty acids are activated by combination with A coenzyme (CoA), the acyl-CoA. Such molecule, by its characteristic, does not cross passively the mitochondrial membrane. Acylcarnitine transferase catalysis the link to the acyl group to carnitine carrying it all into the mitochondria.

In the mitochondria, Acyl-CoA participates in a complex metabolic process, oxidation, with the formation of acetyl-CoA. This molecule, common to sev-

eral paths of the intracellular metabolism, is usually metabolized following two paths: the path oxidation in the Krebs cycle or the path of CoA-malonyl forming fatty acids. In this last one, acetyl-CoA is metabolized in the cytoplasm in malonyl-CoA by the action of carboxylase acetyl-CoA enzyme. This enzyme action depends on the concentration of citrate and insulin influence. In the gluconeogenesis, the acetyl-CoA molecule is metabolized in pyruvic acid. Due to the incapacity of reversing the reaction catalyzed by the pyruvate kinase enzyme, pyruvic acid is firstly carboxylated in oxaloacetyc acid and decarboxylated and phosphorylated in phosphoenolpyruvic.

Regarding the acetyl-CoA availability overtaking its metabolic capacity, an accumulation of acetoacyl-CoA, the oxidation intermediate metabolite is verified. The insulin deficit and the acetyl-CoA excess are responsible for stimulating the enzyme activity of the hydroxymethylglutaryl-CoA with the formation of acetoacetate acid. This is metabolized in β hydroxybutyric acid and acetone. Acetoacetic acid is also a precursor of cholesterol biosynthesis path which is inhibited in the ketoacidosis (*Fig. 1.B*).

In the ketogenesis process, acylcarnitine transferase enzyme is at a limitative stage. This enzyme action is inhibited by the presence of malonyl-CoA. This way, ketogenesis is controlled by three factors: lipolysis, cytoplasmic concentration of malonyl-CoA and carnitine availability. The reduction on the insulin levels is responsible for inhibiting the lipogenesis and subsequent reduction in the intracellular concentration of malonyl-CoA. The relative excess of glucagon potentiates the hepatic ketogenesis stimulating carnitine production and reducing the intracellular level of malonyl-CoA, blocking the conversion of pyruvic acid in acetyl-CoA and subsequent citrate reduction.

In the ketoacidosis not only a production increase of ketonic bodies is seen but also highlights that its metabolization is decreased. Such reduction seems to be explained by a decrease in insulin, an increase on glucocorticoid levels and a reduction on capturing and using the ketonic bodies by peripheral tissues.

Water loss and electrolytes in ketoacidosis results mainly of hyperglycemia with the consequent glycosuria and osmotic diuresis. When the presence of glucose in the glomerular filtrate exceeds the capacity of reabsorption by the proximal convoluted tubule, this remains in the filtrate. Glycosuria reduces water and sodium absorption in the proximal tubule, increasing the volume which reaches the remaining parts of the nephron, being responsible for losing water and sodium. Due to the blood volume reduction emerging from this process, an increase on the release of antidiuretic hormone is seen. This counteracts the sodium loss stimulating the reabsorption by the distal convoluted tubule and the collecting duct; however, its action does not stop the excessive loss of sodium and water. To such losses, small losses and vomits should be added.

The water loss varies but can reach 10% of the body weight, with an estimate of losing three to five liters (50 to 100 ml/kg). The sodium deficit ranges from 4 to 8 mEq/kg, of potassium from 1 to 10 mEq/kg and the phosphorus from 0.1 to 2mmol/kg.[8,12]

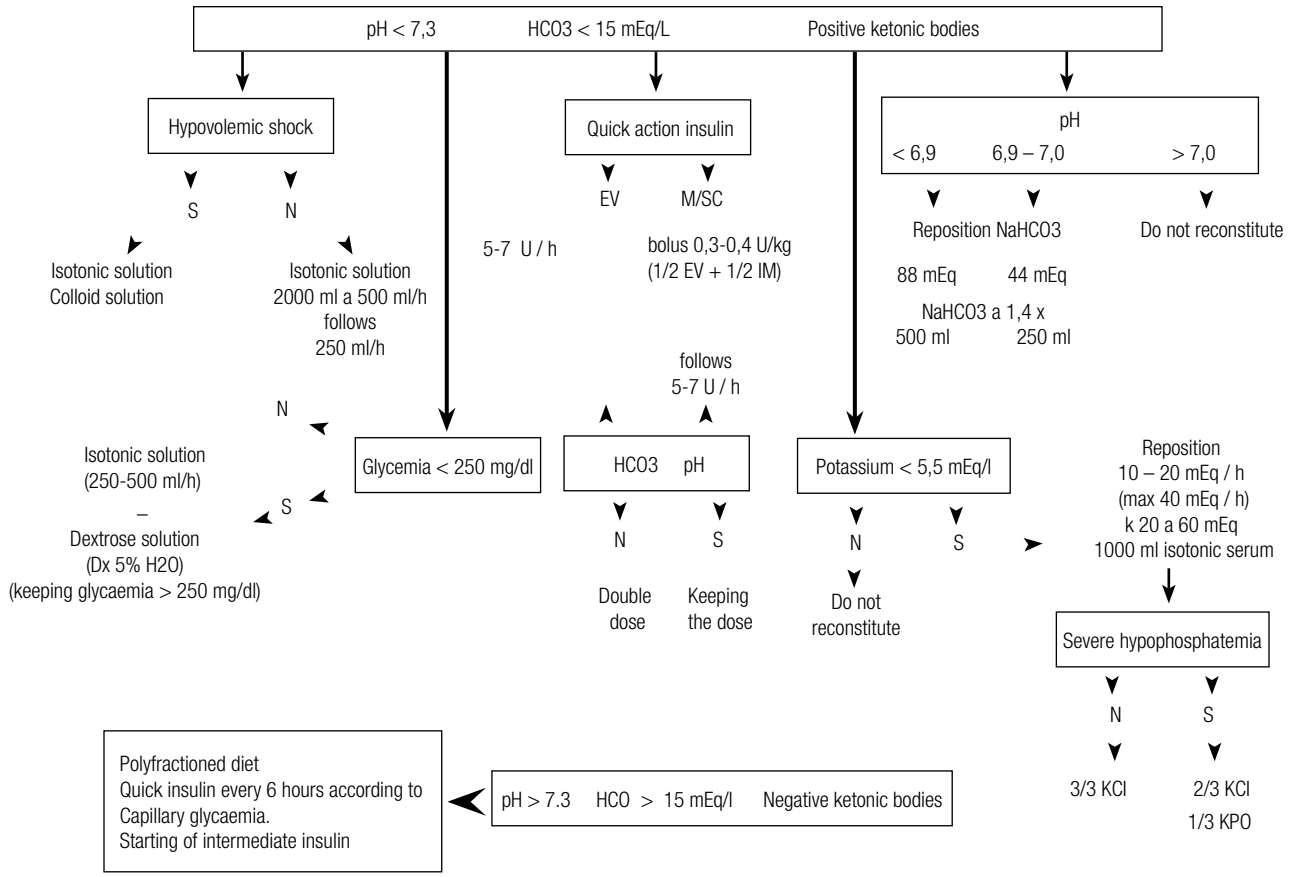
The ketonic bodies behave as cations. Their presence in the glomerular filtrate implies cations reabsorption particularly chlorine ion, as the bicarbonate reabsorption is already stimulated by acidosis and eliminating anions. The antidiuretic hormone is responsible for the potassium preferential loss by stimulating sodium reabsorption. Hyperkalemia, induced by acidemia, intracellular hyperosmolality and insulin deficit, also contributes to a decrease of the total body potassium.

In the diabetic ketoacidosis, acidosis is typically followed by an increase of the gap anion. However, ketoacidosis can present all the metabolic acidosis aspect, depending on the nutrition condition and kidney function. Patients with adequate water intake and working kidneys keep an abundant diuresis with loss of ketonic bodies and glucose. A reduction of a serial concentration of ketonic bodies associated to a decrease of chlorine excretion is responsible for the existence of hyperchloremic metabolic acidosis. On the contrary, dehydration decreasing plasmatic volume and glomerular filtrate, increases plasmatic osmolality , promoting acidosis with an increase on the gap anion due to a retention in ketonic bodies.[13]

Serial osmolality and acidemia are severity factors in the diabetic ketoacidosis. On the contrary, glycaemia values depend on the food intake, on the nutrition condition and the presence of counterregulatory hormones, but it is not a predictive factor for the severity of the clinical condition.

Clinical presentation

The form of usual clinical presentation is subacute with polyuria, polydipsia, asthenia and adynamia. Vo-



Schematic representation in the treatment of diabetic ketoacidosis

FIG. 2

mits can occur later, being secondary to gastric stasis or a direct central effect of the ketonic bodies.[4,12,14]

Pain or abdominal discomfort are frequent being attributed to gastric distension or stretching of the hepatic capsule. Pain is rapidly solved when treating acidosis. Its persistence alerts to other etiologies, namely infectious abdominal processes.[13]

Changes in the awareness state are common, occurring between 60 and 80% of patients. Most of them present only drowsiness; however, 10 to 20% of cases are in coma.[1,12]

The objective exam of the patient with diabetic ketoacidosis reveals ketonic breath, tachycardia and tachypnea. Kussmaul breathing only happens in the presence of severe academia. Dehydration signs with loss of the skin turgor, sunken eyes and sometimes, hypothermia and hypotension, translating a situation of hypovolemic shock.

The semiquantitative analysis of serial ketonic bodies and urinary due to reaction of nitroprussiate it only allow to determine the acetoacetate concentration and, in a less degree, of acetone. Usually, the level of β-hydroxybutiric acid is around three times higher to the acetoacetate, during the treatment of ketoacidosis, the reason between the two of them, is reduced. However, this semiquantification method keeps high levels of ketonic bodies, in spite of the metabolic improvement.

Glycaemia is an extremely variable value in the ketoacidosis. In different series, average values from 500 to 700 mg/dL are mentioned.[1,4,13] There were patients with glycaemia values below 300 mg/dL mainly in pregnant women, for the production of insulin by the fetus; in alcoholic patients, due to gluconeogen-

esis inhibition and in the young; hydrated with high diuresis, by loss of glucose in the urine.[1,15] In patients with diabetes evolving for several years, a decrease on the glucagon excretion is seen, and consequently not so high glycaemia values.

The release of fatty acids by adipocytes is responsible for the increase on triglycerides dosage and, in some patients, by the plasma fatty aspect.

In spite of the sodium depletion, natremia can be low, normal or high. There are multiple causes for this fact. The hyperglycemia level induces the water movement from the intra- to the extracellular space, diluting the latter. Hypertriglyceridemia causes errors while determining laboratorial natremia. Lastly, the resulting dehydration from the osmotic diuresis promotes a loss of water higher than the loss of sodium.[2,4]

The concentration of serial potassium is also variable. At the initial stage, is usually high, in spite of depleting body reserves. The cause of normal or high levels has multiple factors. Acidemia mediates the potassium exit from the intra- to the extracellular compartment. On the other hand, insulin deficiency reduces the activity of the sodium pump and the entry of potassium to the cell interior. Lastly, intracellular hyperosmolality promotes the depletion of intracellular potassium.[2,4]

Amylasemia is usually high in around 80% of patients, with a salivary and pancreatic origin. The clinical cause and meaning are uncertain, but are not related with an increase of morbidity or mortality.[12,13]

Therapy

The success of the ketoacidosis treatment depends on identifying the precipitating factor, its resolution and correction of metabolic and hormonal changes characterizing such situation (*Fig. 2 and Table 1*).

The knowledge of the involved pathophysiological mechanism enabled to establish, in a rational way, the therapy plan aiming to restore adequately the extra- and intracellular volume, reversing the metabolic acidosis, normalizing glycaemia and electrolytes reposition.[2,4,11]

To reach such targets several therapy steps are taken, including endovenous hydration, electrolyte reposition, administration of exogenous insulin and in certain situations, therapy with bicarbonate.

Water reposition

Water reposition is a priority therapy measure and crucial in the treatment of diabetic ketoacidosis. Patients are invariably dehydrated and a sodium, potassium and chlorine deficit.

TABLE I

Ketoacidoses precipitating factors[1,10]

Total lack of insulin
Starting episode of insulin-dependent diabetes
Insulinotherapy withdrawal
Accidental - subcutaneous insulin pump not working properly
Voluntary - psicosis, disease denial ...
Pharmacologic lesion, hydantoid, diazoxyde, pentanidine, asparaginase
Relative lack of insulin (excess of counterregulatory)
Intercurrent disease
Infection
Acute myocardial infarction
Cerebrovascular accident
Trauma
Other
Iatrogenia
Corticoteraphy
Mymetic agents
Pheocromocytoma
Thyrotoxicosis acute crisis
Not monitored pregnancy in insulin-dependent diabetes

Several studies show the safety and efficacy of the hydric therapy before administering insulin, without deteriorating the metabolic acidosis and reducing significantly azotemia and glycaemia. This way, when diabetic acidosis is suspected a venous catheter should be put in place and saline perfusion started while laboratorial confirmations are awaited. [2,13]

Restoring extracellular volume while administering solutions by endovenous route enables to keep the adequate cardiac and urinary output, as well as perfusion of peripheral tissues, adding to this effect a glycaemia reduction by the increase of the urinary output and the reduction on counterregulatory hormones release.[4,13]

Serum insufficient or excessive administration by endovenous route represents the main complication of fluid therapy. The excessive administration can contribute, mainly in children and in the elderly, to

the adult distress respiratory syndrome, cerebral edema and hyperchloremia metabolic acidosis. However, it is more common the non-administration of the necessary volume to restoring the adequate blood volume.

In the initial stage, there is a consensus in the use of isotonic solutions which enable a quick blood volume correction without inducing a quick decrease of extracellular osmolality. In situations of hypovolemic shock, colloid solutions can be administered.[2,3,4,8,16]

It was forecast that in the absence of severe blood volume depletion, hypotonic solutions should be preferred, based in the fact that in ketoacidosis there is water loss above those of ions, namely sodium and chlorine. The endovenous administration of hypotonic solutions decreases rapidly the osmolality in the extracellular compartment, promoting the entry of water to inside the cells which are still in hyperosmolality. Retrospective studies carried out refer the quick decrease of extracellular osmolality as an important factor in the origin of cerebral edema.

The use of isotonic solutions enables a slower correction. The free water deficit always exceeds the ionic deficit should be corrected subsequently by the administration of dextrose solutions.[3]

The quick perfusion of serum has been associated, in retrospective studies, to cerebral edema. Prospective studies meanwhile carried out, document a slower perfusion of serum is more effective in the treatment of the metabolic changes in ketoacidosis when compared with higher perfusion rhythms. [3,16] Serum perfusion at a rate of 500 mL/h in the first four hours, followed by 250 mL/h in the following hours is advocated by some authors.[3,8,16] The perfusion rate should be adjusted in a way it would enable the correction of a hydro electrolytic deficit between 12 and 24 hours and in children in 48 hours.[3]

Potassium reposition

The reduction of body potassium is an electrolytic unbalance more worrying in ketoacidosis. Osmotic diuresis, acidosis and sometimes, vomits are responsible by the loss of potassium which is situated from 300 to 600 mEq, 1 and 10 mEq by kg of body weight.[13]

Only two percent of body potassium is found in the extracellular compartment. However, due to potassium changes between the intra- and extracellular induced by a deficiency in insulin and by metabolic acidosis, the value of serial potassium may be high, normal or low.

Regardless of the initial potassium value, two thirds of patients develop hypokalemia after twelve hours of therapy if, in the meanwhile, potassium reposition is not started.[1] Several factors contribute for such purposes: potassium reentrance in the intracellular space mediated by insulin, an expansion to the extracellular volume, acidemia resolution and the persistence, during the treatment initial stage, of loss of potassium through the urine.[2]

Some authors advocate not restoring potassium in the first serum. Such position is based in the possibility of triggering severe arrhythmias in patients with hyperkalemia. However, if the value of starting serial potassium is lower than 3.5 mEq/L and in the presence of severe acidemia, potassium perfusion should be immediately started, avoiding this way, the presence of severe hypokalemia. [4]

The availability of determining potassium immediately through a gasometry analyzer enables the immediate recognition of severe ionic changes, namely hypokalemia,[17] making the therapy easy.

If a methodology for determining immediately the kalemia is not available, potassium reposition should be restarted in the second serum. The addition of 20 to 60 mEq of each liter of serum is usually used, corresponding to a perfusion of 10 to 20 mEq per hour. However, sometimes, is necessary a quicker reposition up to 30 to 40 mEq/h, in intensive care units.[1,2,4,13]

Serial potassium should be monitored each two hours or hourly if it falls below 3mEq/L. The electrocardiographic monitoring is useful, being an early indicator of severe hyper- or hypokalemia.[1,2]

After resolving the diabetic ketoacidosis, many patients still present a deficit of body potassium, being, sometimes, necessary use of oral supplement for several days.[1]

Phosphorus reposition

Phosphorus is mainly an intracellular ion which migrates from the intra- to the extracellular compartment during ketoacidosis. This way, the initial levels of such ion can be normal and even high. However, osmotic diuresis is responsible for the loss of phosphorus and reduction of body reserve. During treatment, phosphorus reenters the cell, contributing to hypophosphatemia.

The therapy of phosphorus reposition is still a controversial issue in the treatment of ketoacidosis.

As a matter of fact, phosphorus deposits are very depleted, but there is no evidence that he reposition therapy contributes, significantly to an improvement of the patient´s clinical situation.

Theoretically, phosphorus reposition prevents hypophosphatemia potential complications. These include respiratory depression, muscle weakness, hemolytic anemia and cardiac dysfunction. However an excessive administration entails adverse events as hypocalcaemia, tetanus and calcification of soft tissues.

Most random and controlled studies did not demonstrate benefits of use due to a supplement routine in the ketoacidosis treatment. However, regardless of the controversy, the levels of serum phosphorus should be monitored and its reposition started every time these are below 1.0mg/dL.[2,4,18]

Some authors advocate that patients with anemia, heart failure or hypoxemia can be compromised by hypophosphatemia and a low level of erythrocytary 2, 3 DPG, benefitting from reposition therapy.[19]

The reposition of phosphorus deficit, if decided should be performed through a salt, sodium or potassium phosphate. Perfusion should not exceed 10 mmol/hour. Several protocols defend a simultaneous correction of the potassium and phosphorus deficit. They preconize the administration of potassium as potassium chloride and the remaining third under the form of potassium phosphate.[2,4]

Bicarbonate administration

Therapy with bicarbonate in diabetic ketoacidosis has been a controversial subject. The argument in favor of its use presumes that acidosis contributes to morbidity and mortality in ketoacidosis. Acidemia has a negative inotropic effect on the cardiac muscle, induces arrhythmias and peripheral vasodilation, being also responsible for changes in the awareness state.

Insulin therapy and water and electrolytic reposition correct the hydro electrolytic unbalances, reversing acidosis. It is discussed then which the advantages of correcting acidosis through the endovenous administration of bicarbonate.[4]

The perfusion of bicarbonate solutions has several setbacks, among which the deterioration of hypokalemia, due to the entry of potassium into the cellular space and metabolic alkalosis, verified by the association of stopping ketogenesis and continuous metabolism of ketonic bodies and the administration of exogenous bicarbonate.[4,13,20]

In the ketoacidosis, a reduction of the erythrocytary level a 2,3 DPG promoting a deviation to the left of the hemoglobin dissociation curve. This effect is the opposite of acidemia. The use of bicarbonate reverts rapidly acidemia whilst 2,3 DPG concentration can take days to return to normal. From this unbalance results an inadequate delivery of oxygen to the tissues.[13] Apart of the usual setbacks already exposed, some authors describe the appearance of LSF paradoxical acidosis during alkaline therapy.[2,4]

Prospective studies were carried out on the therapy with bicarbonate in ketoacidosis. In these studies there were no significant differences in the decreasing rate of the serial concentration of glucose or hydrogenions.[2] On the other hand the administration of bicarbonate prolongs hepatic ketogenesis.[21] It should be mentioned that no study was carried out in patients with a pH lower than 6.9.[1]

At present, there is no relative consensus regarding when and how much bicarbonate should be administered. Some authors advocate its use every time pH is lower than 7.0 and others when lower than 6.9.[4,11,14,22,23]

Kitabchi argues for a perfusion of 44 mEq of isotonic sodium bicarbonate if pH is found between 6.9 and 7.0 and 88 mEq and if the pH is lower than 6.9.[2]

Insulin therapy

Isolated fluid therapy does not revert ketosis or does it makes the pH normal. Insulin is necessary for the effective treatment of hyperglycemia and the ketoacidosis.

Insulin acts in a multifactorial way. Its actions include glucagon release by the pancreatic alpha cells and the reversion of the glucagon hepatic effects with a resulting gluconeogenesis suppression and ketogenesis by the liver. Other insulin actions include an increase on removing and using glucose by myocytes and adipocytes, lipolysis inhibition in the adipocytes and catabolism of ketonic bodies by hepatocytes.[4]

In the ketoacidosis treatment, the insulin used is of quick action, also called regular insulin. When used subcutaneously it has an acting peak from 2 to 4 hours, lasting for 6 hours. By endovenous route, the biologic half-life is around 20 minutes, and should be administered in continuous perfusion.[2] Only after a resolution of the ketoacidosis condition are introduced the slow release insulins or NPH.

TABLE II

Insulin-therapy scheme[1,2]

1. The insulin initial dose should be from 0.3 to 0.4 U/kg, half administered as endovenous bolus and half by intramuscular or subcutaneous route. If endovenous perfusion is decided, such dose can be ignored.
2. If the patient is in an intensive care unit, is recommended the administration of insulin in continuous perfusion. Such dose should be around 5 to 7 units per hour.
3. If impossible to keep a strict surveillance on the patient, an option of giving 5 to 7 units of insulin per hour, by subcutaneous or intramuscular route.

In the last few years, a discussion has been going on the advantages of low versus high doses of insulin. Until the 70ties, most in the sites foreseen the use of high doses of insulin, based in non-randomized retrospective studies.[1] To perform random prospective studies has demonstrated a similar efficacy of therapy with a lower dose of insulin, with a lower incidence of hypoglycemia and hypokalemia.[24,25,26]

The use of low doses of insulin enables to obtain serial concentrations of insulin in around 100 µU/ml. This level is reached, in healthy individuals, after a rich meal in carbohydrates. This way, the low doses protocol enables to obtain a level of physiologic insulinemia, whilst in the high doses protocol supraphysiologic levels are obtained. Both promote a comparable effect lowering glycaemia and ketonemia but the first with a lower level of complications. [2,25,26]

The administration route is also a controversial subject. Endovenous administration is advocated by several authors instead of the intramuscular or subcutaneous route, resulting in an inconstant and erratic absorption, mainly the latter and in hypotense and hypothermic patients.[13]

About this issue of administration route, prospective studies were carried out. In these studies the efficacy of insulin administration by any of the routes, whether endovenous, intramuscular or subcutaneous was proven. However, in the first hours of therapy, the endovenous route provides a quicker decrease on glycaemia and ketonemia.[26,27] Such difference is explained by the necessary time to reach an insulinemia level effective in insulin administration through an intramuscular and subcutaneous route.[26,27]

To get adequate plasmatic levels quickly, there is no advantage on the administration of an initial dose of insulin in the protocol using endovenous route.[28] In the protocols using the other routes, the initial dose should be administered half by endovenous route, and the reminder by intramuscular or subcutaneous route, enabling this way to obtain effective plasmatic routes since the beginning of the therapy (*Table 2*).[29]

Intensive care units have enabled to reduce significantly morbidity and mortality in ketoacidosis. Severe conditions of ketoacidosis, namely diseases with a change of awareness status, severe dehydration, septic condition among others, should be admitted preferably in intensive care unit with insulin started in continuous endovenous perfusion. The use of endovenous perfusion in the remaining units has some setbacks, with some authors arguing it should be used only in intensive care units or in the possibility of having a constant patient's surveillance. Regardless of the therapy scheme used it is necessary a careful monitoring of the patient's clinical and biochemical condition. To determine the capillary glycaemia at the patient's bedside should be made every hour.

Insulin resistance is a universal fact in ketoacidosis due to an increase of counterregulatory hormones. As a result, much higher insulin doses during the first ketoacidosis day are needed.[4]

Typically, a glycaemia decrease is the initial goal in the ketoacidosis treatment. It is recommended a decrease of around 75 to 100 mg/dL/hour and every time such target is not met, the insulin administration rate should be increased.[4]

At present, the most relevant target is to bring the pH and bicarbonatemia to normal values. This way, if, at the end of two hours of treatment, the level of serial bicarbonate does not increase or the anion gap does not decrease, the insulin dose should be doubled.[3,12]

To correct ketonemia and acidemia takes around the double of time needed to correct glycemia.[2] In such sense, insulin administration must be kept to inhibit ketogenesis, even if glycaemia is normal. To prevent hypoglycemia, dextrose solutions are used every time glycaemia drops below 250 mg/dL. In some patients, it is necessary a dextrose perfusion to 10%.[4,12]

Protocols of low doses of insulin provide physiological insulin levels. However, due to the short plasmatic level of insulin, its administration should not be withdrawn abruptly, mainly when the endovenous route is used. When the bicarbonate level is above 16 mEq/dL and the anion gap lower than

16 mEq, the insulin administration rate should be reduced to half.[12]

Patients in zero diet, in spite of not being in ketoacidosis, the dextrose serum perfusion should be kept and capillary glycaemia assessed every 4 hours. It should be a quick absorption insulin by subcutaneous route, according to the value of glycaemia determined.

When the patients present an effective oral route, the endovenous route can be withdrawn. The patient should start a multifractionated diet for diabetic, with 150 to 200 g of carbohydrates. Capillary glycaemia should be determined before or after a meal, and fast acting insulin administered according to the values obtained.[2] NPH insulin should be started before breakfast and before supper. The value to be administered depends on the insulin administered during the ketoacidosis treatment. Dosage readjustment and administration schemes are made subsequently.

Complications

Hypoglycemia, hypokalemia, hypophosphatemia are possible complications emerging from ketoacidosis treatment. Cerebral edema, adult distress respiratory syndrome, metabolic acidosis and hyperchloremia are also, complications of a hasty ketoacidosis treatment.

Cerebral edema

Cerebral edema and subsequent tonsils herniation is a potentially lethal complication of ketoacidosis treatment. Although the cerebral edema clinic may occur in young adult, most cases occurs in children and teenagers.[7,30] Serial electroencephalography and imagery studies demonstrate a high frequency of subclinical cerebral edema during the first twenty four hours of treatment.[7,31,32]

The clinical condition is of sudden and unpredictable onset. The patient, usually a child, is recovering from ketoacidosis when it refers headaches followed by a change on the awareness condition, papilledema, hypertension, bradycardia and mydriatic pupil. Some patients evolve into diabetes insipidus.[3,7]

The estimated incidence in children is from 0.7 to 1.0 episode per 100 ketoacidosis. Mortality is 70% and a recovery without sequel occurs in only 7 to 14% of cases.[3]

Pathophysiology is hardly known. Risk factors include inaugural diabetes, long lasting ketoacidosis and an exaggerated drop of serial osmolality during treatment.[3]

Hyperosmolarity condition leads to the loss of water of the intracellular space. Such effect is, in the central nervous system, softened by a production of idiogenic osmoles enabling to keep the balance among compartments. When the plasmatic osmolality is abruptly reduced by the infusion of hypotonic solutions, verifying the entry of water into the intracellular space, emerging signs of cerebral edema.[2,3,7]

An increase on vasopressin secretion, occurring usually in ketoacidosis, speeding up this process.[33]

Some authors advocate the presence of precipitating factors, as the excessive serum administration, the use of hypotonic solutions and the use of bicarbonate. However, it was not possible to prove the intervention of any of them in the origin of the cerebral edema.[30,34]

In the presence of some change of the neurologic exam, during the acidosis treatment, one should presume a diagnosis of cerebral edema. Mannitol perfusion in a dosage of one to two grams per kg of body weight should be started immediately, even without image confirmation. Worth of noticing that in the time mediating from the symptomatology onset and starting the therapy depends the treatment success. On the other hand, if a suspicion is verified as incorrect, mannitol perfusion only delays slightly the ketoacidosis recovery. The water reposition therapy should be restarted at a slower pace.[8,30]

Adult respiratory distress syndrome

The non-cardiogenic acute pulmonary edema is one of the potentially lethal complications of the diabetic ketoacidosis treatment.

The osmotic pressure is initially increased in patients with ketoacidosis due to a higher water loss regarding ions. In rehydration, osmotic pressure decreases gradually to values below than healthy individuals. To this effect, it should add a PaO_2 progressive decrease and an increase of the alveoli--capillary gradient. In most patients, such changes are asymptomatic, but a small number evolves to ARDS, mainly in advanced age patients and concomitant cardiac pathology.[2,35,36]

Hyperchloremic metabolic acidosis

Multiple studies show the presence of metabolic acidosis with relative hyperchloremia after ketoacidosis has been resolved. Such acidosis has no adverse clinical effects and it is gradually corrected on the

following days by renal excretion of acid valences.

Big amounts of ketoanions are excreted during ketoacidosis. From this loss results an insufficient amount of ketoanions to correct metabolic acidosis during the metabolism of ketonic bodies mediated by insulin.

Other mechanisms contributing to hypercloremic acidosis include serum infusion containing amounts of chlorine higher than the serum, blood volume expansion with serum with bicarbonate and intracellular consumption of bicarbonate during ketoacidosis correction.[2,3]

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