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BRIEF ARTICLE

Emerging cause of acute metabolic acidosis in the ICU

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Abstract

Background: Metabolic acidosis is a frequently encountered finding in patients admitted to Intensive Care Unit (ICU). The etiological differential diagnosis of metabolic acidosis includes a relatively frequent and often unknown clinical condition which is represented by starvation ketoacidosis. Starvation ketoacidosis (SKA) occurs after the body is deprived of glucose as the primary source of energy for a prolonged time, and fatty acids replace glucose as the major metabolic fuel. We conducted a retrospective observational study we screened medical records of patients admitted to ICU from 2022/10/10 to 2023/04/10, including patients with metabolic acidosis, with ketonuria detected by urine samples or urine stick positivity treated with glucose solutions or enteral/oral nutrition within 2 hours of diagnosis. The primary outcome was to evaluate the prevalence of ketoacidosis in critically ill patients; the secondary outcome was to evaluate the impact of ketoacidosis on hemodynamic instability and the role of early treatment in reducing complications and days of hospitalization in ICU.

Results: In the time period studied, 574 patients were admitted to the ICU, 90 patients had diagnostic criteria for ketoacidosis (15,67%) of which, 19 patients met inclusion criteria. Of these patients 11 were hemodynamically stable and 8 unstable. The unstable patients had a mean norepinephrine support of 0,21 mcg/kg/min. Unstable patients had lower BE value than stable patients (-5,4 vs -1,7, p =0,3), lower pH (7,28 vs 7,33, p=0,13), significantly lower serum albumin (24,5 vs 30,7, p =0,03) and lower HCO3- (20,5 mmol/L vs 24,5, p = 0,21). No statistically significant differences were found in the absolute value of ketonuria (unstable 42,3 vs stable 45,7, p= 0,90) or in the lactate levels at admission.

Conclusion: The presence of ketonuria shows that our patients are often fasting for a variable time lapse depending on the reason for hospitalization, the days of hospitalization preceding entry into the ICU, and the underlying clinical conditions. In our analysis we found that acidosis can lead to transient hemodynamic instability, early treatment could avoid several complications as acidotic electrolyte disorders or major cardiac events related to amine use and could short ICU length of stay or unnecessary ICU admission.

Keywords: metabolic acidosis, starvation ketoacidosis, ketone bodies.

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Background

Metabolic acidosis, defined as the presence of an acid-base imbalance associated with serum reduction of bicarbonate concentration and low pH is a frequent finding in patients admitted to the intensive care unit (ICU) [1]. The most frequent causes of acute metabolic acidosis are sepsis, acute renal failure, drug intoxication, hypovolemia, hemorrhagic shock, cardiac arrest, diabetic ketoacidosis.

This acute metabolic acidosis is a potentially life-threatening condition with several clinical manifestations as myocardial disfunction, cerebral edema, pulmonary vasoconstriction, systemic vasodilatation and fatal arrhythmias [2,3].

A differentiation has recently been introduced in the diagnostic criteria of metabolic acidosis, distinguishing a moderate and severe form based on clinical severity: moderate metabolic acidosis (pH<7.30, base excess < −4 mmol/l and $PaCO^2 \leq 45$ mmHg) occurs in 8,4% of patients admitted to the ICU while severe metabolic acidosis (pH < 7.20, $PaCO^2 < 45$ mmHg, HCO3- < 20 mmol/L and total Sequential Organ Failure Assessment [SOFA] > 4 OR Lactate > 2mmol/L) occurs in 1.5 % of patients. The ICU and hospital mortality rates were 19% and 45%, respectively [4].

In ICU patients, moderate or severe metabolic acidosis seems to be associated with high mortality and increased length of stay [5,6].

Diabetic Ketoacidosis is a life-threatening condition that mostly affect patients with uncontrolled diabetes and it is characterized by hyperglycemia, acidosis and high levels of serum and urinary ketone bodies [7]. However, in several ICU patients, a relatively frequent and often misdiagnosed condition of metabolic acidosis with high serum/urinary ketone levels and normal/low blood glucose level is due to starvation ketoacidosis. Starvation ketoacidosis (SKA) occurs after body is deprived of glucose as the primary source of energy for a prolonged time, and fatty acids replace glucose as the major metabolic fuel. SKA can be also associated to new eating habits such as high-protein diets, low-carb diets, ketogenic diets, intermittent fasting, to the use of drugs that can induce starvation, to the lack of adherence to the Eras protocols [8] and to the late presentation of patients to the hospital after the onset of symptoms. Studies on starvation ketoacidosis are lacking and limited to few case reports [9]. Early recognition and treatment of this condition could prevent several life threating complications, improve survival and shorter the ICU length of stay.

The primary outcome was to evaluate the prevalence of ketoacidosis in critically ill patients admitted to intensive care unit. The secondary outcome was to evaluate the impact of ketoacidosis on hemodynamic instability (MAP < 65 mmHg unresponsive to filling with crystalloids, requiring start of aminic support with noradrenaline and/or other vasopressors as required by normal clinical practice) and the role of early treatment in reducing these complications and the days of hospitalization in intensive care unit.

Materials and methods

We conducted a retrospective observational study. The research protocol was approved by the Local Ethics Committee of Bologna (approval number CE AVEC 519-2023-OSS-AUSLBO of 2023/07/27). We screened all admissions and medical records of patients admitted in the ICU (Ospedale Maggiore-Bologna, Italy) from 2022/10/10 to 2023/04/10. We included patients of more than 18 years old who were admitted to intensive care unit with metabolic acidosis, with ascertained ketonuria detected by urine samples or urine stick positivity and who were treated with glucose solutions or enteral/oral nutrition within 2 hours of diagnosis. We excluded patients with severe renal injury (KDIGO III/IV/V), BPCO Gold classification 3/4, acute drugs intoxications and uncontrolled diabetes. Patients were differentiated into two groups: surgical patients, if admitted to ICU after surgery for monitoring of vital signs or need for intensive treatment, and medical patients. We also assessed each patient if hemodynamic unstable (defined as hypotensive state, with mean arterial pressure < 65 mmhg, unresponsive to volume expansion and requiring norepinephrine support). We collected data at admission and after 12 h: pH, BE, HCO3-, Hb, ketonuria, lactates, albuminemia, $PaCO^2$; we collected the different kind of treatments and their duration to restore a normal pH and to reduce ketonuria.

Data are presented as percentage and numbers,

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means and standard deviations, medians and interquartile ranges. Groups comparisons were performed using chi square test or Fisher exact test for categorical variables and student t-test for normally distributed data. P-value < 0,05 was considered statistically significant.

Results

In the study period 574 patients were admitted to the ICU, 90 patients with diagnosis of ketoacidosis (15.67%) of which, 16 patients met inclusion criteria.
The overall patients' characteristics are shown in **table 1**.

TABLE 1 - patients baseline characteristics at ICU admission

	Tot(n=19)	Stable (n=11)	Unstable (n=8)	P value
Age	57	51	63	0.09
Male	7	4	3	
Surgical patients	10			
Medical patients	9			
Norepineprhine (mcg/kg/min)		0	0.22 ± 0.19	
pH		7.33 ± 0.07	7.28 ± 0.06	0.13
HCO3- (mmol/l)		24.5 ± 6.6	20.5 ± 6.4	0.21
BE (mmol/l)		-1.7 ± 6.6	-5.4 ± 8.3	0.34
Albumin (g/l)		30.7 ± 6.2	24.5 ± 5.4	**0.03***
Lactate (mmol/l)		1.5 ± 2.3	3.1 ± 3	0.23
Creatinine (mg/dl)		0.7 ± 0.4	1.1 ± 0.4	0.06
Hemoglobin (gr/dl)		12.2 ± 2.6	10.4 ± 1.8	0.1

*P value < 0,05

They were 7 men and 12 women, mean age was 56. Three patients had cancer, and 8 underwent major surgery.
Of these patients 11 were hemodynamically stable and 8 unstable. The unstable patients had a mean norepinephrine support of 0.22 mcg/kg/min. Unstable patients had lower BE value than stable patients (-5.4 vs -1.7, p =0.3), lower pH (7.28 vs 7.33, p=0.13), significantly lower serum albumin (23.3 vs 30.4, p =0.04) and lower HCO3- (20.5 mmol/L vs 24.5, p = 0.2). No statistically significant differences were found in the absolute value of ketonuria (unstable 42.5 vs stable 44.5, p=0.90) or in the lactate levels at admission.
Comparing medical (8) and surgical patients (11): the medical patients had a lower ketonuria (12 versus 71 p 0.009) and an higher HCO3- (26 versus 20 p 0.04). (**Figure 1**)
All the patients were treated with 12 h infusion of glucose solutions 5% or 10% at different rates (100-125ml/h, with a total administered volume of 1000 ml) or with enteral feeding (both trough nasogastric/nasojejunal tube) or oral feeding.
After 12 h of treatment all patients improved, amine support was suspended in unstable patients and normal pH was restored. No differences were found in ICU staying between the groups. (**Table 2**)

Discussion

Nineteen patients were admitted to ICU with ketonuria at admission and were treated early with caloric support. The presence of ketonuria in our patients shows that our patients are often fasting for a variable time lapse depending on the reason for hospitalization, the days of hospitalization preceding entry into the ICU, and the underlying clinical conditions.

FIGURE 1 - Ketonuria and HCO3 in surgical and medical patients

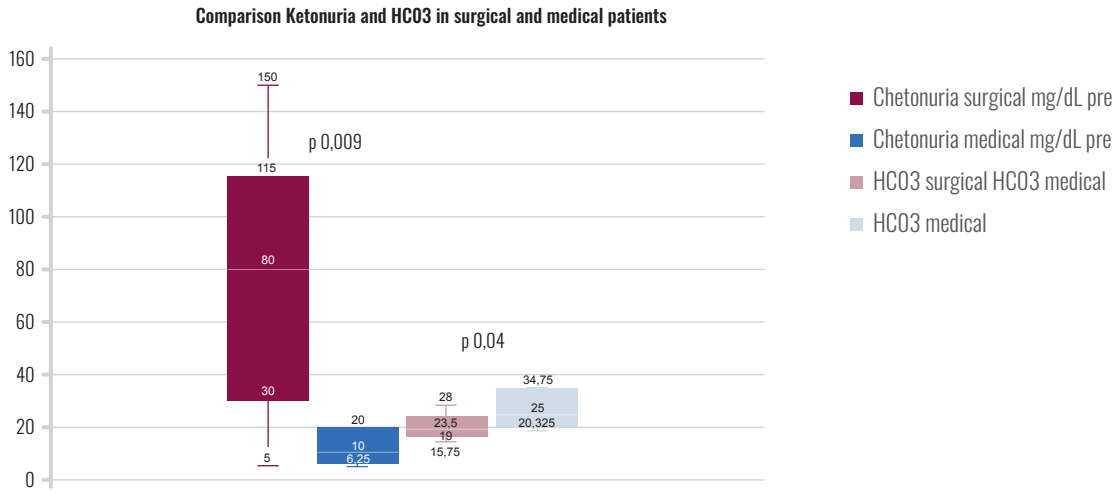

TABLE 2 - patients characteristics after 12 h of treatment

	Tot(n=19)	Stable (n=11)	Unstable (n=8)	P value
pH post		7.40 ± 0.03	7.42 ± 0.03	0.1
BE post (mmol/l)		-0.28 ± 4.2	-2.3 ± 2.3	0.54
HCO3- (mmol/l)		24.7 ± 3.8	22.3 ± 2.6	0.25
Lactate (mmol/l)		1.17 ± 0.6	3.02 ± 4	0.28
ICU LOS mean		2.4	6.1	0.1
Treatment				
-Enteral nutrition		0	1	
-Oral nutrition		4	0	
-Parenteral glucose 5%-10% infusion		7	7	

These conditions are usually added to a hypercatabolic state in which there is a metabolic and hormonal dysregulation in response to stress (e.g. surgery, sepsis, trauma) [10-11].

In healthy adults, in case of prolonged fasting, glucose deficit activates gluconeogenesis and inhibits glycolysis; the Krebs cycle is inhibited (due to lack of oxaloacetate which is oxidized to phosphoenolpyruvate for gluconeogenesis) and the excess AcetylCoA is used for the synthesis of ketone bodies: acetoacetate, betahydroxybutyrate, and acetone (metabolically inert, excreted with exhalation). The activation of lipolysis detemines the transport of free fatty acid chains to the liver mitochondria where they undergo beta-oxidation [12-13].

Under normal conditions, the production of ketone bodies is a protective mechanism; in fact, in the absence of glucose, ketone bodies can be used as an energy substrate and limit the catabolism of amino acids for energy production [14]. Furthermore, in healthy adults, increased blood ketone concentration inhibits further activation of lipolysis, increases insulin production and inhibits further formation of ketone bodies [15,16]. It has been demonstrated that ketone bodies also have an antioxidant effect, indeed, they activate autophagy processes that are involved in the maintenance of

cellular integrity, in the eradication of toxins, cancerous molecules and intracellular damage. Ketogenic diets developed from these mechanisms [17-20]. In cancer patients, ketone bodies could have a protective role, especially for the activation of autophagy [21,22]; in patients with neurovegetative disease a state of ketosis can lead to a reduction of the inflammatory mechanisms involved in the pathogenesis of the disease [23].

In some clinical conditions, ketogenesis is activated early, as in pregnant women and in children [24,25]. Excessive production of ketone bodies can lead to ketoacidosis, a condition of metabolic acidosis with reduced concentration of bicarbonates and excess bases. There are at least two other causes of metabolic ketoacidosis: alcoholic ketoacidosis (AKA) and diabetic ketoacidosis (DKA) [26]. The first occurs in patients with a history of chronic alcohol abuse and usually ketoacidosis is associated with increased lactate levels; indeed, ethanol is metabolized to both acetaldehyde and lactic acid [27]. The second occurs in patients with type 1 or type 2 diabetes mellitus on insulin therapy in which the deficit of insulin production results in an inability of the tissues to use circulating glucose and in an increased production of ketone bodies which can lead to ketoacidosis, usually characterized by hyperglycemia, decreased blood bicarbonate level, high ketone levels and insulin deficiency. A state of "euglycemic" diabetic ketoacidosis can also occur in patients with type II diabetes treated with oral hypoglycemic drugs inhibitors of the sodium- glucose transporter type 2 (SGLT-2), in this case, blood glucose levels are usually normal [28]. Sometimes these causes of acidosis coexist, and it is not possible to make a differential diagnosis; it is also always necessary to exclude all other causes of metabolic acidosis (ethylene glycol, methanol, acetylsalicylic acid, tricyclic antidepressants, etc.) [29-33].

Fasting ketoacidosis (Starvation Ketoacidosis, SKA), often misdiagnosed, can cause acidosis that is unresponsive to volume expansion and bicarbonate administration and can determine hemodynamic instability and consequent hospitalization in an intensive care environment. Patients in the perioperative period, those suffering from pancreatitis [34,35] and septic patients seem to be more exposed to this risk, probably due to stress-induced dysregulation (increased levels of cortisol, decreased insulin/glucagon ratio). The resolution of this acidosis is rapid after administration of glucose or re-feeding, indeed, the increase in blood glucose concentration corresponds to an increased production of insulin and a reduction in the production of glucagon; in the absence of specific guidelines for the treatment, glucose infusion is used as suggested by the guidelines for diabetic ketoacidosis. Ketoacidosis is little studied perioperatively as an index of malnutrition.

In our analysis we found that acidosis can lead to transient hemodynamic instability and most of the unstable patients have low levels of albuminemia and are, thus, malnourished.

Early treatment could avoid several complications as acidotic electrolyte disorders or major cardiac events related to amine use and could short ICU length of stay or unnecessary ICU admission. In fact, in our results hemodynamic stable and unstable patients, both early treated, had the same ICU loss. Our study has several limitations, it is a retrospective observational study, there is a small sample of patients, and the treatments were different depending on clinical practice and different clinicians.

Conclusion

In all patients with metabolic acidosis without an easily identifiable cause ketone bodies in urine or blood samples should be investigated. Indeed, although our series is numerically limited, it is interesting to consider how a simple treatment can resolve apparently complex clinical cases.

More studies are needed to have a comprehensive vision of the incidence of starvation ketoacidosis in ICU, to understand all the physiopatological effects of fasting and starvation in different subgroups of patients (i.e., surgical/medical/trauma patients) and to proper treat this condition.

Declarations

Ethics approval and consent to participate: The clinical study was approved by the Bologna ethics committee.

Consent for publication: not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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