The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 2074-2079

# Predictive Value of Sepsis Markers in Diabetic Ketoacidosis Patients Admitted to Intensive Care Unit

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## ABSTRACT
**Background:** Diabetic Ketoacidosis is one of the leading causes of intensive care unit (ICU) admissions. Recently, evidence suggests that procalcitonin (PCT) and lactate levels are helpful prognostic markers for diabetic ketoacidosis.
**Objective:** To assess the PCT and serum lactate levels as predictors for morbidity and mortality in DKA patients admitted to the ICU.
**Patients and Methods:** A prospective study included 180 patients conducted at Mansoura University Hospitals, Mansoura, Egypt, for a duration of 1.5 year-duration from January 2021 to June 2022. All patients had been subjected to clinical examination and medical history. Laboratory tests, comprising a complete blood count, PCT, and serum lactate levels were reported.
**Results:** The median PCT level in the DKA group was 7.18 ng/ml, the median PCT level in the diabetic group without DKA was 5.8 ng/ml and in the control group, the median level was 0.7 ng/ml. The mean serum lactate level in the DKA group was 7.66 ± 0.86 mmol/L, the mean serum lactate level in the diabetic group without DKA was 4.11±0.77 mmol/L and in the control group, the mean serum lactate level was 2.01 ± 0.39 mmol/L.
**Conclusion:** PCT and lactate levels were significantly higher in the DKA group in comparison to the diabetic without DKA group and the control group.
**Keywords:** Diabetic ketoacidosis, Sepsis, Lactate, Procalcitonin, and ICU.

## INTRODUCTION

The most frequent acute hyperglycemic emergency in persons with diabetes mellitus (DM) is diabetic ketoacidosis (DKA). DKA is more common in cases with uncontrolled type I DM (TIDM), although it can also happen in adults with poorly controlled type II DM (TIIDM) under stressful circumstances, such as acute medical or surgical disorders, and in adolescents with new-onset TIIDM [(1)].

The most common causes of DKA are infections, in particular gastrointestinal infections as well as urinary tract infections (UTIs). The incidence of DKA is approximately 2 episodes per 100 patients per year, with approximately 3% of T1DM patients initially presenting with DKA [(2)].

The American Diabetes Association (ADA), 2001 redefined DKA to involve mild metabolic acidosis, hyperglycemia, and positive ketone testing. In affluent nations, the mortality rate from DKA in pediatrics and adults is 1%. In contrast, mortality rates among impoverished nations are substantially higher, with recorded death rates in youngsters as high as 3-13%. In addition, DKA-related mortality in adults is most common in older people (>60 years old) or those with extensive precipitating diseases [(3)].

DKA can develop in T1DM or T2DM when there is absolute or relative insulin insufficiency or during acute illness, and it is related to a rise in the regulation of the cortisol, growth hormone, glucagon, and catecholamines [(4)].

The pathophysiological mechanisms implicated in DKA are based on changes in hormone levels and the associated inflammatory response [(5)].

Recently, serum procalcitonin (PCT) is a calcitonin precursor with no hormonal activity that has been suggested for the diagnosis of bacterial infections and was hypothesized to be used in the diagnosis of DKA [(6)]. Furthermore; DKA is a significant acute consequence that induces extensive dehydration and raised blood lactate levels; excessive lactate levels frequently imply hypovolemia and microcirculation abnormalities [(7)]. Leading to that, the serum lactate levels and PCT may play a crucial role as predictive biomarkers in DKA diagnosis.

In our study, we aim to discover the role of PCT and lactate level as biomarkers for mortality in DKA patients admitted into the ICU department of Mansoura University Hospitals.

## PATIENTS AND METHODS

The study comprised one hundred twenty diabetic patients, sixty patients were admitted to ICU due to moderate and severe DKA, while the other sixty patients were admitted because of medical emergencies other than DKA to ICU, at Mansoura University Hospitals, Mansoura, Egypt, for a duration of 1.5 year-duration from January 2021 to June 2022.

In our included population, the presence of DKA can be based on the presence of inflammatory symptoms such as respiratory tract infection, UTI, soft tissue infections, and other factors, including renal failure, hepatic encephalopathy, and missing insulin doses.

The inclusion criteria of our study include patients with, insulin-dependent DM (Type 1), complicated with



Received: 15/09/2022
Accepted: 18/11/2022

DKA, and more than 18 years. On the other hand, the exclusion criteria specified cases under the age of 18 years, Patients who met one or more of the following criteria (medullary thyroid carcinoma, cardiac arrest, heat stroke, pancreatitis, malaria, and extensive traumas), or who refused to participate in the trial, were ruled out from the study. All participants in the current study had a clinical examination and personal, family, and drug history taking in addition to their demographic data. Besides, all patients had their laboratory tests, such as complete blood counts, blood procalcitonin, and serum lactate.

**Estimation of blood procalcitonin measurement:**

Prior to the administration of antibiotics, patients' three ml of venous blood was drawn into an additive-free test tube within six hours after the arrival. The serum was centrifuged at 1500 rpm utilizing a double-antibody sandwich immunoassay chemiluminescence measurement of serum PCT levels produced by BRAHMS Diagnostica in Germany. Creatinine and urea nitrogen levels are simultaneously determined from tube samples. Within an hour, all report results were obtained [(8)].

**Estimation of serum lactate measurement:**

Using the Cobas 6000 fully automated analyzer, serum lactate concentrations were measured (Roche Diagnostics) [(9)].

**Ethical consideration:**

**The Faculty of Medicine at Mansoura University's Institutional Review Board (IRB) approved the study design. At every phase of the investigation, confidentiality and personal privacy were respected. Patients can leave the research at any moment without facing any repercussions. No other use was or will be made of the collected data. Before including them in the research, written informed permission was acquired from all participants outlining the purpose of the investigation and the steps that would be taken. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the conduct of this study.**

***Statistical Methods***

The statistical package for social sciences (SPSS 22.0, IBM/SPSS Inc., Chicago, IL) was used to statistically evaluate the results. regarding descriptive statistics. It calculates the mean (X) and SD for the normal distribution of data or the median (Med) and interquartile range (IQR) for skewed data for a summary of the continuous data. The presentation of qualitative data used frequency with a percentage (%). The significance level at which the null hypothesis was rejected was set at 0.05 for all applied tests, meaning that P-values below 0.05 are statistically non-significant, P-values above 0.05 are significant, and P-values over 0.01 are very significant.

**RESULTS**

The current study included 180 (ranging from 18 to 60 years old) patients admitted to ICU (sixty patients due to moderate and severe DKA, sixty patients were admitted because of medical emergencies other than DKA. While normal 60 age and the sex-matched group were included as a control group regarding PCT level and lactate calibration). One hundred ten (61.1%) were males, while the seventy (38.8%) were females **Table (1)**.

Regarding the gender distribution, there were (66.7%, 63.3 and 53.3% males in the DKA group, the diabetic group without DKA, and the control group respectively) while there were (33.3%, 36.7 and 46.7% females in the DKA group, the diabetic group without DKA and the control group respectively) with no significant change in the sex distribution of the cases comprised in the study (p=0.54).

Causes of severe sepsis and septic shock in the DKA group were respiratory tract infection (64.7%), UTI + acute renal failure (17.6%), and soft tissue infection (17.6%). While in the diabetic without DKA group, causes of severe sepsis and septic shock included respiratory tract infection (65.6%), urinary tract infection + acute renal failure (18.8%), and hepatic encephalopathy (15.6%) **Table (1)**.

**Table (1):** Comparison of the demographic data between the study groups

| Variables | DKA with diabetes group (n=60) | Diabetic without DKA group (n=60) | Non-diabetic group (n=60) | Test of significance |
|---|---|---|---|---|
| Age (years) [Mean ± SD] | 49.93 ± 12.81 | 47.93 ± 9.91 | 47.17±10.91 | F =1.275<br>P= 0.285 |
| Gender [n (%)] | | | | c2 = 1.22<br>P= 0.545 |
| Male | 40 (66.7) | 38 (63.3) | 32 (53.3) | |
| Female | 20 (33.3) | 22 (36.7) | 28 (46.7) | |
| BMI (kg/m2) [Mean ± SD] | 26.94 ± 3.35 | 26.24 ± 2.67 | 27.42 ± 3.87 | F =0.868<br>P= 0.394 |
| Severe sepsis and septic shock [n (%)] | | | | c2 = 0.135<br>P= 0.714 |
| Yes | 34 (56.7) | 32 (53.3) | | |
| No | 26 (43.3) | 28 (46.7) | | |
| Cause of severe sepsis or septic shock | N = 34 | N= 32 | | |
| Respiratory tract infection | 22 (64.7%) | 21 (65.6%) | | |
| Urinary tract infection + acute renal failure | 6 (17.6%) | 6 (18.8%) | | |
| Soft tissue infection | 6 (17.6%) | 0 (0%) | | |
| Hepatic encephalopathy | 0 (0%) | 5 (15.6%) | | |
| Other causes of hospital admission | N = 26 | N= 28 | | |
| Respiratory tract infection | 4 (15.4%) | 2 (7.1%) | | |
| Urinary tract infection | 8 (30.8%) | 0 (0%) | | |
| Urinary tract infection + acute renal failure | 0 (0%) | 2 (7.1%) | | |
| Disturbed conscious level + stroke | 0 (0%) | 9 (32.1%) | | |
| Hepatic encephalopathy | 0 (0%) | 9 (32.1%) | | |
| Soft tissue infection | 3 (11.5%) | 0 (0%) | | |
| Missed insulin dose | 2 (7.7%) | 0 (0%) | | |
| Unidentified causes | 9 (34.6%) | 0 (0%) | | |
| HF | 0 (0%) | 6 (21.4%) | | |

The median PCT level in the DKA group was 7.18 ng/ml, the median PCT level in the diabetic group without DKA was 5.8 ng/ml and in the control group, the median level was 0.7 ng/ml. The PCT level was significantly greater in the DKA group in comparison with the Diabetic without DKA group and the control group. Also, the PCT level was statistically significantly higher in the Diabetic without DKA group in comparison with the control group **Table (2)**.

**Table (2):** Comparison of the procalcitonin level in the study groups

| Parameter | DKA with diabetes group (n=60) | Diabetic without DKA group (n=60) | Non-diabetic group (n=60) | significance test | Intergroup Significance |
|---|---|---|---|---|---|
| PCT (ng/mL) [Median (range)] | 7.18 (0.11-38.5) | 5.8 (0.23-28.5) | 0.7 (0.21-2.7) | KW =127.64<br>P <0.001 * | P1<0.001*<br>P2<0.001*<br>P3<0.001* |

Median, range: Non-parametric test.

The mean serum lactate level in the DKA group was 7.66±0.86mmol/L, the mean serum lactate level in the diabetic group without DKA was 4.11 ± 0.77mmol/L and in the control group, the mean serum lactate level was 2.01 ± 0.39 mmol/L. The mean serum lactate level was statistically significantly higher in the DKA group in comparison with the Diabetic without DKA group and the control group. Also, the mean serum lactate level was statistically significantly higher in the Diabetic without DKA group in comparison with the control group **Figure (2) Table (3).**

**Table (3):** Comparison of the lactate level in the study groups

| Parameter | DKA with diabetes group (n=60) | Diabetic without DKA group (n=60) | Non-diabetic group (n=60) | significance test | Intergroup Significance |
|---|---|---|---|---|---|
| Lactate level (mmol/L) [Mean ± SD] | 7.66 ± 0.86 | 4.11 ± 0.77 | 2.01 ± 0.39 | F =36.879<br>P <0.001 * | P1<0.001*<br>P2<0.001*<br>P3<0.001* |

## DISCUSSION

The present study comprised one hundred twenty diabetic patients, sixty patients were admitted to ICU due to moderate and severe DKA, while the other sixty patients were admitted because of medical emergencies other than DKA. Normal 60 age and the sex-matched group were included as a control group regarding PCT level and lactate calibration. Unfortunately, most of our patients were moderate to severe DKA. Mild cases are not admitted to ICU in our locality. All diabetic patients in this study were well-known and treated as IDDM from the start of their diabetic state. The present study aims to investigate the predictive value of PCT, serum lactate, and NLR in DKA patients.

The incidence of DKA has been increasing with increasing prevalence of diabetes. DKA is a hyperglycemic crisis that can be fatal [(10)]. Mortality has been considered a good and clear research benchmark for researching diseases, especially in critical illnesses such as DKA. The mortality rate of DKA has been dropping in developed nations but increasing in developing nations [(11-13)].

The present study revealed that out of 120 patients with critically ill diabetes, seven sepsis, and septic shock could be fulfilled in 55% of the patients (56.6% of the DKA group & 53.3% of the non-DKA group). The most common participating factor in the 60 diabetic DKA group was infection (81.6%), of which lung infection comprised 43.3% & UTI comprised 23.3% and soft tissue infection as cellulitis, diabetic foot, and ulcer comprised 15%.

However, it was previously reported that withdrawal of insulin therapy and infections are the most common activating factors of DKA. They added that the most common cause is bacterial infections with UTI, the phenomenon could explain up to 50% of ketoacidosis [(14-16)].

PCT, a precursor of calcitonin, is produced as a component of the systemic response to bacterial infections [(17)]. PCT is discharged by parenchymal cells, comprising the hepatic, renal, and adipose tissues and muscle cells owing to toxins from bacteria-inducing levels to increase up to 5000 times in about 3 hours [(18)].

The present study revealed that PCT level was far significantly higher in the two diabetic groups versus the control. Moreover, PCT was significantly higher in DKA diabetic patients than in non-DKA diabetes.

However, the contribution of the hyperglycemic crisis to the increase in PCT couldn't be ruled out. **Aksu *et al.*** [(19)] recorded a reduction in PCT levels following the normalization of glycemia in cases with acute hyperglycemic crises. **Blanchard *et al.*** [(17)] found elevated levels of PCT in diabetic cases without any confirmed bacterial infection, with a PCT drop following normalization of glycemia. In addition, high PCT levels were previously recorded in DKA without infection, so, some authors concluded the augmentation of PCT in acute glycemic crisis might be demonstrated in DKA rather than hyperosmolar hyperglycemic syndromes [(20)].

Hyperglycemia in diabetic cases has been demonstrated to be associated with the discharge of pro-inflammatory cytokines which include tumor necrosis factor α (TNFα) and IL-6 [(21)]. Apart from any bacterial infection, TNFα has been identified to induce the discharge of huge amounts of PCT in animal models as well as in humans [(22, 23)]. During infection, bacterial lipopolysaccharides and sepsis released cytokines adjust the liver and peripheral blood mononuclear cells to form PCT. The microbial infection causes an increase in CALC-1 gene expression and then the discharge of PCT which is correlated with the severity of disease and mortality [(24)].

Mortality as one of the endpoints of the course is a good and clear research benchmark for researching a disease, especially in critical illness such as DKA. The present study strengthened the proof of PCT utility in critically ill DKA cases admitted to ICU.

PCT level is a valid indicator of mortality in DKA patients as it describes the degree of inflammation experienced by the patient. **Cheng *et al.*** [(25)] recorded that infection is the commonest predisposing factor for DKA, in an estimated range of 32-60%. Moreover, infection is the commonest cause of death [(16)]. More recently, **Suranadi *et al.*** [(26)] documented that PCT level > 7 ng/ml showed a potent correlation with the incidence of death in cases with sepsis in ICU with RR 1.572 (P< 0.001).

Recently, a review of the use of PCT to guide sepsis diagnosis was published by **Sager *et al*.** [(27)] illustrated that when PCT levels were 0.5-1.0 ng/mL, bacterial infection was judged "probable," and at 1.0 ng/mL, it was regarded "extremely likely". While, a recent study found that when patients are brought to the ICU, combining PCT and the presence of fever might be useful in distinguishing ketoacidosis cases with and without established bacterial infection [(17)]. Meanwhile, PCT's significance in DKA deserves additional

exploration because it does not always indicate bacterial infections [28].

Previous research has been published by **Aksu *et al.*** [19] recorded a reduction in PCT levels after glycemic correction in cases with acute hyperglycemic crises. Although, in our study, the level of sepsis biomarker PCT in the DKA group was found to be substantially higher when compared to the other group. Furthermore, High PCT levels have lately been recorded in several case reports concentrating on diabetic ketoacidosis without infection [20, 29].

PCT levels in a case series of 5 individuals who were hospitalized for DKA ranged from 6.87 to 30.47 ng/mL, this led the author to conclude that diabetic ketoacidosis may be the only condition in which PCT is increased during an acute glucose crisis [20].

On the other hand, blood gas analysis is useful in emergency medicine since it is simple to do and produces quick findings. Lactate or lactic acid (LA) levels, in particular, represent the severity of the condition [30]. Monitoring lactate levels is recommended by the Surviving Sepsis Campaign to assist in early goal-directed therapy [31].

In the context of acute cardiac or respiratory failure, systematic lactate clearance (LC) monitoring within the first two hours of admission may be therapeutically helpful in identifying patients who are at high risk of adverse outcomes and, possibly, informing the choice to intensify the therapeutic approach [32].

This came following the findings of the research carried out by **Ibrahim *et al.*** [30], which demonstrated that LC within the first two hours of admission was a significant predictor of 30-day mortality. According to research, lactic acidosis is more prevalent in DKA patients and is not linked to ICU admission, hospital length of stay, or mortality. On the other hand, another study found that LC is a factor in mortality [33].

Respectively; LA is metabolic acidosis with a high anion gap and a varying cut-off threshold of blood lactate content in various research, ranging from 2.5 mmol/l in a limited number of researches [31, 34, 35].

The current study found a significantly higher in the DKA group than in the diabetic without DKA and control groups Furthermore, the mean serum lactate level in the Diabetic without DKA group was statistically significantly higher than in the control group.

A study of 68 DKA patients indicated that 68% of them had LA, with 40% having lactate levels of more than 4 mmol/l [35]. Another study with 92 pediatric DKA patients found that 63.7% of the patients had LA (2.5 mmol/l), indicating a significant presence of LA among DKA patients [34].

In a different study, it was discovered that 14 patients out of 32 had LA with lactate levels over 2.5 mmol/l and seven had lactate over 4 mmol/l [7]. Overall, these data imply that LA in DKA is a more frequent finding than was previously thought.

However, our research study has several limitations. First, the retrospective analysis was monocentric, which restricts how broadly the findings can be applied. In addition, the sample size is quite limited, which might have contributed to bias.

To confirm the utility and diagnostic cutoffs of these markers, prospective studies will be required. Therefore, prospective clinical randomized control studies may be carried out to verify the clinical added value of such an attitude. This experiment would include a decision rule based on the levels of PCT and lactate during DKA in ICUs.

## CONCLUSION

PCT and lactate levels were statistically significantly higher in the DKA group in comparison with the diabetic without DKA group and the control group. In addition, we found that the most common possible cause of the DKA group was the respiratory tract infection, UTI, soft tissue infection, missed insulin dose, and un-identified causes with ratios (43.3%, 23.3%, 15%, 3.3%, and 15%), respectively.

**Supporting and sponsoring financially:** Nil.
**Competing interests:** Nil.

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