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REVIEW ARTICLE

# Role of Procalcitoninas APrognostic Marker in Patients with Diabetic Ketoacidosis

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**ABSTRACT**

Diabetic ketoacidosis (DKA) is a dangerous and fatal side effect of diabetes. DKA is still poorly managed in spite of all the current guidelines. Therefore, it is important to find clinical and biochemical prognostic indicators of diabetic ketoacidosis to lower morbidity and death. Patients who present with DKA are often offered empiric antibiotics because early diagnosis and treatment of infections are critical components of improved patient outcomes. Due to the similarities in patient presentation between infections and DKA, antibiotics are used excessively in both cases. This may result in higher treatment expenses, adverse drug reactions, and an increased chance of antibiotic resistance. Procalcitonin is one biomarker that has helped clinicians distinguish infectious etiologies from other conditions. It can also be used to delay the start of antibiotics or stop their course entirely. It is not clear how useful procalcitonin is for determining whether bacterial infection is the cause of DKA.
**Keywords:** Diabetic ketoacidosis, DM, insulin.

## INTRODUCTION

One of the top ten primary causes of death worldwide is diabetes mellitus (DM). Diabetes mellitus (DM) is a long-term metabolic disorder of the carbohydrates that is brought on by either insufficient or nonexistent insulin, which raises blood glucose levels. Type 1 diabetes, type 2 diabetes (the most prevalent kind), and gestational diabetes are the three main forms. Long-term uncontrolled diabetes mellitus can lead to micro and macrovascular problems that increase morbidity and death in those with the disease **[1].**

The International Diabetes Federation (IDF) estimates that 15.2% of Egyptian people have diabetes, however this number may be underestimated. Therefore, DM's risk factors, prevention, treatment, and aftereffects should all be thoroughly investigated. One dangerous and sometimes fatal side effect of diabetes mellitus is diabetic ketoacidosis (DKA). The condition is distinguished by three main symptoms: hyperglycemia, large anion gap metabolic acidosis, and ketonemia. It is also known as insulin insufficiency and is accompanied by an increase in counter-regulatory hormones **[2].**Compared to patients with type 2 diabetes mellitus (T2DM),

patients with type 1 diabetes mellitus (T1DM) have DKA more frequently. There are 4.6 to 8 instances per 1,000 diabetic people on a yearly basis. A mortality rate ranging from 2% to 10% is linked to DKA **[2].**

Leukocytosis and a rise in acute-phase proteins, including C-reactive protein, tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6, are known to be linked to DKA. These proteins are also typically elevated in bacterial infections. Procalcitonin (PCT) levels are helpful indicators of bacterial infections because they rise in bacterial infection and sepsis **[3].** Dehydration and elevated blood lactate levels are the main acute consequences of DKA; high blood lactate levels often indicate hypovolemia and abnormalities of the microcirculation **[4]**. As a result, serum lactate levels and PCT may be essential indicators for the diagnosis of DKA

According to reports, PCT levels in DKA patients can rise sharply even in the absence of an occult focus of infection, and they can also fall as their condition improves—even in the absence of antibiotic medication **[5].**The diagnosis and management of bacterial infections have been suggested for serum PCT, a hormone-free precursor of calcitonin. Because PCT is correlated with both illness severity and bacterial load, it is one of the most important and pertinent markers for the identification of bacterial infections **[6].**T1DM patients experiencing DKA where plasma PCT levels are elevated. Since PCT can be helpful in identifying DKA and hyperosmolar hyperglycemia syndrome (HHSP), elevated PCT levels could be a biomarker of DKA in the absence of infection **[7].**

Infants with DKA who do not have an invasive bacterial infection, PCT may have a significant rise. Acidosis and hyperglycemia severity were linked with PCT levels. This was thought to be connected to either high levels of tumor necrosis factor, or the hyperlactatemia linked to DKA **[8].**In diabetic individuals with DKA, PCT has poor diagnostic use for infections. Serum PCT levels significantly rise in DKA patients without infection and are strongly correlated with elevated ALT, hemodiastase, and serum lactic acid levels **[9].**

**Procalcitonin (PCT) in DKA**

PCT is an additional diagnostic technique that has been suggested for the diagnosis of DKA. It is a precursor to calcitonin with no hormone activity. The 116 amino acids that make up PCT are produced by neuroendocrine cells, which include thyroid gland C cells. PCT is a hormokine that produces hormones, but it can also function as a cytokine in an inflammatory environment. Microbial toxins and cellular and humoral immunological responses via interleukin-6, interleukin 1β, and tumor necrosis factor-α (TNF-α) may cause the production of PCT. Hormokines can be released by parenchymal cells, such as those found in the liver, kidney, muscle, and adipocytes, in septic environments **[10].**A healthy individual does not generate PCT in appreciable quantities. A spike in PCT can be caused by conditions such as extreme hyperglycemia, trauma, shock, infection, and surgery. When there is an extreme kind of systemic inflammation, large amounts of PCT may develop. Within two to twenty-four hours, PCT might rise noticeably in cases of acute systemic inflammation, and this

elevation may last until the patient recovers **[5].**

PCT has a longer half-life (22–26 hours) than CRP and other acute phase reactants, hence measuring it is beneficial. Nevertheless, the suppression of TNF-α production by α-interferon generated by macrophages prevents PCT from increasing in viral infection **[5].**

According to the results of multiple studies, the correct use of antibiotics in cases of sepsis and lower respiratory tract infections can be facilitated by employing PCT as a diagnostic tool. In addition to being useful for tracking bacterial infections, PCT may also be a useful diagnostic tool for differentiating between systematic inflammatory response (SIR) and systemic inflammatory response syndrome (SIRS) **[11].**

Numerous investigations have revealed that DKA causes an increase in cytokine production. Additionally, hyperglycemia increases the production of cytokines. Consequently, DKA may result in an inflammatory milieu, which would increase PCT levels **[7, 12].** A study performed by **Ivaska et al.** observed that children with type 1 diabetes mellitus who experienced DKA had elevated PCT levels. An increased PCT level has also been noted in two more investigations involving persons with type 1 diabetes mellitus who have DKA **[8].Aksu et al**. observed that in individuals experiencing acute hyperglycemic crises, PCT levels decreased once hyperglycemia returned to normal **[13].**

Similar results were observed in another investigation, which found that in DKA participants without any evidence of infection, PCT levels decreased following glycemia stabilization. Cipriano et al. also noted elevated PCT levels in DKA patients who did not have an infection **[12].**

**PCT Levels in Infection**

A hyperglycemic crisis encourages bacterial colonization, which might result in elevated PCT. Endotoxin and inflammatory cytokines induce PCT by promoting the transcription of the CALC-I gene and the production of CT mRNA in the liver, kidneys, lungs, and adipose tissue **(**Error! Reference source not found.**1)[14].**

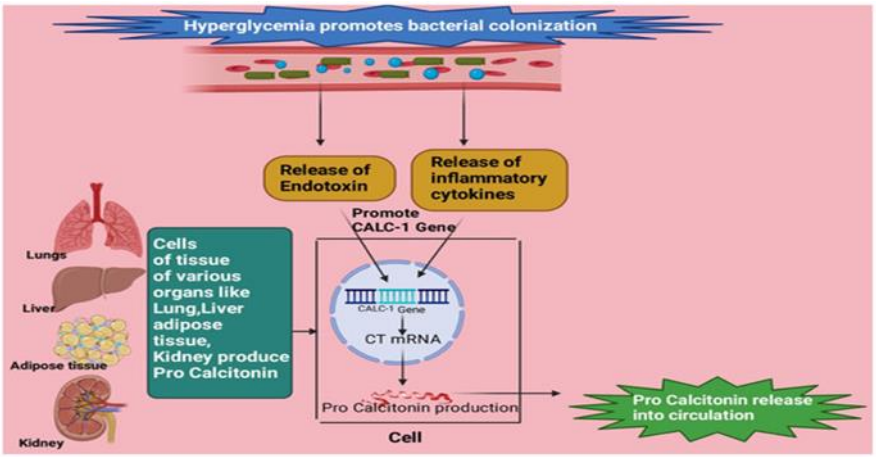


**Figure 1**: Endotoxin and inflammatory cytokines produced due to bacterial colonization in a hyperglycemic environment stimulate the CLAC-1 gene followed by CT mRNA formation, which

causes the production of procalcitonin from tissues of organs like lung, liver, kidney, and adipose tissue [14].

Compared to other laboratory tests, PCT has been shown to be significantly more useful for clinically identifying sepsis and is correlated with the severity of bacterial invasion **[14].**

According to animal research, PCT plays a part in the development of severe sepsis, which makes it useful for prognosis as well. When it comes to predicting mortality risk in critically sick patients who are infected, PCT has proven to be useful. Anti-inflammatory medications, both steroid and non-steroid, do not lower PCT **[15].**

**Hausfater et al.** revealed that the PCT cut-off value for feverish patients admitted to the hospital's emergency room was 0.2 ng/ml, corresponding with a sensitivity and specificity of 0.57 and 0.59 for the diagnosis of bacterial infection **[16].**

A meta-analysis performed by **Wacker et al.** The sensitivity and specificity of PCT were found to be 0.77 and 0.79, respectively, when the clinical usefulness and accuracy of the test for identifying sepsis in critically ill patients were reported **[17].**

A summary of the PCT utilized to guide the sepsis diagnosis was provided by Sager et al. According to their recommendations, patients who were critically unwell and had a PCT value between 0.5 and 1.0 ng/ml were "likely" to have a bacterial infection, and if the value was higher, the patient was "very likely" **[18].**

**PCT in DKA Patients with Infection**

In order to determine the function of PCT in DKA infection, a retrospective investigation was conducted in France. Based on the positive bacterial cultures found in 102 DKA episodes, the study identified cases of proven bacterial infections and designated 20 of them as DKA cases with confirmed bacterial infections **[12].**

PCT levels were considerably greater in those with confirmed bacterial infections than in people without infectious illnesses, according to a univariate study. Proven cases of bacterial infection were associated with PCT levels more than 1.44 ng/mL (OR 1.27 and 95% CI 1.04–1.63) when multiple regression analysis was performed after adjusting for age, ketones, and insulin therapy. The PCT level was 0.52 ng/mlon admission to the hospital and 0.42 ng/mL on the second day for the participants who had no proven bacterial infection **[12].**

When patients were admitted to the hospital, PCT levels had a sensitivity of 0.90 and a specificity of 0.76 for identifying those who had an infection and those who did not. They proposed that a PCT level more than 1.44 ng/mlon the day of hospital admission was a useful indicator of infection in DKA patients **[12].**

An additional investigation conducted in Iraq discovered that individuals with diabetic foot infections had higher PCT levels than the control group, which was made up of people without infectious diseases **[19].**

According to an Indonesian investigation, PCT was found to be higher in infected children with DKA than in DKA-free infected children, with $p < 0.001$ **[14].**

PCT should be used cautiously for diagnosing DKA with infection because it can be elevated by a number of stressful circumstances. PCT modified for hypovolemia may assist achieve a more

accurate result that can help detect DKA with infection in the emergency department, as DKA leads to hypovolemia and dehydration **[12].**

**Procalcitonin-to-Lactate Ratio (PLR) for Diagnosing DKA with Infection**

The aforementioned section raises the possibility that PCT alone may not be adequate for evaluating DKA patients who have infections. Lactate levels may also be limited in their ability to diagnose infectious illnesses in DKA, despite their high levels **[6].** Significant fluid loss occurs in DKA, which may result in reduced tissue perfusion and the production of lactate. The amount of lactate present in DKA can be used to measure the degree of stress and bodily fluid volume. Since the procalcitonin level in this instance is adjusted for the generated stress and hypovolemia in DKA, determining the ratio of procalcitonin to lactate may therefore be of great utility as a diagnostic tool **[20].**

According to a study, people who develop DKA may benefit from early detection of infection, and a PLR threshold level of >0.438 may be taken into consideration **[6].**

According to a Chinese study, people with DKA and infection had a PLR of 0.25 ± 0.11%, substantially higher than the control group ($p < 0.05$). Additionally, PLR has a high 84.46% sensitivity and 87.23% specificity for identifying DKA with infection **[21].**Further research may help establish this factor as a useful tool for identifying DKA with infection in the emergency environment. This novel factor PLR may have a high diagnostic value in both forms of diabetic mellitus **[22].**

**Declaration of interest**

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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