Procalcitonin and White Blood Cells as an Infection Marker in Children with Diabetic Ketoacidosis

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Abstract

Introduction: Diabetic ketoacidosis (DKA), an acute complication of type 1 (insulin dependent) diabetes mellitus (T1DM), can be precipitated by infection. Procalcitonin (PCT) is an accurate marker of bacteremia, sepsis, and inflammation, however white blood cells (WBC) are still often used by clinicians. We aimed to analyze PCT levels and WBC counts in children with DKA.

Methods: A cross-sectional study was conducted in Dr. Soetomo General Hospital, Surabaya, Indonesia, between 2015 and 2019. T1DM and DKA diagnosis was based on the International Society for Pediatric and Adolescent Diabetes. PCT levels and WBC counts were measured in samples from patients with and without DKA, and were compared using the Mann-Whitney test.

Results: A total of 41 samples were included, with 15 samples (36.6%) from children with DKA, and 26 (63.4%) from children without DKA. PCT levels and WBC counts were significantly higher in those with DKA (p<0.001). The receiver operating characteristic curve analysis of WBC was lower than PCT (0.849 vs. 0.982). PCT had a higher sensitivity and spesificity as an infection marker than WBC (93.3 vs. 86.7; 92.3 vs. 88.5, respectively).

Conclusion: PCT is a better infection marker in children with DKA than WBC

Keywords: type 1 diabetes mellitus, diabetic ketoacidosis, white blood cells, procalcitonin, biomarkers

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Prokalsitonin dan Sel Darah Putih sebagai Penanda Infeksi pada Anak dengan Ketoasidosis Diabetikum

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Abstrak

Pendahuluan: Ketoasidosis diabetikum (KAD), suatu komplikasi akut diabetes melitus tipe 1 (DMT1 - tergantung insulin), dapat dipicu oleh infeksi. Procalcitonin (PCT) adalah penanda bakteremia, sepsis, dan peradangan yang akurat, namun sel darah putih (SDP) masih sering digunakan oleh klinisi. Studi kami bertujuan untuk menganalisis kadar PCT dan jumlah SDP pada anak-anak dengan KAD.

Metode: Studi potong lintang dilakukan di RSUD Dr. Soetomo, Surabaya, Indonesia, antara tahun 2015 dan 2019. Diagnosis DMT1 dan KAD didasarkan pada International Society for Pediatric and Adolescent Diabetes. Kadar PCT dan jumlah SDP diukur dalam sampel dari pasien dengan dan tanpa KAD, dan dibandingkan menggunakan uji Mann-Whitney.

Hasil: Sebanyak 41 sampel dimasukkan dalam penelitian, di antaranya 15 sampel (36,6%) dari anak-anak dengan KAD, dan 26 (63,4%) dari anak-anak tanpa KAD. Kadar PCT dan jumlah SDP secara signifikan lebih tinggi pada anak-anak dengan KAD (p <0.001). Analisis kurva karakteristik operasi penerima SDP lebih rendah daripada PCT (0,849 vs 0,982). PCT memiliki sensitivitas dan spesifisitas yang lebih tinggi sebagai penanda infeksi dibandingkan SDP (masing-masing 93,3 vs 86,7; 92,3 vs 88,5).

Kesimpulan: PCT merupakan penanda infeksi yang lebih baik pada anak dengan KAD dibandingkan SDP.

Kata kunci: diabetes melitus tipe 1, diabetik ketoasidosis, sel darah putih, prokalsitonin, biomarker

Introduction

Diabetes mellitus (DM) is a chronic systemic disease due to insulin secretion deficiency, characterized by hyperglycemia.[1] Diabetic ketoacidosis (DKA) is a preventable, but life-threatening acute complication of DM, that occurs more often in children with type 1 DM (T1DM) than in those with type 2 DM (T2DM). The triad of features of DKA are hyperglycemia, metabolic acidosis, and ketonemia.[2,3] In 60% of T1DM cases, the first clinical manifestation is DKA.[4,5] Infections predispose to DKA and increase mortality rate.[6] Several DKA patients with infections have mild or no symptoms and signs. Early diagnosis of bacterial infection in DKA guides antibiotic treatment to reduce antibiotic resistance, and improves outcome.[7] Procalcitonin (PCT) has been known as a marker of bacterial infection, sepsis, and non-bacterial inflammation since 1993. PCT is a peptide consisting of 116 amino acids.[8,9] The synthesis of PCT is triggered by bacterial endotoxins and inflammatory cytokines, when their levels increase in blood (>0.5 ng/mL).[8] However, white blood cell (WBC) count is an examination to aid diagnosis and prognosis of infectious patients, and indicates the presence of inflammatory processes in clinical practice.[10]

PELOD-2 score and PCT values were used to be a predictor of mortality in Indonesian children with sepsis.[11] To date, studies of PCT levels and WBC counts as infection markers in Indonesian children with T1DM (with or without DKA) are not available. The purpose of our study; therefore, was to compare PCT levels and WBC counts in such children.

Methods

This study was a cross-sectional study, conducted in 2015-2019, and approved by the Health Research Ethics Committees (605/Panke.KKE/XI/2015) of Dr. Soetomo Gen-

eral Hospital, Surabaya, Indonesia. The patients included in the study were children with T1DM children, aged less than 18 years, who attended the pediatric endocrinology outpatient clinic, or who came to the emergency room without congenital disease. Parents signed informed consent on behalf of all children. We grouped the participants into group 1 (DKA) and group 2 (non-DKA). Diagnostic criteria for T1DM and DKA were according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) guideline.[3]

Data from medical records was extracted, including gender, age, weight, height, body mass index (BMI), location of infection, and body temperature. PCT levels were measured and were classified as normal (<0.5 ng/mL), or abnormal (≥0.5 ng/mL). WBC counts were classified as normal (4x109/L - 15x109/L), or abnormal (<4x109/L or >15x109/L).

Data were analyzed with SPSS 17.0, using the Mann-Whitney test to compare both PCT levels and WBC counts patients with and without DKA. The Youden index from the receiver operating characteristic (ROC) curve analysis was used to determine the cutoff value of PCT levels and WBC count.[12]

Results

A total of 41 samples were included, 15 samples (36.6%) from the DKA group, and 26 (63.4%) from the non-DKA group. Of the 41 subjects, there were 17 boys (41.5%) and 24 girls (58.5%) with the mean of age 12.6±3.4 years and body mass index (BMI) 16.8±3.9 kg/m2. About 9 of 41 children had a focus of infection, which the most frequent site of infection was urogenital system (14.6%). Thirteen subjects (31.7%) had a fever with the temperature of body ≥37.5°C. The basic characteristics of each group are shown in Table 1.

Table 2. Comparison of Procalcitonin (PCT) Levels and White Blood Cell (WBC) Counts between Two Groups

Parameter	Group one (DKA)	Group 2 (non-DKA)	p
PCT levels (ng/mL)	3.32 (0.47-127.75)	0.04 (0.02-2.70)	0.000*
WBC counts (x10⁹/L)	16.5 (5.01-33.93)	8.05 (5.45-22.27)	0.000*

*The results of Mann-Whitney test between two groups are differences significantly (p<0.05)

DKA diabetic ketoacidosis; PCT procalcitonin; WBC white blood cell

Table 1. Baseline Characteristics of Studied Subject

Characteristics	Group one (DKA)	Group two (non-DKA)
Gender (n %)		
Boy	7 (46.7)	10 (38.5)
Girl	8 (53.3)	16 (61.5)
Age (year)*	12.7±3.3	12.5±3.4
Weight (kg)†	36.0 (18.5-71.0)	32.0 (12.0-51.0)
Height (cm)*	144.0±9.9	137.4±18.6
BMI (kg/m2)*	17.6±3.7	15.9±4.2
Focal infection (n %)		
Gastrointestinal disorder	1 (6.7)	0 (0)
Urogenital disorder	4 (26.7)	2 (7.7)
Integumentary disorder	1 (6.7)	0 (0)
Dental and oral disorder	1 (6.7)	0 (0)
None	8 (53.2)	24 (92.3)
Body temperature (n %)		
≥37.5°C	6 (40.0)	1 (3.9)
<37.5°C	9 (60.0)	25 (96.1)
PCT levels (n %)		
<0,5 ng/mL	1 (6.7)	23 (88.5)
≥0,5 ng/mL	14 (93.3)	3 (11.5)
WBC counts (n %)		
4x10⁹/L – 15x10⁹/L	8 (53.3)	23 (88.5)
<4x10⁹/L or >15x10⁹/L	7 (46.7)	3 (11.5)

DKA diabetic ketoacidosis; BMI body mass index; PCT procalcitonin; WBC white blood cell; SD Standard Deviation.

The median of PCT levels and WBC counts in each group are demonstrated in Table 2. At the time of study, children with DKA have increased PCT levels and WBC counts compared to the children without DKA (p<0.05).

The PCT levels showed a higher area under the receiver operating characteristic (ROC) curve (AUC) values as an infection marker than the WBC counts (AUC: 0.982 vs 0.849). The sensitivy and specificity of PCT were higher than WBC, that can be used as an infection predictor (Table 3, Figure 1).

Discussion

The median PCT levels were 80 times higher in the DKA group than the non-DKA group in our study (3.32 vs. 0.04 ng/mL, p<0.001), which was similar to a recent study (11.74 vs. 0.06 ng/mL, p=0.014).[13] PCT levels are positively associated with metabolic disorders,

Table 3. The Area Under the Curve (AUC), Cutoff Value, Sensitivity, and Specificity of Procalcitonin (PCT) and White Blood Cell Count (WBC) in Receiver Operating Curve Analysis

Parameter	AUC	p	Cutoff value	Sensitivity (%)	Specificity (%)
PCT levels (ng/mL)	0.982	0.000	0.63	93.3	92.3
WBC counts (x10⁹/L)	0.849	0.000	12.8	86.7	88.5
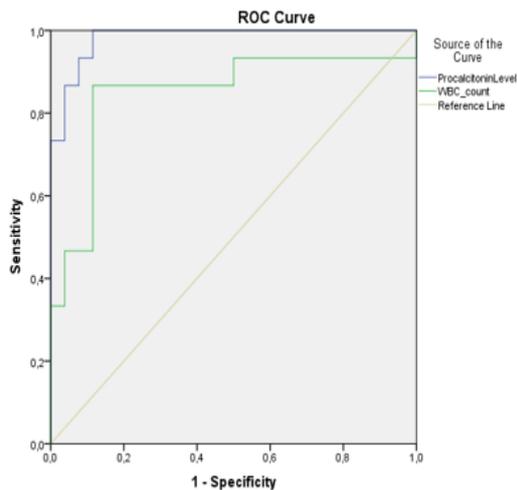
Figure 1. The Receiver Operating Characteristic (ROC) Curve Analysis of Procalcitonin (PCT) and White Blood Cell (WBC) Count

bacteremia, and sepsis. Hyperglycemic crisis will increase bacterial colonization, so PCT levels in the blood will increase.[8,14]

PCT release is induced by infection in two ways: firstly, a direct pathway induced by lipopolysaccharide (LPS) or bacterial endotoxin; and secondly, an indirect pathway induced by inflammatory cytokines (e.g interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α). This process will induce CALC-I gene transcription and CT mRNA expression in the cells of some tissues (lung, liver, kidney, adipose tissue) to produce PCT.[8,9] An Iraqi study showed significantly higher PCT levels in a group of patients with diabetic foot disease with infections when compared with a control group, a group with DM, or a group with diabetic foot disease but no infections.[15]

In our study, WBC counts were significantly higher in the DKA group than the non-DKA group. This was similar to a study of Chinese children, where WBC counts increased in children with DKA, with significantly higher WBC counts in a DKA group compared with a non-DKA group, reflecting the severity of the DKA.[16] The WBC count reflects both the presence of acute infection, and hyperglycemia crisis, with significantly higher WBC counts in patients with both DKA and infec-

tion. DKA occurs as an acute complication of poor metabolic control, or as an early manifestation of T1DM. The severity of DKA is related to the arterial pH value, and high H+ values increase WBC production.[17] Hyperketonemia increases systemic inflammatory activity processes and oxidative stress. It will increase various cytokines, such as IL-6, IL-8, IL-10, so WBC production will increase too.[18]

ROC curve analysis revealed that PCT (area under the curve (AUC) 0.982, sensitivity 93.3%, specificity 92.3%) was better than WBC count (AUC 0.849, sensitivity 86.7%, specificity 88.5%) as a marker of infection in DKA. Studies in Spain showed that the AUC of PCT (0.79) had the highest prognostic value in septic shock, when compared with C-reactive protein (CRP) (0.64) and WBC count (0.60). The sensitivity and specificity of PCT were 53% and 94.7%, respectively.[19] Examination of single PCT levels, or PCT combined with WBC, showed the best diagnostic and prognostic power as a marker of infection and sepsis in an ROC analysis.[10]

The appearance of PCT as a marker of inflammation or bacterial infections is earlier than a rise in WBC count or CRP. PCT can be detected in blood 2 to 4 hours after stimulation, with a maximum in 6 to 24 hours. CRP levels begin to increase in 12 to 24 hours after inflammation, and reach a maximum after 48 hours. Procalcitonin is a stable marker, not influenced by neutropenia, immune deficiency conditions, or NSAID drug use.[8,19] PCT is also superior to CRP, IL-6, or serum amyloid A as a marker of bacteremia in patients with symptoms and signs such as fever.[20]

Conclusion

We conclude that PCT levels and WBC counts were significantly higher in children with DKA than in those without DKA. In addition, PCT has better sensitivity and specificity for diagnosis of infection than WBC counts.

Acknowledgments

Conflict of Interest

The authors declare no conflicts of interest.

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