Efficacy of Quantitative Capillary Beta-Hydroxybutyrate Measurement in the Diagnosis of Diabetic Ketoacidosis: A Comparison to Quantitative Serum Ketone Measurement by Nitroprusside Reaction

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Objective: *To examine the efficacy of using capillary beta-hydroxy butyrate (β-OHB) levels in comparison with serum ketone levels in distinguishing diabetic ketoacidosis (DKA) from non-DKA states in patients who had severe hyperglycemia and to determine a cut-off level of capillary β-OHB that is best for the diagnosis of DKA.*
Material and Method: *Diabetic patients who presented with capillary blood glucose of ≥400 mg/dL were studied. Capillary β-OHB levels were measured by using a ketometer (OptiumXceed™) at the same time as blood sample collection for biochemical tests and serum ketone measurement using nitroprusside reaction. The American Diabetes Association (ADA) criteria 2012 were used as the gold standard in the diagnosed of DKA.*
Results: *There were 13 cases (34.2%) with DKA (DKA group) and 25 cases (65.8%) without DKA (non-DKA group). There was no difference in plasma glucose levels between both groups. (DKA group = 714.2±367.6 mg/dl vs. non-DKA group = 589.4±220.2 mg/dl). The DKA group had significantly higher serum ketone (7.2±3.6 vs. 0.28±0.05 mmol/L, p<0.001) and capillary β-OHB levels (4.3±0.7 vs. 1.0±1.1 mmol/L, p<0.001) than did the non-DKA group. Capillary β-OHB levels significantly correlated to serum anion gap values (r = 0.828, p<0.001), serum bicarbonate (r = 0.715, p<0.001), and ketone (r = 0.72, p<0.001) levels. ROC analyses showed that a capillary β-OHB level of >3.1 mmol/L was the best cut-off level for the diagnosis of DKA, and yielded a sensitivity of 100% (95% CI = 75.1-100) with a specificity of 96% (95% CI = 79.6-99.3).*
Conclusion: *Using a cut-off capillary β-OHB level of >3.1 mmol/L is highly effective in the diagnosis of DKA in patients who presented with hyperglycemia. Quantitative measurement of capillary β-OHB levels using a ketometer offers an immediate result that is useful for a reliable triage of screening for DKA in patients presented with severe hyperglycemia.*

Keywords: *Triage, Diabetic ketoacidosis, Ketone, Beta-hydroxybutyrate*

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Ketoacidosis is a serious complication of diabetes that needs prompt diagnosis and treatment. The diagnosis of diabetic ketoacidosis (DKA) is generally based on the presence of severe hyperglycemia in accompanying with wide-anion gap metabolic acidosis resulting from accumulation of ketone bodies including acetoacetate (AcAc) and beta-hydroxybutyrate (β-OHB) which possess acid property and acetone that does not possess acid property[1-3]. The β-OHB is generated by reduction of AcAc in mitochondria whereas acetone is developed by decarboxylation of AcAc[4-7]. During the development of DKA, the ratio of serum β-OHB to AcAc levels usually rises from 1: 1 to as high as 10: 1[8,9]. In clinical practice, the diagnosis of ketone accumulation is usually based on quantitative and semi-quantitative measurements of AcAc and acetone in blood or urine made by using a nitroprusside reaction that does not detect β-OHB. Accordingly, the diagnosis of DKA through the conventional use of the nitroprusside reaction may be missed or delayed in some situations

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in which β-OHB is produced much more than AcAc, such as in hypotension and hypoxemia[10]. Currently, β-OHB can be measured instantly by using a capillary blood ketone meter and has been shown to be useful in the rapid diagnosis and treatment of DKA[11-22] that resulting in reduction of complications, morbidity and mortality, as well as total hospital cost[11,23]. The objectives of the present study were to examine the efficacy of using capillary β-OHB level in the diagnosis of DKA in diabetic patients who presented at the emergency room with severe hyperglycemia and to determine the cut-off level of capillary β-OHB that is best for the diagnosis of DKA.

Material and Method

Patients

Type 1 and type 2 diabetic patients who presented at the Emergency Department of Siriraj Hospital with capillary blood glucose levels of ≥400 mg/dL were studied. Before initiating the treatment, standard laboratory tests for the diagnosis and evaluation of DKA were performed in all patients including measurements of plasma glucose, serum electrolytes, blood urea nitrogen (BUN), creatinine, serum and urine ketones. Simultaneous measurement of capillary blood β-OHB was also performed in all patients. The results of capillary β-OHB measurement were not provided to the attending physicians and were not used for determining the diagnosis and treatment of patients' hyperglycemic states. Arterial blood gas analyses were performed in selected patients who had mixed acid-base disturbances. The diagnosis of DKA was based on the consensus statement of the American Diabetes Association (ADA) 2009[24] including 1) plasma glucose level >250 mg/dL, 2) metabolic acidosis as defined by arterial pH <7.3 and/or serum bicarbonate level <18 mmol/L, and 3) wide serum anion gap of >10 mmol/L in accompanying with the presence of ketonemia/ketonuria. Patients who did not meet the criteria for diagnosis of DKA were classified as non-DKA. The diagnosis of hyperglycemic hyperosmolar non-ketotic state (HHNS) was based on the ADA's consensus statement 2009[24] including 1) plasma glucose levels >600 mg/dL, 2) absence of ketoacidosis or serum bicarbonate level >15 mmol/L with negative or small amount of blood ketone, and 3) effective serum osmolarity >320 mOsm/L. Type 1 and type 2 diabetes were defined according to the diagnosis reported in the patients' medical records based on clinical features with or without results of serum anti-glutamic acid decarboxylase antibody. This study was approved by Siriraj Institutional Review Board.

Biochemical methods

Capillary blood glucose was measured by point of care testing system using glucose strips and glucometers for which the methods and results were standardized and approved by ISO 22870. Plasma glucose, serum electrolytes, BUN, and creatinine were measured by using an autoanalyzer (Hitachi 917, Japan) with the methods and results standardized and approved by ISO 15189. Serum ketone was quantitatively measured by nitroprusside reaction. Capillary blood β-OHB was quantitatively measured by using strips and a ketone meter (OptiumXceed™, Abbott, USA) which were able to detect β-OHB concentration within the range of 0.0-6.0 mmol/L from a single 5 μL of capillary blood sample at 10 seconds of reaction. Effective serum osmolarity was calculated by the formula: 2 [Na^+ (mmol/L) + K^+ (mmol/L)] + plasma glucose (mg/dL)/18. Serum anion gap was calculated by the formula: Na^+-[Cl^- + HCO_3^-].

Statistical analyses

Data were expressed as percents (%) or mean ± standard deviation (SD) as appropriate. The Fisher exact and Mann Whitney U test were used to compare the categorical variables and continuous variables data including baseline patients' characteristics and other metabolic parameters between DKA and non-DKA groups respectively. Pearson correlation and simple linear regression model were used to determine association between capillary β-OHB and serum anion gap, serum bicarbonate and serum ketone. A p-value <0.05 was considered statistically significant. Kolmogorov-Smirnov test was used to determine the distribution of the data. Receiver operating characteristic curve (ROC) analyses were performed to determine a cut-off level of capillary β-OHB that would be best for diagnosis of DKA using the ADA criteria as the gold standard tool for the diagnosis of DKA.

Results

There were 38 patients recruited in the study. Using the ADA criteria for the diagnosis of DKA[24], the patients were divided into 2 groups: DKA group (13 cases, 34.2%) and non-DKA group (25 cases, 65.8%). All of the patients in non-DKA group had type 2 diabetes. Table 1 shows characteristics and metabolic parameters of patients in DKA and non-DKA groups. There was no significant difference in age, gender, plasma glucose, serum BUN, creatinine, chloride levels,

Table 1. Patients' characteristics and metabolic parameters

	DKA* group (13 cases)	Non-DKA group (25 cases)	p-value
Female: male (cases)	10: 3	10: 15	0.492
Age (years)	47.8±22.2	55.7±18.0	0.247
Type 1 DM (cases (%))	4 (30.8)	0 (0)	0.017
Serum BUN (mg/dL)	31.1±17.2	42.9±28.9	0.288
Serum creatinine (mg/dL)	1.6±0.7	2.3±2.1	0.527
Blood glucose (mg/dL)	714.2±367.6	589.4±220.2	0.332
Serum Na^+ (mmol/L)	128.0±7.3	131.0±9.9	<0.001
Serum K^+ (mmol/L)	5.3±1.2	4.3±1.0	0.007
Serum Cl^- (mmol/L)	89.8±7.8	93.3±11.0	0.223
Serum HCO_3 (mmol/L)	7.2±5.5	21.6±5.1	<0.001
Serum anion Gap (mmol/L)	31.0±6.7	16.0±5.3	<0.001
Effective serum osmolarity (mOsmol/L)	295.7±15.0	294.7±19.2	0.286
Serum ketone (mmol/L)	7.2±3.6	0.28±0.05	<0.001
Capillary β-OHB (mmol/L)	4.3±0.7	1.0±1.1	<0.001

Data expressed as mean ± SD, A p-value of <0.05 was statistically significant
* DKA was diagnosed according to the ADA criteria

Table 2. Capillary β-OHB, serum and urine ketone levels in DKA and non-DKA groups

DKA* group (13 cases)				Non-DKA group (25 cases)			
Case number	Serum β-OHB	Serum ketone	Urine ketone	Case number	Serum β-OHB	Serum ketone	Urine ketone
Case 1	4.6	8.0	Large	Case 14	0.4	0.0	Negative
Case 2	4.7	8.0	Large	Case 15	2.7	0.5	Negative
Case 3	4.4	3.0	Large	Case 16	0.2	0.0	Negative
Case 4	4.2	8.0	Large	Case 17	4.3**	1.5	Moderate
Case 5	3.5	16.0	Large	Case 18	0.9	0.0	Negative
Case 6	4.6	8.0	Moderate	Case 19	1.3	0.0	Negative
Case 7	4.7	4.0	Large	Case 20	3.1	0.5	Large
Case 8	4.7	6.0	Large	Case 21	0.5	0.5	Large
Case 9	3.7	8.0	Moderate	Case 22	0.7	0.0	Negative
Case 10	3.4	8.0	Large	Case 23	1.3	0.0	Small
Case 11	3.5	0.5	Large	Case 24	0.2	0.0	Negative
Case 12	5.9	8.0	Large	Case 25	0.3	0.0	Negative
Case 13	4.1	8.0	Large	Case 26	1.8	0.0	Moderate
				Case 27	0.4	0.0	Negative
				Case 28	1.2	1.5	Moderate
				Case 29	0.1	0.5	Negative
				Case 30	0.1**	0.0	Negative
				Case 31	0.0	0.0	Negative
				Case 32	2.2	1.5	Moderate
				Case 33	0.4	0.5	Negative
				Case 34	0.0	0.0	Negative
				Case 35	2.1	0.5	Small
				Case 36	0.1	0.0	Negative
				Case 37	0.2	0.0	Moderate
				Case 38	0.4	0.0	Negative

* DKA was diagnosed according to the ADA criteria
** Patients who had hyperglycemic hyperosmolar non ketotic state

and effective serum osmolarity between two groups. The DKA group had significantly lower serum sodium and bicarbonate levels and higher serum potassium levels and anion gap values than did the non-DKA group. The DKA group had significantly higher serum ketone (7.2±3.6 vs. 0.28±0.05 mmol/L, p<0.001) and capillary β-OHB levels (4.3±0.7 vs. 1.0±1.1 mmol/L, p<0.001) than did the non-DKA group. Table 2 shows results of serum ketone and capillary β-OHB levels of individual patients in DKA and non-DKA groups. In the DKA group, all except 2 cases (case numbers 3 and 11) had serum ketone levels of ≥4 mmol/L. In the non-DKA group, there were 2 cases (case numbers 17 and 30) had HHNS, 16 cases had negative serum ketone, 9 cases (case numbers 15, 17, 20, 21, 28, 29, 32, 33, and 35) had positive serum ketone at low levels of 0.5-1.5 mmol/L, 16 cases had negative or low capillary β-OHB levels of <1 mmol/L, and 9 cases (case numbers 15, 17, 19, 20, 23, 26, 28, 32, and 35) had significant capillary β-OHB levels of 1-4.3 mmol/L. None of the non-DKA group had metabolic acidosis as determined by serum bicarbonate levels and/or arterial pH. Kolmogorov-Smirnov test was used to determine the distribution of the data. Capillary β-OHB levels significantly correlated to serum anion gap values (r = 0.828, p<0.001), serum bicarbonate (r = 0.715, p<0.001), and ketone (r = 0.72, p<0.001) levels (Fig. 1).

ROC analyses were performed by using different levels of capillary β-OHB as cut-off points for diagnosis of DKA and the ADA criteria as the gold standard tool. Capillary β-OHB level of >3.1 mmol/L was the best cut-off point for diagnosis of DKA which yielded a sensitivity of 100% (95% CI = 75.1-100), a specificity of 96% (95% CI = 79.6-99.3), a positive likelihood ratio of 25, a negative likelihood ratio of 0, and an area under curve of 0.982 (Fig. 2).

Discussion

The present study was aimed to examine the efficacy of using capillary β-OHB levels measured by a ketometer in comparison with that of using serum ketone levels measured by nitroprusside reaction in

Table 3. Efficacy of using different capillary β-OHB levels as cut-off points in the diagnosis of DKA

β-OHB	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
≥0	100.00	75.1-100.0	0.00	0.0-13.8	1.00	0.00
>0	100.00	75.1-100.0	8.00	1.2-26.1	1.09	0.00
>0.1	100.00	75.1-100.0	20.00	6.9-40.7	1.25	0.00
>0.2	100.00	75.1-100.0	32.00	15.0-53.5	1.47	0.00
>0.3	100.00	75.1-100.0	36.00	18.0-57.5	1.56	0.00
>0.4	100.00	75.1-100.0	52.00	31.3-72.2	2.08	0.00
>0.5	100.00	75.1-100.0	56.00	34.9-75.6	2.27	0.00
>0.7	100.00	75.1-100.0	60.00	38.7-78.8	2.50	0.00
>0.9	100.00	75.1-100.0	64.00	42.5-82.0	2.78	0.00
>1.2	100.00	75.1-100.0	68.00	46.5-85.0	3.13	0.00
>1.3	100.00	75.1-100.0	76.00	54.9-90.6	4.17	0.00
>1.8	100.00	75.1-100.0	80.00	59.3-93.1	5.00	0.00
>2.1	100.00	75.1-100.0	84.00	63.9-95.4	6.25	0.00
>2.2	100.00	75.1-100.0	88.00	68.8-97.3	8.33	0.00
>2.7	100.00	75.1-100.0	92.00	73.9-98.8	12.50	0.00
>3.1 *	100.00	75.1-100.0	96.00	79.6-99.3	25.00	0.00
>3.4	92.31	63.9-98.7	96.00	79.6-99.3	23.08	0.08
>3.5	76.92	46.2-94.7	96.00	79.6-99.3	19.23	0.24
>3.7	69.23	38.6-90.7	96.00	79.6-99.3	17.31	0.32
>4.1	61.54	31.6-86.0	96.00	79.6-99.3	15.38	0.40
>4.2	53.85	25.2-80.7	96.00	79.6-99.3	13.46	0.48
>4.3	53.85	25.2-80.7	100.00	86.2-100.0		0.46
>4.4	46.15	19.3-74.8	100.00	86.2-100.0		0.54
>4.6	30.77	9.3-61.4	100.00	86.2-100.0		0.69
>4.7	7.69	1.3-36.1	100.00	86.2-100.0		0.92
>5.9	0.00	0.0-24.9	100.00	86.2-100.0		1.00

* The best cut-off level of capillary β-OHB for distinguishing DKA from HHNS and simple hyperglycemia

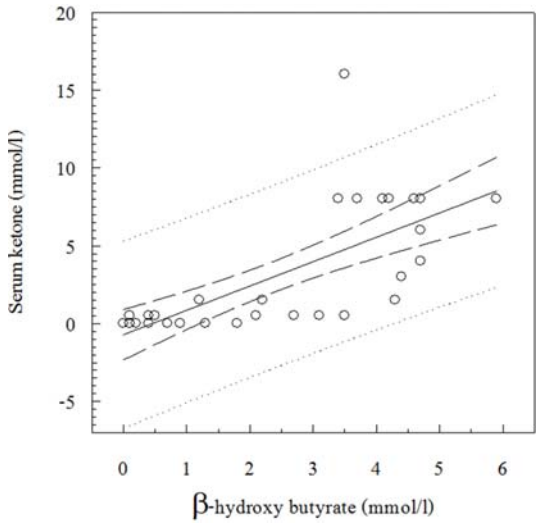

Fig. 1 Linear correlation between capillary β-OHB and serum ketone levels. The figure showed that both factors had linear correlation with a correlation coefficient of 0.720 and R^2 of 0.518 ($p<0.001$). The correlation could be expressed as an equation: serum ketone level = -0.702 + (1.563 * capillary β-OHB level). An open circle (O) represents a serum ketone level of an individual patient. Solid line (—) represents serum ketone levels from equation. Broken line (---) represents serum ketone for 95% CI. Dot line (····) represents range of serum ketone levels.

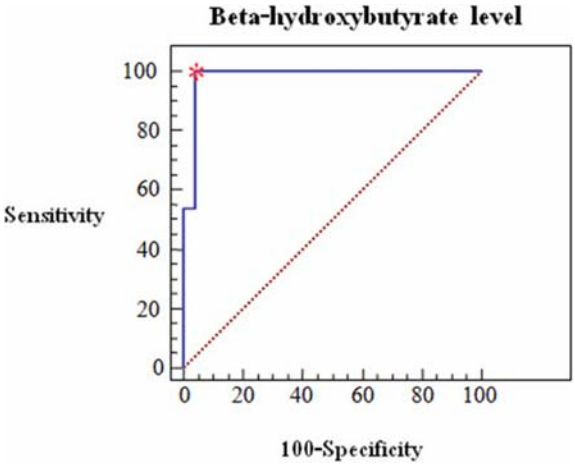

Fig. 2 An ROC curve of using different capillary β-OHB levels as cut-off points in the diagnosis of DKA. The best cut-off level of capillary β-OHB was >3.1 mmol/L.

distinguishing DKA from non-DKA states in patients who had severe hyperglycemia and to determine a cut-off level of capillary β-OHB that is best for the diagnosis of DKA. The results showed that a capillary β-OHB level of 3.1 mmol/L is the best cut-off value for the diagnosis and prediction of DKA in hyperglycemic patients with a high sensitivity of 100%, specificity of 96%, positive likelihood ratio of 25, and negative likelihood ratio of 0, as shown in Table 3 and Fig. 2. The cut-off level of 3.1 mmol/L was comparable to that reported in other studies[12-16]. Harris et al have shown that hyperglycemic patients with capillary β-OHB levels of >3 mmol/L had high risk of DKA whereas those with capillary β-OHB levels of <1 mmol/L had no risk of DKA[12]. A study in type 1 diabetic patients by Wallace et al with poor glycemic control (20 cases) and DKA diagnosed according to the same criteria as the present study (14 cases) showed that capillary β-OHB measurement is useful in adjunct to blood glucose monitoring in distinguishing between ketosis and simple hyperglycemia. The patients with capillary β-OHB levels of >3 mmol/L required intensive evaluation for the presence of DKA and those with capillary β-OHB levels of <1 mmol/L were not associated with DKA[13]. A retrospective study in uncontrolled diabetic patients by Sheikh-Ali et al have reported that serum β-OHB levels of >3.0 mmol/L in children and >3.8 mmol/L in adults can be used to diagnose DKA more effectively than using serum bicarbonate levels[18]. A large study by Voulgari et al of insulin-treated type 2 diabetic patients, who presented at the emergency room with hyperglycemia with DKA (50 cases) and without DKA (400 cases), has shown that the use of capillary β-OHB levels of >3.0 mmol/L had the highest performance in distinguishing DKA from simple hyperglycemia with a sensitivity of 99.87%, specificity of 92.89%, and positive predictive value of 92.89%[14], comparable to those observed in the present study. Another large study in hyperglycemic patients with DKA (54 cases) and without DKA (462 cases) showed that the use of a capillary β-OHB level of >1.5 mmol/L as the cut-off level suggested by manufacturer had a sensitivity of 98% and a specificity of 79%[15] which are lower than those of ours and Voulgari's studies that used capillary β-OHB level of >3.0 mmol/L as cut-off level. The use of capillary β-OHB levels of >3 mmol/L is not only effective in distinguishing hyperglycemia with DKA from without DKA, but also has been demonstrated to be as effective as using serum ketone levels measured by nitroprusside reaction in distinguishing DKA from other causes of metabolic acidosis in hyperglycemic patients[16].

The comparable levels of mean plasma glucose in both DKA and non-DKA groups observed

in the present study suggested that only high plasma glucose level is not helpful in the diagnosis of DKA. The diagnosis of DKA hence needs additional parameters, especially serum bicarbonate levels, to determine the presence of metabolic acidosis and blood or urine ketone levels conventionally, quantitatively or semi-quantitatively as measured by nitroprusside reaction; these measurement methods are time consuming and require laboratory procedures. As quantitative capillary β-OHB measurement can be performed instantly by using a ketometer which yields the results within 10 seconds and the capillary β-OHB level has been shown to diagnose reliably or predict DKA[12-16,18-22,25], it has been, therefore, recommended to be used in the triage of screening for DKA at the emergency room[16,18,20-21,26] or in addition to self blood glucose monitoring, for the prediction of developing DKA, at home in diabetic patients with hyperglycemia[13,27]. This is useful in the rapid diagnosis and treatment of DKA that will result in reduction of complications, morbidity and mortality, and total hospital cost[11,23].

Conclusion

Using a cut-off capillary β-OHB level of >3.1 mmol/L is highly effective in the diagnosis of DKA in patients who presented with hyperglycemia. Quantitative measurement of capillary β-OHB levels using a ketometer offers an immediate result, which is useful for a reliable triage of screening for DKA in patients presented with severe hyperglycemia.

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Potential conflicts of interest

None.

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ประสิทธิภาพในการใช้ระดับบีตา-ฮัยดร็อกซีบิวทีเรทซึ่งตรวจวัดเชิงปริมาณจากเลือดแคปิลลารีที่ปลายนิ้วมือในการวินิจฉัยภาวะคีโตอะซิโดสิสจากโรคเบาหวานโดยเปรียบเทียบกับการใช้ระดับซีรัมคีโตนซึ่งตรวจวัดเชิงปริมาณโดยปฏิกริยาไนโตรปรัสไซด์

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วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพในการใช้ระดับบีตา-ฮัยดร็อกซีบิวทีเรท (β-OHB) ซึ่งตรวจวัดเชิงปริมาณ จากเลือดแคปิลลารีในการวินิจฉัยภาวะคีโตอะซิโดสิสจากโรคเบาหวาน (DKA) และกำหนดระดับ β-OHB ซึ่งสามารถวินิจฉัยภาวะ DKA ได้ดีที่สุดในผู้ป่วยเบาหวานที่มีระดับกลูโคสสูงในเลือด

วัสดุและวิธีการ: ผู้ป่วยเบาหวานที่มีระดับกลูโคสในเลือด >400 มิลลิกรัม/เดซิลิตร (มก./ดล.) จะได้รับการเจาะเลือดแคปิลลารีเพื่อตรวจวัดระดับ β-OHB โดยใช้คีโตมิเตอร์ (OptiumXceed™) พร้อมกับการเก็บตัวอย่างเลือดดำเพื่อตรวจวัดระดับชีวเคมีเลือดชนิดต่างๆ โดยวิธีมาตรฐานและวัดระดับซีรัมคีโตนโดยปฏิกริยาไนโตรปรัสไซด์

ผลการศึกษา: ผู้ป่วยเบาหวานที่มีระดับกลูโคสในเลือด >400 มก./ดล. เข้าร่วมการวิจัย 38 ราย โดยที่ 13 ราย มีภาวะ DKA (กลุ่ม DKA) และ 25 ราย ไม่มี DKA (กลุ่ม non-DKA) ไม่พบว่ามีความแตกต่างกันของระดับพลาสมากลูโคสของผู้ป่วยทั้งสองกลุ่ม (714.2±367.6 มก./ดล. ในกลุ่ม DKA vs. 589.4±220.2 มก./ดล. ในกลุ่ม non-DKA) กลุ่ม DKA มีระดับซีรัมคีโตนและระดับ β-OHB สูงกว่ากลุ่ม non-DKA อย่างมีนัยสำคัญ (ซีรัมคีโตน 7.2±3.6 vs. 0.28±0.05 mmol/L, p<0.001 และ ระดับ β-OHB 4.3±0.7 vs. 1.0±1.1 mmol/L, p<0.001 ในกลุ่ม DKA vs. กลุ่ม non-DKA ตามลำดับ) ระดับ β-OHB มีความสัมพันธ์อย่างมีนัยสำคัญกับค่า anion gap (r = 0.828, p<0.001), ระดับซีรัมไบคาร์บอเนท (r = 0.715, p<0.001) และระดับซีรัมคีโตน (r = 0.72, p<0.001) การวิเคราะห์ ROC curve พบว่าระดับ β-OHB ที่สูงกว่า 3.1 มิลลิโมล/ลิตร จะเป็นค่าที่เหมาะสมที่สุดในการใช้เป็นเกณฑ์ ในการวินิจฉัยภาวะ DKA โดยมีค่าความไวร้อยละ 100 (95% CI = 75.1-100) และความจำเพาะร้อยละ 96 (95% CI = 79.6-99.3)

สรุป: การใช้ระดับ β-OHB ที่สูงกว่า 3.1 มิลลิโมล/ลิตร สำหรับการวินิจฉัยภาวะ DKA ในผู้ป่วยเบาหวานที่มีระดับกลูโคสในเลือด >400 มก./ดล. จะช่วยให้สามารถวินิจฉัยภาวะ DKA ได้อย่างรวดเร็ว และมีประสิทธิภาพสูงซึ่งช่วยให้สามารถรักษาผู้ป่วยได้อย่างรวดเร็ว