Comparing Finger-stick β-Hydroxybutyrate with Dipstick Urine Tests in the Detection of Ketone Bodies

Keton Cisimciklerinin Tespitinde Parmakucu β-Hidroksibütirat ile İdrar Daldırma Testlerinin Karşılaştırılması

Baris KURU,[1] Mustafa SEVER,[1] Ersin AKSAY,[1] Tarik DOGAN,[1] Necmiye YALCIN,[1] Ezgi SEKER EREN,[1] Fusun USTUNER[2]

[1]Department of Emergency Medicine, Tepecik Training and Research Hospital, Izmir;
[2]Department of Biochemistry, Tepecik Training and Research Hospital, Izmir

SUMMARY

Objectives

Blood ketone (beta-hydroxybutyrate) measurements are suggested instead of urine ketone (acetoacetate) measurements in the diagnosis of diabetic ketoacidosis. Urine ketone examination is difficult and time consuming, and may result in an incorrect interpretation. Studies performed in emergency departments on blood ketones are limited. Our objective is to compare urine ketones and capillary blood ketones in patients whose serum glucose levels were ≥150 mg/dl.

Methods

In our cross-sectional prospective study, finger-stick blood beta-hydroxybutyrate, arterial blood gas and urine ketone measurements of patients whose serum glucose levels were 150 mg/dL and higher were performed in the emergency department.

Results

A total of 265 patients were included in the study. The mean age of the patients was 62.4±14.9 years, and 65.7% of them were female. The mean of the capillary blood ketone levels of the patients was determined to be 0.524±0.9 mmol/L (min: 0 mmol/L, max: 6.7 mmol/L). In 29 (13.1%) of the 221 patients whose urine ketone levels were negative, the finger-stick blood ketone levels were positive. Three of these patients were severely ketonemic, six were moderately ketonemic, and 20 were mildly ketonemic.

Conclusions

In patients admitted to the emergency department with a blood glucose level of 150 mg/dL or higher, performing a capillary blood ketone measurement instead of a urine ketone measurement was a better predictor of ketonemia.

Key words: Diabetic ketoacidosis; hydroxybutyrates; ketosis.

ÖZET

Amaç

Diyabetik keto asidoz tanısında idrar ketonu (asetoasetat) yerine kan ketonu (beta-hidroksibütirat) ölçümü önerilmektedir. İdrar ketonu bakılması zahmetli, zaman alıcı ve yanlış yorumlara yol açabilen bir testtir. Acil servislerde kan ketonu ile ilgili yapılan çalışmalar sınırlıdır. Bu çalışmadaki amacımız serum glikoz düzeyi ≥150 mg/dl tespit edilen hastalarda idrar ketonu ile kapiller kanda keton varlığını karşılaştırmaktır.

Gereç ve Yöntem

İleriye yönelik kesitsel çalışmada, acil serviste serum glikoz düzeyi 150 mg/dL ve üzerinde olan hastaların parmak ucu kan beta-hidroksibütirat, venöz kan gazı ve idrar ketonu ölçümü yapıldı.

Bulgular

Bu çalışmaya toplam 265 hasta dâhil edildi. Hastaların yaş ortalaması 62.4±14.9 yıl, %65.7'si kadındı. İdrar ketonu negatif olan 221 hastanın 29'unda (%13.1) parmak ucundan kan ketonu pozitif olarak saptandı. Bu hastaların üçü ağır, altısı orta düzeyli, 20'si hafif düzeyli ketonemikti. Olguların kapiller kan keton düzeyleri ortalaması 0.524±0.9 mmol/L (min.: 0 mmol/L, maks.: 6.7 mmol/L) tespit edildi.

Sonuç

Acil servise başvuran ve kan glikoz değeri 150 mg/dL üzerindeki hastalar içinde, idrar keton ölçümü yerine kapiller kan keton ölçümünün kullanılması hastaların yönetiminde önemli değişikliğe yol açabilir.

Anahtar sözcükler: *Diyabetik ketoasidoz; hidroksibütirat; ketozis.*

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Correspondence: Dr. Mustafa Sever. Manavkuyu Mahallesi, 275/10 Sokak, No: 12 Platinium Sitesi, C Blok., D: 4, 35330 Izmir, Turkey.
e-mail: adanasever@yahoo.com

Introduction

It has been reported that 25% of patients who are admitted to the emergency department (ED) are diabetic, and the routine glycemic control results of nearly half of these patients were negative. In emergency medicine practice, diabetic ketoacidosis (DKA) should be considered in patients whose blood glucose level is ≥250 mg/dL, regardless of symptoms.[1] DKA is a severe complication of diabetes that is characterized by hyperglycemia, ketone body production and metabolic acidosis.[2-4] Early diagnosis of DKA patients is critical because of the high mortality rate (2-5%).[5]

In current emergency medicine practice, ketonemia is frequently tested using a urine dipstick that measures acetoacetate (AA) concentrations.[1] A urine dipstick does not measure the concentration of β-hydroxybutyrate (β-OHB), a major ketone body that plays an important role in DKA pathogenesis.[2-4]

Studies of blood ketone concentrations in ED patients are limited.[1,6-9] Detection of ketone bodies in capillary blood provides analytical, technical, and clinical advantages compared to a urine dipstick test.[3] The objective of our study was to compare urine ketone (AA) and capillary blood ketone (β-OHB) levels in ED patients whose serum glucose levels were ≥150 mg/dl.

Materials and Methods

Our cross-sectional prospective study was performed over a period of three months in the Department of Emergency Medicine of Izmir Tepecik Training and Research Hospital, a tertiary training clinic. Ethics committee approval was obtained before the study. All the patients included in the study gave consent.

Patient Selection

All the patients admitted to our ED who were older than 14 years and whose serum glucose level was 150 mg/dL or higher were consecutively enrolled in the study. The criteria of the American Diabetes Association (ADA) were used for the definition of DKA as follows: blood glucose levels higher than 250 mg/dl, the existence of an anion gap greater than 10, bicarbonate levels lower than 18 mEq/L, and 3 mmol/L ketonemia or significant ketonuria ("≥3+" by standard urine dipstick) with blood pH lower than 7.3.[1,4,10,11]

Patients who declined to participate in the study as well as any patients whose blood biochemical tests, blood gas analysis, or urine or capillary ketone measurements could not be performed for any reason were excluded from the study.

Study Protocol

Patients whose finger-stick blood glucose level was measured to be 150 mg/dL and higher for any reason were identified. Serum glucose levels, serum electrolyte (Na+1, K+1, Cl-1; to calculate the anion gap) measurements, complete urine tests, arterial blood gases (pH, lactate, HCO3-, base excess), and capillary blood ketone measurements were performed.

Serum electrolytes and glucose levels were measured with an Olympus AU640 auto-analyzer. Arterial blood gas parameters were evaluated with a GEM Premier 3000 S/N 17839 blood gas analyzer®. To avoid observer bias, complete urine tests were evaluated using DIRUI H10–800 urine dipsticks with a DIRUI H800 Urine Analyzer® device with a spectrophotometric measurement technique. Urine ketone levels were grouped as no ketonemia, "trace quantity", "1+", "2+", or "3+".

Capillary blood glucose levels were measured with a Glucometer® (HMD Biomedical Inc., Hsinchu, Taiwan) in mg/dL at the bedside using a finger-stick test. Measurement of capillary blood ketone levels was performed at the bedside using β-ketone test strips (Optium-meter, Optium TM Xceed TM/Abbott®). Capillary blood ketone levels were grouped as follows: no ketonemia (0–0.5 mmol/L), mild ketonemia (0.6–

Table 1. Comparison of capillary blood ketone levels with dipstick urine ketone levels

Blood ketone levels	Urine ketone levels										Total	
	–		Trace		1+		2+		3+			
	n	%	n	%	n	%	n	%	n	%	n	%
No	192	72.4	18	6.8	1	0.4	0	0	0	0	211	79.6
Mild	20	7.5	7	2.6	5	1.9	0	0	2	0.8	34	12.8
Moderate	6	2.3	1	0.4	5	1.9	0	0	0	0	12	4.5
Severe	3	1.1	2	0.8	1	0.4	1	0.4	1	0.4	8	3
Total	221	83.4	28	10.6	12	4.5	1	0.4	3	1.1	265	100

1.5 mmol/L), moderate ketonemia (1.6–3.1 mmol/L) and severe ketonemia (3.2 mmol/L and higher). Patients whose blood ketone levels were determined to be higher than 0.5 mmol/L were classified as "ketonemia positive".

The socio-demographic (age, gender) and clinical properties (biochemical laboratory test results, finger-stick ketone levels) required for the study were transferred from the patient medical records onto data collection forms for evaluation.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows Ver. 17.0, (SPSS Inc., IL, USA). Non-parametric (qualitative) variables were shown as a number and percentage (%), and Mann-Whitney U and chi-square tests were used for evaluation. In the crosstab values, when the expected value in at least one cell was less than five, Fisher's Exact Test was used. Parametric (quantitative) data were shown as the mean ± standard deviation (SD). For parametric data, analysis of variance (ANOVA), correlation, and regression analyses were used. In the statistical analysis, $p<0.05$ was accepted as significant.

Results

The serum glucose levels of 408 patients who were admitted to ED in the course of our study were higher than 150 mg/dl. A total of 143 patients were excluded from the study for the following reasons: 43 patients' the urine ketones could not be studied; 56 patients' blood gas analysis could not be studied; 27 patients' blood biochemistry parameters could not be studied; and 17 patients refused to participate in the study. A total of 265 patients were included in the study, and 174 (65.7%) of the patients were female. The mean age of the patients was 62.4±14.9 years (range: 15-96 years).

In 221 of the cases (83.4%), no ketones were found in the urine. In 29 (13.1%) of the patients who did not have ketonuria, the capillary blood ketone (ketonemia) was determined to be positive (>0.5 mmol/L). Three (1.3%) of these patients were severely ketonemic, six (2.6%) were moderately ketonemic, and 20 (9.2%) were mildly ketonemic (Table 1). The mean capillary blood ketone level was determined to be 0.524±0.9 mmol/L (range: 0-6.7 mmol/L). The relationship between the patients' biochemical test results and capillary blood ketone levels is shown in Table 2. The comparisons of the capillary blood ketone levels and serum glucose, pH, lactate and bicarbonate levels are shown in Table 3.

In 211 (79.6%) patients, no ketones were found in the capillary blood. Twenty-nine (53.7%) of the 54 patients whose capillary blood ketone levels were positive had no ketonuria. Of these patients, 34 (12.8%) had mild ketonemia, 12 (4.1%) had moderate ketonemia, and 8 (3%) had severe ketonemia (Table 1).

Ten patients (3.8%) were identified who were positive for ketonemia by capillary blood and who had a blood pH value of <7.3. Four (1.5%) of these patients were diagnosed as DKA according to the ADA criteria; one had a urine ketone level of "3+", two had trace quantities, and one had a negative urine ketone test. These patients' capillary blood ketone levels were determined as 6.7, 5.2, 3.5 and 6.3 mmol/L, respectively.

Table 2. Relationship between capillary ketone levels and laboratory results

		Ketone levels (mmol/L)				
Variables	**All patients**	**0–0.5 (no)**	**0.6–1.5 (mild)**	**1.6–3.1 (moderate)**	**≥3.2 (severe)**	**p**
Capillary glucose (mg/dL)	282.1±107.4	273.3±98.6	279.6±118.6	362.1±144.6	404.7±114.7	=0.402
Serum glucose (mg/dL)	309.7±131.1	301.6±121.7	292.5±138.5	398.3±156.1	463.5±174	=0.878
Serum base excess	-1.7±6.4	-1.1±5.4	-3.8±8.9	-1.6±5.7	-10.4±12.4	=0.001
Serum bicarbonate (mmol/L)	22.8±5.5	23.7±4.7	20.7±6.2	22.5±4.8	10.2±5.5	=0.594
Serum pH	7.38±09	7.38±.1	7.37±.1	7.41±.1	7.32±0.1	=0.017
Anion gap	12.9±5.7	11.8±4.7	15.6±5.4	17.3±9.3	25.4±5.5	=0.011
Serum Lactate (mmol/L)	2.2±2.1	2.1±1.8	2.5±2.8	2.8±2.9	3.6±4.4	=0.064
Serum Sodium (Na^+) (mEq/L)	136.2±5.9	136.5±5.2	136.1±7.8	133.6±10	133.9±8.9	=0.07
Serum Potassium (K^+) (mEq/L)	4.4±0.7	4.5±.6	4.6±.8	4.1±.6	4.5±.8	=0.209
Serum Chlorine (Cl^-) (mEq/L)	100.5±7.2	101.1±6	99.8±8.7	93.7±13.5	98.2±9.6	=0.01

Data are given as mean±standard deviation. p values are results of Fisher's exact test.

Table 3. Comparison of capillary blood ketone levels and serum glucose, pH, lactate and bicarbonate levels

Variable	Ketone levels										
	Ketosis (-)				Ketosis (+)						
Serum glucose level (mg/dL)	0–0.5 (No)		0.6–1.5 (mild)		1.6–3.1 (moderate)		≥3.2 (severe)		Total		p
	n	%	n	%	n	%	n	%	n	%	
150–249	92	34.7	17	6.4	1	0.4	0	0	110	41.5	=0.03
≥250	119	44.9	17	6.4	11	4.2	8	3	155	58.5	
Acidosis											
Yes (pH<7.3)	18	6.8	6	2.3	0	0	4	1.5	28	10.6	=0.001
No (pH≥7.3)	193	72.8	28	10.6	12	4.5	4	1.5	237	89.4	
Bicarbonate level (mEq/L)											
<18	11	4.2	6	2.3	1	0.4	6	2.3	24	9.1	<0.001
≥18	200	75.5	28	10.6	11	4.2	2	0.8	241	90.9	
Lactate level (mmol/L)											
≥4	197	74.3	28	10.6	11	4.2	6	2.3	242	91.3	=0.042
<4	14	5.3	6	2.3	1	0.4	2	0.8	23	8.7	

p values are results of Fisher's exact test.

Although six patients' pH values were <7.3, they were not considered to be DKA according to the ADA criteria, as three had blood glucose levels lower than 250 mg/dL; two had bicarbonate levels higher than 18 mmol/L; and one had capillary blood ketone levels lower than 3 mmol/dL. Two of those patients had ketonuria (one patient had a trace quantity and the other "1+"), whereas no ketonuria was identified in the other four patients. All six patients had mild ketonemia (0.6, 0.6, 1.2, 1.1, 0.9, 0.8 mmol/L, respectively).

Four (1.5%) patients who met the ADA DKA criteria except for having an arterial blood gas pH value greater than 7.3 were considered to have compensated metabolic acidosis. The capillary blood ketone levels of these patients were 3.2, 3.9, 5.6, and 5.2 mmol/L. No ketonuria was found in the urine tests of two of these patients, whereas one had "1+", and the other had a trace quantity of ketonuria.

One hundred and eighty-one (68.3%) of the patients were discharged from the hospital. Four (1.5%) patients died, seven (2.6%) refused treatment and fifteen (5.7%) were referred. Additionally, 17 (6.4%) patients were admitted to the intensive care unit and 41 patients (15.5%) to other departments.

Discussion

The main objective of our study was to compare blood ketone levels with the presence of urine ketones in hyperglycemic ED patients. We found that capillary ketone levels were high in 13% of the patients who had no ketonuria. Severe ketonemia was identified in 10% of these patients. In DKA, the β-OHB/AA ratio can increase from 1/1 to 5/1. With treatment, β-OHB will be oxidized to AA. As a result, the measurable blood ketone levels (β-OHB) will decrease, whereas the measurable urine ketone levels (AA) will increase.[2] In our study, there were four patients who were diagnosed with DKA according to the ADA criteria. In spite of the fact that significant ketonemia was determined in these patients, the urine dipsticks only identified significant ketonuria ("3+") in one of these patients. In the early stages of DKA, some cases might be missed if urine dipsticks for ketone detection are used instead of capillary blood ketone measurement.

It was determined that only four (1.5%) of the ten patients who had ketones in the capillary blood and whose pH value was <7.3 met the ADA DKA criteria. In our study, the capillary blood ketone levels of the four adults who were diagnosed with DKA were determined to be 3.5, 5.2, 6.3 and 6.7 mmol/L.

Additionally, in six patients who did not meet the ADA criteria, acidosis was determined with mild (0.6-1.5 mmol/L) ketonemia. Charles et al. reported a blood β-OHB threshold level of 3.5 mmol/L for the diagnosis of DKA,[8] whereas Savage et al. reported this value to be ≥3 mmol/L.[11] Laffel et al. reported that all capillary blood ketone body values higher than 0.5 mmol/L are abnormal. In the populations that are a specific risk group for DKA (e.g. those who use insulin pumps), this value decreases to the lower limit value of 0.3

mmol/L.[12] Thus, although the aforementioned six patients are not considered as DKA according to ADA criteria, they might be diagnosed as being in the early stages of DKA. We hypothesize that, even at low levels, early stage DKA cases can be diagnosed with capillary blood ketone measurement. Otherwise, these patients, whose blood ketone levels are less than 3 mmol/L, might be discharged from the hospital without being adequately treated because they do not meet ADA criteria and are not diagnosed as DKA.

In current clinical practice, urine dipsticks are frequently used for ketone detection in patients presenting with hyperglycemia in the ED. Urine dipsticks measure AA via a semi-quantitative method dependent on a sodium-nitroprusside reaction. This test gives a weak reaction with acetone, whereas it has no reaction with β-OHB. When the spectrophotometric method is not used, the accuracy of the urine dipstick is user-dependent in the manner of sensing the color change on the dipstick.[2] The literature and the ADA encourage serum ketone measurement instead of urine dipstick tests because the specificity of urine dipsticks is low (<50%), and urine dipsticks frequently give false positive results, which cause an increased workload and inappropriate treatment.[1-8,11,13-15] Umperriez et al. reported that, in more than half of patients, even after the ketoacidosis attack was eliminated, ketones were detected in the urine.[16] Urine dipstick tests can create an incorrect impression that ketosis has not been eliminated. The delay in urine sample collection in seriously dehydrated patients can cause delays in diagnosis. In anuric patients with end-stage renal failure, a urine dipstick cannot be used.[2] False negatives in urine ketone measurements might result from faulty urine dipsticks, urinary tract infections, and medications such as acetylcysteine, captopril and vitamin C.[1,3,6,8-10,13,14]

Blood ketones (β-OHB) can be measured in less than 30 minutes with bedside finger-stick tests. Bedside finger-stick tests have several advantages over urine dipstick measurements, including quick and quantitative results, ease of use, and repeatability in the ED.[1,3,6,8-10,13,14]

It has been reported that capillary ketone measurements are highly accurate, sensitive (98.1%) and specific (78.5%) for detection of DKA.[1] Bektas et al. found the sensitivity and specificity of urine ketone dipstick testing and capillary blood ketone testing in determining DKA were 66% and 78%, and 72% and 82%, respectively.[6]

In our study, the urine ketone level was determined to be negative in more than half of the patients whose capillary blood ketone level was positive. It should be considered that, in the management of hyperglycemic ED patients, 53% of the patients might be inappropriately treated if a urine dipstick is used. In cases in which the incidence and prognosis of hyperglycemic patients admitted to the ED is based on an inappropriate diagnosis, the treatment administered might adversely affect the quality of patient care. Inadequate treatment could result in the re-admission of some patients to the ED.

Limitations

Because pregnant women and children were not included in our study, our data must not be generalized to these populations. We did not compare urine AA or capillary β-OHB ketone levels to serum β-OHB ketone levels, which is the gold standard in ketonemia diagnosis. There are studies reporting that the bedside capillary β-OHB ketone level test is as accurate and reliable as the serum β-OHB ketone level.[1,6-10,13,14]

Conclusion

Capillary blood ketone measurement should be considered for use instead of urine ketone measurement in hyperglycemic ED patients.

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Conflict of Interest

The authors declare that there is no potential conflicts of interest.

References

1. Arora S, Henderson SO, Long T, Menchine M. Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: {beta}-hydroxybutyrate versus the urine dipstick. Diabetes Care 2011;34:852-4. CrossRef
2. Wallace TM, Matthews DR. Recent advances in the monitoring and management of diabetic ketoacidosis. QJM 2004;97:773-80. CrossRef
3. Guerci B, Tubiana-Rufi N, Bauduceau B, Bresson R, Cuperlier A, Delcroix C, et al. Advantages to using capillary blood beta-hydroxybutyrate determination for the detection and treatment of diabetic ketosis. Diabetes Metab 2005;31:401-6. CrossRef
4. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, et al. Hyperglycemic crises in diabetes. Diabetes Care 2004;27 Suppl 1:S94-102. CrossRef
5. Umpierrez GE, Murphy MB, Kitabchi AE. Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. Diabetes Spectrum 2002;15:28-36. CrossRef
6. Bektas F, Eray O, Sari R, Akbas H. Point of care blood ketone testing of diabetic patients in the emergency department. Endocr Res 2004;30:395-402. CrossRef
7. Taboulet P, Haas L, Porcher R, Manamani J, Fontaine JP, Feu-

geas JP, et al. Urinary acetoacetate or capillary beta-hydroxybutyrate for the diagnosis of ketoacidosis in the Emergency Department setting. Eur J Emerg Med 2004;11:251-8. CrossRef

8. Charles RA, Bee YM, Eng PH, Goh SY. Point-of-care blood ketone testing: screening for diabetic ketoacidosis at the emergency department. Singapore Med J 2007;48:986-9.
9. Naunheim R, Jang TJ, Banet G, Richmond A, McGill J. Point-of-care test identifies diabetic ketoacidosis at triage. Acad Emerg Med 2006;13:683-5. CrossRef
10. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006;29:2739-48. CrossRef
11. Savage MW, Hammersley MS, Rayman G, et al. The Management of Diabetic Ketoacidosis in Adults. Joint British Diabetes Societies Inpatient Care Group. March 2010. Available in: http://www.bsped.org.uk/clinical/docs/DKAManagementOfDKAinAdultsMarch20101.pdf. Accessed 28 May 2012.
12. Laffel L. Sick-day management in type 1 diabetes. Endocrinol Metab Clin North Am 2000;29:707-23. CrossRef
13. Byrne HA, Tieszen KL, Hollis S, Dornan TL, New JP. Evaluation of an electrochemical sensor for measuring blood ketones. Diabetes Care 2000;23:500-3. CrossRef
14. Wallace TM, Meston NM, Gardner SG, Matthews DR. The hospital and home use of a 30-second hand-held blood ketone meter: guidelines for clinical practice. Diabet Med 2001;18:640-5. CrossRef
15. Sheikh-Ali M, Karon BS, Basu A, Kudva YC, Muller LA, Xu J, et al. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? Diabetes Care 2008;31:643-7. CrossRef
16. Umpierrez GE, Watts NB, Phillips LS. Clinical utility of beta-hydroxybutyrate determined by reflectance meter in the management of diabetic ketoacidosis. Diabetes Care 1995;18:137-8.