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Practical method in the diagnosis of diabetic ketoacidosis: end-tidal carbon dioxide

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ABSTRACT

Objectives: Diabetic ketoacidosis (DKA) poses a life-threatening risk in uncontrolled diabetes. Current diagnostic criteria rely on invasive measures, leading to potential delays in treatment initiation. This study aimed to assess the diagnostic utility of noninvasive end-tidal carbon dioxide ($EtCO_2$) measurements in DKA patients.

Methods: A prospective, cross-sectional study was conducted in a tertiary-level Emergency Medicine Clinic from January 2021 to January 2023. Participants included adults with DKA symptoms and those with stable vital signs as controls. $EtCO_2$ levels were measured using a capnograph device. Diagnostic criteria for DKA were blood glucose ≥250 mg/dL, ketonuria, ketonemia, and metabolic acidosis (pH<7.3 or bicarbonate <15 mEq/dL). Statistical analysis was performed using SPSS Statistics.

Results: Of 730 participants, 120 had DKA, 410 did not, and 200 served as controls. EtCO2 levels significantly differed between DKA, non-DKA, and control groups (P<0.05). $EtCO_2$ correlated with pH, lactate, base deficit, and bicarbonate (P<0.05). ROC analysis showed an AUC of 0.86 for EtCO2 in diagnosing DKA (P<0.01), with 91.67% sensitivity and 74.39% specificity at a cut-off value 23.7.

Conclusion: This study suggests that $EtCO_2$ measurement is a valuable noninvasive tool for diagnosing and assessing the severity of DKA in the emergency department. An $EtCO_2$ threshold of <23.7 could prompt consideration of DKA in patients with elevated blood glucose levels. More extensive multicenter studies are warranted to validate these findings further. $EtCO_2$ measurement could facilitate early DKA diagnosis and improve patient outcomes.

Keywords: Diabetic ketoacidosis, end tidal CO_2, fast diagnosis, emergency medicine

Diabetic ketoacidosis (DKA) is a life-threatening metabolic complication that can result from poorly managed diabetes mellitus. DKA) occurs due to decreased insulin effectiveness and an increase in counter-regulatory hormones. Diabetic ketoacidosis was consistently fatal before the identification of insulin in the 1920s. However, the mortality rate associated with DKA has decreased significantly over time [1, 2].

Diabetic ketoacidosis sometimes occurs in newly diagnosed diabetic patients but more commonly in uncontrolled diabetic patients presenting to the emergency department with hyperglycemia, ketonemia, ketonuria, metabolic acidosis, and dehydration [3]. Rapid diagnosis and treatment are of great importance in this disease, which is a mortal picture affecting the

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state of consciousness. Apart from physical examination, there is still no noninvasive method that will lead the physician to a rapid diagnosis except for blood glucose level ≥ 250 mg/dL, ketonuria, ketonemia, metabolic acidosis (pH<7.3, bicarbonate level <18 mEq/dL), anion gap > 10 mEq/L (biochemistry, blood gas, and urinalysis) [4]. This may lead to prolonged treatment initiation and undesirable results in DKA patients who cannot be predicted by physical examination [4].

End-tidal carbon dioxide ($EtCO_2$) measured with a capnograph device indicates end-expiratory carbon dioxide pressure [5]. While it was first used in operations in patients undergoing anesthesia, it has started to be used in non-intubated patients over time [6]. Studies have shown that it can provide information about the patient's metabolic status, and it has been observed to be correlated with pH, bicarbonate, and PCO_2. $EtCO_2$, a noninvasive, rapid, easy-to-apply method, is increasing daily, especially in cardiopulmonary arrest management [7].

This study aimed to investigate the diagnostic feature of end-tidal carbon dioxide measurement with a capnograph device, which is a noninvasive, practical, and rapid application suitable for use in prehospital and hospital triage in diabetic ketoacidosis patients in a prospective, cross-sectional, controlled plan.

METHODS

Study Design

Our study was conducted as a prospective, cross-sectional, controlled, and single-center study between 01.01.2021 and 01.01.2023 in the Emergency Medicine Clinic of a tertiary-level Izmir Atatürk Training and Research Hospital in Izmir province. Consent was obtained from all volunteers participating in the study by face-to-face interview. The Declaration of Helsinki was complied with at all stages of the study.

Study Population

Patients over 18 who presented to the emergency department were included in the study. Patients presenting to the emergency department with symptoms and signs of diabetic ketoacidosis, nausea, vomiting, altered consciousness, polyuria/polydipsia, weakness, and abdominal pain were included in the study. The study did not include patients with respiratory pathology or diseases such as pneumonia, asthma, or COPD that may affect end-tidal carbon dioxide value. Unconscious patients, patients in whom end-tidal carbon dioxide measurement could not be adequately performed, and intubated patients were excluded from the study. The study did not include patients whose treatment was started before the measurement.

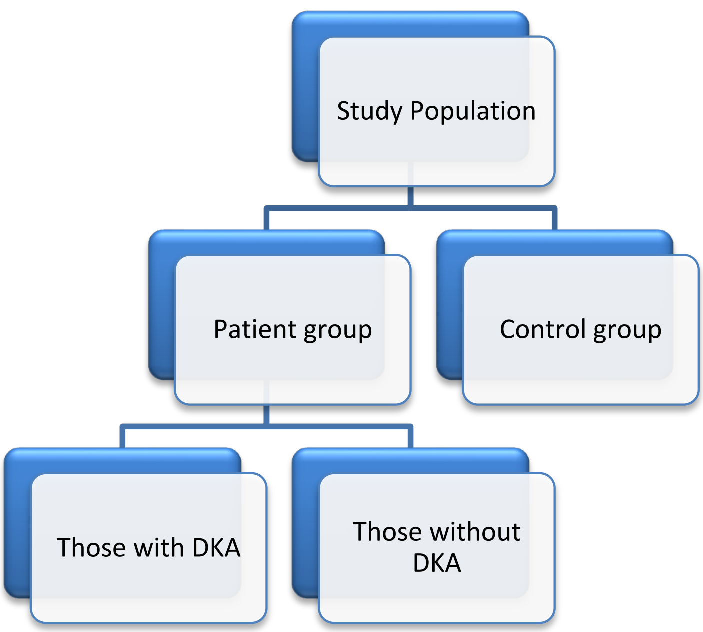

Fig. 1. Graphical explanation of the study population. DKA=Diabetic ketoacidosis.

Study Protocol and Data Collection

Patients presenting to the emergency department with symptoms and signs of diabetic ketoacidoses, such as nausea, vomiting, altered consciousness, polyuria/polydipsia, weakness, and abdominal pain, were evaluated. In the triage area, the SD Gluconavii Pro blood glucose meter is used to measure fingertip stick blood glucose and other vital signs in patients presenting to the emergency department. Those with a blood glucose value of 250 mg/dL and above were included in the study and named as the patient group. Those who met the diagnostic criteria for diabetic ketoacidosis (blood glucose level ≥ 250 mg/dL, ketonuria, ketonemia, metabolic acidosis (pH<7.3 or blood bicarbonate level <15 mEq/dL)) were divided into two groups as patient group-DKA patients and those who did not meet the diagnostic criteria as patient group-non-DKA patients.

Patients who presented to the emergency department for different reasons, whose stick blood glucose level was below 250 mg/dL, who had no respiratory disease or pathology that could affect the end-tidal CO_2 value, and whose vital signs were stable were included in the study as the control group (Fig. 1).

End-tidal CO_2 measurement was performed simultaneously with blood gas collection from the patients included in the study before any treatment was administered. End-tidal CO_2 measurement was performed with the VS2000 Vital Sign Monitor (UTECH CO., LTD. (UTMI) device, which measures with the sidestream technique using a side flow measurement mask.

The patient's vital signs, end-tidal CO_2 values, complaints, blood and urine tests, and outcomes were recorded on the case form. These data were used for statistical analysis.

Outcome Measurements

The primary outcome planned to be achieved in this study is to evaluate the effectiveness of end-tidal CO_2 measured with a mask in diagnosing diabetic ketoacidosis. For this purpose, end-tidal CO_2 levels were measured before treatment in patients grouped as control group, DKA, and non-DKA patients. The secondary outcome was to determine the efficacy of end-tidal CO_2 levels in determining the severity of diabetic ketoacidosis.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA) statistical package program. Descriptive statistics were given as number of units (n), percentage (%), and mean ± standard deviation (x±ss) values. The Shapiro-Wilk normality test evaluated the normal distribution of the data of numerical variables. One-way Analysis of Variance (ANOVA) and Tukey HSD test, one of the multiple comparison tests, was used when the data were normally distributed; Kruskal Wallis and Bonferroni-Dunn test, one of the multiple comparison tests, were used when the data were not normally distributed. The Spearman correlation coefficient was used to analyze the relationships between the data. $P<0.05$ was considered statistically significant.

RESULTS

Seven hundred thirty people were included in the study. Among the participants, 56.16% were women. The mean age of the women was 59.45±17.04 years, and the mean age of the men was 58.95±14.88 years. In the study groups, there were 120 participants with DKA, 410 participants without DKA, and 200 participants in the control group. There was no statistically significant difference between these groups regarding mean age ($P=0.41$). Other demographic data about the patient groups are given in Table 1.

Systolic blood pressure, pH, base deficit, HCO_3, and end-tidal CO2 parameters showed a statistically significant difference between the patient group with DKA and the other two study groups, the patient group without DKA and the control group ($P<0.05$). Pulse rate glucose parameters showed a statistically significant difference between the patient and control groups ($P<0.05$). The lactate parameter showed a statistically significant difference in all study groups ($P<0.05$). PO_2 and PCO_2 parameters showed no statistically significant difference between the study groups. Age, vital signs, blood gas, and end-tidal CO_2 values and p values of the patient groups are shown in Table 2.

The relationship between end-tidal and blood gas parameters, which were statistically significantly different between the study groups, was evaluated. End-

Table 1. Demographic characteristics of patients

			Patient group-Those with DKA	Patient group-Those without DKA	Control group	Total
Gender	Woman	n	13	51	18	82
		%	15.9%	62.2%	22.0%	100.0%
	Male	n	11	31	22	64
		%	17.2%	48.4%	34.4%	100.0%
Arrival complaint	Weakness	n	4	15	12	31
		%	12.9%	48.4%	38.7%	100.0%
	Abdominal pain	n	1	5	11	17
		%	5.9%	29.4%	64.7%	100.0%
	Nausea/vomiting	n	6	7	6	19
		%	31.6%	36.8%	31.6%	100.0%
	Chills/shivering	n	0	3	2	5
		%	0.0%	60.0%	40.0%	100.0%
	Shortness of breath	n	0	5	7	12
		%	0.0%	41.7%	58.3%	100.0%
	Dizziness	n	4	7	2	13
		%	30.8%	53.8%	15.4%	100.0%
	Polyuria/polydipsia	n	1	4	0	5
		%	20.0%	80.0%	0.0%	100.0%
Hypertension	None	n	17	30	18	65
		%	26.2%	46.2%	27.7%	100.0%
	There is	n	7	52	22	81
		%	8.6%	64.2%	27.2%	100.0%
Coronary artery disease	None	n	21	65	27	113
		%	18.6%	57.5%	23.9%	100.0%
	There is	n	3	17	13	33
		%	9.1%	51.5%	39.4%	100.0%
Congestive heart failure	None	n	24	76	33	133
		%	18.0%	57.1%	24.8%	100.0%
	There is	n	0	6	7	13
		%	0.0%	46.2%	53.8%	100.0%
Outcome	Discharge	n	6	61	24	91
		%	6.6%	67.0%	26.4%	100.0%
	Service hospitalization	n	11	18	15	44
		%	25.0%	40.9%	34.1%	100.0%
	Intensive care hospitalization	n	7	3	1	11
		%	63.6%	27.3%	9.1%	100.0%

Table 2. Vital signs, blood gas, and end-tidal CO_2 values of the patient groups

	DKA Patients	Non-DKA patients	Control group	P value
Age (years)	50.75±18.53	59.84±14.55	63.08±16.1	¥0.41
SBP (mmHg)	122.46±25.42^{a}	138.3± 25.16^{b}	127.43±19.89^{b}	¥**0.01**
DBP (mmHg)	70.88±13.38^{a}	77.51±13.83^{b}	71.68±11.92^{a}	£**0.02**
Saturation (%)	96.88±1.75	96.21±2.14	96.6±2.27	£0.34
Pulse (bpm)	99.08±17.53^{a}	89.91±13.84^{a}	86.8±14.23^{b}	¥**0.01**
Temperature (°)	50.02±66.45	40.53±36.07	36.43±0.3	£0.38
pH	7.23±0.1^{a}	7.39±0.05^{b}	7.41±0.07^{b}	¥**0.001**
PCO_2 (mmHg)	37.7±30.09	48.35±47.11	38.15±7.88	£0.26
PO_2 (mmHg)	63.46±34.22	51.55±38	54.83±29.69	£0.35
Glucose (mg/dL)	488.08±181.33^{a}	411.72±104.46^{a}	125.43±31.32^{b}	¥**0.001**
Lactate (mmol/L)	2.27±1.89^{a}	2.25±1.12^{b}	1.53±1.01^{c}	£**0.01**
Base excess (mEq/L)	12.82±7.84^{a}	3.3±2.66^{b}	3.4±2.9^{b}	¥**0.001**
HCO_3 (mEq/L)	15.33±5.28^{a}	24.41±3.26^{b}	23.59±3.41^{b}	¥**0.001**
End-tidal CO_2 (mmHg)	18.88±4.71^{a}	26.28±5.1^{b}	28.08±5.3^{b}	¥**0.001**

¥One-Way Anova- Post Hoc Test Tukey, SBP= Systolic blood pressure, DBP=Diastolic blood pressure

Table 3. Correlation values of end-tidal CO_2 and blood gas values of the patient group - DKA patients

DK groups			End-tidal CO_2	pH	PO_2	Lactate	Base minus
Patient group-DK patients	pH	r	0.421 *				
		P value	0.040				
		n	24				
	PO_2	r	-0.365	-0.174			
		P value	0.080	0.415			
		n	24	24			
	Lactate	r	-0.476*	-0.031	-0.072		
		P value	0.019	0.885	0.739		
		n	24	24	24		
	Base minus	r	-0.437*	-0.857	0.482	0.020	
		P value	0.033	0.000	0.017	0.928	
		n	24	24	24	24	
	HCO_3	r	0.440*	0.843**	-0.300	-0.095	-0.923
		P value	0.032	0.000	0.154	0.658	<0.001
		n	24	24	24	24	24

*P<0.05, **P<0.01

Table 4. **ROC analysis showing the diagnostic accuracy of $ETCO_2$**

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI
≤23.7	91.67	73.0-99.0	74.39	63.6-83.4	3.58	2.43-5.28	0.11	0.030-0.42

tidal CO_2 was found to be statistically significantly correlated with pH, lactate, base minus, and bicarbonate (P<0.05) (Table 3).

ROC analysis was performed to examine the sensitivity and specificity of end-tidal CO_2 in diagnosing DKA patients with increased blood glucose levels. The surface area under the curve (AUC) was calculated as 0.86 with 91.67% sensitivity and 74.39% selectivity below the end-tidal CO_2 cut-off value of 23.7, and this result was statistically significant (P<0.01). (Table 4, Figs. 2 and 3).

DISCUSSION

More studies must be done on the diagnostic value of End-tidal CO_2 patients presenting to the emergency department. This study is one of the rare studies evaluating the use of capnography in prehospital and emergency department triage for the diagnosis of diabetic ketoacidosis.

Assessment of end-tidal CO_2 by capnography is a valuable method used in the emergency department and critical care settings, especially in the context of cardiac arrest and procedural sedation [8]. This study demonstrated that $EtCO_2$ measured with a capnograph device has diagnostic value in DKA patients.

Capnography has shown a consistent ability to aid in identifying and diagnosing metabolic acidemia. Linearity has been observed between $EtCO_2$ and serum bicarbonate levels. Many studies have investigated this relationship, particularly in DKA and diarrhea [9-14]. As the severity of acidemia increases, there is a decrease in bicarbonate levels, which leads to respiratory compensation and a subsequent decrease in $EtCO_2$ levels [9-12]. There is a direct relationship between the severity of acidemia and the decrease in bicarbonate and $EtCO_2$ levels. Furthermore, these $EtCO_2$ levels are closely related to venous pH and bicarbonate levels, which may aid the diagnostic process

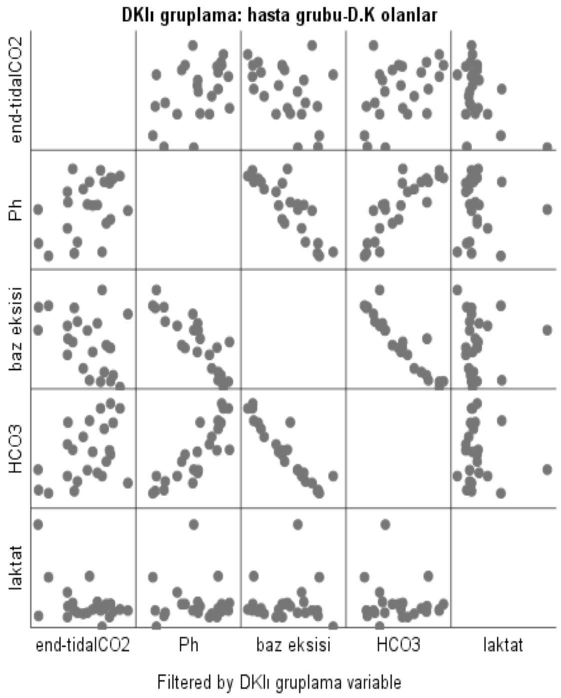

Fig. 2. **Graph showing the correlation of end-tidal CO2 with pH, lactate, base deficit, and bicarbonate.**

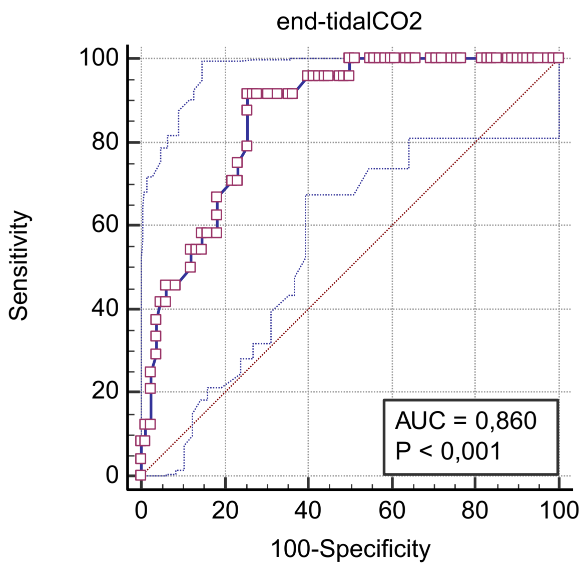

Fig. 3. **ROC curve showing the diagnostic accuracy of ETCO2.**

[13-15]. This finding has potential for diabetic individuals in the evaluation of the presence of ketoacidosis [13, 14].

Recent studies investigate the relationship between metabolic acidosis and end-tidal CO_2 measured by capnography. However, the majority of these studies were performed in pediatric patients. In a study by Fearon and Steele [9] investigating the presence and severity of acidosis in children with diabetes mellitus by end-tidal CO_2 measurement, it was reported that end-tidal CO_2 <29 and below suggested a diagnosis of DKA. A recently published study by Bhattaram *et al.* [16] investigated the relationship between end-tidal CO_2 measurement and prognosis in adult DKA patients. They concluded that the diagnosis of DKA should be considered in patients with $EtCO_2$ values ≤24 measured by capnography [16]. Soleimanpour *et al*. [17] investigated the diagnostic utility of end-tidal CO_2 measurement in patients with suspected DKA presenting to the emergency department. They concluded that capnography could rule out DKA in patients with $EtCO_2$>24.5 and elevated blood glucose [17]. This study concluded that an end-tidal CO_2 limit value below 23,7 may be significant for diagnosing DKA. This result is similar to other studies.

This supports the idea that end-tidal CO_2 can be used for diagnostic purposes in DKA patients, where mortality and morbidity can be changed with rapid diagnosis in emergency departments.

Among the limited number of studies conducted on adult patients on this subject, in a single-center study conducted by Bou *et al*., [18] it was reported that $EtCO_2$ may be helpful in adults in the differential diagnosis of DKA in patients presenting to the emergency department with glucose levels >550 mg/dL [18]. However, Taghizadieh *et al*. [19] compared arterial blood gas (ABG) with $EtCO_2$ and reported that capnographic $EtCO_2$ helped detect metabolic acidosis in spontaneously breathing patients. However, it should be remembered that ABG is the gold standard [19]. Similarly, this study showed a significant correlation between blood gas and capnographic $EtCO_2$ values.

In our study, it was concluded that there was a significant correlation between $EtCO_2$ and bicarbonate ($P<0.05$). Similarly, previous studies have reported a significant linear correlation between end-tidal CO_2 and bicarbonate [20-22]. As low bicarbonate level explains the metabolic acidosis present in patients with DKA, the linear significant correlation found between $EtCO_2$ and bicarbonate is another result supporting that $EtCO_2$ measurement can be used for diagnostic purposes in these patients.

In this study, we indirectly suggest that including $EtCO_2$ measurements in the diagnostic process may facilitate rapid triage of patients in the emergency department. By quickly identifying potential cases of DKA using $EtCO_2$, healthcare providers can prioritize these patients for immediate intervention. This would reduce the burden on the healthcare system while optimizing resource allocation and ensuring that critically ill individuals receive care quickly.

We also see the potential of $EtCO_2$ as a screening tool. By using $EtCO_2$ measurements as a first diagnostic step, healthcare providers can avoid unnecessary laboratory tests and imaging procedures in patients with hyperglycemia but not DKA. This would not only save time and resources, but it would also reduce patient discomfort and radiation exposure.

Limitations

The limitations of our study include the fact that it was a single-center study and the number of patients was limited. The study exclusion criteria included conditions that caused significant changes in end-tidal CO_2 value, and it may not have been possible to exclude all other confounding factors that affect $EtCO_2$ value. In addition, no comparison of end-tidal CO_2 measurement with other diagnostic methods was performed in the study. In addition, since the types of diabetic ketoacidosis were not analyzed separately, the possibility of different results in some types should not be overlooked.

CONCLUSION

This study showed that the $EtCO_2$ measurement may be an effective diagnostic tool in identifying DKA patients in the emergency department and evaluating their severity. DKA should be among our preliminary diagnoses in patients with elevated blood glucose levels if the end-tidal CO_2 value is <23,7. Larger scale and multicentre studies are needed in this regard.

Ethics Approval

Ethics committee approval was obtained from İzmir Katip Çelebi University non interventional Ethics Committee (No: 01/05.01.2023).

Authors' Contribution

Study Conception: AK, ESB; Study Design: AK, ESB; Supervision: N/A; Funding: N/A; Materials: AK, ESB; Data Collection and/or Processing: N/A; Statistical Analysis and/or Data Interpretation: N/A; Literature Review: AK, ESB; Manuscript Preparation: AK, ESB and Critical Review: N/A.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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