

# Point-of-care blood ketone testing: screening for diabetic ketoacidosis at the emergency department

Charles R A, Bee Y M, Eng P H K, Goh S Y

## ABSTRACT

**Introduction:** We piloted the use of a blood beta-hydroxybutyrate meter as a point-of-care testing in an emergency department (ED) to establish its role in distinguishing ketosis/ketoacidosis from simple hyperglycaemia, and develop guidelines for its use in the ED.

**Methods:** 111 consecutive patients presenting with capillary glucose levels exceeding 14 mmol/L had a simultaneous blood ketone measurement at triage. This was correlated with clinical diagnosis, venous bicarbonate levels and urine ketone testing.

**Results:** The median beta-hydroxybutyrate levels was 5.7 (range 4.3-6.0) mmol/L for patients with diabetic ketoacidosis (DKA) and 0.1 (0.0-3.2) mmol/L for the remaining patients. Only 47.7 percent could provide urine samples in the ED. A blood ketone result of 3.5 mmol/L yielded 100 percent specificity and sensitivity for the diagnosis of DKA.

**Conclusion:** This is a useful tool that allows clinicians to immediately distinguish between simple hyperglycaemia and potentially life-threatening ketotic states. We formulated simple guidelines for its utilisation in an ED setting.

**Keywords:** beta-hydroxybutyrate, blood ketone testing, diabetes emergencies, diabetes mellitus, diabetic ketoacidosis

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## INTRODUCTION

Ketone testing is an integral part of the management of diabetes mellitus.<sup>(1)</sup> We undertook this study to (a) establish the role of measurement of blood beta-hydroxybutyrate ( $\beta$ -OHB) in distinguishing ketoacidosis from simple hyperglycaemia, and (b) develop guidelines

for the use of the ketone meter in the emergency room setting.

## METHODS

Near-patient blood  $\beta$ -OHB testing was piloted as a point-of-care testing tool in the emergency department (ED) of a tertiary-care 1,500-bed hospital. Over three months, all patients who presented to the ED with a capillary glucose level equal to or exceeding 14 mmol/L (252 mg/dL) were subjected to a simultaneous measurement of capillary blood ketones at triage, and a venous bicarbonate level and/or arterial blood gas drawn. All patients with any of the following had a capillary glucose level tested: a history of diabetes mellitus, current or past use of oral hypoglycaemic agents and/or insulin, and a presenting complaint suggestive of hyperglycaemia, e.g. polyuria, polydipsia. Urine ketone testing was performed at the ED if a urine sample could be procured. Diabetic ketoacidosis (DKA) has no universally agreed definition – attending doctors used standard clinical criteria (metabolic acidosis pH < 7.3 and/or bicarbonate < 18 mmol/L, blood glucose > 14 mmol/L, urine ketones  $\geq$  2+) and were blinded to the  $\beta$ -OHB result. The blood  $\beta$ -OHB meter (Optium, Abbott/Medisense Laboratories, Abingdon, UK) gave a quantitative measurement of  $\beta$ -OHB in a range of 0.0–6.0 mmol/L from a single five microlitre prick capillary blood sample by an electrochemical method.

## RESULTS

We analysed 111 consecutive cases. The median age was 60 years, with a slight male predominance (54.5%, 61/111) and the racial group distribution reflected the multi-ethnic population of Singapore. 95.5% had type 2 diabetes mellitus. 52.3% of patients could not provide urine samples, including nine cases with anuric end-stage renal failure. Respective median times from arrival to  $\beta$ -OHB testing was 12 (range 5–47) minutes, availability of arterial/venous bicarbonate result was 37 (range 23–56) minutes, and urine ketone testing was 52 (range 25–149) minutes. The average length of stay in the ED from time of registration to time of disposition was 156.3  $\pm$  30.2 minutes. The median  $\beta$ -OHB level was 5.7 (range 4.3–6.0) mmol/L for patients

Department of Emergency Medicine, Singapore General Hospital, Outram Road, Singapore 169608

Charles RA, FRCS Consultant

Department of Endocrinology

Bee YM, MRCP Registrar

Eng PHK, MRCP, FAMS Senior Consultant

Goh SY, MRCP Associate Consultant

**Correspondence to:** Dr Rabind A Charles  
Tel: (65) 6326 5884  
Fax: (65) 6321 4783  
Email: rabindcharles@yahoo.com.sg

**Table I. Characteristics of the study population.**

Characteristics	DKA	Others	p-value
Gender M:F	3:4	58:46	0.310
Age (years)	61 (18–86)	59 (17–83)	0.846
$\beta$ -OHB (mmol/L)*	5.7 (4.3–6.0)	0.1 (0–3.2)	< 0.001
Capillary glucose (mmol/L)#	29.5 (14.4–33.0)	21.9 (14.2–33.0)	0.014
Venous blood glucose (mmol/L)	37.4 (14.1–50.9)	22.5 (12.3–57.3)	0.010
Bicarbonate (mmol/L)	8.1 (2.8–14.0)	21.6 (9.4–31.8)	< 0.001
Type 1 diabetes mellitus	1	3	0.232
Type 2 diabetes mellitus	6	101	

Data expressed as median (range)

\* Upper limit of ketone meter: 6.0 mmol/L

# Cut-off for entry into study: 14.0 mmol/L, upper limit of glucometer: 33.0 mmol/L

**Table II. Variables stratified according to blood ketone levels.**

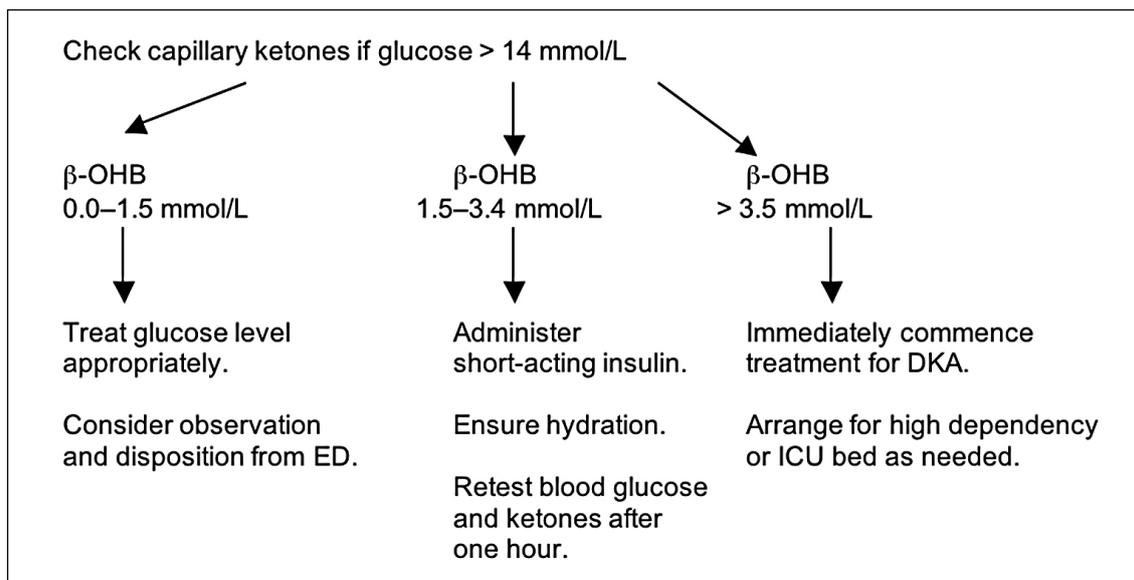
Variables	Blood ketone levels			p-value
	< 1.5	1.5–3.4	> 3.5	
Type 1 diabetes mellitus	3	0	1	0.268
Type 2 diabetes mellitus	94	7	6	
Capillary glucose (mmol/L)	22.1 (14.2–33.0)	18.7 (15.7–21.4)	29.5 (14.4–33.0)	0.032
Venous glucose (mmol/L)	22.5 (14.4–57.3)	22.8 (12.3–44.4)	37.4 (14.1–50.9)	0.035
Bicarbonate (mmol/L)	21.8 (9.4–31.8)	19.0 (16.8–22.8)	8.1 (2.8–14.0)	0.002
Number with DKA	0	0	7	< 0.001

with DKA and 0.1 (range 0.0–3.2) mmol/L for the remaining patients with uncomplicated hyperglycaemia (Table I). There were three mortalities among the seven cases of DKA, yet all three cases had urinary ketones  $\leq$  1+ at first presentation. Seven patients had blood ketone levels of between 1.5 and 3.4 mmol/L (Table II), and none of these fulfilled the clinical criteria for DKA, nor did their clinical course in the hospital indicate the diagnosis of DKA. All patients with presenting blood ketone levels < 3.5 mmol/L were discharged well from hospital. At the manufacturer suggested  $\beta$ -OHB cut-off level of 1.5 mmol/L, cross-classification of DKA versus  $\beta$ -OHB level yielded a sensitivity of 100% (95% confidence interval [CI] 59.0–100), a specificity of 93.3% (95% CI 86.6–97.2), a positive predictive value of 50% (95% CI 23.0–77.0) and a negative predictive value of 100% (95% CI 96.3–100). Using a level of 3.5 mmol/L yielded 100% sensitivity (95% CI 59.0–100), 100% specificity (95% CI 96.5–100), 100% positive predictive value (96% CI 59.0–100) and 100% negative predictive value (95% CI 96.5–100).

## DISCUSSION

This study suggests that point-of-care blood ketone testing has a role in optimising the assessment and

management of hyperglycaemic emergencies. Prolonged insulin insufficiency can progress rapidly to life-threatening ketosis and ketoacidosis. In the ED and hospital setting, this is usually confirmed with a battery of tests including blood gases, pH and bicarbonate levels, as well as urine ketone dipstick testing.  $\beta$ -OHB is the predominant ketone in most pathological states of ketosis,<sup>(2)</sup> and diabetic ketoacidosis is the most common cause of pathological ketosis. The normal level of  $\beta$ -OHB in the blood, in a patient with or without diabetes mellitus, is between 0.0 and 0.5 mmol/L;<sup>(3)</sup> this level corresponds to a negative or trace amount of urine ketones. While urine ketone testing is cheap and convenient, existing tests are based on a nitroprusside reaction and give an imprecise reflection of blood levels. The reading of the urine dipstick tests depends on a colour change and accuracy is user-dependent. False-negative readings may occur with strip degradation, vitamin C contamination or urinary tract infections. The difficulty of relying on urinalysis was underscored by our findings that only 47.7% of patients could produce a urine sample. Taboulet et al's retrospective study concurs that capillary blood ketone measurement is faster and more effective than urine dipstick usage to detect ketoacidosis in the ED setting.<sup>(4)</sup> Our study confirms suspicions that patients are often unable to produce



**Fig. 1** Guidelines for use of the ketone meter at the emergency department.

a urine specimen when they first present to hospital, whether it is from dehydration, inconvenience of having to void a urine specimen in a crowded ED, or being anuric from end-stage renal failure. Arterial blood sampling is an invasive and often painful procedure that can only be performed by a physician, while fingerprick capillary sampling is easily performed by paramedical staff and patients. Although arterial blood sampling is a traditional “must”, recent papers suggest that the results of blood gas testing rarely affect the treatment of or disposition of patients with DKA.<sup>(5-7)</sup>

The clinical use of a point-of-care ketone sensor is to distinguish a moderate-to-markedly elevated  $\beta$ -OHB level from that of a normal level, so that the emergency diagnosis of ketoacidosis can be made and appropriate care instituted immediately. The majority of DKA cases in our series were not the typical adolescent or young person with type 1 diabetes mellitus; six of the seven cases were older than 50 years of age and had type 2 diabetes mellitus. It is even more pertinent to note that in 71.4% (5 out of 7) of the episodes, urinary ketones were either not available or  $\leq 1+$ , and all three episodes which resulted in mortality did not test positive for urinary ketones at first presentation. The diagnosis of DKA may well have been missed in these cases if not for blood  $\beta$ -OHB testing, as acidosis is often attributed to concomitant sepsis or mild lactic acidosis if there is a component of hypotension. As a result of our study, we have established a threshold level of blood  $\beta$ -OHB values exceeding 3.5 mmol/L as a guideline to distinguish DKA cases at the point of triage or early in the ED consult (Fig. 1). Our findings

correlate well with reports available in the current literature,<sup>(8)</sup> in which the value of 1.5 mmol/L yielded a sensitivity of 98% and a specificity of 85% for the diagnosis of DKA. In our study, at a ketone level of 1.5 mmol/L, cross-classification of DKA versus  $\beta$ -OHB level yielded a sensitivity of 100% and a specificity of 93.3%. Using a level of 3.5 mmol/L, it yielded 100% sensitivity, specificity, positive and negative predictive values.

There are several limitations in our study. In our local setting, we do not have any laboratory enzymatic method to correlate or ascertain the precision of the capillary blood ketone meter. However, the performance of the meter has been verified in multiple studies.<sup>(9-11)</sup> This is a small non-blinded study, but the values derived are similar to those found in another population of ED patients, as well as quoted values above which medical assistance is recommended in an outpatient study of patients with poorly controlled diabetes.<sup>(9,12-14)</sup> Reflective of our local population, the prevalence of type 1 diabetes mellitus is low. Finally, any assessment of  $\beta$ -OHB as a diagnostic tool is complicated by the fact that ketonaemia (and therefore  $\beta$ -OHB levels) is part of the definition of DKA, and incorporation bias would prevent the calculation of sensitivity and specificity for diagnosis of DKA. As such, we elected to utilise standard criteria for the diagnosis of DKA, as elaborated in the Methods section, and attending physicians were blinded to the  $\beta$ -OHB results.

The manufacturer-suggested cut-off for “at risk” of having DKA is 1.5mmol/L. We tested the sensitivity, specificity, positive and negative predictive values for blood ketone testing at various levels. All cases of

DKA had values exceeding 3.5 mmol/L, albeit there were only seven cases, and none of the cases had values lower than that. As one of our objectives of this study was to establish practical guidelines for its utilisation in the setting of a busy ED, the figure of 3.5 mmol/L yielded both acceptable sensitivity/specificity as well as practicality for the physicians to remember. This study has provided us with useful diagnostic thresholds for our clinical practice and in formulating our guidelines. We conclude that blood ketone testing is a useful adjunct in the diagnosis of diabetic emergencies, and allows us to rapidly distinguish between ketoacidosis and simple hyperglycaemia.

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This investigator-initiated study was approved by the Singapore General Hospital Institution Review Board (reference number #119/2004). As this was an observational study, waiver of consent was granted. We thank Abbott Laboratories for the provision of meters and test electrodes, and the staff of the Emergency Department at Singapore General Hospital for their effort and enthusiastic support and participation in this study.

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