# Comparing Finger-stick Beta-hydroxybutyrate with Dipstick Urine Tests in the Detection of Ketone Bodies in the Diagnosis of Children with Diabetic Ketoacidosis

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**ABSTRACT**

**Objective:** To compare the finger-stick β-hydroxybutyrate (β-OHB) method accuracy with dipstick urine test for the detection of ketone bodies to diagnose diabetic ketoacidosis in children.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Department of Pediatrics, National Institute of Child Health, Karachi, from March to August 2021.

**Methodology:** Ninety-six known or newly diagnosed diabetic patients aged 2-15 years with suboptimal glycemic control and diabetic ketoacidosis were included in the study. A urine dipstick test was utilised to evaluate the absence or presence of ketones in the urine. In point-of-care, blood β-OHB levels were recorded.

**Results:** Among 96 children, with median age of 10 years (IQR=6-11), 11 (11.5%) children had traces of urine ketones, 7 (7.3%) had + urine ketones, 19 (19.8%) had ++ urine ketones, 26 (27.1%) had +++ ketones and 19 (19.8%) had ++++ ketones. In 66 patients (68.75%), capillary blood ketone was observed to be positive by a finger-stick β-OHB method. The finger-stick β-OHB method had a higher sensitivity (90.4% *vs*. 84.9%), specificity (100% *vs*. 91.3%), and accuracy (92.7% *vs.* 86.5%) than the dipstick urine test.

**Conclusion:** Finger-stick β-OHB method can serve as a more accurate alternative to the urinary dipstick method for the measurement of ketones and to exclude ketosis and diagnosis of diabetic ketoacidosis (DKA) in hyperglycemic children.

**Key Words:** *Diabetes mellitus, Hyperglycemia, Diabetic ketoacidosis, Point-of-care testing, Ketosis, Urine ketones, Acetoacetates.*

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## INTRODUCTION

Diabetes is the most frequent endocrine condition in all age groups children and teenagers.[1] Diabetic ketoacidosis (DKA) is a life-threatening complication of type 1 diabetes (T1DM) that can be avoided. DKA affects almost 21% of the children and teenagers with T1DM at the time of diagnosis, with severe cases accounting for 6%, moderate for 5%, and mild cases accounting for 10%.[1] It is the leading cause of increased hospitalisation time, severe morbidity, and mortality.[1,2] Because of the high fatality rate of 2-5%, early detection and proper management of DKA are essential.[1-3]

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DKA is induced by a decline in circulating insulin along with an increase in counter-regulatory hormones (*i.e*. cortisol, catecholamines, glucagon, and growth hormone), leading to underutilisation and overproduction of glucose, resulting in hyperosmolarity and hyperglycemia.[2,4] Increased ketogenesis and lipolysis result in an excess of ketone bodies accumulating to induce metabolic acidosis and ketonemia. In the current clinical practice, a urine dipstick is used to detect concentrations of acetoacetate (AcAc) to determine ketonemia.[5] The major ketone body in the pathophysiology of DKA is β-hydroxybutyrate (β-OHB), which is not measured by a urine dipstick.[5]

Although rarely, DKA may develop even if blood glucose levels are normal. As a result, all diabetics with appropriate glucose levels should have their acid-base, urine glucose, and ketone readings evaluated. In such patients, hyperlipidemia may lead to pseudo-normoglycemia. It is important to be aware of this rare but treatable life-threatening disease.[6] Studies of blood ketone concentrations have been conducted worldwide, but data from Pakistani population are limited. New methods that can detect blood ketone β-OHB rather than traditional urine ketones (AcAc) appear to offer the possibility of early detection

and treatment of impending DKA, perhaps limiting the need for hospitalisation and reducing costs.

Since the majority of patients with DKA have uncontrolled diabetes, teaching and reinforcing sick-day guidelines that include enhanced self-care, consistent self-monitoring of blood glucose and ketones, and prompt administration of extra insulin and fluids, can be beneficial. When compared to a urine dipstick test, the detection of ketone bodies in the capillary blood may have analytical, technical, and clinical advantages.

The goal of this study was to compare the finger-stick β-OHB method with the dipstick urine test in detecting ketone bodies in children at a tertiary care hospital to identify DKA.

## METHODOLOGY

From March to August 2021, a cross-sectional study was conducted at the Department of Pediatrics, National Institute of Child Health, Karachi. A sample size of 96 patients was estimated using the open Epi online sample size calculator, by taking statistics as 53.7% for the patients whose capillary blood ketone levels were positive; but no ketonuria, a margin of error of 10% and 95% confidence level.[7] Known or newly diagnosed diabetic patients aged 2 to 15 years, visiting the emergency room or outpatient department with blood glucose greater than 11 mmol/L [200 mg/dL], were enrolled in the study. Patients with non-medical (traumatic) complaints were excluded from the study. Non-probability consecutive sampling was applied for sample selection. This study was conducted after getting approval from IERB of NICH (IERB No: 35/2020). The consenting cases, who met inclusion criteria, were enrolled in the study.

A urine dipstick (URS-1K reagent strips for urine analysis) was utilised to evaluate the absence or presence of ketones in the urine. The results of urine dipstick were categorised as either negative, +/− (Trace), +, ++, +++ or ++++. The ketonuria was labelled as positive when the urine dipstick had ketones ≥2+. Venous pH, $HCO_3$, RBS, urea, creatinine, and serum electrolytes were determined for participating patients. A point-of--care blood β-OHB level was recorded with freestyle optium neo-blood ketone. The ketonemia was labelled as positive when a finger-stick blood ketones level >3 mmol/L (10 mg/dl) was observed. DKA was defined as blood glucose >11 mmol/L [200 mg/dL]; serum bicarbonate <15 mmol/L or venous pH ≤7.30; ketonuria or ketonemia.[8] The age and gender of all the subjects were also recorded on a predesigned study proforma.

SPSS version 23 was used to enter and analyse all of the data. For quantitative data, mean and standard deviations were determined along with median and interquartile range (IQR), if the data was not normally distributed. Shapiro-Wilk test was used to check normality where the data was considered "not normally distributed," if p-value was less than or equal to 0.05. For qualitative variables, frequencies and percentages were determined. Kappa statistic was also estimated to assess the level of agreement between the two methods, *i.e.* finger-stick β-OHB method and dipstick urine test for the detection of ketone bodies to detect DKA. Sensitivity, specificity, NPV, PPV, and diagnostic accuracy for urinary ketones and blood ketones were also estimated by taking biochemical criteria for DKA (including blood glucose, serum bicarbonate or venous pH, and ketonuria or ketonemia with normal values as defined previously in the text) as a reference standard.

## RESULTS

The registered children had a median age of 10 years (IQR=6-11). Of the 96 patients, 60 were girls (62.5%) and 36 were boys (37.5%). Other baseline characteristics are shown in Table I.

**Table I: Baseline characteristics of study variables.**

| Variables | Range | Median | IQR |
|---|---|---|---|
| Age (years) | 2-15 | 10 | 6-11 |
| Weight (Kg) | 10-40 | 20 | 15-27 |
| RBS at admission (mg/dL) | 220-650 | 458 | 375-550 |
| pH | 6.5-7.9 | 7.2 | 7.0-7.3 |
| $HCO_3$ (mmol/L) | 0.5-25.0 | 7.9 | 5.2-12.9 |
| Urea (mg/dL) | 8-104 | 26 | 20-32 |
| Creatinine (mg/dL) | 0.30-2.0 | 0.5 | 0.4-0.6 |
| Na+ (mEq/L) | 120-157 | 136.5 | 132-140 |
| K+ (mEq/L) | 2.5-5.8 | 3.6 | 3.3-4.2 |
| Cl- (mEq/L) | 90-124 | 104.5 | 101-110 |

At the time of presentation, no ketones were detected in the urine of 14 children (14.6%). About 11 children (11.5%) had traces of urine ketones, and 7 (7.3%) had + urine ketones. About 64 (66.7%) children were identified as DKA using urinary ketones, where 19 children (19.8%) had ++ urine ketones, 26 (27.1%) had +++ ketones, and 19 (19.8%) had ++++ ketones.

In 66 patients (68.75%), capillary blood ketone [ketonemia: blood ketones level >3 mmol/L (10 mg/dl)] was observed to be positive by finger-stick β-OHB method and in 30 patients (31.25%), it was negative for DKA.

The median blood ketone level was estimated as 3.75 mmol/L (IQR=2.15-4.9). In patients with negative urine ketones, the median blood ketones were 1.30 mmol/L (IQR=0.50-1.60). The highest mean value for blood ketones was estimated for patients with "++++" urine ketones, *i.e.* 4.88 ± 1.15 mmol/L.

On comparing the accuracy of the finger-stick β-OHB method with a dipstick urine test for the detection of ketone bodies to detect DKA, the authors found that blood ketones had higher sensitivity (90.4% *vs.* 84.9%), specificity (100% *vs.* 91.3%), and accuracy (92.7% *vs.* 86.5%) than urinary ketones (Table II).

## DISCUSSION

DKA is a severe complication of T1DM, and the early detection improves prognosis. DKA is identified *via* the detection of metabolic acidosis, hyperglycemia, and ketonuria or ketonemia.[9,10] The evaluation of urine AcAc, using a dipstick test; and the identification of β-OHB, using a hand-held ketone sensor are all proposed techniques for detecting elevated ketone bodies. However, the measurement of β-OHB, using a laboratory assay, is not universally accessible, so it is impractical in most emergency scenarios.

**Table II: Comparison of accuracy of finger-stick β-OHB method and dipstick urine test for the detection of ketone bodies to detect DKA by taking biochemical criteria for DKA as a reference standard.**

| | DKA | | Statistics |
|---|---|---|---|
| | Positive | Negative | |
| **Urinary ketones ≥2+** | | | |
| Positive | 62 | 2 | *Sn=84.9%, Sp=91.3%, PPV=96.9%, NPV=65.6%, DA=86.5% |
| Negative | 11 | 21 | |
| **Blood ketone levels >3mmol/L** | | | |
| Positive | 66 | 0 | Sn=90.4%, Sp=100%, PPV=100%, NPV 76.7%, DA=92.7% |
| Negative | 7 | 23 | |

**Sn,= Sensitivity, SP = Specificity, PPV = Predictive value, NPV = Negative predictive value, DA = Diabetic ketoacidosis.*

The most widely used approach for identifying ketones is a urine dipstick test, although there are certain limitations with its usage. For example, the dipstick method depends upon the nitroprusside, which changes its colour to purple with ketones, and can have subjective variations. It measures acetoacetate, but not β-OHB, which is the top-tier ketone in DKA. Moreover, urine collection can be troublesome and consume a lot of time or may even be very difficult in critically ill children in the emergency room. In addition, numerous researchers have discovered that this instrument is associated with a high risk of false-negative and false-positive results.[11-14] A false-positive rate is less hazardous depending on the severity of the disease because the disease may then be ruled out by blood gas analysis. A false-negative rate, on the other hand, may result in an underestimation of the ketotic status of the patient and, as a result, a DKA misdiagnosis.[15] In contrast, a finger-stick method is a tool for detecting the capillary blood ketone concentrations primarily β-OHB; and when compared with the laboratory assay methods of measuring β-OHB, the point-of-care technique only requires 5-µL capillary blood sample; and the results are commonly available in 30 seconds. Since 2014, the International Society of Pediatric and Adolescent Diabetes (ISPAD) has recommended to measure blood β-OHB for the diagnosis of ketoacidosis, whenever possible.[16]

According to Yu *et al.,* ketone levels in urine typically rise despite lowering blood β-OHB concentrations because β-OHB is metabolised to acetoacetate during therapy.[17] Furthermore, in children with T1DM, home-based monitoring of ketones enhances compliance with assessing the ketotic status during sick days and reduces the number of emergency department visits and hospitalisations.[18] In the present study, when children were assessed for ketone levels using urine dipstick (urine ketone levels ≥ 2+), 64 of 96 children had ketonuria. Furthermore, 66 of 96 children had ketonemia (β-OHB >3 mmol/L by finger-stick method). In another similar study, the β-OHB assay was compared with the semi-quantitative urine ketone assay and found a weak to moderate agreement between the two methods (Kappa = 0.66; 95%, CI: 0.55 to 0.77).[11] Another study by Taboulet *et al*. also revealed a good concordance between urine ketones and blood ketone levels for small values in the adult population; whereas, poor agreement was found for higher values.[19]

In this research, it was found that β-OHB >3 mmol/L had higher sensitivity (90.4% *vs*. 84.9%), specificity (100% *vs.* 91.3%), and accuracy (92.7% *vs*. 86.5%) than urinary ketones for the detection of DKA. While previous research revealed that β-OHB >3 mmol/L is 100% sensitive and 88% specific in detecting DKA, urine dipstick had a sensitivity of 100% and specificity of 58%, respectively.[20] As a result, appropriate β-OHB sensitivity and specificity have the potential to reduce needless DKA work-ups in hyperglycemic patients by up to 57%.[13] It is not unanticipated that β-OHB in the blood is a more accurate marker than AcAc in urine for insulin deficiency detection as β-OHB levels in the event of sudden insulin deficiency increase rapidly, while urinary AcAc excretion is delayed as it relates to glomerular filtration and, therefore, renal function and hydration.[19,21-23] Urine ketones also reflect the NAD+ or NADH balance, which is changed in some individuals with insulin deficiency or liver disease. Finally, urine dipsticks give a semi-quantitative assay and the finding may be affected by the presence of some medicines or food.[24,25] Due to the high accuracy of blood ketones, most of the researchers now suggest this tool in high-risk patients, especially in the emergency room.[11,13,16,19]

Despite the obtained results, this research had a few limitation. The sample size of the present study was relatively small. Furthermore, it was a single institute-based study. Therefore, more research with a larger sample size based on more centres should be done in the future to improve the accuracy of results.

## CONCLUSIONS

For the measurement of ketones in hyperglycemic children, the finger-stick β-OHB method can be used instead of the urine dipstick approach. It can be utilised to rule out ketosis, and diagnose DKA in hyperglycemic children. Being the point-of-care method, which is more convenient and accurate, it will aid in early detection and reduce unnecessary delays in DKA management.

### ETHICAL APPROVAL:

Ethical approval was obtained from the Institutional Review Board (IRB) of the National Institute of Child Health, Karachi under IERB No. 35/2020.

### PATIENTS' CONSENT:

Informed consents were obtained from all patients to publish the data concerning this case.

### CONFLICT OF INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

PDL: Concept and design, critical revision, acquisition of data, final approval.

MI, SJR, MG: Concept and design, drafting, critical revision, final approval.
SHB: Concept and design, data analysis, interpretation and final approval.

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