

USE OF CAPILLARY β -HYDROXYBUTYRATE FOR THE DIAGNOSIS OF DIABETIC KETOACIDOSIS AT EMERGENCY ROOM: OUR ONE-YEAR EXPERIENCE

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Key words: diabetic ketoacidosis, ketone body, β -hydroxybutyrate

SUMMARY

Diabetic ketoacidosis (DKA) is a life threatening acute complication of diabetes characterized by metabolic derangements caused by an imbalance of glucoregulatory hormones. Ketone bodies (the terminology is traditional, not scientific) as one of the main manifestations are usually tested in urine where their occurrence does not reflect their actual blood levels. Quantitative measurement of the blood ketone bodies (β -hydroxybutyrate) in capillary blood is now available. We conducted a retrospective study by reviewing laboratory data of patients treated at Emergency Room. The primary objective of this study was to assess the relationship between urine ketones and blood ketones. The study included 122 patients. Six patients met the criteria for DKA, whereas the others had either diabetic ketosis or were free from hyperglycemic complications. The main finding of the study was elevation of blood ketones beyond 3.5 mmol/L, which correlated much better with diabetic

ketoacidosis than +++ urine ketones. Good correlation between urine ketones and blood ketones was observed at a low concentration of urine ketone bodies.

INTRODUCTION

Diabetic ketoacidosis (DKA) is a life threatening acute complication of diabetes that is associated with considerable mortality and morbidity (1,2). Although the mortality rate has diminished, little improvement has been evident in recent years and the incidence of DKA remains over 20% in patients over 65 years of age (3). DKA is characterized by elevated blood glucose, elevated levels of ketone bodies in the blood, and metabolic acidosis (4). These metabolic derangements are caused by an imbalance of glucoregulatory hormones, mainly glucagon/insulin ratio (5). The lack of insulin and elevations of the counter-regulatory hormones lead to activation of enzymes which stimulate lipolysis in the adipose tissue and ketogenesis in the liver (6,7). During the process of ketogenesis, free fatty acids are transformed into acetoacetate (AcAc) and β -hydroxybutyrate (3-OHB). 3-OHB is formed from the reduction of AcAc in the mitochondria. Acetone, the least abundant ketone body, is generated by spontaneous decarboxylation of AcAc (8). The ketone body ratio,

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defined as the ratio of circulating 3-OHB to AcAc, is approximately 1:1 (9). This ratio rises in DKA to 3:1 or higher, to as high as 10:1, resulting in 3-OHB being the most concentrated blood ketone body. In DKA, the rate of ketone body generation always exceeds the combined rates of ketone body utilization and renal excretion (10). Ketone bodies are usually tested in urine where their occurrence does not reflect their actual blood levels, given that the commonly used nitroprusside strips for ketone body monitoring in the urine react only with AcAc and acetone but not with the most prevalent form of ketone body in the blood, i.e. 3-OHB (5). DKA may be preventable in patients with diabetes if the presence of ketones is recognized early and treatment is initiated (12,13). It is estimated that 50% of hospital admissions for DKA could be prevented with improved outpatient treatment and better adherence to self-care (14,15). Quantitative measurement of 3-OHB in capillary blood with an accurate near patient meter is now available. The method is reliable and precise, and results are available in 20 s (11). Since 2004, the American Diabetes Association (ADA) no longer recommends the nitroprusside method to test for ketone bodies in the blood or urine and prefers quantitative determination of blood 3-OHB for the diagnosis and follow up of DKA (20). In this retrospective study, we evaluated the usefulness of blood ketone body determination in detecting DKA in Emergency Room (ER). Statistical analyses were performed using the SAS statistical software system.

MATERIALS AND METHODS

We conducted a retrospective study by reviewing laboratory data of patients treated at ER of the Vuk Vrhovac University Clinic in Zagreb during a one-year period, where capillary blood glucose, urine ketones, blood ketones, arterial pH, plasma bicarbonate level and plasma osmolality were available.

Ketonuria was measured with dipsticks (Multistix[®]) read by Clinitek 50 (Bayer). With this dipstick, +, ++ or +++ urine ketones correspond to 1.5, 5.0 or 8.0 mmol/L of AcAc, respectively. Capillary blood ketones were measured with a dipstick read by a Medisense Optium meter (Abbott Laboratories,

MediSense). The meter enables quantitative measurement of 3-OHB in a range of 0.0-6.0 mmol/L. The accuracy of capillary 3-OHB measurements has been documented. Its accuracy tested against a reference laboratory instrument is optimal in the range between 0 and 6 mmol/L (11,17). Blood glucose was measured in the laboratory by the spectrophotometric method. The diagnosis of DKA was made according to ADA 2004 guidelines: plasma glucose >13.9 mmol/L with: (1) arterial pH <7.30 and serum bicarbonate level <15 mmol/L and (2) moderate ketonuria and/or ketonemia (18). Diabetic ketosis was defined as ketonemia by either urine dipstick finding of AcAc >1.5 mmol/L or 3-OHB level >1.0 mmol/L in capillary blood and evidence for compensated metabolic acidosis (pH >7.3 and bicarbonate 15-24 mmol/L) (19). A blood ketone level less than 0.5 mmol/L is considered to be physiological, hyperketonemia is defined by a value greater than 1 mmol/L and ketoacidosis is considered to be probable above 3 mmol/L (1,11). To describe the relationship between urine ketones and blood ketones in hyperglycemic subjects in ER, we studied blood ketone values in correlation with various urine ketone values, plasma glucose level, arterial pH value and plasma bicarbonate value. A structured questionnaire contained data on patient sex, type of diabetes and urine glucose level. Correlations between various urine ketones, blood ketones, plasma bicarbonate level, plasma glucose level, arterial pH and plasma osmolality were analyzed.

RESULTS

In the files reviewed for the study, the required tests were performed in 122 patients. There was a slight male predominance (71/122, 58.1%). The median age was 58 years (men: 55 years, range 28-80, and women: 62 years, range 26-83). Type 2 diabetes mellitus was diagnosed in 111 (90.1%) patients. Six of 122 (5%) patients met the criteria for DKA. Ketoacidosis was detected in 100% of patients with blood ketones greater than or equal to 4.9 mmol/L. Twelve patients had blood ketone levels between 1.5 and 3.5 mmol/L, and none of these met the clinical criteria for DKA. The median 3-OHB level was 5.25 (range 5.2-5.9)

Table 1. Clinical and metabolic characteristics of study patients

Characteristic	Diabetic ketoacidosis ^a	Others ^a	Z χ^2	P ^b
Sex (M:F ratio)	2:4	49:67	0.57	0.45
Age (yrs)	49 (26-58)	58 (50-68)	2.03	0.04*
Type 1 diabetes mellitus	1	12		
Type 2 diabetes mellitus	5	104	0.04	0.63
3-OHB (mmol/L)	5.25 (5.2-5.9)	0.4 (0.2-0.9)	4.1	<0.001**
Plasma glucose (mmol/L)	25.5 (23.3-39.5)	16.6 (13.9-19.7)	3.4	<0.001**
Bicarbonate (mmol/L)	14.2 (9.7-15.5)	22.1 (20.0-23.7)	-3.90	<0.001**
Arterial pH	7.25 (7.16-7.29)	7.39 (7.37-7.42)	-3.95	<0.001**
Plasma osmolality mosm/L	302.5 (292-315)	299 (296-303.5)	0.66	0.50

a = data expressed as median (interquartile range) or frequency; b = P value refers to either Mann-Whitney test or χ^2 ; *significance at 95% confidence level; **significance at 99% confidence level

Table 2. Relationship between blood and urine ketone bodies in patients with ketonuria (\geq +))

Urinary ketones (+) ^b	Range of capillary blood ketones (mmol/L) ^a			
	0-0.6	0.6-1.0	1.0-3.0	>3.0
(+)	45 (82)	6 (11)	4 (7)	0 (0)
(++)	7 (39)	7 (39)	3 (16)	1 (6)
(+++)	5 (15)	4 (12)	18 (54)	6 (19)

a = data expressed as number of patients (%); b = urine acetoacetate: +: 1.5 mmol/L; ++:5.0 mmol/L; +++:>8.0 mmol/L

mmol/L in patients with DKA and 0.4 (range 0.2-0.9) mmol/L in patients with ketonuria \geq +. In DKA patients, the mean plasma glucose was 25.5 mmol/L (range; 23.3-39.5) and mean plasma bicarbonate level 14.2 (range 9.7-15.5) mmol/L (Table 1). In the group of patients with negative or traces of urine ketones, all patients (100%) had blood ketones \leq 0.5 mmol/L. Patients with ++ and +++ urine ketones were distributed within the following blood ketone ranges: 0.2-1.6 and 0.3-5.9 mmol/L, respectively (Table 2).

At three-cross cut-off point for ketonuria, the sensitivity was 100% but specificity was only 15.4% (5/33). In all DKA cases, arterial pH was <7.3 and serum bicarbonate level <15.0 mmol/L. The most severe case of DKA had arterial pH 7.16, serum bicarbonate level 5.9 mmol/L and osmolality 348 mosm/L.

DISCUSSION

The primary objective of this study was to assess the relationship between urine ketones and blood ketones of patients admitted to ER. The secondary objective was to compare the value of these two tests and of other laboratory data.

We compared data on urine ketones, blood ketones, arterial pH, plasma bicarbonate level and plasma osmolality of 122 patients treated at our ER. The main finding of our study was that elevation of blood ketones beyond 3.5 mmol/L showed considerably better correlation with diabetic ketoacidosis than +++ of urine ketones. The measurement of 3-OHB in capillary blood is faster and more effective than the use of dipsticks in the urine to detect ketoacidosis (25,26).

Our results confirmed good correspondence between the low value of urinary AcAc (0 to trace \pm) and a significantly low (0-0.5 mmol/L) β -hydroxybutyrate in capillary blood, as 100% of non-ketonuric patients had blood ketones in the normal range of 0-0.5 mmol/L. It also showed the risk of ketoacidosis to be zero at blood ketones <1.0 mmol/L and/or urinary ketones less than ++, and to be high at blood ketones \geq 5 mmol/L but not at urinary ketones +++ (24). There was a broad range of blood ketones comparing with urinary ketones, especially with +++ urinary ketones. In study patients, plasma bicarbonate levels <15.0 mmol/L and 18-20 mmol/L were demonstrated to correspond to capillary blood 3-OHB levels >3.0 mmol/L and 2.0-3.0 mmol/L, respectively. It appears useless to assay serum bicarbonate in a patient with blood ketones less than or equal to 1 mmol/L and it seems acceptable to treat patients with blood ketones greater than or equal to 5 mmol/L without waiting for serum bicarbonate results (29). We also found an advantage of urine ketone body determination in diagnosing DKA comparing with plasma bicarbonate level. The urine ketone dipstick test is superior to anion gap or serum bicarbonate as a screening test for DKA and diabetic ketosis (28).

We found a number of patient files lacking data of urine analyses. The reason is that patients are often unable to produce a urine specimen when they first present to ER. The voiding problem has been emphasized in several studies (24,25). It is one of the main disadvantages of urinary ketone determination.

The quantitative assay of β -hydroxybutyrate in blood is more precise than urine dipstick detection of AcAc, as blood levels of β -hydroxybutyrate increase rapidly in case of sudden insulin deficiency, while urinary excretion of AcAc is delayed, as it is dependent on glomerular filtration and therefore on renal function and degree of hydration (5). Health care professionals should be aware, however, that currently available urine ketone tests are not reliable for diagnosing or monitoring the treatment of ketoacidosis. Blood ketone testing methods that quantify β -hydroxybutyric acid as the predominant ketone body are available and are preferred to urine ketone testing for diagnosing and monitoring ketoacidosis. Home tests for β -

hydroxybutyric acid are available (20). Several authors have emphasized that measurement of 3-OHB is preferable because it does not require any additional work at hospital department (21). This method offers the advantage of producing results that are much faster since it is not necessary to wait and collect urine (18,21). Using a level of 3.5 mmol/L, it yielded 100% sensitivity, specificity, positive and negative predictive values. Our findings were consistent with the literature reports available (22). In the present study, all cases diagnosed with DKA were hospitalized and there was no mortality. Most of cases with hyperketonemia and/or hyperketonuria were successfully treated at ER. Our study showed both methods, i.e. quantitative determination of 3-OHB and urine dipstick analyses of AcAc, to be equally effective in patients free from hyperglycemic complications.

This new method of blood ketone body determination carries a higher cost than the method of urinary measurement. Health authorities of some EU countries have limited its reimbursement to populations of diabetic patients who are most vulnerable to the risks of ketosis and ketoacidosis, including type 1 diabetes with insulin pump, children and teenagers up to 18 years of age and pregnant diabetic women (23).

Even though this study confirmed the excellent diagnostic accuracy of quantitative determination of blood 3-OHB, it has some limitations due to its retrospective and selective nature and a small number of patients with DKA. However, our findings can be applied to uncomplicated DKA patients.

In conclusion, our retrospective study showed that DKA was more accurately predicted by quantitative determination of 3-OHB than by urine dipstick analysis of AcAc in patients with higher concentration of ketones in the blood. Good correlation between urine ketones and blood ketones was recorded at a low concentration of urine ketone bodies. At a 3-OHB level >3.5 mmol/L, there is no doubt that treatment for DKA should be immediately initiated at ER, without waiting for arterial pH or serum bicarbonate level.

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