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Original Article

The diagnosis of diabetic acute complications using the glucose-ketone meter in outpatients at endocrinology department

Xu Cao, Xuejue Zhang, Yang Xian, Jichuan Wu, Mingjing Bao, Yan Yang, Xianjun Zhu, Lei Zhang, Limei Liu, Yi Yang, Hui Zhou, Pengqiu Li

Department of Endocrinology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Sichuan, China

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Abstract: Objective: To determine urine ketone and blood β-hydroxybutyrate acid (β-HBA) in outpatients of endocrinology department and to investigate the association between urine ketone or blood β-HBA and diabetic ketosis (DK) or diabetic ketoacidosis (DKA). Methods: Urine ketone, blood β-HBA, body mass index (BMI) and glycosylated hemoglobin (HbA_{1c}) were determined in 134 patients with blood glucose ≥ 13.9 mmol/L. Results: In 134 patients with severe hyperglycemia, there were 30 patients (22.4%) with acute complications of diabetes, including 24 patients (17.9%) diagnosed with DK and 6 patients (4.5%) diagnosed with DKA. Among them, 6 patients (20%) were withdrawal, 2 (6.7%) were infected, and 19 (63.3%) were not treated. When there was a negative urine ketone, 10% patients would have had blood β-HBA ≥ 0.3 mmol/L. When there was a positive urine ketone (+ to +++), 22.62% patients would have had blood β-HBA < 0.3 mmol/L. Conclusions: Blood β-HBA had a positive correlation with blood glucose (r = 0.34, P < 0.001). Complications of severe hyperglycemia could be diagnosed quickly and accurately by analyzing blood β-HBA using the glucose-ketone meter.

Keywords: Diabetic ketoacidosis, urine ketone, β-hydroxybutyrate acid, glucose-ketone meter

Introduction

Diabetes is a chronic disease which is associated with serious complications. Severe hyperglycemia is a sign of acute diabetic complications, including diabetic ketosis (DK) and diabetic ketoacidosis (DKA). The ketone bodies formed in DK or DKA are β-hydroxybutyrate acid (β-HBA) and acetoacetate [1]. It is important for diagnose complications in diabetic patients to determine the levels of ketone in urine or blood. The test used in urine ketone test strips is based on the reaction of sodium nitroprusside (nitroferricyanide). In this reaction, the acetoacetic acid in an alkali medium reacts with the sodium nitroprusside producing a magenta coloured complex. But urine test strips can't determine the β-HBA concentration. Because β-HBA is the most important ketone body to produce DKA, diseases are usually underestimated by only analyzing the urine ketone. Moreover results of urine ketone test will be affected by medicines which patients take. There are false-negative results when patients take medicines with sulfydryl, such as captopril, N-acetyl cysteine, dimercaprol dimercaptopropanol and penicillamine, or when patients take much vitamin C [2]. Urine ketones are also related to renal function, so blood β-HBA test is recommended by more and more researchers [3, 4]. In this study, acetoacetic acid (urine ketone) and β-HBA (blood ketone) were both determined in patients with severe hyperglycemia in endocrinology department to find the association between them and to investigate their relationships to DK or DKA.

Patients and methods

Patients

134 patients with fasting blood glucose (FBG) or random blood glucose (RBG) no less than 13.9 mmol/L were recruited from endocrinology out-patient department of Sichuan Provincial People's Hospital from June, 2013 to December, 2013. Patients with blood β-HBA from 0.6 to 3

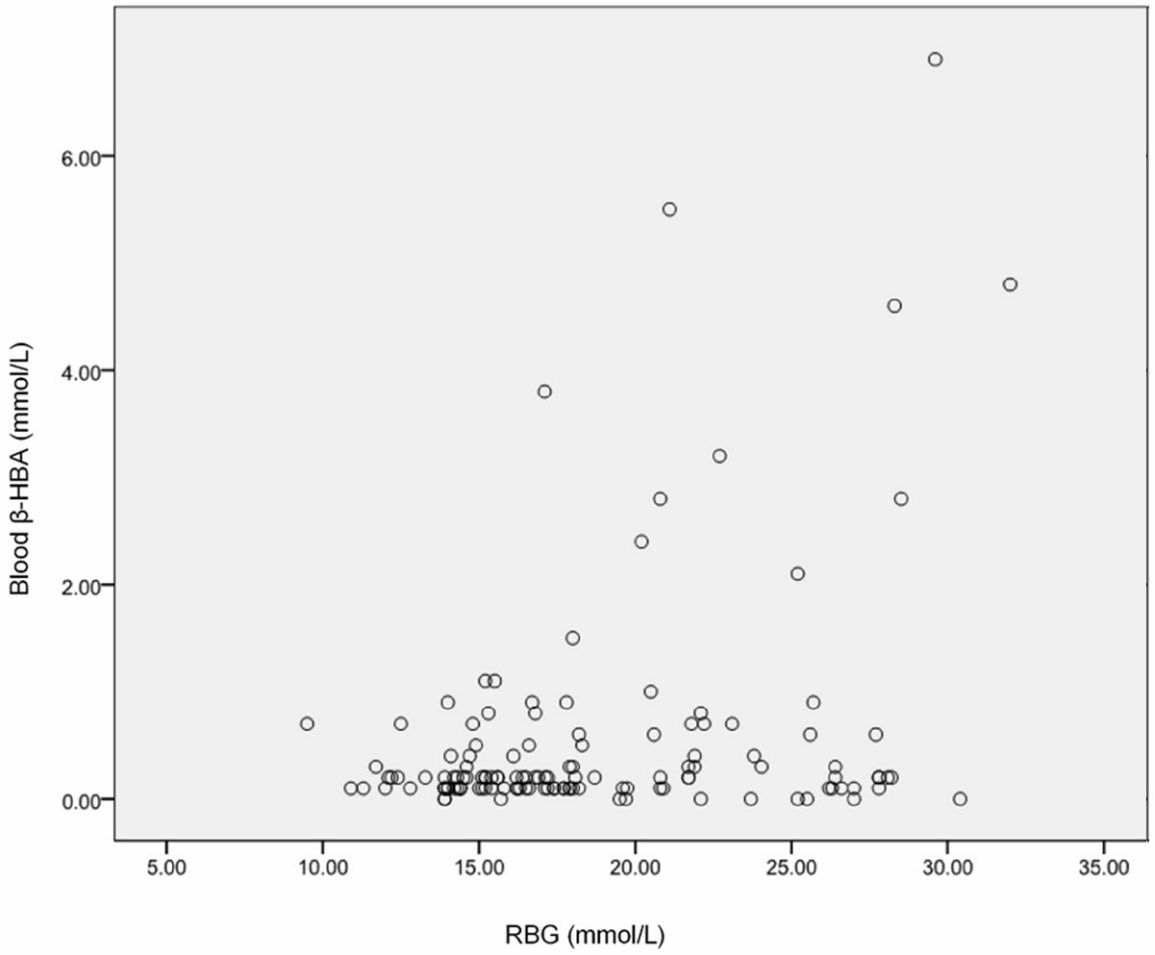

Figure 1. Correlation analysis of the blood β-HBA concentration and the level of blood glucose in diabetic patients. There was a positively correlation between them ($r = 0.34$, $P < 0.001$).

mmol/L and positive urine ketone were diagnosed with DK; patients with blood β-HBA ≥ 3 mmol/L and negative urine ketone were diagnosed with DKA. All subjects gave their informed consent.

Blood β-HBA and urine ketone tests

One drop capillary blood from fingertip was collected from every patient, and blood β-HBA was determined by MediSense Optium Blood Glucose-Ketone Meter (MediSense Optium Blood Glucose Sensor, USA). Urine ketone was tested using Multistix 10SG reagent strips (Siemens, Germany).

HbA_{1c} tests

2 ml venous blood was collected from every patient, and HbA_{1c} Kit (BIO-RAD, USA) for HPLC was used to determine the level of HbA_{1c} according to the manufacturer's instructions.

Statistical analysis

SPSS 18.0 was used for statistical analysis. All data were expressed as mean ± SD ($\bar{x} \pm s$), and the statistical differences between two groups were assessed by *t* test. Spearman's correlation was used to analyze the relationship between two variables. $P < 0.05$ indicated a significant difference, $P < 0.01$ indicated that there was a very significant difference.

Results

Diagnosis of patients

134 patients with severe hyperglycemia were composed of 73 males and 61 females, with an average duration of 2.83 ± 5.01 years, average BMI of 24.38 ± 4.0 kg/m^2, mean FBG of 8.72 ± 8.29 mmol/L, mean RBG of 12.46 ± 10.22 mmol/L, mean blood β-HBA of 0.55 ± 1.07 mmol/L, mean HbA_{1c} of 11.39 ± 2.07%. There

Table 1. Clinical data of low blood β-HBA group and high blood β-HBA group

	Low blood β-HBA group (< 0.6 mmol/L, n = 104)	High blood β-HBA group (≥ 0.6 mmol/L, n = 30)
Male	59 (56.7%)	14 (46.67%)
Age, y	52.13 ± 13.83	50.50 ± 14.97
Duration of diabetes, y	2.98 ± 5.23	2.58 ± 4.41
BMI, kg/m^2	24.43 ± 3.93	24.20 ± 4.18
FBG, mmol/L	15.57 ± 3.16	16.62 ± 3.96
RGB, mmol/L	20.14 ± 4.79	23.26 ± 4.58*
blood β-HBA, mmol/L	0.17 ± 0.14	1.84 ± 1.71*
HbA_{1c}, %	11.38 ± 1.83	11.78 ± 1.77

*, $P < 0.05$ *vs* Low blood β-HBA group.

Table 2. Urine ketone and blood β-HBA of patients with severe hyperglycemia

	Urine ketone					Sum
	(-)	(±)	(+)	(++)	(+++)	
Blood β-HBA (mmol/L)						
0.0-0.2	37	28	15	4	0	84
0.3-0.5	3	7	7	3	0	20
0.6-1.0	0	5	7	4	1	17
1.1-2.0	0	0	0	3	0	3
2.1-3.0	0	0	1	2	1	4
> 3.0	0	0	0	2	4	6
Sum	40	40	30	18	6	134

were 30 patients (22.4%) diagnosed with acute complications of diabetes, including 24 patients (17.9%) with DK and 6 patients (4.5%) with DKA. Among them, 6 patients (20%) were withdrawal, 2 (6.7%) were infected, and 19 (63.3%) were not treated.

The correlation between blood β-HBA and other indexes

As the correlation analysis, the blood β-HBA concentration and the level of blood glucose in diabetic patients were positively correlated (r = 0.34, $P < 0.001$) (**Figure 1**). However blood β-HBA and HbA_{1c} were not correlated (r = 0.161, P = 0.063).

Differences between low blood β-HBA group and high blood β-HBA group

RBG levels were significantly different between patients with blood β-HBA < 0.6 mmol/L and ≥ 0.6 mmol/L (**Table 1**). There were no significant differences between two groups in other indexes except blood β-HBA.

Urine ketone and blood β-HBA

As shown in **Table 2**, 10% patients (3/30) with negative urine ketone (-) had blood β-HBA ≥ 0.3 mmol/L. While 22.62% patients (19/84) with positive urine ketone (+ to +++) had blood β-HBA < 0.3 mmol/L.

Discussion

The three endogenous ketone bodies are acetone, acetoacetic acid, and β-HBA [5]. The β-HBA elevates much faster than acetoacetic acid and acetone at the early stage of DKA. Therefore DKA patients might be easily missed since urine ketone would be false-negative at early DKA. In treatment process, β-HBA is oxidized to acetoacetic acid resulting in elevated urine ketone and that might lead to the misleading mistaken exacerbations of DKA. But in fact has already declined. Shi Y *et al.* monitored urine ketone and blood β-HBA in 66 patients with DK or DKA, finding that 17.86% patients with negative urine ketone (-) had blood β-HBA ≥ 0.3 mmol/L and 19.41% patients with positive urine ketone (+ to +++) had blood β-HBA < 0.3 mmol/L [6]. Li Q [7] reported that the blood β-HBA was 0.3 mmol/L or over in 18.2% patients with negative urine ketone (-) and the blood β-HBA was less than 0.3 mmol/L in 44.18% patients with positive urine ketone (+ to +++). Our results and these reports all suggested that it is more reliable to diagnose DK or DKA by blood β-HBA than urine ketone.

A portable blood glucose-ketone meter determines blood β-HBA concentration accurately by using only 5 μL capillary blood sample within 30 s. Using this meter, patients with DK or DKA can be diagnosed at the early stage of illness and can be treated in time. Point-of-care test of blood ketone has been reported as an accurate and repeatable method to monitor patients with DK or DKA rather than urine ketone test [8]. Luo W *et al.* checked blood ketone by using rapid glucose-ketone meter in 113 cases of suspected DKA patients to point that the rapid

blood ketone assay was positive correlated with the automated chemistry assay ($P < 0.01$) and gave a sensitive of 100% and specificity of 100% in the diagnosis of DKA [9]. Voulgari C and Tentolouris N's study also indicated that serum and capillary β-HBA values were highly correlated ($r = 0.99$, $P < 0.001$) [10].

Voulgari C *et al.* reported that 50 patients (11.1%) had DKA from 450 type 2 diabetes mellitus insulin-treated patients attending the emergency room with a capillary glucose level > 13.9 mmol/L. In their study, 80% patients with DKA compared to 20% of patients without DKA were inadequately treated with insulin and missed clinic appointments [10]. In our study, 22.4% patients with blood glucose ≥ 13.9 mmol/L were diagnosed with DK or DKA. In these patients, 20% were withdrawal, 6.7% were infected and newly diagnosed non-treated patients were up to 63.3%. Therefore besides controlling the blood glucose level, early detection and treatment was very important for Chinese diabetic patients.

Compared to patients with low blood β-HBA, patients with high blood β-HBA had greater random blood glucose (23.26 ± 4.58 mmol/L *vs* 20.14 ± 4.79 mmol/L, $P < 0.05$). It suggested that the level of blood ketone was only associated with blood glucose rather than HbA_{1c}, the duration of illness, age, BMI or gender. So to avoid missed diagnosis or inadequacy treatment, patients with severe hyperglycemia must be examined to exclude DK or DKA firstly.

There are several limitations in our study. One problem is that there is no ELISA for β-HBA. Since there have already been many reports to prove the accuracy and reliability of the rapid blood ketone test, we didn't repeat the correlation test. Otherwise blood gas analyze was not performed in outpatients, so we used positive urine ketone and blood β-HBA ≥ 3 mmol/L as the diagnostic criteria of DKA. In Voulgari C and Tentolouris N's study capillary ketonemia (β-HBA > 3.0 mmol/L) had the highest performance (sensitivity 99.87%, specificity 92.89%, positive predictive value 92.89%) for the diagnosis of DKA compared with serum ketonemia (sensitivity 90.45%, specificity 88.65%, positive predictive value 87.76%) or ketonuria (sensitivity 89.89%, specificity 52.73%, positive predictive value 41.87%) [10]. Therefore we believed urine ketone test combined with blood β-HBA test would have a high sensitive and specificity.

In conclusion, a rapid fingertip β-HBA test using the glucose-ketone meter can determine β-HBA concentration easily and accurately. Doctors of endocrinology department using a glucose-ketone meter can diagnose diabetic acute complications rapidly and patients would be treated in time to prevent adverse outcomes caused by missed diagnosis and delayed treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Pengqiu Li, Department of Endocrinology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu 610072, China. E-mail: pengqiuli612-@163.com

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