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Usefulness of a blood glucose and ketone monitoring device as a screening tool for lethal diabetic ketoacidosis

Pierre-Antoine Peyron¹ · Maëlle Plawecki² · Maisy Lossois¹ · Manuela Lotierzo² · Eric Baccino¹ · Jean-Paul Cristol²

Abstract

Diabetic ketoacidosis (DKA) is a frequent and life-threatening complication, whose diagnosis remains challenging in forensic practice. We aimed at assessing the performance of a commercially available blood glucose and ketone monitoring device (BGMD) in measuring glucose and ketone levels in post-mortem vitreous (VH) and blood samples, in order to determine if such a device can be used for screening lethal cases of DKA at autopsy. VH and blood samples were collected in cases of unexplained causes of death at autopsy. Glucose and β -hydroxybutyrate (BHB) were measured in VH and BHB in blood using the BGMD. The values were compared to those obtained with validated enzymatic methods. Values ≥ 10 mmol/L were considered to be elevated for glucose, and BHB values ≥ 2.5 mmol/L were considered to indicate ketoacidosis. There was a strong and significant correlation between VH glucose and blood BHB concentrations measured with the BGMD and the validated method ($r = 0.78$ and $r = 0.80$, $p < 0.0001$, respectively), whereas no correlation was found for VH BHB values ($r = 0.19$, $p = 0.19$). The sensitivity and specificity of the BGMD were both excellent (1.0) to detect elevated VH glucose levels with a threshold of 14.4 mmol/L, and to detect elevated blood BHB levels with a threshold of 2.85 mmol/L. In contrast, the specificity of the BGMD to detect high BHB levels in VH was poor (0.50) with an optimal threshold of 2.5 mmol/L. We showed that a commercially available BGMD is suitable for identifying cases of lethal DKA and other metabolic disorders at autopsy, through the investigation of vitreous glucose and blood BHB. We therefore recommend the systematic use of a BGMD for screening these conditions in cases of unexplained deaths.

Keywords Diabetic ketoacidosis · Blood glucose monitoring device · Screening · Autopsy · Post-mortem biochemistry · Forensic pathology

Introduction

Diabetic ketoacidosis (DKA) is a frequent and potentially lethal complication of diabetes mellitus [1]. It is characteristically associated with type 1 diabetes (DM1) but can also occur in type 2 (DM2). Lack of insulin associated with concomitant enhanced release of counter-regulatory hormones results in a

significant decrease in glucose uptake and in an increase in glucose production, leading to hyperglycemia. In parallel, increased lipolysis leads to the production of ketone bodies followed by acidosis, resulting in ketoacidosis [2].

As DKA is a life-threatening condition, it is therefore a potential forensic issue. A recent study showed that in a forensic setting, acute metabolic complications mainly consisted in DKA and were the second most common cause of death in type 1 diabetics regardless of the ages, after cardiovascular disease [3].

In forensic practice, the diagnosis of lethal DKA can only be made using post-mortem biochemistry, due to the lack of specific changes associated with DKA neither at autopsy nor at the histological exam [4]. Vitreous humor is the matrix of choice, in which glucose and β -hydroxybutyrate (BHB, the most specific ketone for the diagnosis of DKA) are measured post-mortem to assess ante-mortem hyperglycemia and ketoacidosis [5–8]. Blood BHB values can alternatively be

Pierre-Antoine Peyron and Maëlle Plawecki contributed equally to this work.

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measured to assess ante-mortem ketoacidosis [5]. However, such a biochemical diagnosis may be technically challenging, as it requires validated laboratory methods, which involve well-defined pre-analytical and analytical procedures [1]. Other drawbacks include rapid and appropriate sample transportation to the laboratory and delayed results due to the process time. An efficient approach would therefore consist in limiting such laboratory analyses to pre-selected cases, in order to reduce unnecessary investigations.

It has been suggested that a commercially available blood glucose and ketone monitoring device (BGMD) could be of possible interest for the screening of high glucose and ketone levels in post-mortem vitreous [9]. Such a device requires a small sample size, it is known to provide rapid results and can be easily used at the time of the autopsy or external examination. However, further research is necessary as post-mortem blood remains to be investigated and appropriate thresholds need to be confirmed.

In the present study, we aimed at assessing the suitability of a BGMD for screening lethal cases of DKA. Our objectives were (1) to confirm the performance of such a device in measuring high glucose and ketone levels in post-mortem vitreous, (2) to assess its performance in measuring high ketone levels in post-mortem blood, and (3) to determine appropriate thresholds to be applied based on those recommended in the literature.

Material and methods

Study population

From August 2018 to January 2020, deceased adult subjects whose cause of death was unexplained at the scene and who were brought for a post-mortem examination to the medicolegal institute of the University Hospital of Montpellier, France, were included. Medical records, police reports, and post-mortem investigations were reviewed in each case. For the purpose of the study, we paid particular attention to the inclusion of cases with a medical history of DM1/DM2. Decomposed bodies were not included.

Blood glucose and ketone monitoring device

We used a commercially available FreeStyle® Optium Neo BGMD (Abbott, diabetes healthcare, UK), with its specific test strips for glucose and ketone, according to the manufacturer's instructions. The ketone test strips are specifically designed for measuring BHB, which is the ketone of interest for the diagnosis of DKA. The measuring range for glucose is 1.1–27.8 mmol/L and for BHB 0–8 mmol/L.

Sample collection and BGMD analyses

Vitreous samples were collected in dry tubes at autopsy, using a 5 mL syringe equipped with an 18-gauge needle. Glucose and BHB concentrations were immediately measured with the studied BGMD. In some cases, vitreous samples from both eyes were collected separately to compare glucose and BHB concentrations between eyes with the device. In parallel, peripheral blood specimens from some of the same subjects were collected, and BHB levels were measured with the BGMD. Blood samples were placed in lithium heparin and EDTA tubes for further analyses (Fig. 1). For some vitreous and blood samples, glucose and BHB concentrations were measured twice in the same sample to assess the measurement repeatability with the BGMD.

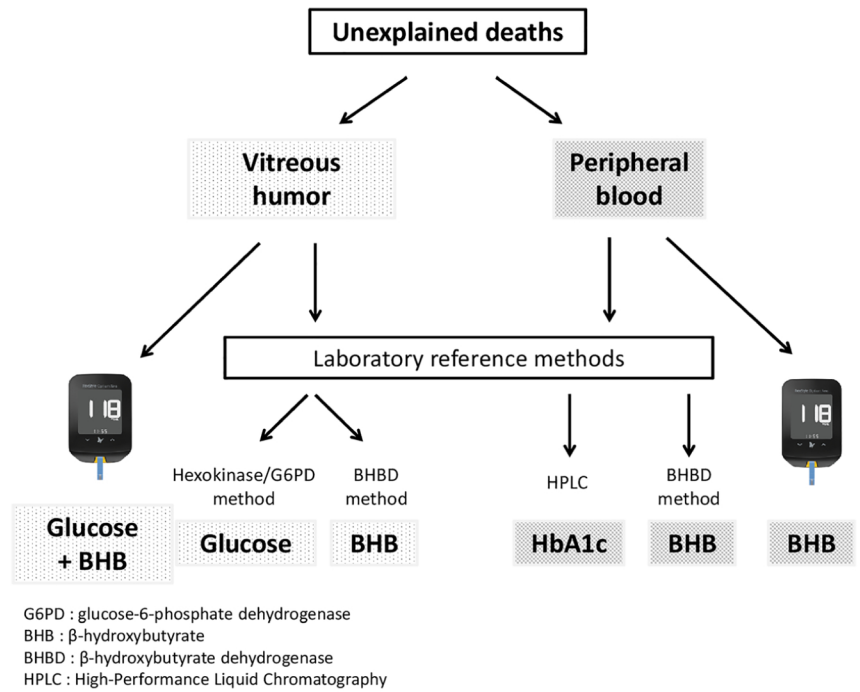
Biochemical analyses

Vitreous and blood samples were immediately sent on ice to the biochemistry laboratory. Upon receipt, samples were deproteinized with perchloric acid then centrifuged (2000 g, 10 min, +4 °C), except EDTA tubes that were directly stored at +4 °C. Supernatant was stored at –20 °C until analysis. After neutralization of the supernatant, vitreous glucose and BHB levels from both eyes were measured. Vitreous glucose levels were determined on a Cobas 8000 c701 (Roche diagnostics, Switzerland) with a reference enzymatic method using hexokinase/glucose-6-phosphate dehydrogenase. BHB concentrations in vitreous and deproteinized blood were determined on a BS-480 analyzer (Mindray, China) with a commercial enzymatic method using BHB dehydrogenase (BHBD) (Biosentec, France). Glycated hemoglobin (HbA1c) was determined by high-performance liquid chromatography (HPLC) (Tosoh, Japan) on EDTA blood samples. HbA1c ≥ 6.5% (48 mmol/mol) was considered as diagnostic criteria for diabetes [10, 11]. The thresholds applied to the reference methods for the diagnosis of lethal DKA were based on recommendations in the literature: 10 mmol/L for vitreous glucose and 2.5 mmol/L for vitreous and blood BHB [1, 5, 7, 12–16].

Statistical analysis

The Mann-Whitney *U* test and the unpaired *t* test were used to compare glucose and BHB concentrations between eyes. The measurement repeatability and the general agreement between the BGMD and the biochemical methods were assessed using Lin's concordance correlation coefficient (CCC) [17] and Bland-Altman analyses. Glucose and BHB levels measured with the BGMD and

Fig. 1 General workflow of the study



the biochemical methods were compared using a simple linear regression analysis, and Spearman’s rank correlation coefficient was computed for correlation analyses. ROC curves were used to determine appropriate thresholds for high glucose and BHB levels with the BGMD. A p value <0.05 was considered statistically significant. Graphpad Prism® (version 8.4) was used for graphics and statistical analysis.

Results

A total of 68 individuals (51 men, 17 women) were included, with a mean age of 56.5 ± 15.0 years. Thirty-four subjects were known or suspected to be diabetic (5 DM1, 19 DM2, and 10 with unclear subtype of diabetes). The PMI ranged from 0 to 9 days (mean 3.5, SD 1.9).

Table 1 Comparison of vitreous glucose and BHB concentrations between eyes

		Mean	95%CI	P value
Glucose ($n = 28$)	VH1	8.47	6.64; 10.31	0.74 ^a
	VH2	8.39	6.39; 10.39	
BHB ($n = 31$)	VH1	2.75	2.28; 3.22	0.88 ^b
	VH2	2.80	2.30; 3.31	

VH1 and VH2 represent the two different eyes

^a Mann-Whitney U test

^b Unpaired t test

Between-eye vitreous concentrations and measurement repeatability

There was no statistically significant between-eye difference in vitreous glucose and BHB concentrations (Table 1), and we observed almost perfect repeatability and correlation of the measurements in vitreous and blood (Table 2).

Vitreous glucose concentrations

There was a strong and significant correlation between concentrations measured with the BGMD and the validated method ($n = 51$; $r = 0.78$, $R^2 = 0.74$, $p < 0.0001$) (Fig. 2). Despite this strong correlation, a moderate concordance between both methods was noted (CCC = 0.57) (Table 3), and the Bland-Altman analysis showed a great variation between the differences in concentrations measured by both methods, with a

Table 2 Repeatability of the measurements in vitreous and blood with the BGMD

	Matrix	CCC ^a	95% CI	P value
Glucose ($n = 13$)	VH	0.91	0.74; 0.97	0.92 ^b
BHB ($n = 17$)	VH	0.99	0.96; 1.00	0.99 ^c
BHB ($n = 16$)	Blood	0.98	0.93; 0.99	0.98 ^b

^a Lin’s concordance correlation coefficient

^b Spearman’s rank correlation coefficient

^c Pearson correlation coefficient

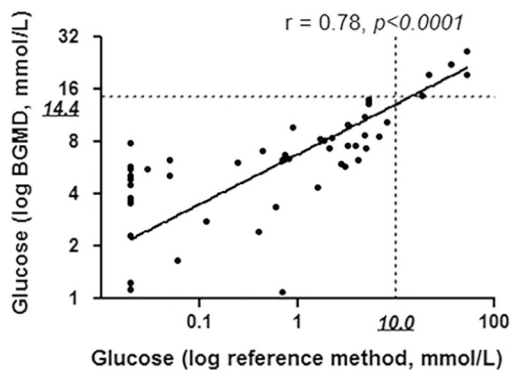


Fig. 2 Correlation between vitreous glucose concentrations measured with the BGMD and the biochemical reference method ($n = 51$)

bias in favor of the BGMD (Fig. 3). Mean values measured with the BGMD were significantly higher to those obtained with the validated method. However, the BGMD tended to underestimate high glucose values. The sensitivity and specificity of the BGMD to detect elevated VH glucose levels were both 1.0 when the threshold value was set to 14.4 mmol/L (Fig. 2).

Vitreous BHB concentrations

We observed no correlation between values obtained with both methods ($n = 51$; $r = 0.19$, $R^2 = 0.18$, $p = 0.19$), and a poor concordance between both methods was noted ($CCC = 0.09$) (Table 3). With an optimal threshold value of 2.5 mmol/L, the sensitivity and specificity of the BGMD to detect elevated vitreous BHB were 1.0 and 0.5, respectively.

Blood BHB concentrations

There was a strong and significant correlation between concentrations measured with the BGMD and the validated method ($n = 29$; $r = 0.80$, $R^2 = 0.74$, $p < 0.0001$) (Fig. 4). As with vitreous glucose, the Bland-Altman analysis showed, however, a great variation between the differences in concentrations measured by both methods, with a bias in favor of the BGMD which tended to overestimate BHB levels, except for high values (Fig. 5). A fair concordance between both methods was noted ($CCC = 0.50$) (Table 3). A threshold value of

Table 3 Agreement between the BGMD and the biochemical methods

	Matrix	CCC ^a	95%CI	<i>P</i> value ^b
Glucose ($n = 51$)	VH	0.57	0.45; 0.68	0.78
BHB ($n = 51$)	VH	0.09	-0.03; 0.20	0.22
BHB ($n = 29$)	Blood	0.50	0.36; 0.62	0.78

^a Lin's concordance correlation coefficient

^b Spearman's rank correlation coefficient

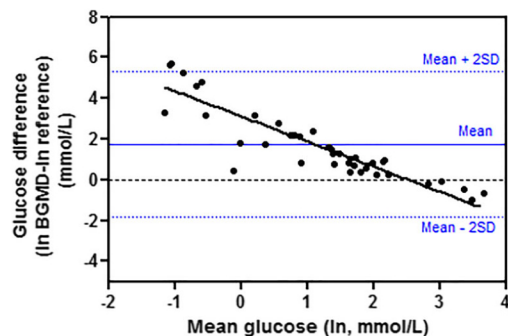


Fig. 3 Bland-Altman plots for method comparison as regards vitreous glucose measurements

2.85 mmol/L gave excellent sensitivity and specificity (both 1.0) (Fig. 4).

Discussion

The aim of this study was to assess the performance of a commercially available BGMD in measuring glucose and BHB levels in post-mortem vitreous and blood samples, in order to determine if such a device could be used for screening potential DKA cases at autopsy.

The studied BGMD allowed the detection of high vitreous glucose levels, and proved to be highly sensitive (1.0) and specific (1.0) with a cutoff value of 14.4 mmol/L. These results are in line with those of Walta et al. [9], who found a sensibility and specificity of 1.0 and 0.94, respectively. Among the 51 subjects these authors included in their study, they were able to identify 19/21 cases with high vitreous glucose levels (versus 5/5 in our study), using the same BGMD. However, the inclusion criteria of the population they studied were not specified, and they applied a lower cutoff value to the biochemical reference method (7.0 mmol/L) that could have significantly overestimated positive cases. As suggesting by prior research [18, 19], we observed no significant between-eye difference in glucose concentrations (Table 1), confirming that BGMD analyses can be performed in one or the other eye. In addition, the measurement repeatability was found to be

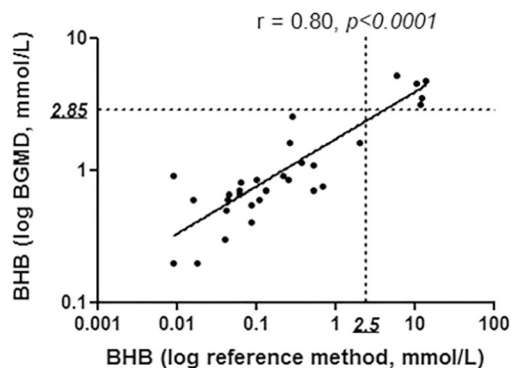


Fig. 4 Correlation between blood BHB concentrations measured with the BGMD and the biochemical reference method ($n = 29$)

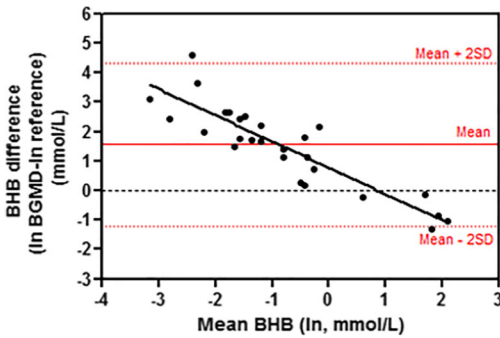


Fig. 5 Bland–Altman plots for method comparison as regards blood BHB measurements

excellent (Table 2), and the correlation between concentrations measured with the BGMD and the reference enzymatic method was strong (Fig. 2). Our study therefore confirmed the performance of the studied BGMD in detecting increased glucose values in vitreous, and thus ante-mortem hyperglycemia.

In contrast, high vitreous ketones could not be reliably investigated with the studied BGMD, which showed an excellent sensitivity (1.0) but a poor specificity (0.50) with an optimal threshold of 2.5 mmol/L, leading to many false-positives and unnecessary laboratory analyses. These findings were partly consistent with those of Walta et al. [9], who found the same BGMD to be as sensitive (1.0) but more specific (0.72). However, the authors used in their study an alternative analytical method (Headspace Gas Chromatography) and quantified total ketone bodies, instead of solely quantifying BHB [1]. In addition, they applied an arbitrary cutoff of 3.0 mmol/L as the reference threshold. These differences in the methodological approach could explain such a discrepancy with our results.

Our findings were significantly different as regards blood BHB levels. We showed that blood could be used as an alternative matrix to vitreous to measure ketones with the studied BGMD. As with vitreous glucose, there was a great measurement repeatability and the BGMD proved to be highly sensitive (1.0) and specific (1.0) to detect high blood ketone levels with a threshold value of 2.85 mmol/L [5, 15]. However, only

twenty-nine blood samples could be investigated in our study. Additional samples would therefore be needed to support these findings as such analyses have never been performed so far in forensic settings.

Based on BGMD and biochemical analyses, and on further data from post-mortem investigations (clinical history, autopsy findings, ancillary testing including toxicology), we were eventually able to diagnose 4 cases of lethal DKA among the individuals included in our study (5.9% of the study population, 11.8% of diabetic subjects) (Table 4). Furthermore, 1 case of alcoholic ketoacidosis and 1 hyperosmolar hyperglycemic state were identified. It is noteworthy that most of these conditions would probably not have been unveiled without the systematic screening that we performed in our study. In this regard, Zilg et al. showed that the frequency of DM-related deaths doubled when systematic biochemical analyses were carried out in unexplained deaths (Zilg 2009). In the present study, metabolic-related deaths represented the second most common cause of death in the diabetic sub-population (14.7%; $n = 5$), cardiovascular disease remaining the leading cause of fatality (47.1%; $n = 16$). Two additional cases with isolated but significant increase of vitreous and blood BHB levels were reported. Death was attributed to hypothermia in one case, and to an infection (pneumonia) in the other case. These two conditions have been reported to be associated with high ketone values in the literature [6].

It should be pointed out that despite the strong correlation between the BGMD and the biochemical methods for VH glucose and blood BHB (Figs. 2 and 4), measurements performed with the BGMD resulted in overestimation of the mean glucose and BHB concentrations, as shown by Bland-Altman analyses (Figs. 3 and 5). This discrepancy may be explained by several factors. Enzymatic methods require a pre-analytical processing of the samples consisting in protein precipitation, which primarily aims at preventing in vitro enzymatic degradation, but which also avoids analytical interferences that could be caused by the viscosity or cell content (retinal and red blood cells) of post-mortem vitreous and blood. Such interferences may affect the electrochemical

Table 4 Results of the BGMD and biochemical analyses in DKA-related deaths

Case	Age (year)/sex	Type of diabetes	BGMD analyses			Biochemical analyses				PMI (days)
			VH BHB (mmol/L)	VH glucose (mmol/L)	Blood BHB (mmol/L)	VH BHB (mmol/L)	VH glucose (mmol/L)	Blood BHB (mmol/L)	HbA1c (%)	
1	57/F	DM1	2.8	19.6	Not tested	4.6	21.6	3.9	9.6	3
2	57/F	DM1	2.6	19.4	Not tested	20.4	54.0	17.6	10.6	3
3	46/M	DM1	4.1	22.3	3.2	15.1	36.8	11.8	10.1	6
4	74/M	Unknown	4.7	27.7	4.9	20.2	53.7	13.6	16.0	3

M male; *F* female, *DM1* type 1 diabetes, *BGMD* blood glucose monitoring device, *VH* vitreous humor, *BHB* β -hydroxybutyrate, *PMI* post-mortem interval

detection of glucose and BHB when using the BGMD, as samples are directly applied to the test strip, which has not been initially designed for use with vitreous. Moreover, BGMD are intended to be used by diabetics to monitor their blood glucose levels, so they cannot be expected to be effective tools for measuring extreme values close to the lower or upper detection limits of the device. That could explain the great underestimation of high glucose and BHB concentrations with the BGMD. Nevertheless, this relative lack of precision of the BGMD for measuring glucose and BHB levels was considered of little concern in our study, as the BGMD was intended to be exclusively used for screening purposes.

Short PMI (up to 72 h) has been reported not to significantly affect glucose and BHB levels in vitreous and blood, respectively [12, 13]. In our study, high vitreous glucose concentrations were detected up to 6 days post-mortem, and high blood ketone concentrations up to 8 days, suggesting that longer PMI does not hamper the detection of such high concentrations. As positive cases displayed values well above the set thresholds for both glucose and BHB, it is very unlikely that potential cases with high initial values could have been disregarded due to the influence of the PMI. Interestingly, HbA1c also appeared to remain stable in case of PMI longer than 72 h, which is the cutoff that has been considered in the literature [11, 20].

The main limitation of this research is the relative small number of cases included, despite an inclusion period of more than a year. This is partly due to the fact that natural causes of death are unfortunately insufficiently explored in the French medicolegal system, which primarily focuses on investigation of non-natural fatalities. As a consequence, a few cases with elevated vitreous glucose and/or blood ketone were detected among the individuals who were included. Nevertheless, we did not find any false-negatives that could have jeopardized the performance of the studied BGMD.

Conclusion

Our study confirmed that a commercially available BGMD can assist forensic pathologists in identifying cases of lethal DKA at the time of the autopsy or external examination. Glucose can be reliably investigated in vitreous, while BHB has to be tested in blood, using threshold values of 14.4 mmol/L and 2.85 mmol/L, respectively. Interestingly, such a device also allows the investigation of other metabolic disorders such as alcoholic ketoacidosis and hyperosmolar hyperglycemic states, as shown in our study. We therefore recommend the systematic use of a BGMD for screening these conditions in cases of unexplained deaths, especially when dealing with diabetic and alcoholic subjects. However, it should be kept in mind that positive results should still be

confirmed by validated biochemical methods since such a device remains a screening tool.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with live human participants or animals performed by any of the authors. Ethical approval was obtained from the Ethics Committee of the University Hospital of Montpellier, Nr. 2018_IRB-MTP_05–08.

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