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Article

2012

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How to cite

PALMIERE, Cristian et al. Is the formula of Traub still up to date in antemortem blood glucose level estimation? In: International journal of legal medicine, 2012, vol. 126, n° 3, p. 407–413. doi: 10.1007/s00414-011-0659-1

This publication URL: <https://archive-ouverte.unige.ch/unige:25173>

Publication DOI: [10.1007/s00414-011-0659-1](https://doi.org/10.1007/s00414-011-0659-1)

Is the formula of Traub still up to date in antemortem blood glucose level estimation?

Cristian Palmiere · Frank Sporkert · Paul Vaucher ·
Dominique Werner · Daniel Bardy · François Rey ·
Christelle Lardi · Christophe Brunel ·
Marc Augsburger · Patrice Mangin

Received: 10 August 2011 / Accepted: 14 December 2011 / Published online: 11 February 2012
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Abstract According to the hypothesis of Traub, also known as the ‘formula of Traub’, postmortem values of glucose and lactate found in the cerebrospinal fluid or vitreous humor are considered indicators of antemortem blood glucose levels. However, because the lactate concentration increases in the vitreous and cerebrospinal fluid after death, some authors postulated that using the sum value to estimate antemortem blood glucose levels could lead to an overestimation of the cases of glucose metabolic disorders with fatal outcomes, such as diabetic ketoacidosis. The aim of our study, performed on 470 consecutive forensic cases, was to ascertain the advantages of the sum value to estimate antemortem blood glucose concentrations and, consequently, to rule out fatal diabetic ketoacidosis as the cause of death. Other biochemical parameters, such as blood 3-beta-hydroxybutyrate, acetoacetate, acetone, glycated haemoglobin and urine glucose levels, were also determined. In addition, postmortem native CT scan, autopsy, histology, neuropathology and toxicology were performed to confirm diabetic ketoacidosis as the cause of death.

According to our results, the sum value does not add any further information for the estimation of antemortem blood glucose concentration. The vitreous glucose concentration appears to be the most reliable marker to estimate antemortem hyperglycaemia and, along with the determination of other biochemical markers (such as blood acetone and 3-beta-hydroxybutyrate, urine glucose and glycated haemoglobin), to confirm diabetic ketoacidosis as the cause of death.

Keywords Postmortem biochemistry · Glucose · Vitreous · Diabetes · Ketoacidosis

Introduction

Diabetes mellitus is a chronic metabolic disease responsible for many deaths [1]. Any intercurrent illness can disrupt the metabolic balance in diabetics, particularly in individuals with type 1 diabetes. The stress of infection, injury, surgery and even emotional turmoil are associated with an enhanced release of the counterregulatory hormones (glucagon, adrenaline, noradrenaline, cortisol and growth hormone). Even relatively mild illnesses, such as respiratory infections or gastrointestinal upsets, can cause an increased secretion of counterregulatory hormones, which increase hepatic glucose production, stimulate ketogenesis and induce a state of insulin resistance with decreased peripheral glucose use. Hyperglycaemia followed by ketosis commonly results when absolute or relative insulin deficiency and unopposed action of counterregulatory hormones coexist. Absolute insulin deficiency occurs in patients with type 1 diabetes, whereas a relative insulin deficiency may occur in patients with type 2 diabetes, who cannot increase their endogenous insulin release in response to illness or stress [2–4].

Starting from the assumption that glucose is converted into lactate after death and to eliminate the negative effect of

C. Palmiere (✉) · F. Sporkert · P. Vaucher · C. Lardi · C. Brunel ·
M. Augsburger · P. Mangin
University Centre of Legal Medicine,
Lausanne-Geneva, Rue du Bugnon 21, 1011 Lausanne,
Rue Michel-Servet 1,
1211 Genève 4, Switzerland
e-mail: cristian.palmiere@chuv.ch

D. Werner · D. Bardy
Laboratory of Clinical Chemistry, University Hospital,
Rue du Bugnon 46,
1011 Lausanne, Switzerland

F. Rey
Division of Endocrinology, Diabetology and Metabolism,
University Hospital,
Rue du Bugnon 46,
1011 Lausanne, Switzerland

postmortem glycolysis, Traub [5] proposed that antemortem blood glucose concentration could be estimated by summing the postmortem values of glucose and lactate found in the cerebrospinal fluid. The basis of this hypothesis was the assumption that two molecules of lactic acid are the final product of postmortem glycolysis of one molecule of glucose ('formula of Traub'). Subsequent to Traub, other authors have proposed the establishment of the sum values of glucose and lactate in the vitreous humor and/or cerebrospinal fluid to estimate antemortem blood glucose concentrations [1, 6–11].

More recently, other authors [12, 13] postulated that using the sum value of glucose and lactate to estimate antemortem glycaemia could lead to overestimations of the cases of glucose metabolic disorders with fatal outcomes, such as diabetic ketoacidosis. Thus, vitreous glucose concentration (individually considered) has been proposed to be the most reliable marker to estimate antemortem blood glucose levels. However, in a review of the literature concerning glucose metabolism disorders and postmortem biochemistry, Hess et al. [14] reasserted the postmortem biochemical evaluation of glucose metabolism based on the combination of glucose and lactate concentrations, especially when the analyses are performed in the vitreous humor.

The aim of our study, which was performed on 470 consecutive forensic cases, was to evaluate the diagnostic accuracy of the sum values of glucose and lactate in the vitreous humor or in cerebrospinal fluid to estimate antemortem blood glucose levels and rule out fatal diabetic ketoacidosis as the cause of death. To do this, we compared the sum values of glucose and lactate with individually considered glucose levels. In accordance with previous observations, we decided to test whether fatal diabetic ketoacidosis could be accurately suspected when vitreous glucose levels were higher than 10 mmol/l or the sum value was higher than 23.7 mmol/l (in the vitreous humor) and 23.4 mmol/l (in the cerebrospinal fluid). Other biochemical parameters, such as blood 3-beta-hydroxybutyrate, acetoacetate, acetone, glycated haemoglobin and urine glucose levels, were determined. Postmortem native CT scan, autopsy, histology, neuropathology and toxicology were also performed to confirm diabetic ketoacidosis as the cause of death.

Materials and methods

Population

During 2008–2010, vitreous humor and cerebrospinal fluid samples were systematically collected from consecutive deceased subjects immediately after their arrival at the morgue (1–12 h after death). Blood and urine samples were also collected from the same cases during autopsy. In total, 470 cases were included in this study (315 males and 155 females),

with a mean age of 61.4 years. The criteria for including cases were postmortem interval, medical records and circumstances of death. Samples from severely decomposed bodies and from bodies with severe cranial destruction were rejected. Only cases with both vitreous humor and cerebrospinal fluid were considered. Diabetic and non-diabetic subjects were selected for this study, which included 119 subjects (79 males and 40 females) with a previous diagnosis of diabetes mellitus (68 insulin-dependent) and 351 subjects (236 males and 115 females) with no history of diabetes mellitus based on the medical records. Because the study samples originated from forensic practice and most of the deaths occurred outside the hospital, data on antemortem glucose levels shortly before death were not available.

Reference standard

In accordance with previous observations, diabetic ketoacidosis was determined to be the cause of death when vitreous glucose concentrations were above 10 mmol/l and blood 3-beta-hydroxybutyrate levels were higher than 2,500 $\mu\text{mol/l}$. Other biochemical parameters, such as blood acetoacetate and acetone, glycated haemoglobin and urine glucose levels, were also determined. Glycated haemoglobin and urine glucose concentrations were not considered as parameters necessary to establish the diagnosis of diabetic ketoacidosis but were measured to better characterise the metabolic profiles of diabetic ketoacidosis cases. Postmortem native CT scan, autopsy, histology, neuropathology and toxicology were also performed to exclude other possible causes of death.

Index test

The formula of Traub in the vitreous humor and cerebrospinal fluid was calculated by adding half of the lactate concentration value to the glucose concentration value. Methods for sampling and laboratory analyses are described in the following subsections.

Biological samples

Postmortem vitreous samples were collected by aspiration using a sterile needle and syringe. Right and left vitreous samples were collected through a scleral puncture at the lateral canthus, aspirated from the centre of each eye, pooled in the same syringe and mixed together. Cerebrospinal fluid samples were collected by aspiration using a sterile needle and a syringe by suboccipital puncture. After collection, the vitreous humor and cerebrospinal fluid samples were immediately centrifuged at $3,000\times g$ for 15 min. The separated supernatant was collected, stored in tubes containing sodium fluoride and frozen at -20°C . No specimens were excluded because of insufficient sample volume.

Postmortem blood samples were collected by aspiration with a sterile needle and a syringe from the femoral vein during autopsy, typically performed 24–48 h after death. The blood samples were stored in tubes containing sodium fluoride and in tubes containing ethylenediaminetetraacetic acid (EDTA) then frozen at -20°C . Postmortem urine samples were also collected by bladder aspiration during autopsy (24–48 h after death), stored in tubes with no preservatives and frozen at -20°C .

Laboratory analyses

Determination of glucose and lactate in the vitreous humor and cerebrospinal fluid

Glucose and lactate in the vitreous humor and cerebrospinal fluid were systematically determined by enzymatic assays on a Dimension® Xpand® Plus Integrated Chemistry System (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA).

Determination of 3- β -hydroxybutyrate and acetoacetate in the blood

Frozen samples of blood (stored in tubes containing sodium fluoride) were thawed overnight at 4°C and deproteinized with perchloric acid. Supernatant was used for analysis. 3- β -hydroxybutyrate (3HB) and acetoacetate concentrations were both determined by an enzymatic photometric method.

Determination of glycated haemoglobin

Glycated haemoglobin was determined on whole blood samples (stored in tubes containing EDTA) by ion-exchange high-performance liquid chromatography (Bio-Rad D-10 Dual Program, Hercules, CA, USA).

Determination of glucose in urine

Glucose in urine was analysed on the Roche Modular P clinical chemistry system (Roche glucose hexokinase method calibrated using manufacturer-supplied materials and values).

Determination of acetone in blood

Blood acetone was systematically determined by the use of headspace gas chromatography with flame ionisation detection on an Agilent 1888 headspace and a 6850 GC (Palo Alto, CA, USA). The blood samples were incubated for 20 min at 80°C and then expanded to the GC column. Analyses were performed on the blood samples stored in tubes containing sodium fluoride.

Statistical methods

Receiver operating curves were traced for both methods (glucose and sum value) and area under the curve (AUC) was statistically compared. Differences of $p < 0.05$ were considered statistically significant. Sensitivity, specificity, predicting values and the likelihood ratio (LR) were measured for glucose with a cut-off value of 10 mmol/l in the vitreous humor and for the sum value of 23.7 mmol/l (in the vitreous humor) and 23.4 mmol/l (in the cerebrospinal fluid). The LR was weighed by prevalence and a 95% confidence interval (CI 95%) was reported. Linear regression was used to verify the similarities of concentrations between measures in the vitreous humor and cerebrospinal fluid.

Ethical aspects

Ethical aspects were discussed with the local ethics committee, and this study was authorised as a part of an investigation into medico-legal autopsies ordered by the judicial authorities.

Results

In total, 470 cases were included in this study. We identified 12 cases of hypothermia, showing blood 3HB values ranging from 2,350 to 6,700 $\mu\text{mol/l}$, vitreous glucose levels lower than 3.0 mmol/l and no ethanol in the blood. We also observed four cases of alcoholic ketoacidosis, which revealed blood 3HB values ranging from 1,650 to 2,400 $\mu\text{mol/l}$ and glucose levels in the vitreous humor and cerebrospinal fluid lower than 3.0 mmol/l. All hypothermia and alcoholic ketoacidosis cases showed glycated haemoglobin levels lower than 6.5%. Blood 3HB determination was performed in all cases of sudden death, suspected hypothermia, suspected alcohol misuse-related death and suspected glucose metabolic disorders (250 out of 470 cases).

Figure 1a illustrates the correlation between glucose concentrations in the vitreous humor and cerebrospinal fluid ($R^2=0.978$). The addition of lactate (Fig. 1b) and glucose values (using the formula of Traub) decreased the correlation between both samples ($R^2=0.608$), suggesting that lactate levels, but not glucose levels, are differently affected in the vitreous humor and in cerebrospinal fluid after death.

Eleven cases out of 470 (Table 1) showed vitreous glucose concentrations over 10.0 mmol/l. For eight of these cases, diabetic ketoacidosis was determined to be the cause of death (blood 3HB concentrations between 6,730 and 17,600 $\mu\text{mol/l}$, glycated haemoglobin levels over 10.6%, urine glucose levels between 100 and 205 mmol/l, blood acetone levels between 3,450 and 10,860 $\mu\text{mol/l}$ and acetoacetate levels lower than 20 $\mu\text{mol/l}$ in seven out of eight

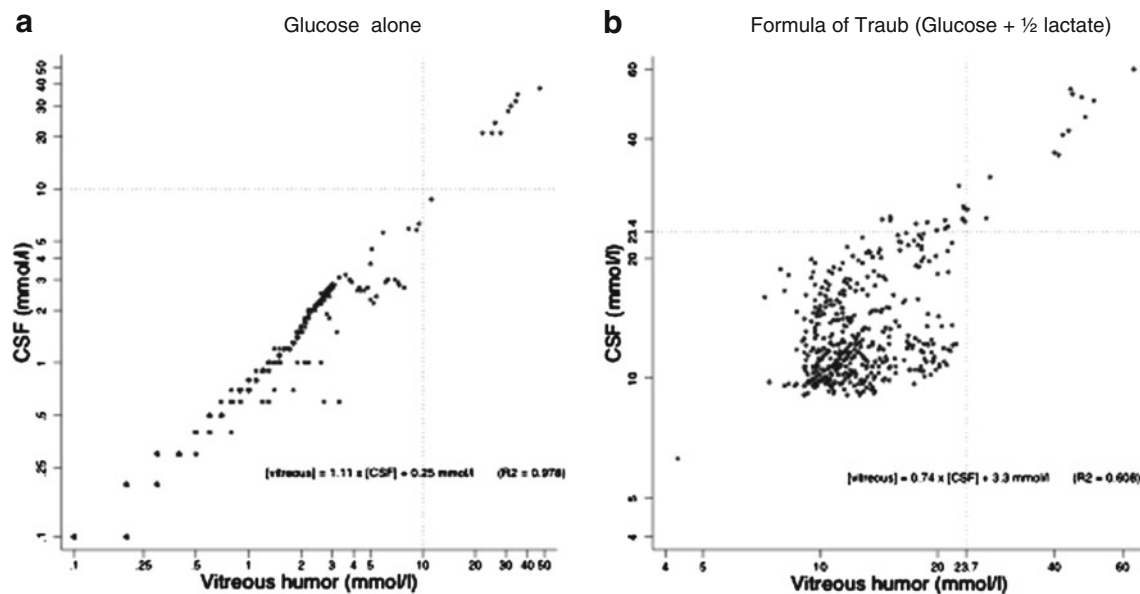


Fig. 1 Relationship between concentrations in the vitreous humor and cerebrospinal fluid (CSF) samples for glucose alone (a) and formula of Traub (b). R^2 =coefficient of determination (proportion of shared variance)

cases). In two other cases (cases 9 and 10), the causes of death were determined to be global cardiac hypertrophy with mitral–aortic valvulopathies (heart weight of 850 g) and gastric haemorrhage with massive blood aspiration into the airways. In both cases, pathological findings were associated with a hyperglycaemic state, which was not considered to be the cause of death.

Eleven cases out of 470 (Table 1) showed glucose concentrations in the cerebrospinal fluid over 8 mmol/l. For eight of these cases, diabetic ketoacidosis was determined to be the cause of death. A concentration of 21 mmol/l of glucose (Table 1 and Fig. 2) was found in one case of fatal diabetic ketoacidosis (case 7) as well as in cases 9 and 10, which presented a hyperglycaemic state associated with other pathologies responsible for death.

Fatal diabetic ketoacidosis was ruled out for vitreous humor glucose concentrations lower than 26 mmol/l and sum values lower than 42 mmol/l. For both methods, the AUC was 100% and no significant difference between both methods could be observed ($p=1.000$). However, using standard cut-off values (Table 2), positive predictive values were better for determining the cause of death using glucose alone rather than the sum value.

Finally, we observed 11 out of 470 cases with cerebrospinal fluid sum values over 23.4 mmol/l and glucose concentrations lower than 3 mmol/l, which was not consistent with the hypothesis of antemortem hyperglycaemia with fatal outcome. Moreover, according to all our results (postmortem native CT scan, autopsy, toxicology, histology, postmortem biochemistry and neuropathology), in none of these cases was the cause of death attributed to diabetic ketoacidosis.

Discussion

The aim of this study was to evaluate the diagnostic accuracy of the sum values of glucose and lactate in the vitreous humor or cerebrospinal fluid for the postmortem biochemical evaluation of the glucose metabolism and to rule out glucose metabolic disorders with fatal outcomes, such as diabetic ketoacidosis. Therefore, we compared the sum values of glucose and lactate with individually considered glucose concentrations.

Out of the 470 cases included in our study, 11 cases revealed vitreous glucose levels higher than 10 mmol/l. The diagnosis of diabetic ketoacidosis as the cause of death was proposed in eight cases. In accordance with the results of our investigations, antemortem hyperglycaemia could be detected by measuring only glucose levels in the vitreous humor or cerebrospinal fluid. Relying on a vitreous glucose cut-off level at 10 mmol/l guarantees the exclusion of antemortem hyperglycaemia with diabetic ketoacidosis (sensitivity 100%, negative predictive value 100%, specificity >95% and positive predictive value >70%). The results of our study also indicated that using the sum value of glucose and lactate for the postmortem biochemical evaluation of glucose metabolism could lead to an overestimation of the number of cases of antemortem glycaemia with fatal outcomes. In fact, according to the formula of Traub, as well as the limit of 23.4 mmol/l for the sum value in the cerebrospinal fluid, the cause of death would have been erroneously linked to a glucose metabolic disorder in 15 cases. Among these cases, 11 revealed glucose concentrations lower than 3 mmol/l, which is completely inconsistent with the

Table 1 Description of subjects ($n=11$) showing vitreous glucose concentrations over 10 mmol/l

ID no.	Cause of death	Vitreous humor			CSF		Blood			Urine		
		Glucose mmol/l	Lactate mmol/l	Traub mmol/l	Glucose mmol/l	Lactate mmol/l	Traub mmol/l	Acetone μmol/l	Acetoacetate μmol/l	3HB μmol/l	HbA1c%	
												Glucose mmol/l
1	Diabetic ketoacidosis	47	34	64	38	44	60	9,830	43	16,410	11.4	205
2	Diabetic ketoacidosis	35	24	47	35	32	51	8,620	<20	13,910	11.4	162
3	Diabetic ketoacidosis	34	33	50.5	32	36	50	10,860	<20	13,550	12.2	172
4	Diabetic ketoacidosis	34	21	44.5	32	40	52	6,210	<20	9,500	12.1	161
5	Diabetic ketoacidosis	32	24	44	30	47	53.5	3,450	<20	6,730	13.4	100
6	Diabetic ketoacidosis	31	34	48	28	35	45.5	6,900	<20	17,600	11.5	190
7	Diabetic ketoacidosis	28	31	43.5	21	42	42	5,000	<20	16,500	10.6	181
8	Diabetic ketoacidosis	26	32	42	24	34	41	6,650	<20	11,490	11.4	168
9	Mitral and aortic valvulopathy	25	32	41	21	31	36.5	n.d.	<20	1,050	9.2	22
10	Gastric haemorrhage and blood aspiration	22	36	40	21	32	37	5,690	<20	1,710	8.9	78
11	Subarachnoid haemorrhage	11.2	24	23.2	8.7	33	25.2	n.d.	<20	215	5.5	n.d.

3HB 3- β -hydroxybutyrate, CSF cerebrospinal fluid, HbA1c glycated haemoglobin, n.d. not detected

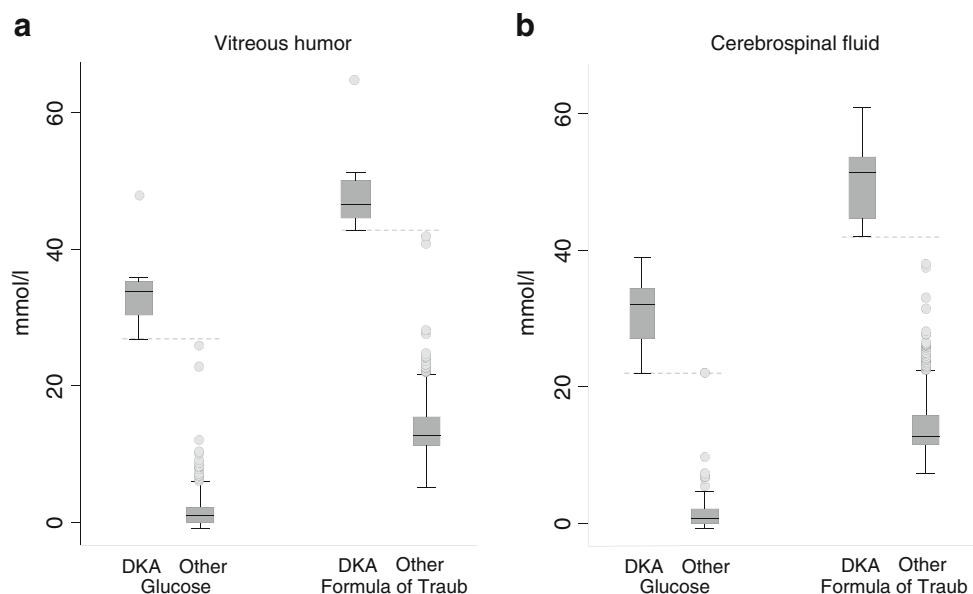
hypothesis of antemortem hyperglycaemia. Based on these results, we concluded that the sum value is primarily comprised of glucose in situations of antemortem hyperglycemia and of lactate in the other situations.

Initial studies on postmortem glycolysis and postmortem blood glucose were performed by Hamilton–Paterson and Johnson [15], Tonge and Wannan [16] and Fekete and Kerenyi [17]. Glycolysis is thought to continue spontaneously after death, and blood glucose concentration falls extremely rapidly. Furthermore, death may be preceded by agonal processes and cardiopulmonary resuscitation, which are often associated with the secretion or administration of catecholamines. This results in further mobilisation of liver glycogen and release of glucose into the blood circulation as a counterbalancing phenomenon [18]. Due to the difficulty interpreting postmortem blood glucose levels, other fluids have been proposed as being more reliable in the estimation of antemortem blood glucose concentrations, particularly the cerebrospinal fluid and vitreous humor [19–24]. Investigation of the biochemical constituents of the vitreous humor have been periodically performed by several authors [25–27]. However, the postmortem identification of hypo- and hyperglycaemia still remains interesting subjects of research. Coe [20, 21, 23, 28] demonstrated that there was a consistent but variable decrease in vitreous glucose concentrations with increasing postmortem time in non-diabetic individuals, whereas postmortem glycolysis had little effect on the elevated vitreous glucose values of uncontrolled diabetics. Given the assumption that glucose is converted into lactate after death and to eliminate the negative effect of postmortem glycolysis, Traub proposed that antemortem blood glucose concentration could be estimated by combining the postmortem values of glucose and lactate found in the cerebrospinal fluid. The basis of this hypothesis was the assumption that two molecules of lactic acid are the final product of the postmortem glycolysis of one molecule of glucose [5]. Several authors following Traub have attempted to define the diagnostic meaning of the sum values of glucose and lactate in the cerebrospinal fluid and/or vitreous humor to estimate antemortem blood glucose concentrations and to investigate metabolic disorders in diabetics and alcohol misuse-related deaths [1, 6–11, 29, 30].

Karlovsek [6, 7] investigated glucose and lactate levels in the vitreous humor and cerebrospinal fluid in a group of diabetic individuals and in a control group and proposed that vitreous glucose levels over 13 mmol/l (234 mg/dl) or combined values of glucose and lactate in the vitreous humor or cerebrospinal fluid greater than 23.7 mmol/l (427 mg/dl) and 23.4 mmol/l (422 mg/dl), respectively, could be an indicator of an antemortem hyperglycaemic state with fatal outcome.

Zilg et al. [13] postulated that, after an initial drop of vitreous glucose during the very early postmortem period,

Fig. 2 Relationship between diabetic ketoacidosis cases, formula of Traub values and glucose concentrations in the vitreous humor and cerebrospinal fluid. Round dots correspond to outside values (>95th percentile). DKA diabetic ketoacidosis



glucose levels remained stable for an appreciable time after death, whereas lactate levels (and consequently, the sum value of glucose and lactate) rise with increasing postmortem time. Hence, they concluded that vitreous glucose concentration alone was more appropriate than the sum value of glucose and lactate in the estimation of antemortem blood glucose concentrations. The authors emphasised that the decrease in vitreous glucose is limited to the early postmortem period, probably due to the residual metabolic activity of the surviving hyalocytes and inner retinal cells. Subsequent to this phase, glucose levels remain stable. Moreover, the authors postulated that the presence of lactate in the vitreous humor could be due not only to the postmortem metabolism of glucose, but other sources could also be responsible for its formation and subsequent increased concentrations in the vitreous humor after death. Consequently, the authors assumed that the sum value was primarily

comprised of lactate levels, which increase with postmortem time and that vitreous humor glucose concentrations alone should be used to estimate antemortem blood glucose concentrations. To corroborate their hypothesis, Zilg et al. reported the results of a study performed on more than 3,000 cases in which no cases of diabetic deaths revealing only high vitreous lactate levels were observed.

Herein, the results of the study are consistent with these conclusions and indicate that the sum value of glucose and lactate in the vitreous humor or cerebrospinal fluid does not add any further information when estimating antemortem blood glucose concentrations. Moreover, the use of the sum value could lead to an overestimation of cases of glucose disorders with fatal outcomes, such as diabetic ketoacidosis. Thus, the vitreous glucose concentration appears to be the most reliable marker to estimate antemortem blood glucose concentrations. Its determination, together with the

Table 2 Diagnostic accuracy for ruling out diabetic ketoacidosis using glucose and lactate postmortem concentrations

	Sensitivity% (CI 95%)	Specificity% (CI 95%)	Predictive values		Likelihood ratios	
			Positive% [TP/(TP + FP)]	Negative% [TN/(TN + FN)]	Positive LR (CI 95%)	Negative LR (CI 95%)
Vitreous humor						
Glucose alone (>10 mmol/l)	100% (59.8 to 100)	99.4% (98.0 to 99.8)	72.7% (8/11)	100% (459/459)	2.7 (0.95 to 7.5)	0 (–)
Traub (>23.7 mmol/l)	100% (59.8 to 100)	98.9% (97.3 to 99.6)	61.5% (8/13)	100% (457/457)	1.6 (0.71 to 3.6)	0 (–)
CSF						
Glucose alone (>10 mmol/l)	100% (59.8 to 100)	99.6% (98.3 to 99.9)	80.0% (8/10)	100% (460/460)	4.0 (1.1 to 14.4)	0 (–)
Traub (>23.4 mmol/l)	100% (59.8 to 100)	95.7% (93.3 to 97.3)	28.6% (8/28)	100% (442/442)	0.4 (0.21 to 0.75)	0 (–)

CI 95% confidence interval 95%, CSF cerebrospinal fluid, FN false negative, FP false positive, LR likelihood ratio, TN true negative, TP true positive

measurements of other biochemical markers, such as blood 3HB and acetone, urine glucose and glycated haemoglobin, can confirm diabetic ketoacidosis as the cause of death and better characterise the metabolic profiles in these situations. Finally, we concluded that the determination of acetoacetate levels does not add any further information in order to estimate the importance of ketonemia when glucose metabolic disorders are associated with ketoacidosis.

Acknowledgements The authors are grateful to the anonymous reviewers, whose constructive and useful comments improved the quality of the article.

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