Correlation between urine ketones (acetoacetate) and capillary blood ketones (3-beta-hydroxybutyrate) in hyperglycaemic patients


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Abstract

Aims. – To facilitate the transition from urine ketones (acetoacetate) to capillary blood ketones (3-beta-hydroxybutyrate), we studied the correlation between these two tests.

Methods. – Retrospective study of all patients with blood glucose greater than or equal to 2.5 g/l on arrival in the Emergency Department. We studied the correlation between urine ketones (Clinitek 50, Bayer) and capillary blood ketones (Optium, Abbott). We then compared the relative risks (RR) of ketoacidosis and hospitalization associated with each of these tests.

Results. – In 33 months, 529 adult patients with both urine and blood testing for ketones were enrolled (ketoacidosis 8%, admission rate 49%). Urine ketones scored as +, ++ and +++ corresponded to median capillary blood ketone levels of 0.5 mmol/l (IQR: 0.1–0.9), 0.7 mmol/l (IQR: 0.2–1.8) and 3 mmol/l (IQR: 1.4–5.2), respectively. RRs of ketoacidosis or hospitalization associated with blood ketones greater than or equal to 3 mmol/l were higher than those associated with +++ urine ketones: 74 (95% confidence interval [CI]: 48–88) and 2.9 (95% CI: 2.5–3) versus 31 (95% CI: 18–45) and 2 (95% CI: 1.7–2.1), respectively.

Conclusions. – In hyperglycaemic patients in the Emergency Department, a good correlation was observed between urine ketones and capillary blood ketones for low values, but a poor correlation was observed for high values. Either test can therefore be used to exclude ketosis, but the capillary blood ketones test is more accurate to confirm ketoacidosis.

Résumé

Corrélation entre cétonurie (acétoacétate) et cétonémie capillaire (3-bêta-hydroxybutyrate) chez les patients hyperglycémiques.

Objectif. – Afin de faciliter la transition entre cétonurie (acétoacétate) et cétonémie capillaire (3-bêta-hydroxybutyrate), nous avons étudié la corrélation entre ces deux tests.

Méthode. – Étude rétrospective de tous les patients hyperglycémiques (2,5 g/l) à l’arrivée dans une structure d’urgence. Nous avons étudié la corrélation entre la cétonurie (Clinitek 50, Bayer) et la cétonémie (Optium, Abbott). Nous avons ensuite étudié les risques relatifs d’acidocétose et d’hospitalisation associés à chacun de ces tests.

Résultats. – En 33 mois, 529 patients adultes avec dosages urinaire et capillaire de cétones ont été inclus (acidocétose 8 %, taux d’hospitalisation 49 %). Une cétonurie à +, ++ ou +++ correspondait à une médiane de cétonémie de 0,5 mmol/l (intervalle interquartile ou IQR : 0,1–0,9), 0,7 mmol/l (IQR : 0,2–1,8) ou 3 mmol/l (IQR: 1,4–5,2), respectivement. Les risques relatifs d’acidocétose et d’hospitalisation associés à une cétonémie supérieure ou égale à 3 mmol/l étaient supérieurs à ceux associés à une cétonurie à +++ : 74 (IC 95 % : 48–88) et 2,9 (IC 95 % : 2,5–3) versus 31 (IC 95 % : 18–45) et 2 (IC 95 % : 1,7–2,1), respectivement.

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1. Introduction

The reference technique to estimate a patient’s ketotic state is based on semiquantitative determination of acetoacetate in the urine. This technique uses nitroprusside which produces a colorimetric reaction in the presence of ketosis and is generally performed with reagent dipsticks. The semiquantitative result provides an indication of the level of ketone bodies in the urine (from zero to +++ or ++++, depending on the dipsticks used). This ketone body concentration is dependent on renal function and requires a urine sample, which can take time or may even be impossible in seriously ill patients in the emergency setting [1]. Furthermore, the nitroprusside test does not quantify 3-β-hydroxybutyrate [2], the main and sometimes the only ketone body responsible for ketoacidosis [3,4].

For the last 10 years, the patient’s ketotic state can now be estimated by fingerstick capillary blood 3-hydroxybutyrate assay, requiring only 5 µl of blood. This method is reliable and precise and the results are available in 20 s [5,6]. This new assay, called blood ketones, is gradually replacing urine ketones (acetoacetate) to evaluate insulin deficiency in hyperglycemic patients [7]. Since 2004, the American Diabetes Association [8] no longer recommends the nitroprusside method to test for ketone bodies in the blood or urine and prefers quantitative determination of blood 3-hydroxybutyrate for the diagnosis and follow-up of ketoacidosis. 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 [5,7,9]. To facilitate the transition from urine ketones to blood ketones in clinical practice, physicians must have a better understanding of the relationship between these two tests. The primary objective of this study was to describe the relationship between urine ketones and blood ketones in hyperglycemic subjects in the Emergency Department. The secondary objective was to compare the value of these tests to assess the degree of insulin deficiency in hyperglycemic patients.

2. Patients and methods

We conducted a retrospective study over 32 months by reviewing the case files of all patients attending the Emergency Department of a Paris teaching hospital for whom capillary blood glucose, urine ketones and blood ketones were available. The start of the inclusion period (1st October 2001) corresponded to the date of first use of the blood ketones meter. All patients included had a capillary blood glucose greater than or equal to 250 mg/dl determined by the triage nurse. The capillary blood glucose cut-off value corresponded to the American Diabetes Association 1998 guideline [10]. According to our protocol, capillary blood glucose had to be determined on arrival in the Emergency Department on all patients complaining of malaise, polydipsia-polyuria, disorders of consciousness, life-threatening situations and in all known diabetic patients. In patients with capillary blood glucose greater than or equal 13.75 mmol/l, the triage nurse had to test for ketone bodies on a urine sample (urine ketones) and/or on a capillary blood sample (blood ketones). During the first year of the study, the nurse was required to perform both assays whenever possible [1]. After this year of comparison of the two tests, the urine analysis was recommended in all hyperglycaemic patients, whereas capillary blood ketones was recommended only in patients unable to urinate rapidly after arrival or who presented positive urine ketones (at least +). Ketonuria was measured with dipsticks (Multistix®) read by Clinitek 50 (Bayer). With this dipstick, +, ++ or +++ urine ketones correspond to 1.5, 5 or 8 mmol/l of acetoacetate, respectively. Capillary blood ketones were measured with a dipstick read by the Medisense Optium meter (Abbott, MediSense, Bedford, MA, USA). As the blood ketones meter displays “HI” (for high) when blood ketones were ≥ 6 mmol/l, we considered the “HI” value to be equal to 6 mmol/l. The results of the two tests were reported on the case report form accessible to clinicians.

To describe the relationship between urine ketones and blood ketones in hyperglycemic subjects in the Emergency Department, we studied blood ketone values associated with various urine ketone values. To compare the respective capacities of these two tests to evaluate the severity of insulin deficiency in hyperglycemic patients, we compared the relative risks (RRs) of ketoacidosis and hospitalization as a function of urine ketones and blood ketones. Ketoacidosis was defined as positive ketosis (+ urine ketones or blood ketones ≥ 1 mmol/l) and metabolic acidosis defined by a low pH (arterial pH ≤ 7.35 or venous pH ≤ 7.32) or a low plasma bicarbonate concentration (< 20 mmol/l on arterial blood gases, venous gases or, when blood gases were not performed, on serum electrolytes) with a high anion gap (> 16 mmol/l) unexplained by blood lactate [1].

The correlation between the various urine ketone or blood ketone levels and the RR of ketoacidosis or hospitalization was analyzed by logistic regression. The results are expressed in terms of RR together with their 95% confidence intervals (CI) [11]. The capacities of these tests to predict ketoacidosis or hospitalization are expressed by the area under the curve.
(AUC) of receiver operating characteristic (ROC) curves and were compared by the test described by DeLong et al. [12].

3. Results

In a series of 949 hyperglycaemic patients seen in the Emergency Department over a period of two and a half years, both tests were performed in 529 (62%) patients (men: 64%, mean age ± standard deviation: 53 ± 17 years, range: 15–96 years), and these patients were included in this study. The 173 patients included during the first year of use of capillary blood ketones have been described elsewhere [1]. This previous study included during the first year of use of capillary blood ketones and these patients were included in this study. The 173 patients age ± standard deviation: 53 ± 17 years, range: 15–96 years, were compared by the test described by DeLong et al. [12].

Fig. 1 shows the distribution of blood ketone test results as a function of the reference standard urine ketone results (Fig. 1). In patients with negative or traces of urine ketones, the median blood ketones were zero and 95% of patients had blood ketones ≤ 0.5 mmol/l. In patients with +, ++ and +++ urine ketones, the median blood ketone value did not increase linearly, but exponentially and the distribution around the median was increasingly large. Patients with +++ urine ketones were distributed with an equal probability in the following blood ketones ranges: [0.1–1.3], [1.4–2.9], [3–5.2] and [5.3–6] mmol/l.

The incidence of ketoacidosis was 7.7%. This rate increased with increasing blood ketones and to a lesser degree with elevation of urine ketones (Table 1). No difference was seen between the insulin treated patients and the other ones. The RR of hospitalization with +++ urine ketones (2, CI: 1.7–2.1) was higher than that observed for negative reference urine ketones (P < 0.0001). This RR was similar to that observed for blood ketones between 0.6 and 0.9 mmol/l (2, CI: 1.4–2.4) or between 1 and 2.9 mmol/l (2.2, CI: 1.7–2.5), but lower than that observed for blood ketones greater than or equal to 3 mmol/l (2.9, CI: 2.5–3.0). The area under the ROC curve was significantly higher for blood ketones (0.984) than for urine ketones (0.941) (P < 0.0001) (Fig. 2).

The hospitalization rate was 49.7% and increased with elevation of blood ketones, and to a lesser degree with elevation of urine ketones (Table 2). No difference was seen between the insulin treated patients and the other ones. The RR of hospitalization with +++ urine ketones (2, CI: 1.7–2.1) was higher than that observed for negative reference urine ketones (P < 0.0001). This RR was similar to that observed for blood ketones between 0.6 and 0.9 mmol/l (2, CI: 1.4–2.4) or between 1 and 2.9 mmol/l (2.2, CI: 1.7–2.5), but lower than that observed for blood ketones greater than or equal to 3 mmol/l (2.9, CI: 2.5–3.0). The area under the ROC curve was significantly higher for blood ketones (0.984) than for urine ketones (0.941) (P < 0.0001) (Fig. 2).

Table 1
Relationship between the presence of ketone bodies and ketoacidosis (520 patients)

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Patients with ketoacidosis [n, (%)]</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood ketones (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>215 (41)</td>
<td>0 (0)</td>
<td>1*</td>
</tr>
<tr>
<td>0.1</td>
<td>92 (18)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>0.2–0.5</td>
<td>90 (17)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>0.6–0.9</td>
<td>37 (7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>1–2.9</td>
<td>40 (8)</td>
<td>5 (13)</td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>46 (9)</td>
<td>36 (78)</td>
<td>74 (48–88) &lt; 0.0001</td>
</tr>
<tr>
<td>Urine ketones (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>277 (53)</td>
<td>0 (0)</td>
<td>1*</td>
</tr>
<tr>
<td>Traces</td>
<td>69 (13)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>71 (14)</td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td>++</td>
<td>33 (6)</td>
<td>3 (9)</td>
<td></td>
</tr>
<tr>
<td>+++</td>
<td>70 (14)</td>
<td>34 (49)</td>
<td>31 (18–45) &lt; 0.0001</td>
</tr>
</tbody>
</table>

NB: metabolic data were not available for nine patients with positive ketosis.

Table 2
Relationship between the presence of ketone bodies and hospitalization (n = 529)

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Number of hospitalizations (%)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood ketones (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>215 (41)</td>
<td>70 (33)</td>
<td>1*</td>
</tr>
<tr>
<td>0.1</td>
<td>92 (17)</td>
<td>39 (42)</td>
<td>1.3 (0.9–1.7) 0.10</td>
</tr>
<tr>
<td>0.2–0.5</td>
<td>90 (17)</td>
<td>52 (58)</td>
<td>1.8 (1.4–2.1) 0.0001</td>
</tr>
<tr>
<td>0.6–0.9</td>
<td>37 (7)</td>
<td>24 (65)</td>
<td>2 (1.4–2.4) 0.0003</td>
</tr>
<tr>
<td>1–2.9</td>
<td>47 (9)</td>
<td>33 (70)</td>
<td>2.2 (1.7–2.5) &lt; 0.0001</td>
</tr>
<tr>
<td>≥ 3</td>
<td>48 (9)</td>
<td>45 (94)</td>
<td>2.9 (2.5–3.0) &lt; 0.0001</td>
</tr>
<tr>
<td>Urine ketones (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>277 (53)</td>
<td>117 (42)</td>
<td>1*</td>
</tr>
<tr>
<td>Traces</td>
<td>69 (13)</td>
<td>27 (39)</td>
<td>0.9 (0.6–1.2) 0.64</td>
</tr>
<tr>
<td>+</td>
<td>72 (14)</td>
<td>37 (51)</td>
<td>1.2 (0.9–1.5) 0.16</td>
</tr>
<tr>
<td>++</td>
<td>36 (7)</td>
<td>20 (56)</td>
<td>1.3 (0.9–1.7) 0.13</td>
</tr>
<tr>
<td>+++</td>
<td>75 (14)</td>
<td>62 (84)</td>
<td>2 (1.7–2.1) &lt; 0.0001</td>
</tr>
</tbody>
</table>

* Reference category.
for the capacity to predict hospitalization was significantly greater for blood ketones (0.704) than for urine ketones (0.620) \((P < 0.0001)\).

### 4. Discussion

This study compared urine ketones, the reference test for detection of ketoacidosis, and blood ketones in 529 hyperglycaemic patients attending the Emergency Department. It completes a previous retrospective study on 173 patients [1]. The results confirm the good correspondence between the absence of acetoacetate in urine (0 or traces) and the absence of a significant quantity of 3-hydroxybutyrate in capillary blood, as 95% of non-ketonuric patients had blood ketones less than or equal to 0.5 mmol/l. They also confirm the exponential relationship between urine ketones and blood ketones and the marked variability of blood ketones among patients with high urine ketones. For example, the median blood ketones was 0.3 mmol/l for patients with +++ of urine ketones, with a broad distribution of blood ketone values [mmol/l] with equal probabilities of low [0.1–1.3], medium [1.4–2.9], high [3–5.2] or very high values [5.3–6]. To determine which of the two tests more accurately reflected insulin deficiency, we studied the correlation between the two tests and the RRs of ketoacidosis or hospitalization.

Our study confirms that elevation of blood ketones beyond 2.9 mmol/l is associated with a higher risk of ketoacidosis than +++ urine ketones. It also confirms that the risk of ketoacidosis is zero for blood ketones less than 1 mmol/l [13,14], but high for blood ketones greater than or equal to 5 mmol/l. Future Emergency Department management protocols should therefore be based on these data. In particular, it appears useless to assay serum bicarbonate in a patient with blood ketones less than or equal to 1 mmol/l and it appears justified to treat patients with blood ketones greater than or equal to 5 mmol/l without waiting for serum bicarbonate results.

This study also showed that elevation of blood ketones beyond 2.9 mmol/l is associated with a higher risk of hospitalization than +++ urine ketones. Negative blood ketone assay was associated with a particularly low risk of hospitalization, but this risk rapidly increased with the slightest elevation of blood ketones, even at values usually considered to be physiological. This suggests that blood ketones could be a good prognostic marker, reflecting the stress of a patient through the relative or absolute insulin deficiency, but this hypothesis needs to be confirmed.

These results confirm the excellent diagnostic accuracy of blood ketones [15–17]. It is not surprising that quantitative assay of 3-hydroxybutyrate in blood is a more precise marker of insulin deficiency than urine dipstick detection of acetoacetate, as blood levels of 3-hydroxybutyrate increase rapidly in the case of sudden insulin deficiency, while urinary excretion of acetoacetate is delayed, as it is dependent on glomerular filtration and therefore on renal function and degree of hydration [3]. Urine ketones also reflect the NAD+/NADH balance, which is altered in some patients with liver disease or insulin deficiency [18]. Finally, dipsticks provide a semiquantitative assay and the result can be influenced by the presence of certain foods or drugs [3,19,20]. Due to the excellent bedside diagnostic performance of blood ketones, most authors now recommend this test in high-risk patients, particularly in the Emergency Department [3,8,9,13–17,21–24].

This study presents a number of limitations due to its retrospective and selective nature. Analysis of the correlation between blood ketones and urine ketones would have been more precise if these tests had been performed systematically and simultaneously. The patient population with both blood ketones assay and dipstick test for urine ketones may have differed from the overall patient population seen in the department during the study period. Nevertheless, our sample represented 62% of the overall population and most of the patients not included were non-ketonuric and/or non-ketonic patients, subgroups that were well represented in our study.

We used an unconventional definition for comparison of the risk of ketoacidosis, as ketoacidosis is classically defined by at least a low arterial or venous blood pH, with varying degrees of severity [15,24–27]. However, this definition excludes numerous patients with severe ketoacidosis but compensated metabolic acidosis. For example, one patient of our series had blood ketones of 5.1 mmol/l, arterial blood bicarbonate of 14 mmol/l and arterial pH of 7.39. According to the classical definition, this patient did not present ketoacidosis, as his pH was normal. However, he required treatment with high doses of insulin, correction of fluid and electrolyte disorders and close surveillance, corresponding to a similar management protocol to that conventionally proposed in patients with a similar general state but low arterial pH. In order to include all patients with severe ketosis in our study, the criterion of low pH was not mandatory in our definition of ketoacidosis. Moreover, blood pH appears to be of limited practical value in severe ketoacidosis [17,28,29].

The fact that blood ketones results were given to clinicians probably biased comparison of the RR of hospitalization, as these results may have modified their behavior. However, the
use of this new marker was not defined for the first 173 patients included in the study, as this study was observational and the risk related to high blood ketones was unknown to the clinical team [1]. Furthermore, if the decision to hospitalize patients had been significantly influenced by blood ketones, it is surprising to find that the risk of hospitalization rapidly increased for values usually considered to be normal (e.g. 0.1 and values between 0.2 and 0.5 mmol/l), (32%, 42% and 56%, respectively).

In conclusion, this retrospective Emergency Department Study in adult hyperglycaemic patients shows a correlation between urine ketones and blood ketones which varies with the degree of ketonuria. A good relationship between urine ketones and blood ketones was observed for low urine ketones and the RRs of ketoacidosis and hospitalization were comparable with the two tests. For higher levels of urine ketones, the relationship between urine ketones and blood ketones was poorer, but the RRs of ketoacidosis and hospitalization were more accurately predicted by blood ketones than by urine ketones. These data should be used to construct diagnostic and management algorithms for hyperglycaemic patients in the Emergency Department based on the use of blood ketones.

References