Is capillary ketone determination useful in clinical practice? In which circumstances?

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SUMMARY

A new method is now available to measure capillary levels of 3-hydroxybutyrate (3HB), one of the three ketone bodies. It is a quantitative and enzymatic test that uses the same equipment as for home capillary blood glucose determination but with specific strips. In comparison to urine ketone test, there is no false negative or false positive results, it is highly correlate to standard automate assays and patients find it more acceptable. Clinical implementations of this new test begin to be reported. Some studies showed an advantage of ketonemia *versus* ketonuria measurement to detect and to treat diabetic ketoacidosis in the emergency room. In diabetic patients treated with continuous subcutaneous insulin infusion, ketonemia seems to be more relevant to detect lack of insulin. In the current care of patient with type 1 diabetes and especially in children blood ketone test is more effective than urine ketone test to prevent hospitalisation during sick days. For other situations such as diabetic pregnancy or type 2 diabetes, more data are needed to determine if capillary measurement of 3HB is really useful. This new test is easier and less unpleasant than doing urinary test but it is still far more expensive. Further clinical studies are needed to define whether self 3HB monitoring should substitute urinary test in outpatient care.

Key-words: Ketonemia · 3-hydroxybutyrate · Ketonuria · Ketoacidosis · Self-monitoring.

RÉSUMÉ

La détermination de la cétonémie capillaire est-elle utile en pratique clinique ? Dans quelles circonstances ?

La mesure des concentrations capillaires de 3-hydroxybutyrate (3HB), un des trois corps cétoniques, est maintenant disponible. Elle repose sur une méthode enzymatique quantitative réalisée par un appareil identique à un lecteur glycémique avec des bandelettes spécifiques. Comparativement au test urinaire, il n'y a pas de faux négatif ou de faux positif, les résultats sont hautement corrélés à ceux obtenus par automates standards et les patients la trouvent plus acceptable. Les intérêts cliniques de cette nouvelle méthode commencent à être rapportés dans la littérature. Certaines études ont montré un avantage de la mesure de la cétonémie par rapport à celle de la cétonurie pour détecter et traiter la céto-acidose diabétique aux Urgences. Chez les patients traités par pompe sous cutanée d'insuline, la mesure de la cétonémie capillaire semble plus intéressante pour détecter la carence en insuline. Dans la prise en charge courante des patients diabétiques de type 1, en particulier chez l'enfant, la mesure de la cétonémie capillaire est plus efficace que celle de la cétonurie pour prévenir une hospitalisation en cas d'affection intercurrente. Dans d'autres situations telles que le diabète au cours de la grossesse ou le diabète de type 2, des données supplémentaires sont nécessaires pour déterminer si la mesure capillaire du 3HB est vraiment utile. Ce nouveau test est simple et moins pénible que la réalisation des tests urinaires mais il est beaucoup plus cher. D'autres études sont nécessaires pour savoir si l'auto-surveillance du 3HB doit supplanter les tests urinaires dans le suivi ambulatoire des patients.

Mots-clés : Cétonémie · 3-hydroxybutyrate · Cétonurie · Céto-acidose · Auto-surveillance.

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Until recently, only semi-qualitative urinary ketone measurement was available using strip tests. The detection of ketone bodies in the blood from finger prick offered new options for monitoring and treating diabetes. In this paper we will depict the method and evaluate the interest of capillary ketone measurement in comparison to urinary ketone measurement. We will try to propose clinical practice guidelines according to what have been reported in the literature.

Ketone bodies: physiology and pathophysiology

The term "ketone bodies" refers to three molecules, acetoacetate (AcAc), 3-hydroxybutyrate (3HB), and acetone. Acetoacetate accumulates during fatty acid metabolism under low carbohydrate conditions. 3-hydroxybutyrate is formed from the reduction of AcAc in the mitochondria *(Fig. 1)*. These biochemical activities enable fat-derived energy to be generated in the liver and used by other organs such as brain, heart, kidney cortex and skeletal muscle when there is limited availability of carbohydrate or when carbohydrate cannot be used effectively.

Ketogenesis is the process by which fatty acids are transformed into AcAc and 3HB. This process takes place into the mitochondria of perivenous hepatocytes [1]. Fatty acid release by adipose tissue is stimulated by epinephrine and glugagon and inhibited by insulin. When glucose level is low (during fasting) or when insulin is lacking (poorly controlled diabetes) oxaloacetate (derived from pyruvate during glycolysis) is preferentially utilized in the process of gluconeogenesis, instead of condensing with acetyl-CoA. Acetyl-CoA accumulates due to the high level of fatty acid beta-oxidation and is then diverted to ketone body formation. Acetoacetate and 3HB are short chain (4-carbon) organic acids that can freely diffuse across cell membranes. Therefore, ketone bodies can serve as source of energy for the brain (which can not utilize fatty acids) and other organs. The control of ketogenesis depends on the glucagon-to-insulin ratio. A low insulin-to-glucagon ratio is associated with a stimulation of ketogenesis.

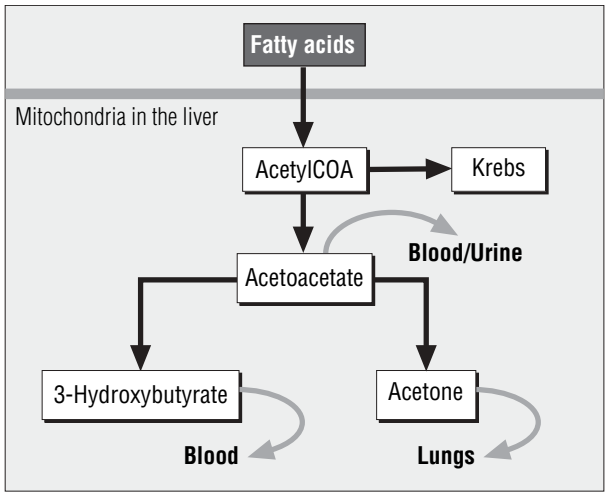

Figure 1
Pathway of the formation of the three major ketone bodies.

Ketolysis is the process by which ketone bodies are converted into energy that can be used as fuel for various intracellular metabolic activities. It occurs in the mitochondria of several extra hepatic organs [1].

Ketosis is a transient condition that is characterized by elevated serum levels of ketone bodies. The most common causes of ketosis are physiological responses to fasting (especially during infancy and pregnancy), prolonged exercise or a ketogenic (high-fat) diet [2, 3]. In infancy, children are more susceptible to physiological ketosis because of their lower hepatic glycogen stores. The most common pathological causes of ketosis are diabetes and toxics, especially binge drinking (alcoholic ketoacidosis) and salicylate overdose. However, in these situations, ketone body concentrations do not rise to very high levels [4].

Mechanisms of diabetic ketoacidosis (DKA): DKA is a serious acute metabolic complication of diabetes associated with elevated levels of ketone bodies in the blood to such a level that leads to acidosis. DKA is precipitated by omission or inadequate use of insulin, infection, new onset of diabetes, and concomitant affections (the stress induced by a surgery, hyperthyroidism…). These metabolic derangements are caused by an effective lack of insulin and simultaneous elevation of counter regulatory hormones such as glucagon, catecholamines, cortisol and growth hormone. Consequently, lipolysis in adipose tissue and ketogenesis in the liver are stimulated while lipid synthesis is inhibited, inducing a large quantity of circulating free fatty acids. In addition to the generation of abnormally high levels of ketone bodies in the blood, DKA is associated with an alteration in the ratio of 3HB to AcAc. This ratio rises to 3:1 or higher. A metabolic acidosis occurred since 3-hydroxybutyrate and AcAc are strong organic acids. The third ketone body, acetone, is formed from spontaneous decarboxylation of AcAc. Acetone does not contribute to metabolic acidosis since it does not dissociate to yield hydrogen ions. Acetone is fat soluble and is excreted slowly via the lungs. It generates the distinctive aromatic smell of the breath of patients with DKA.

Measurement of ketone bodies in the urines

In the seventies, home urine tests for ketone and glucose determination have been developed. In contrast to the striking advances in blood glucose monitoring, urinary ketone bodies evaluation did not progress over the last 30 yrs.