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The emerging risks of ketoacidosis and its detection by an innovative Breath Ketone Analyser - KetoMetrics

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Abstract

Ketoacidosis is a dangerous condition, of which diabetic ketoacidosis and euglycemic diabetic ketoacidosis are increasingly common in the community due to uncontrol diabetes and its medical management. This paper describes the common situations leading to ketoacidosis and the dilemma facing clinicians in handling this life-threatening condition. The development of an innovative Breath Ketone Analyser has improved the point of care in diabetes management by detecting and preventing the development of dangerous ketoacidosis.

Keywords: Ketoacidosis; Diabetic Ketoacidosis; DKA; Euglycaemic Diabetic Ketoacidosis; SGLT2 inhibitor; Emergency

1. Introduction

When a person does not have enough sugar (known as glucose) for energy, the body starts to break down the stored fat into ketones and use it as an alternative fuel source. Normally, the body does not produce ketone because it has glucose from carbohydrates as its main energy source. However, today, we face many situations when carbohydrate intake is limited; this occurs during diet restriction for weight management, having low-carbohydrate and high-fat diets, prolonged strenuous exercise, or treatment with antidiabetic medications. In these situations, the liver converts fats into fatty acids and ketones, which the body uses as energy. By further severely reducing carbohydrate intake, the body will be forced to rely on fats for energy, leading to ketosis. However, when the level of ketone reaches a dangerously high level, ketoacidosis occurs. It is a serious medical condition that significantly lowers the body's pH, which leads to ketoacidosis, and it is an abnormal and potentially dangerous condition.

1.1. Situations leading to dangerous ketoacidosis

Nowadays, ketoacidosis occurs more commonly in the community than we expect. In people with diabetes, particularly those with Type 1 Diabetes Mellitus (DM), glucose cannot be taken in for energy because of a lack of insulin. This can lead to rising levels of ketone, causing the blood to become acidic and ending with dangerous ketoacidosis. Sometimes, in this group of patients, if insulin treatment is inadequate or not available, the patient may go into life-threatening ketoacidosis condition, with severe dehydration, electrolyte imbalances, and even coma (1). However, in addition to Type 1 DM and occasionally Type 2 DM, there are many other situations in which doctors should be aware of the dangerous and potentially life-threatening ketoacidosis.

1) Nutritional ketoacidosis is different and uncommon to give rise to severe ketoacidosis. It is a normal metabolic ketosis. Taking a ketogenic diet, or fasting, is a controlled and safe condition that occurs with special dietary intake

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because some people intentionally want to lose weight by inducing ketosis. The ketogenic diet is a diet with a very low carbohydrate but high fat content. Thus, by severely limiting carbohydrate intake, the body will rely on fats for energy, producing ketones and a state of ketosis. This can have various weight loss effects on the body. However, it can induce ketoacidosis when there is a coexisting infection, exhaustive overexercise, and adverse effects of medication.

2) Infection or illnesses. Infections can increase the risk of ketoacidosis, particularly in patients with diabetes. It can cause an elevation of stress hormones, increasing insulin resistance and decreasing insulin action (2); thus, glucose cannot enter cells effectively, and the body burns fat instead of glucose for energy. Certain medical conditions like pancreatitis or kidney disease can also increase the risk of ketoacidosis because they affect the insulin, leading to impaired glucose and ketone metabolism. Reduced fluid and food intake during an infection can lead to dehydration and insufficient carbohydrate intake, creating an imbalance between glucose and ketone.

3) Diabetes Mellitus: The primary risk factor for developing ketoacidosis is having diabetes, particularly Type 1 diabetes. However, it is important to note that ketoacidosis can also occur in Type 2 diabetes patients under certain circumstances. Prolonged hyperglycaemia can contribute to the development of ketoacidosis. The body constantly lacks enough insulin or is in an insulin-resistant condition, leading to increased ketone production. Patients with longstanding Type 2 diabetes are more likely to face this situation, especially when stressful conditions, such as a major operation or infection, end with ketoacidosis.

4) Novel diabetic medications: Sodium Glucose Cotransporter 2 inhibitors (SGLT2i), a new class of oral antidiabetic medications, help to lower blood sugar by promoting kidney excretion of glucose filtered from the blood into the urine. They can also stimulate the production of glucagon. With lower glucose availability to the body and increased glucagon/ insulin ratio, the body will burn more fat instead of glucose, thus increasing ketone formation. Therefore, their use may increase the risk of diabetic ketoacidosis (DKA). Patients taking SGLT2i have a higher risk of diabetic ketoacidosis, with increased risks to 1.3 events per 1000 patient-years in Type 2 diabetic patients (3). In some of these patients, the blood glucose levels may be normal, a condition known as euglycaemic ketoacidosis (EDKA) (4), of which the symptoms are nonspecific, such as tiredness, drowsiness, nausea, and shortness of breath. Although blood tests may show metabolic acidosis, and urine dipstick may show ketones +++, the diagnosis is often delayed without clinical awareness due to relatively normal glucose levels. Therefore, it is recommended that a ketone check should be performed in patients taking SGLT2i with develop symptoms of DKA or having ketosis precipitating factors, even if blood glucose levels are only mildly elevated or normal.

5) Pregnancy, weight reduction surgery, and fasting: The other dangerous ketoacidosis is euglycemic diabetes ketoacidosis, which can occur during pregnancy, fasting, and after bariatric surgery (5) Euglycemic diabetic ketoacidosis (EDKA) is an acute life-threatening metabolic emergency characterized by ketoacidosis and normal to modestly raised blood glucose (less than 14 mmol/L)(4, 6). This condition is difficult to diagnose because the blood sugar is relatively normal, and a diabetic condition is not suspected. Euglycemic DKA is uncommon but can occur in patients with either Type 1 or 2 diabetes mellitus. With the availability of new diabetic medications like SGLT2i in DM management, EDKA incidence has increased.

6) Others: Prolonged or vigorous exercise with dehydration, like running a marathon, can result in dehydration and dangerous ketoacidosis. A faulty Insulin pump or disruption of the usual schedule of insulin regimen in travel may also lead to dangerous ketoacidosis.

All of the above might result in unexpected and life-threatening ketoacidosis. Even in severe ketoacidosis, the patient's symptoms could be nonspecific. Doctors in the emergency department and their clinics may not suspect this complication, leading to potentially worse outcomes due to delay in diagnosis. Individuals with diabetic conditions must monitor their blood sugar and ketone levels regularly and seek immediate medical advice if they feel unwell or develop nonspecific symptoms of ketoacidosis. Treatment typically involves intravenous fluids to correct dehydration, insulin therapy to lower blood sugar and ketone levels, and addressing any underlying causes or complications associated with the condition (2).

2. Dilemmas facing clinicians in handling this dangerous ketoacidosis

1) The symptoms of ketoacidosis can be nonspecific, including headache, rapid breathing, weakness, excessive thirst, frequent urination, nausea and vomiting, confusion, and abdominal pain (7). When patients present without a history of known diabetes, ketoacidosis might not be easily suspected at the emergency room or outpatient clinic. All blood or urine ketone tests will not be promptly or routinely performed. Misdiagnosis of a serious ketoacidosis might lead to delayed treatment to save a life-threatening condition.

2) Also, surgeons sometimes face a dilemma of whether to postpone or cancel an operation when a patient with no known history of diabetes presents with high urine sugar and ketone. Today, an increasing number of patients are taking SGLT2i. However, they often do not know the need to stop the medication three days before the surgery as recommended (8). Surgeons are increasingly faced with these scenarios nowadays. When dangerous ketoacidosis exists before the operation or develops perioperatively, if the condition is left undetected or not treated promptly, it can progress to a life-threatening condition, causing severe dehydration, electrolyte imbalances, and complications of the surgery.

3) Even when a patient has a history of diabetes, the diagnosis of ketoacidosis at present still relies on urine and blood ketone tests. Because prompt treatment can help prevent the progression of ketoacidosis and associated complications, it is important to have an instant blood test with finger pricks or venepuncture. However, the tests are invasive and unpleasant to the patients. They are also not easily available in general outpatient clinics, and results would not be available quickly.

4) During prolonged and strenuous exercise, patients on diabetic medications, ketogenic diets, or prolonged fasting may collapse unexpectedly. Healthcare providers will have difficulty finding out whether they suffer from cardiovascular collapse, other dangerous conditions, or dangerous ketoacidosis.

5) Cases of euglycaemic ketoacidosis at various times of pregnancy have been reported in women with gestational diabetes and also in those without any history of diabetes(1). The precipitating factors appear to be related to decreased oral intake due to sickness, nausea, vomiting, ketogenic diet leading to starvation. Despite women with ketoacidosis can be diagnosed and treated with complete recovery after hospitalization, there are fetal demises reported at 27 weeks (9), 34 weeks (10) and premature birth at 32 weeks of gestation (11).

Given the above issues facing clinicians and surgeons, developing a breath ketone test to provide convenient and accurate ketone measurement is ideal and timely. In the commercial markets, a few breath ketone test devices are available, which are portable devices designed to detect and measure the amount of ketones in a person's breath. They are also non-invasive alternatives to traditional urine or blood tests used to monitor ketosis for various conditions.

3. An innovative detector KetoMetrics@

A novel device, KetoMetrics (from AusMed Global Limited, Hong Kong) from Hong Kong, is a US Food and Drug Administration (FDA) listed medical device for detecting ketone (as acetone) in the breath. It is a hand-held device with a main device, disposable testing kits, and a bottle sampler (one-off or reusable version) (Figure 1). After collecting a breath sample, it measures the acetone levels in the exhaled breath photonically. It provides an instant numerical reading of the breath acetone concentration. Most nonspecific volatile organic compounds, including ethanol and methanol from exhaled breath, do not interfere with the KetoMetrics results (12, 13). It is reported to correlate with blood ketone levels well (12, 14-16).

Figure 1 KetoMetrics Breath Ketone Analyser (from AusMed Global Limited, Hong Kong)

Compared to other ketone testing modalities(blood and urine), the advantages of this device are 1) its operation is easy, non-invasive, and intuitive. It is more convenient and result-friendly than blood sampling and urine collection; the measurement takes less than three minutes. 2) it is cost-effective over time, especially for patients requiring frequent blood ketone checking. 3) Frequent ketone testing is feasible for those who need to monitor their ketone levels to adapt

to their dietary choices and avoid lifestyle factors that precipitate ketosis formation. 4) its real-time measurement can synchronize with another wearable device for remote monitoring and digital recording of the ketone levels.

It does not have the limitations of other breath ketone test devices. Various factors like hydration status, alcohol consumption, and oral hygiene can affect their ketone recordings. Cost considerations may be higher compared to other commercially available devices. However, many devices in the market have not been validated clinically. For this innovative device, ongoing clinical trials are underway in Type 1 diabetes, vigorous sports, and fitness programs to validate its usefulness in detecting and preventing dangerous ketoacidosis.

4. Conclusion

When facing a dangerous ketoacidosis, the patient should be hospitalized. A team of medical and nursing professionals should closely monitor the patient. Ketoacidosis treatment is on the same principles as diabetic ketoacidosis, with the urgent correction of dehydration, blood glucose levels, and electrolyte deficit. Intravenous insulin infusion in 10% Dextrose is given to return blood glucose to a safe range. It aims to correct metabolic acidosis and ketonemia and avoid hypoglycemia. However, this life-saving approach is only possible when dangerous ketoacidosis can be detected early. The development of a breath ketone test device can now provide a convenient and rapid method that can be done repetitively to monitor the levels of ketosis and detect ketoacidosis.

Blood ketone measurements are generally considered the most accurate and reliable method to measure ketone levels. However, they may not be easily available in clinics or emergency rooms. Even blood ketone test is taken, there will be a practical delay in the diagnosis of ketoacidosis. As the device described in this paper correlates well with the blood ketone test, it is promising as a diagnostic test in emergencies, inconvenient situations, and conditions requiring frequent monitoring uses.

Compliance with ethical standards

Disclosure of Conflict of Interest

Dr. Wong and Dr. Yeung are honorary medical advisors to AusMed Global Limited, Hong Kong. Christine Yip, Dr Addy Chau, and Dr. Benedict Chau are from AusMed Global Limited. The authors understand the importance of disclosing potential conflicts of interest and ensuring that the provided information is accurate and based on the best knowledge available.

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Author's short biography

Dr. Wu Shun Felix Wong. He is a retired Professor at the University of New South Wales, Sydney, Australia. He had contributed to medical education in Asia Pacific Countries over the past 30 years. In recognition of his contributions to teaching, he received many awards and honors. Dr Wong has co-edited 16 medical books and had published more than 250 papers in local and international journals.