Use of capillary ketones monitoring in treatment of mild ketotic crisis in people with ketosis-prone atypical diabetes

Eugene Sobngwi,[1] Christine Ghislaine G Ngo Ngai ,[1] Martine Etoa Etoga,[1] Eric Lontchi-Yimagou ,[2] Armand Mbanya,[1] Mesmin Dehayem,[1] Jean-Claude Mbanya[1]

[1]Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaounde I, Yaounde, Cameroon
[2]Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA

Correspondence to
Professor Eugene Sobngwi, Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, University of Yaounde I, Yaounde 99999, Cameroon; sobngwieugene@yahoo.fr

Accepted 12 May 2020
Published Online First 14 July 2020

To cite: Sobngwi E, Ngo Ngai CGG, Etoga ME, *et al*. *J Investig Med* 2020;**68**:1193–1195.

ABSTRACT

This study was carried out to assess the potential reduction in duration of intensive diabetic ketoacidosis treatment in adults with ketosis-prone atypical diabetes (KPD) when using capillary versus urinary ketones. In this cross-sectional study, we included 20 people with KPD presented at the National Obesity Center of the Yaoundé Central Hospital with hyperglycemic decompensation (random capillary glucose ≥13 mmol/L) and significant ketosis (ketonuria≥++) requiring intensive insulin treatment. In all subjects, intensive insulin treatment was initiated at 10 UI per hour with simultaneous measurement of capillary beta-hydroxybutyrate and ketonuria every 2 hours until disappearance of ketonuria. Time-to-disappearance of urine ketones was compared with the time-to-normalization of capillary β-hydroxybutyrate concentrations. Subjects were aged 46±13 years with a median duration of diabetes of 1.5 (IQR: 0–2.5) years. On admission, the mean blood glucose was 22.8±5 mmol/L and capillary ketones level was 2.9±2.7 mmol/L. The median time-to-disappearance of ketonuria was 5 (IQR: 3–8) hours compared with the time-to-normalization of capillary β-hydroxybutyrate of 4 (IQR: 2–6) hours, p=0.0002. The absolute difference in time-to-normalization of ketonuria versus ketonemia was 2 (IQR: 1–3) hours and the relative time reduction of treatment was 32.5%±18.0%. Our results suggested that the use of capillary ketones versus ketonuria would allow a significant reduction in duration of intensive insulin treatment by one third in people with KPD.

INTRODUCTION

Ketosis is recognized as one of the major complications of diabetes with respect to severity and urgency for care.[1] It is a leading cause of death in people with diabetes (2%–5% mortality rate)[2 3] and usually occurs in people with type 1 diabetes mellitus (T1DM). Among African American and sub-Saharan African patients, this complication is one of the main circumstances of diagnosis of diabetes among mature patients, particularly in ketosis-prone atypical diabetes (KPD).[4] KPD is characterized by acute initial presentation with severe hyperglycemia and ketosis, absent autoimmune markers of diabetes, and subsequent long-term insulin-free remission few days or weeks after initial treatment, occasionally interrupted by unexplained hyperglycemic ketotic relapses. People with KPD have features of both T1DM and type 2 diabetes mellitus, thus complicating its classification on clinical grounds. The causes and mechanism underlying KPD are still unclear.[5 6] In general, ketotic crises are managed using an intensive insulin protocol, careful rehydration and constant ketone monitoring. According to the American Diabetes Association (ADA), the most appropriate ketone monitoring method during ketosis is the measurement of blood ketone levels.[7] These recommendations had been established for the management of ketotic crisis in T1DM population.

To the best of our knowledge, there is no existing study using this approach for the management of ketotic crisis in people with KPD. Therefore, we carried out this study to assess the potential reduction in the duration of intensive diabetic ketoacidosis treatment in adult sub-Saharan African population with KPD when using capillary versus urinary ketone measurement. If proved useful, the limited access and affordability of capillary ketones could thus be balanced and exceeded by cost saved through reduction of the duration of intensive treatment.

METHODS

Setting and study population

We carried out a comparative study at the National Obesity Center of Yaoundé Central Hospital, a reference center for diabetes care in the capital city of Cameroon. From February to March 2015, we consecutively enrolled all adult people with KPD presenting with hyperglycemic crisis defined as random blood glucose ≥13.89 mmol/L and ketonuria ≥++. Subjects under free sulfhydryl drugs such as captopril, aminopenicillins, acetylcysteine, and with chronic kidney disease were excluded from the study. Overall, 20 patients with KPD

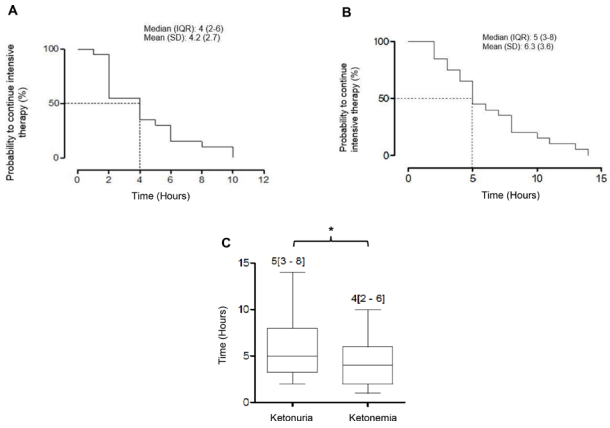

Figure 1 (A) Kaplan-Meier curves displaying the estimated survival probability for the normalization of ketonemia after intensive insulin treatment. (B) Kaplan-Meier curves displaying the estimated survival probability for the normalization of ketonuria after intensive insulin treatment. (C) Median time to normalization for ketonemia and ketonuria.

participated in the study. KPD was defined as new-onset diabetes without precipitating events such as infection, stress or corticotherapy, with significant ketosis (urine ketones≥ ++) or diabetes ketoacidosis requiring initial insulin treatment to achieve glucose control in the absence of cytoplasmic islet cells (ICA), insulin (IAA), glutamate decarboxylase 65 (GADA) and islet antigen-2 (IA-2A) autoantibodies.[5 6] People with type 1 diabetes were not included in the study.

Procedure

For all the study subjects, the treatment was initiated using an intensive intramuscular insulin therapy,[2] and rehydration was performed according to the clinical assessment of the level of dehydration and the monitoring of blood glucose and urine ketones. An intramuscular dose of insulin was given every hour depending on blood glucose levels (10 IU for blood glucose levels above 22 mmol/L, and 5 IU for blood glucose levels between 13.75 and 21.94 mmol/L), combined with rehydration as needed and follow-up of ketonuria. Intensive treatment was discontinued and data were collected immediately after the disappearance of ketonuria and blood glucose was normalized. As a result, the insulin delivery pathway was changed to subcutaneous insulin therapy.

Endpoints

The primary endpoints of the study were the times to normalization of capillary β-OH levels and ketonuria and the secondary one was the absolute difference in time to normalization and the relative time reduction of intensive insulin treatment.

Data collection

Data were collected using a standardized questionnaire which included anthropometric data, medical history, clinical, and biological data. Blood samples were collected for biological assessment of diabetes-associated antibodies, random blood glucose, and blood ketones. Urine samples were collected to assess urine ketone bodies.

Analytical methods

From the initiation of the treatment to the end of the intensive insulin protocol, we recorded hourly the capillary blood glucose levels by a One Touch Ultra 2 (LifeScan, USA, Milpitas) using glucokinase method. Monitoring of blood ketones was based on the same principle, requiring a larger sample of capillary blood on the test strip, attached to a device for measuring blood ketones.

Every 2 hours, the capillary β-OH levels were measured with an electrochemical meter (MediSense Optium, Abbott, UK, Oxon) until the normalization of those levels. Semi-quantitative urinary ketones were concomitantly measured every 2 hours using Ketodiastix strips test until the absence of ketonuria.

Statistical analysis

Data were coded, entered and analyzed using SPSS 12.0. Results were presented as counts with percentages and means with SD or medians with IQR. The nonparametric Mann Whitney U was used to compare data between non-normally distributed variables. The different times to normalization were obtained by using the Kaplan-Meier curves for overall survival. $P<0.05$ was set as statistically significant.

RESULTS

Characteristics of the study population at admission

A total of 20 people with KPD in a hyperglycemic state were included in this study. The age of the patients ranged from 21 to 66 years with a mean of 46±13 years. Women represented 55% (11/20) of all subjects. The median duration of diabetes was 1.5 years (IQR: 0–2.5), with a maximum of 10 years. Systolic and diastolic blood pressures were 127±16 mm Hg and 82±8 mm Hg, respectively. The mean body mass index was 25.4±7 kg/m^2. The mean waist circumference was 88±14 cm. Mean capillary glucose and mean β-OH level at admission were 22.8±5 mmol/L and 2.9±2.7 mmol/L, respectively.

Time to normalization ketonuria and capillary β-OH levels

The time-to-normalization of ketonuria ranged between 2 and 14 hours (median 5 (IQR: 3–8) hours) and that of ketonemia between 1 and 10 hours (median 4 (IQR: 2–6) hours) (figure 1). There was a significant difference in the time-to-disappearance of ketonuria compared with the time-to-normalization of capillary β-hydroxybutyrate (median 5 (IQR: 3–8) hours vs 4 (IQR: 2–6) hours, p=0.0002).

Absolute difference in time to normalization and the relative time reduction of treatment

The absolute difference in time-to-normalization of ketonuria versus ketonemia was 2 (IQR: 1–3) hours and relative time reduction of treatment to 32.5%±18.0%.

DISCUSSION

This study aimed to assess the potential reduction in the duration of intensive diabetic ketosis treatment in adult

people with KPD when using capillary versus urinary ketone measurement. We showed that the measurement of capillary ketones was more advantageous than the use of urinary ketones during the treatment of ketotic crisis in people with KPD.

Ketonuria took 5 hours (median time) to disappear in this specific population. This result is similar to that of Mosnier Pudar's study, which estimated a T1DM population in ketoacidosis state to have a median time of normalization of ketonuria of 4 hours 45 min.[8] In the same way, we got a rapid normalization of blood ketones trending towards 4 hours (median time). In the aforementioned study, Mosnier-Pudar *et al* obtained a lower time of normalization of ketonemia estimated to 2 hours 5 min.[8] Apart from the fact that during this study the study population was exclusively T1DM, a conventional treatment was used based on the intravenous intensive insulin and intravenous rehydration as recommended by ADA. Wiggam *et al*, who used the same methods in a comparative study between normalization of blood ketone levels and clinical recovery as a treatment goal, obtained the normalization of ketonemia in 5.9 hours which is significantly higher than our results.[9] Umpierrez *et al*, by establishing a subcutaneous protocol in resolving ketoacidosis estimated a correction time estimated to 10±3 hours, but with different endpoints: PH and HCO3 levels.[10]

The simple insulin therapy protocol as applied in this study was based on the one recently introduced in our setting,[2] used for treatment of hyperglycemic emergencies. Oral rehydration was better suited to this therapy's ambulatory nature, as it was easier to perform, and none of the admitted patients showed signs of severe dehydration. Furthermore, the use of this protocol led to a result similar to those found in the literature, giving an advantage to using the measurement of blood ketones in the treatment of diabetic ketosis in people with KPD.

Ketogenesis is a physiological phenomenon resulting from lipolysis that is normally inhibited by insulin and promoted under the action of glucagon and counter-regulation hormones. Through this mechanism, acetyl CoA is produced which is a precursor of acetoacetic acid, a precursor of Beta-hydroxybutyric acid and acetone which is excreted in the urine. In the case of insulinopenia, ketogenesis is amplified, resulting in hyperproduction of these ketone bodies.[11] This mechanism, which is well known in decompensations in patients with T1DM, may be the same in patients in ketotic phase of KPD. Thus, at the setting of ketoacidosis, a measurement of Beta-hydroxybutyric acid reveals a concentration much higher than that of other ketone bodies. Under the effect of intensive insulin therapy, ketogenesis is inhibited, and Beta-hydroxybutyric acid is converted into acetoacetate which continues its excretion into urinary acetone.[12] This may explain why for ketonemia the time of elimination of blood ketones is shorter than that of the ketonuria that persists despite the disappearance of Beta-hydroxybutyric acid in the blood.

This study implies a reduction of processing time and better monitoring of patients during ketotic crisis treatment and therefore could be used in a resource-limited setting especially for patients with mild ketosis as observed in most cases of KPD. Capillary ketones give the advantage of being more accurate than urine ketones while being a real reflection of the severity of the ketotic crisis, it will help to better classify emergencies and reduce undue burden. By reducing the duration of treatment, its use will limit the risks due to a prolonged treatment. It will allow better ambulatory cares and reduce the hospitalization times. In a limited-resource environment, considering the lack of health insurance for most of the patients, this approach could reduce the costs for patients and health systems.

Acknowledgements We are grateful to all the subjects of the study. These results of this study have been presented as a poster discussion at the International Diabetes Federation congress in 2015 in Vancouver.

Contributors CGGNN, ES, and J-CM: study design and conception, data collection and analysis, drafting, and review of the manuscript. EL-Y, AM, MD, and MEE: data interpretation, editing, and review of the manuscript. All authors read and approved of the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was performed in accordance with the guidelines of the Helsinki Declaration and was approved by the Institutional Research Ethical Committee of the Faculty of Medicine and Biomedical Sciences of Yaoundé and by the institutional review board of the Yaoundé Central Hospital of Cameroon. All subjects provided written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The principal investigator, Professor Sobngwi Eugene, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ORCID iDs
Christine Ghislaine G Ngo Ngai http://orcid.org/0000-0001-5162-5973
Eric Lontchi-Yimagou http://orcid.org/0000-0003-1071-3154

REFERENCES

1 Kitabchi AE, Umpierrez GE, Murphy MB, *et al*. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American diabetes association. *Diabetes Care* 2006;29:2739–48.
2 Sobngwi E, Lekoubou AL, Dehayem MY, *et al*. Evaluation of a simple management protocol for hyperglycaemic crises using intramuscular insulin in a resource-limited setting. *Diabetes Metab* 2009;35:404–9.
3 Sacks DB, Arnold M, Bakris GL, *et al*. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care* 2011;34:e61–99.
4 Csako G, Elin RJ. Spurious ketonuria due to captopril and other free sulfhydryl drugs. *Diabetes Care* 1996;19:673–4.
5 Sobngwi E, Gautier J-F. Adult-Onset idiopathic type I or ketosis-prone type II diabetes: evidence to revisit diabetes classification. *Diabetologia* 2002;45:283–5.
6 Mauvais-Jarvis F, Sobngwi E, Porcher R, *et al*. Ketosis-Prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. *Diabetes* 2004;53:645–53.
7 Sheikh-Ali M, Karon BS, Basu A, *et al*. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? *Diabetes Care* 2008;31:643–7.
8 Mosnier-Pudar H, Cuperlier A, Le Devehat C, *et al*. Mise en place et validation de recommandations de traitement et de surveillance basés sur la détermination capillaire des corps cétoniques chez le patient diabétique en cétose (résultats intermédiaires d'une étude multicentrique). *Diabetes Metab* 2003;29(suppl 1):1S52.
9 Wiggam MI, O'Kane MJ, Harper R, *et al*. Treatment of diabetic ketoacidosis using normalization of blood 3-hydroxybutyrate concentration as the endpoint of emergency management. A randomized controlled study. *Diabetes Care* 1997;20:1347–52.
10 Umpierrez GE, Latif K, Stoever J, *et al*. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. *Am J Med* 2004;117:291–6.
11 Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metab Res Rev* 1999;15:412–26.
12 McGarry JD, Foster DW. Regulation of ketogenesis and clinical aspects of the ketotic state. *Metabolism* 1972;21:471–89.