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Case Report

Life-Threatening Ketoacidosis in a Patient with Type 2 Diabetes Precipitated by LCHF Diet and SGLT2 Inhibition

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Abstract

Patients with type 2 diabetes may develop severe ketoacidosis. A low carb high fat (LCHF) diet is popular among these patients but is ketogenic. Antidiabetic SGLT2 inhibitors increase glucagon and may predispose to ketoacidosis, which is euglycemic and thus makes it more difficult to suspect. We present a case of life-threatening ketoacidosis in type 2 diabetes patients on LCHF diet and concomitant SGLT2 inhibitor therapy.

Keywords: *Diabetes; Diet; Ketoacidosis; SGLT-2; LCHF*

Abbreviations

DKA: Diabetic Ketoacidosis; ICU: Intensive Care Unit; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; SGLT2: Sodium-Glucose Co-Transporter-2 Inhibitors

Introduction

Type 2 diabetes (T2D) constitutes approximately 90% of the 450 million people diagnosed with diabetes globally and its incidence is increasing [1]. The majority of patients are elderly and the disease is associated with obesity, physical inactivity, excess caloric intake, and a clear hereditary linkage.

Plasma glucose levels are regulated in healthy subjects mainly by the two pancreatic hormones insulin and glucagon [2]. Shortly after food intake, glucose undergoes oxidative metabolism in pancreatic beta cells in a chain reaction that culminates in insulin secretion [3]. Similarly, glucose inhibits the release of glucagon from pancreatic alpha cells [4,5]. These two pancreatic hormones are each other's opposites where insulin is anabolic and anaplerotic [3] while glucagon stimulates catabolism and cataplerosis [4-6], not only in terms of glucose metabolism but also lipid and protein metabolism.

In patients with T2D the homeostatic system does not work. Among other things, the disease is characterized an early loss of glucose-sensitive insulin release [7]. Relative insulin deficiency, usually in combination with peripheral insulin resistance in obese individuals, leads to defective uptake of glucose in predominantly skeletal muscle and adipose tissue. There is also a disproportionate hyperglucagonemia [2,4-6]. This not only contributes to hyperglycemia - primarily by stimulating hepatic glucose production - but also ketogenesis is stimulated by glucagon's lipolytic effects.

Diabetic ketoacidosis (DKA) usually affects patients with type 1 diabetes (T1D), *e.g.* at disease onset or at times of insufficient insulin supply in relation to current needs [8]. It is generally considered that patients with T2D, because they still produce insulin, only very rarely develop DKA, for example in severely catabolic situations. However, T2D is characterized by a progressive loss of insulin-producing beta cells [9,10], which causes many patients with T2D to eventually develop insulinopenia similar to that of T1D and thus need add-on insulin therapy. For these reasons, these patients are prone to develop DKA in situations such with rapid and highly increased insulin requirements. In addition, recurrent DKA occur in patients with Flatbush diabetes, also known as ketosis-prone T2D, which is a common form of T2D in individuals of non-Caucasian ethnicity and characterized by episodic insulinopenia as well as disorders of glucagon production [11].

We present a Caucasian patient with T2D of short duration who developed severe DKA that required intensive care unit (ICU) treatment.

Case Report

A 43-year old male with T2D since five years and obesity (body mass index > 33 kg/m^2) was admitted to the emergency room with Kussmaul breathing, nausea, vomiting, abdominal pain, polydipsia, polyuria, and acetone odor. Arterial blood gas analysis showed pH 7.15, base excess (BE) -24.7 mmol/L, pO_2 17.3 kPa, pCO_2 1.3 kPa, P-glucose 22.1 mmol/L, B-lactate 1.1 mmol/L, and B-ketones of 5.1 mmol/L. The patient had been treated with metformin in the past but due to gastrointestinal side effects he had discontinued it. The patient was transferred to the ICU for DKA therapy with i.v. insulin and fluids. Upon discharge the patient was prescribed the sulfonylurea glimepiride for his T2D.

A month later, he fell ill again with similar symptoms. Arterial blood gas analysis showed pH 7.14, BE -24 mmol/L, pO_2 17.8 kPa, pCO_2 1.5 kPa, P-glucose 11.5 mmol/L, B-lactate 0.9 mmol/L, and B-ketones of 7.0 mmol/L. Notably, the hyperglycemia this time, despite a more pronounced ketosis, was only moderate. Between the first and second hospital admissions, a primary care physician had replaced glimepiride with Synjardy™ which is a combination of metformin and the (sodium-glucose co-transporter-2) SGLT2 inhibitor empagliflozin. Again, the patient was admitted to the ICU for DKA treatment. His endogenous insulin production was very high (C-peptide in serum of 2.7 nmol/L), despite continuous treatment with high-dose i.v. insulin.

Recapitulating the medical history in detail revealed that the patient had been on a low carb high fat (LCHF) diet for a long time, even before the first hospital admission. In fact, he had intensified this diet after discharge as he badly wanted to lose weight by "burning fat". Upon discharge from the hospital, the patient was informed of the risks associated with LCHF dieting in diabetes and prescribed metformin, the GLP-1 receptor agonist liraglutide, and insulin glargine.

Discussion

The LCHF diet involves reduced intake of carbohydrates in favor of increased fat intake. Dieting with LCHF diet is popular, not least in patients with T2D as they usually have become diabetic as a result of obesity [1]. Our patient exhibited pronounced ketosis, which is usually considered very unusual among T2D patients with remaining insulin production. We propose that the LCHF diet was the main contributing factor for this ketosis. Due to its high fat content, this diet is ketogenic, something that is well-known among LCHF- dedicated individuals. One of the authors (Å.S.) has lectured for groups of people on LCHF diet at several times and then noticed a weak, but distinctly sensible, odor of acetone in the room. Blood ketone concentrations of up to 5 mmol/L can occur in people on strict LCHF diet, whereas simultaneous acidosis (ketoacidosis) is rare unless insulin deficiency is also present [12-16].

However, it is important to realize that insulin deficiency does not have to be absolute, but relative to current needs in a dynamic process where the balance between insulin and glucagon may be critical [2,4,5]. In addition to the LCHF diet, norepinephrine treatment and severe infection are catabolic processes believed to may further accelerated the ketogenic situation.

The latest class of drugs against T2D, SGLT2 inhibitors [17,18], has, through convincing beneficial effects on clinically relevant endpoints [19], been given strong endorsements by regulatory agencies globally.

SGLT2 inhibitors reduce the reabsorption of glucose in the kidneys, promoting glucosuria and thereby reducing glycemia independently of insulin [17,18]. This class of drugs may, under certain stressful circumstances, cause euglycemic DKA in patients with T1D as well as T2D [20-22]. The mechanisms underlying this unexpected effect started to be unraveled when it was reported that endogenous glucose production increased in T2D patients treated with the SGLT2 inhibitor dapagliflozin [23]. It was subsequently found that SGLT2 is expressed in the glucagon-producing alpha cells and that inhibition of SGLT2 results in increased glucagon secretion [24,25]. This glucagon surplus, relative to low concentrations of insulin, is believed to induce and drive the ketosis as it may occur in SGLT2 inhibitor-treated patients. Since SGLT2 inhibition also reduces glycemia through increased glucosuria, an atypical - euglycemic - ketoacidosis may evolve. The usual symptoms of ketoacidosis, nausea and vomiting, do occur but in the absence of an expected hyperglycemia such an insidious ketoacidosis may easily be missed.

The potential risk attributed to SGLT2 mechanisms should not call for reduced prescription of SGLT2 inhibitors in T2D. On the contrary, in the light of very positive results on hard endpoints [19], these agents should definitely be prescribed more often. However, caution is warranted in patients with long-term (potentially insulinopenic) T2D and/or on LCHF diet and in severely catabolic situations. Patients should be taught the symptoms of ketoacidosis and be advised to seek emergency care should such symptoms develop.

Since patient had been started on SGLT2 inhibitor therapy between the first and second hospital admissions and had more pronounced ketonemia at the latter occasion (7.0 mmol/L vs 5.1 mmol/L) despite significantly lower P-glucose (11.5 mmol/L vs 22.1 mmol/L), it is likely that SGLT2 inhibition had contributed to aggravating the patient's DKA that was close to euglycemic. It is also interesting to note that this patient's DKA developed in spite of a particularly mighty insulin production.

It is important for health care providers to know how to best measure ketosis. The three ketone bodies that have human pathological relevance are beta-hydroxybutyrate, acetoacetate, and acetone. Beta-hydroxybutyrate is the ketone present in the circulation and which is measured as B-ketones. The concentration in healthy adults after a night's fast usually does not exceed 0.2 mmol/L. Acetoacetate is excreted in the urine and is the ketone detected by urinary dip sticks. Acetone is metabolized and eliminated mainly via the lungs. Thus, different ketones are measured in blood and urine, which may not be well known, and this is also relevant from a time perspective. B-ketone analysis gives a snapshot, whereas U-ketones accumulate over longer periods. The situation is analogous to the measurement of P-glucose vs U-glucose. Each emergency room and ICU must have access to B-ketone meters (including sticks). These are now simple and inexpensive and many diabetes patients with labile glycemia have such meters in their homes.

Conclusion

Patients with type 2 diabetes may develop severe ketoacidosis. The LCHF diet is popular in patients with type 2 diabetes but is also ketogenic which may suffer profound ketoacidosis despite marked hyperinsulinemia. The SGLT2 inhibitors, may induce or aggravate euglycemic ketoacidosis by increasing glucagon release and glucosuria.

Conflicts of Interest

Kamila Avander reports no disclosures. Peter Magnusson received speakers fee/grants from Abbott, Alnylam, Bayer, Boeringer-Ingelheim, Novo Nordisk, Octopus Medical, and Pfizer. Åke Sjöholm received speaker's fee from AstraZeneca and Boehringer-Ingelheim.

Bibliography

1. Zimmet P., *et al*. "Diabetes mellitus statistics on prevalence and mortality: facts and fallacies". *Nature Reviews Endocrinology* 12.10 (2016): 616-622.

2. Holst JJ., *et al*. "Insulin and glucagon: partners for life". *Endocrinology* 158.4 (2017): 696-701.

3. Rorsman P and Ashcroft FM. "Pancreatic β-cell electrical activity and insulin secretion: of mice and men". *Physiological Reviews* 98.1 (2018): 117-214.

4. Unger RH and Cherrington AD. "Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover". *Journal of Clinical Investigation* 122.1 (2012): 4-12.

5. Hædersdal S., *et al*. "The role of glucagon in the pathophysiology and treatment of type 2 diabetes". *Mayo Clinic Proceedings* 93.2 (2018) : 217-239.

6. Drucker DJ., *et al*. "Discovery, characterization, and clinical development of the glucagon-like peptides". *Journal of Clinical Investigation* 127.12 (2017): 4217-4227.

7. Pfeifer MA., *et al*. "Insulin secretion in diabetes mellitus". *The American Journal of Medicine* 70.3 (1981): 579-588.

8. Tran TTT., *et al*. "Review of evidence for adult diabetic ketoacidosis management protocols". *Frontiers in Endocrinology* 8 (2017): 106.

9. UK Prospective Diabetes Study Group. "U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44.11 (1995): 1249-1258.

10. Sjöholm Å. "Diabetes mellitus and impaired pancreatic beta-cell proliferation". *Journal of Internal Medicine* 239.3 (1996): 211-220.

11. Patel SG., *et al*. "Pathogenesis of $A^{-}\beta^{+}$ ketosis-prone diabetes". *Diabetes* 62.3 (2013): 912-922.

12. Bergqvist AG., *et al*. "Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy". *Epilepsia* 46.11 (2005): 1810-1819.

13. Paoli A. "Ketogenic diet for obesity: friend or foe?". *International Journal of Environmental Research and Public Health* 11.2 (2014): 2092-2107.

14. Courchesne-Loyer A., *et al*. "Inverse relationship between brain glucose and ketone metabolism in adults during short-term moderate dietary ketosis: A dual tracer quantitative positron emission tomography study". *Journal of Cerebral Blood Flow and Metabolism* 37.7 (2017): 2485-2493.

15. Neal EG., *et al*. "A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy". *Epilepsia* 50.5 (2009): 1109-1116.

16. Payne NE., *et al*. "The ketogenic and related diets in adolescents and adults-a review". *Epilepsia* 52.11 (2011): 1941-1948.

17. Ferrannini E and Solini A. "SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects". *Nature Reviews Endocrinology* 8.8 (2012): 495-502.

18. Ferrannini E. "Sodium-glucose co-transporters and their inhibition: clinical physiology". *Cell Metabolism* 26.1 (2017): 27-38.

19. Zinman B., *et al*. "EMPA-REG OUTCOME investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes". *The New England Journal of Medicine* 373 (2015): 2117-2128.

20. Peters AL., *et al*. "Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition". *Diabetes Care* 38.9 (2115): 1687-1693.

21. Taylor SI., *et al.* "SGLT2 inhibitors may predispose to ketoacidosis". *The Journal of Clinical Endocrinology and Metabolism* 100.8 (2015): 2849-2852.

22. Bonora BM., *et al.* "Sodium-glucose co-transporter-2 inhibitors and diabetic ketoacidosis: An updated review of the literature". *Diabetes, Obesity and Metabolism* 20.1 (2018): 25-33.

23. Merovci A., *et al.* "Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production". *Journal of Clinical Investigation* 124.2 (2014): 509-514.

24. Bonner C., *et al.* "Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion". *Nature Medicine* 21.5 (2015): 512-517.

25. Hattersley AT and Thorens B. "Type 2 diabetes, SGLT2 inhibitors, and glucose secretion". *The New England Journal of Medicine* 373.10 (2015): 974-976.

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