Ketosis in type 2 diabetes mellitus: complication or compensatory mechanism?

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Data Availability Statement: All relevant data are within the paper.

Key words: ketogenesis; diabetes mellitus type 2; ketone bodies; outcomes

REVIEW

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Abstract

The exact clinical role of diabetic ketosis in patients presenting to emergency departments with hyperglycemic crises is largely unknown. The aim of this brief review is to provide insights into possible mechanisms and clinical impact of diabetic ketosis in patients with hyperglycemic crises and clinical features of type 2 diabetes mellitus (T2DM). Patients with T2DM have impaired ketogenesis and lower blood ketone levels. High insulin, low glucagon, IGF-I, ghrelin and adiponectin levels are associated with suppressed ketogenesis. Adenosine 5’-monophosphate-activated protein kinase is an enzyme expressed in skeletal muscle and seems to have pivotal role in impaired ketogenesis. An increase in ketogenesis is associated with weight loss, increase in insulin sensitivity and serum IGF-I levels, which have beneficial effects on glycemia but also on cardiovascular morbidity and mortality. Ketone bodies are far more efficient fuel sources than glucose, especially in diabetics with heart failure and kidney disease. In theory, ketogenesis in patients with T2DM can be improved by low-carbohydrate and low-calorie diet, physical activity, moderate alcohol use, metformin, dipeptidyl peptidase 4 inhibitors, glucagon–like peptide-1 agonists and sodium/glucose cotransporter 2 (SGLT-2) inhibitors. SGLT-2 inhibitors are the most potent inducers of ketogenesis. They induce profound glycosuria with a consequent shift to fatty acid metabolism and increased ketogenesis. This could potentially explain how SGLT-2 inhibitor empagliflozin lowers cardiovascular mortality and slows progression of kidney disease. Therefore, we believe that diabetic ketosis in patients with hyperglycemic crisis may be a compensatory mechanism, rather than a complication itself. Further prospective studies are needed to test this hypothesis.
1. Introduction

Ketosis in patients with type 1 diabetes mellitus (T1DM) precedes the development of diabetic ketoacidosis (DKA)\[1\]. Ketosis may be precipitated by infection, withdrawal of insulin therapy, and use of alcohol or illicit drugs[2]. Catecholamine excess coupled with insulinopenia promotes lipolysis of peripheral fat stores to free fatty acids and glycerol, which serve as substrates for the formation of ketone bodies. The key regulator of fatty acid oxidation is carnitine palmitoyltransferase 1, which is inhibited by malonyl coenzyme A (CoA) in the normal non-fasted state. The increased ratio of glucagon and other counter regulatory hormones to insulin promote fatty acid oxidation and incoming fatty acids from fat tissue can be converted to ketone bodies. Increased production of ketone bodies (acetoacetate, and β-hydroxybutyrate) leads to ketonemia and subsequent development of DKA[1]. Ketosis in patients with T1DM requires careful monitoring and treatment in order to prevent the development of DKA, a life threatening acute complication of T1DM[3].

The role of ketosis in patients with features of type 2 diabetes mellitus (T2DM) is unknown. According to our unpublished data, diabetic ketosis and ketoacidosis occurs frequently in patients with T2DM. Among 3409 admissions of patients with hyperglycemic crisis over a five-year period, we observed 630 episodes of DK and 215 episodes of DKA. Only 8.6% of DK episodes and 34.4% of DKA episodes were attributed to T1DM. Moreover, patients with DK had both higher pH and bicarbonate levels than patients with non-ketotic hyperglycemia, implying that DK may not precede the development of DKA in T2DM. DKA in patients with T2DM is a well-recognized complication, but the exact mechanism of development is poorly understood. This subtype of T2DM is also referred to as ketosis-prone diabetes or atypical diabetes, a poorly understood subgroup of T2DM. It occurs predominantly in obese middle-aged men of Hispanic and Afro-American ethnicity and in regions of sub-Saharan Africa[4]. These patients usually lack autoimmunity markers and present with DKA [4,5]. They are prescribed with insulin therapy after the episode of DKA, but after several months usually have normoglycemia without insulin or any other anti-diabetic drug. However, they present again with DKA after several months or years [4]. Absolute or relative insulin deficiency is the cornerstone of DK and DKA pathogenesis in T1DM. On the other hand, evidence exists that the pathogenesis of DKA greatly differs in T2DM. DKA in T2DM occurs presumably due to impaired uptake and metabolism of ketone bodies rather than increased synthesis. Moreover, ketone bodies are mostly synthesized from aminoacids (mostly leucine) rather than fatty acids [6,7]. However, the exact precipitating factors and regulatory mechanisms are unknown. Moreover, the exact clinical role of DK in patients presenting to emergency departments with hyperglycemic crises is largely unknown.

The aim of this brief review is to provide insights into possible mechanisms and clinical impact of DK in patients with hyperglycemic crises and clinical features of T2DM. We hypothesize that DK may be a compensatory mechanism to increased insulin resistance, which does not necessarily lead to DKA.

![Figure 1](image_url). Impact of changes in metabolic hormones and gene expression on ketogenesis.

2. Pathogenesis of diabetic ketosis in T2DM

Evidence exists that patients have impaired ketogenesis [8,9]. The exact mechanism is unknown, but several metabolic hormones may be involved in ketogenesis (Figure 1).
2.1. Insulin and glucagon

The majority of patients with T2DM are obese and have high insulin and c-peptide levels. Hyperinsulinemia directly suppresses ketogenesis in the liver, but also suppresses growth hormone secretion in the pituitary gland [9-16]. Therefore, patients with T2DM have lower levels of circulating non-esterified fatty acids and ketone bodies. On the contrary, insulin deficiency is associated with increased ketogenesis and predisposes patients with T1DM to ketoacidosis. Blood insulin levels are far more important in suppressing ketogenesis than insulin action on insulin receptors. Hence, patients with inactive insulin receptors do not develop ketoacidosis. High insulin levels in these patients exert an insulinomimetic activity via type 1 insulin-like growth factor receptor [17].

Glucagon has a stimulatory effect on ketogenesis; hence, ketone bodies are increased during starvation and hypoglycemia [10,18]. Glucagon is the most potent stimulus for ketogenesis. For instance, patients with fibrocalculous pancreatic diabetes who have both alpha- and beta-cell dysfunction are unable to develop diabetic ketoacidosis [19]. Moreover, octreotide administration in patients with T1DM suppresses glucagon secretion and ketogenesis [20].

2.2. Growth hormone and ghrelin

Starvation increases secretion of ghrelin from neuroendocrine cells in the gastric wall. Ghrelin is the most potent stimulus for growth hormone secretion [21,22]. High growth hormone and ghrelin levels increase insulin sensitivity and lower serum insulin levels, which is necessary for proper ketogenesis [23-25]. Patients with T2DM tend to have lower IGF-1 and ghrelin levels, which could explain impaired ketogenesis [26,27]. The role of growth hormone deficiency and low IGF-I levels is underestimated in diabetes. For instance, treatment with synthetic IGF-I dramatically enhances insulin sensitivity and reduces insulin dose by 70% in patients on insulin therapy [28,29].

Growth hormone and IGF-1 levels are also influenced by fibroblast growth factor 21 (FGF-21), which was considered to be an important factor in inducing ketogenesis [18,30]. FGF21 deficiency is associated with impaired adaptation to ketosis. However, recent studies have shown that an increase in FGF21 during starvation is a consequence of, rather than a stimulatory mechanism in ketogenesis [18].

2.3. Adiponectin

High adiponectin levels are associated with improved insulin sensitivity and lower serum insulin levels [31,32]. Increased adiponectin was also shown to reduce the incidence of cardiovascular diseases [33]. The exact association between adiponectin and ketogenesis is unknown. However, studies have shown that moderate alcohol consumption increases serum adiponectin and ghrelin levels and improves insulin sensitivity [34-36]. Moreover, alcohol consumption is associated with increased ketogenesis and ketonemia, which could therefore be mediated by adiponectin.

3. Clinical impact of metabolic hormones

High insulin levels, low IGF-I and adiponectin levels are independently associated with higher cardiovascular morbidity and mortality [37-39]. Consequently, insulin therapy and treatment with sulfonylureas increase overall mortality in patients with T2DM, despite lowering glycated hemoglobin (HbA1c) levels [40-42]. On the other hand, metformin, DPP4 inhibitors and GLP-1 analogues are associated with lower mortality and cardiovascular morbidity, independently from changes in HbA1c levels and glycemia [40-42]. This implies that changes in metabolic hormones induced by antidiabetic drugs are far more important than simply lowering plasma glucose levels. Increased ketogenesis is a common denominator of increased insulin sensitivity, lower serum insulin and high IGF-1 and adiponectin levels. Interestingly, no one has ever linked impaired ketosis with decreased mortality and cardiovascular morbidity.
Table 1. List of all intrinsic and environmental factors that may lead to impaired ketogenesis in patients with type 2 diabetes mellitus.

<table>
<thead>
<tr>
<th></th>
<th>Effect on ketogenesis</th>
<th>Mechanisms of action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environmental factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low carbohydrate diet</td>
<td>↑</td>
<td>Low insulin, leptin</td>
</tr>
<tr>
<td>Low calorie diet</td>
<td>↑</td>
<td>Low insulin, leptin, T3, High IGF-I, ghrelin</td>
</tr>
<tr>
<td>Physical activity</td>
<td>↑</td>
<td>Low insulin, High AMPK gene expression, High IGF-I</td>
</tr>
<tr>
<td>Moderate alcohol consumption</td>
<td>↑</td>
<td>High adiponectin, ghrelin, Low insulin</td>
</tr>
<tr>
<td><strong>Intrinsic factors</strong></td>
<td></td>
<td></td>
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<tr>
<td>AMPK activity</td>
<td>↑</td>
<td>Directly induces ketogenesis</td>
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<tr>
<td>ARNT/HIF1beta</td>
<td>↑</td>
<td>Stimulates AMPK activity</td>
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<tr>
<td><strong>Medication</strong></td>
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<tr>
<td>Insulin therapy</td>
<td>↓</td>
<td>High insulin</td>
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<td>Metformin</td>
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<td>Low insulin</td>
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<td>Sulfonylureas</td>
<td>↓</td>
<td>High insulin</td>
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<tr>
<td>SGLT2 inhibitors</td>
<td>↑</td>
<td>Low insulin, High glucagon</td>
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<tr>
<td>Octreotide analogues</td>
<td>↓</td>
<td>Low GH, glucagon</td>
</tr>
</tbody>
</table>
4. Intrinsic and exogenous factors associated with ketogenesis

4.1. Intrinsic factors

4.1.1. Genetic factors and gene expression

Patients who present with DK may have improved function of enzymes that regulate ketogenesis. Adenosine 5'-monophosphate-activated protein kinase (AMPK) is a key enzyme that regulates ketogenesis, but is also responsible for mediating the stimulation of glucose uptake induced by muscle contraction. It stimulates hepatic fatty acid oxidation and ketogenesis, inhibits cholesterol synthesis, lipogenesis, and triglyceride synthesis, inhibits adipocyte lipolysis and lipogenesis, stimulates skeletal muscle fatty acid oxidation and muscle glucose uptake, and modules insulin secretion by pancreatic beta-cells. In skeletal muscle, AMPK is activated by contraction. Defects or disuse (due to a sedentary lifestyle) of AMPK signaling in patients with T2DM may be associated with impaired ketogenesis [43] (Table 1).

Expression of the transcription factor ARNT/HIF1beta is reduced in islets cells and liver of patients T2DM [44]. In animal model, L-ARNT knock out mice have normal blood glucose but increased insulin levels and exhibited features of type 2 diabetes with increased hepatic gluconeogenesis, increased lipogenic gene expression, and low serum ketone bodies. These effects may be associated with reduction in phosphorylation of AMPK without changes in the expression of enzymes involved in ketogenesis, fatty acid oxidation, or FGF21, emphasizing the pivotal role of AMPK in diabetes and impaired ketogenesis [44] (Table 1).

4.1.2. Alpha-cell dysfunction

Glucagon and insulin are key hormones that regulate ketogenesis. Hyperinsulinism inhibits ketogenesis, while hyperglucagonemia caused by starvation or hypoglycemia stimulates ketogenesis. Patients with decreased beta-cell mass and beta-cell failure tend to have impaired alpha cell function [45]. The main clinical implication of alpha cell dysfunction is a tendency towards severe asymptomatic hypoglycemia, but in theory, impaired ketogenesis in T2DM could be explained by alfa-cell dysfunction.

4.1.3. Insulin resistance

Hyperinsulinemia in patients with T2DM suppresses growth hormone and glucagon secretion [16]. Hence, profound insulin resistance and hyperinsulinemia may be the cause of impaired ketogenesis. Evidence exists that insulin inhibits ketogenesis by suppressing Foxa2 transcriptional factor. In the fasted (low insulin) state, Foxa2 activates transcriptional programmes of lipid metabolism and ketogenesis. In insulin-resistant or hyperinsulinaemic mice, Foxa2 is inactive and permanently located in the cytoplasm of hepatocytes. Chronic hyperinsulinaemia in insulin-resistant syndromes results in the cytoplasmic localization and inactivation of Foxa2, thereby promoting lipid accumulation and insulin resistance in the liver [15].

4.2. Environmental factors

4.2.1. Medication

Metformin, DPP-4 inhibitors and GLP-1 analogues improve insulin sensitivity and decrease serum insulin levels[40-42]. This may lead to improved secretion of growth hormone and glucagon and consequently to increased ketogenesis in the state of starvation or acute hyperglycemic crisis. On the other hand, sulfonylureas and insulin do quite the opposite, which in theory disables ketogenesis. Although these hypotheses have not been tested in randomized clinical trials, impaired ketogenesis may explain the increased mortality in patients with high cardiovascular risk. The best rationale for this hypothesis is the fact that sodium-glucose transporter 2 inhibitor empagliflozin, was the first anti-diabetic drug that decreased mortality in patients with T2DM at high cardiovascular risk [46]. Empagliflozin inhibits
sodium-glucose transporter 2 in the proximal tubules and induces profound glycosuria and carbohydrate depletion. This leads to increased serum glucagon levels and increase in ketogenesis [47]. SGLT-2 inhibitors are very potent stimulators of ketogenesis and may even precipitate the development of DKA in some patients [48,49]. Although the increased ketogenesis may explain favorable outcomes, the data on serum ketone levels and their association with mortality is lacking (Table 1).

4.2.2. Alcohol use

Evidence exist that moderate alcohol intake in obese patients with and without diabetes improves insulin sensitivity and leads to improvements in lean body mass [50]. Alcohol increases serum adiponectin and ghrelin levels, both of which may improve insulin sensitivity [34-36]. Therefore, moderate alcohol use may improve ketogenesis via adiponectin- and ghrelin-mediated decrease in insulin levels.

4.2.3. Low-calorie and low-carbohydrate diet

Low-calorie and low-carbohydrate diets in obese non-diabetic subjects are associated with long-term weight loss, decrease in serum insulin and LDL cholesterol and increase in HDL cholesterol [51-53]. Low-calorie diets have been demonstrated as safe and effective treatments of T2DM in terms of achieving normoglycemia and lowering HbA1c [54]. Low-carbohydrate diets are even more effective but with a considerable risk for hypoglycemia [55]. Both low-calorie and low-carbohydrate diets promote ketogenesis. Several cases of normoglycemic DKA mostly in patients with gestational diabetes have been associated with ketogenic diets. This means that patients with T2DM can completely rely on ketone bodies as a fuel source with excellent changes in their metabolic profiles (Table 1).

4.2.4. Physical activity

The effects of physical activity in patients with T2DM are similar to those observed during the ketogenic diet. Physical activity also promotes ketogenesis through decrease in serum insulin levels, but may induce long-term changes in terms of improved ketogenesis through increased expression of AMPK in muscle tissue [56].

5. Clinical implications of increased ketogenesis in T2DM

Studies have shown that patients with T1DM and recurrent ketoacidosis have increased mortality and a higher prevalence of both microvascular and macrovascular complications, which can be explained by excessive oxidative stress [57]. DKA in T1DM implies lack of serum insulin, which also has important anabolic and antioxidative effects. However, lowering serum insulin levels in T2DM implies a decrease in insulin resistance, which is the main feature in patients with T2DM. Despite the decrease in serum insulin levels, patients with T2DM rarely have absolute insulin deficiency and therefore are not at risk for developing DKA (except for patients with ketosis-prone diabetes). Ketone bodies are far more efficient fuel than glucose in patients with diabetes, since insulin is not required for their utilization. Previous studies have found that hypertrophied and failing hearts shift to increased utilization of ketone bodies [58,59]. Hence, patients with increased serum ketone bodies and diabetic cardiomyopathy may have a lower risk for heart failure, which is the leading cause of death in these patients. Moreover, ketone bodies have protective effects on the kidney and improve glomerular filtration rates in healthy subjects and in patients with T1DM [60,61]. Diabetic nephropathy is also an independent prognostic factor for increased mortality; therefore, slowing progression of kidney disease may also reduce mortality. Exogenous ketone supplements also have potent antioxidative properties via inhibition of class I histone deacetylases, which may contribute to favorable outcomes in patients with DK [62].

6. Conclusions

Evidence exists that patients with T2DM have impaired ketogenesis and lower blood ketone levels. The exact etiology is unknown, but may be influenced by several intrinsic and environmental factors. There is no evidence that increased ketogenesis in patients with non-insulinopenic T2DM could predispose to DKA.
Increased ketogenesis is associated with weight loss, increase in insulin sensitivity and serum IGF-I levels, which have beneficial effects on glycemia but also on cardiovascular morbidity and mortality. Moreover, ketone bodies are far more efficient fuel sources than glucose, especially in diabetics with developed complications. Therefore, we believe that DK in patients with hyperglycemic crisis may be a compensatory mechanism, rather than a complication itself. Further prospective studies are needed to test this hypothesis.

Author contributions

IK gave the idea for the article, wrote the article and gave the final approval. MĆ and PĆ performed literature review, participated in drafting the article and gave the final approval. MV critically revised the manuscript, gave suggestions regarding data presentation and gave the final approval.

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