

## REVIEW

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# Ketogenic diets in the management of type 1 diabetes: Safe or safety concern?

## ABSTRACT

The jury is still out on whether a low-carbohydrate, ketosis-inducing diet is an effective and safe adjunctive therapy to insulin in type 1 diabetes. The limited published literature reports an association with weight loss and improved glycemic control and may, over the long-term, lead to reduced macrovascular and microvascular harm. However, the attendant increased risk of dyslipidemia, diabetic ketoacidosis, and hypoglycemia warrant caution, close monitoring of patients who embark on the diet, and further research.

## KEY POINTS

Ketogenic diets are high in fat, moderate in protein, and low in carbohydrate; they should be well formulated for maximal nutritional benefit and well-being.

Ketogenic diets have been reported to improve hemoglobin A1c and glycemic variability in patients with type 1 diabetes and may improve biochemical and physical markers of cardiovascular risk.

Key safety concerns include the risk of dyslipidemia, diabetic ketoacidosis, and hypoglycemia.

Insulin therapy usually requires adjustment when starting a ketogenic diet, and patients should be closely monitored.

Sodium-glucose cotransporter 2 inhibitors should be discontinued when following a ketosis-inducing diet, but metformin is considered safe. Glucagon-like peptide 1 receptor agonists can be continued with close monitoring.

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A 31-YEAR-OLD MAN WITH A 14-YEAR HISTORY of type 1 diabetes presented for routine follow-up. He had been on hybrid closed-loop insulin pump therapy for 6 months. Before using this system, he used multiple daily injections of insulin, with hemoglobin A1c (HbA1c) levels ranging from 7.5% to 9.0% (target range < 7%). Glycemic control improved on insulin pump therapy but was still subpar (HbA1c 7.7%) and highly variable. He self-initiated a very-low-carbohydrate, ketosis-inducing diet (< 30 g of carbohydrates per day), self-adjusted his insulin pump settings, and subsequently reported that his glucose control improved with minimal hypoglycemia.

His HbA1c was 5.7%, and he weighed 18 lbs less than at his previous visit (pre-diet body mass index [BMI] 30.4 kg/m<sup>2</sup>). Glucose levels were reported as within the desired range (3.9–10.0 mmol/L [70–180 mg/dL]) 97% of the time, with very few boluses of insulin required. The patient inquired if this dieting program was safe in patients with type 1 diabetes.

## ■ KETOGENIC DIET AND DIABETES TYPE

Ketogenic diets have risen in popularity in recent years as a strategy for weight loss and treatment of a variety of diseases. For patients with type 2 diabetes mellitus, the diet can lead to clinical improvement, including better glycemic control, lower cholesterol, and weight reduction.<sup>1–3</sup>

The diet is also becoming popular among patients with type 1 diabetes, but its clinical impact remains unclear, as much of the literature consists of retrospective case reports and series. The subject has not been well investigated, likely because of concern about induc-

ing ketoacidosis and hypoglycemia in patients already at high risk for these complications.

This article reviews potential risks and benefits of a ketogenic diet for managing type 1 diabetes based on available evidence.

### ■ KETOGENIC DIET PARAMETERS

Ketogenic diets are generally high in fat (60%–85%), moderate in protein (15%–30%), and low in carbohydrates (5%–10%).<sup>4</sup> This leads to the body using fat as its principal energy source.

Total caloric needs and preferred macronutrient distribution can be calculated using one of a variety of formulas (eg, Mifflin-St. Jeor).<sup>5</sup> Unfortunately, the literature of ketogenic and very-low carbohydrate diets varies in defining diet composition. Feinman et al<sup>6</sup> define a very-low carbohydrate ketogenic diet as containing 20 to 50 g of carbohydrate in a 2,000 calorie diet, or less than 10% of total energy intake.

Common misconceptions about ketogenic diets are that followers can consume few vegetables and must eat excessive amounts of meat. But a well-formulated diet can incorporate a variety of protein-containing foods, including fish, cheese, and Greek-style yogurt. The diet may also include 4 or 5 servings of vegetables daily, which contain about 20 to 30 grams of carbohydrate in total; hence, the low amount of allowable carbohydrate may be obtained entirely from vegetables. Fat calories can also come from plants and fish that are on the Mediterranean diet, such as olives, olive oil, nuts, seeds, avocado, tuna, and salmon.

A long-term ketogenic diet should be designed to meet all nutritional needs. Using a hypothetical case study design, Zinn et al<sup>7</sup> demonstrated that a low-carbohydrate, high-fat diet (10% of calories from carbohydrate) could be formulated to be micronutrient replete. Further, nutrition counseling and attention to hydration can ensure that appropriate amounts of electrolytes such as sodium, potassium, and magnesium are achieved.

### ■ BIOCHEMISTRY OF KETOSIS

Under normal physiologic circumstances, glucose is the main substrate for glycolysis, resulting in the production of adenosine triphosphate (ATP), the body's main energy source.

Under circumstances of starvation or dietary carbohydrate restriction, the body breaks down glycogen (ie, the storage form of glucose) in the liver to provide the body with glucose.

In a prolonged fasting or carbohydrate-restricted state (> 48–72 hours), liver glycogen stores become depleted. Without glucose as a substrate for ATP production, the liver breaks down triglycerides to make ketone bodies that travel to target tissues (eg, brain, muscles) and ultimately generate ATP.<sup>8,9</sup> This process of ketogenesis is regulated by insulin; low carbohydrate intake leads to low insulin levels, promoting ketosis.<sup>10</sup>

### ■ MONITORING KETONES

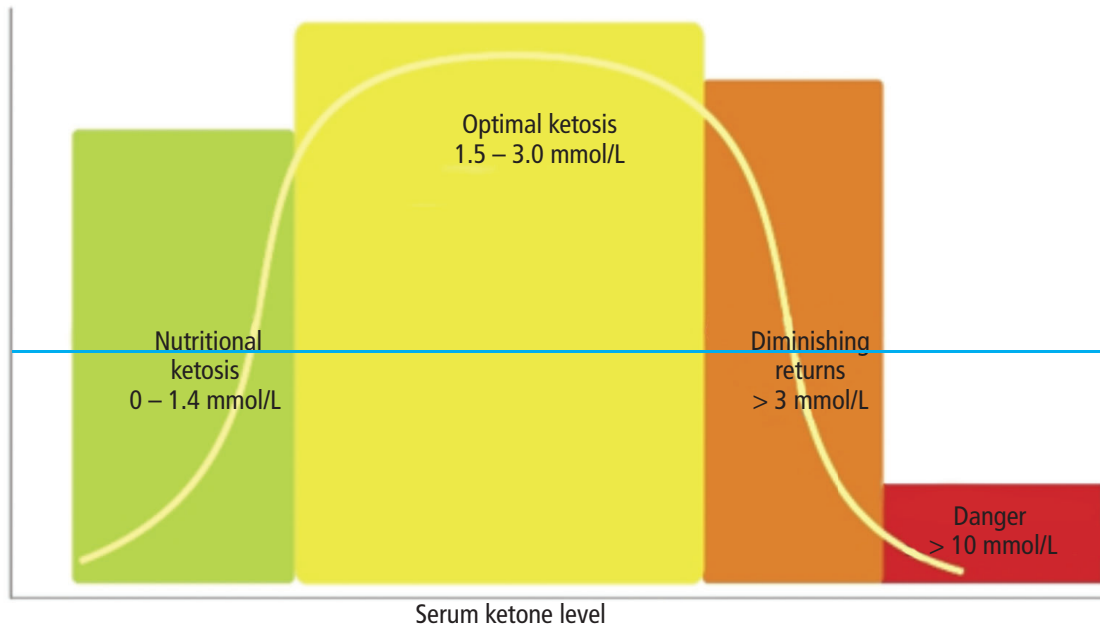
For patients with type 1 diabetes, monitoring ketones is important to identify and prevent diabetic ketoacidosis (DKA). Three types of ketone bodies, resulting from the liver metabolizing fatty acids, are measured in different ways, each with advantages and disadvantages: acetone, acetoacetic acid, and beta-hydroxybutyrate.<sup>11</sup>

**Acetone** is measured with a breath test. Breath analyzers are painless, convenient, and noninvasive. Although they can cost more than blood ketone meters, breath analyzers typically do not have recurring costs. However, research on the accuracy of breath analyzers is limited, and several available devices are not approved by the US Food and Drug Administration.

**Acetoacetic acid** is measured in urine. Urine ketone tests are painless, inexpensive, and noninvasive. However, they are not ideal for early detection of DKA, as results provide an average of urine ketone concentration since the last void rather than reflect current ketone levels.

**Beta-hydroxybutyrate** is measured in capillary blood. Blood ketone measurements provide timely identification of DKA, as they measure the current plasma concentration of beta-hydroxybutyrate, the ketone body that appears earliest in DKA. They also are more sensitive and specific than urine tests. However, blood tests are invasive, and the cost includes the initial purchase of a meter in addition to the recurring expense for disposable test strips and lancets.

**Ketogenic diets are becoming popular for type 1 diabetes, but the clinical impact remains unclear**



**Figure 1.** Safety ranges of serum ketone levels.

Based on data from reference 12.

## DKA OR DESIRED KETOSIS?

Differentiating DKA from desired nutritional ketosis for a patient following a ketogenic diet poses a challenge when interpreting monitored test results. According to Volek and Phinney,<sup>12</sup> blood ketone levels ranging from 0.5 to 3.0 mmol/L are expected in nutritional ketosis, with the upper end (1.5–3.0 mmol/L) being optimal (Figure 1).<sup>12</sup> Although such levels are not high enough to indicate DKA, they can be a warning sign. As such, the clinical picture should be considered. Patients should be educated regarding symptoms of DKA, including nausea, vomiting, and difficulty breathing.

Diligent and more frequent blood glucose monitoring should be a mainstay in patients with diabetes on a ketogenic diet. Although euglycemic DKA is possible while following a ketogenic diet, blood glucose levels above 250 mg/dL may be seen and are a sign of potential DKA.

Glucose monitoring can also be helpful for preventing hypoglycemia, a potential consequence of reduced carbohydrate intake. Clinical studies indicate that a continuous glucose monitor (CGM) can be a useful tool in reducing hypoglycemia.<sup>13,14</sup>

## ADJUSTING DIABETES THERAPIES

Little has been published on how to adjust medications in people with type 1 diabetes who follow a ketogenic diet.

### Insulin requirements change

Ranjan et al<sup>15</sup> conducted a small, randomized crossover study of a high-carbohydrate vs low-carbohydrate diet in patients with type 1 diabetes. All patients used an insulin pump with a CGM. Insulin pump settings were optimized in a 2- to 3-week period before the diet. The diets resulted in similar basal insulin requirements, but the total bolus dosage was lower in the low-carbohydrate diet group (defined as  $\leq 50$ g carbohydrates per day), with the total daily insulin dose reduced by 44.3%. This is similar to that observed in clinical trials in patients with type 2 diabetes starting a low-carbohydrate diet, in which insulin dosages are typically decreased by 50%.<sup>1,16,17</sup> A key difference is that people with type 2 diabetes on a low-carbohydrate diet can usually completely stop bolus doses in addition to reducing basal insulin.<sup>18</sup>

In clinical practice, it is not uncommon to escalate basal insulin rather than add or increase bolus doses, thus allowing the long-acting insulin to cover some or all of a patient's

**A low-carbohydrate, high-fat diet can be formulated to be micronutrient-replete**

post-meal insulin needs. In such cases, excessive basal coverage can increase the risk of hypoglycemia when a patient reduces mealtime carbohydrate intake when starting a ketogenic diet. Furthermore, many people with type 1 diabetes have an elevated BMI, and insulin resistance is expected to improve and insulin requirements decrease as weight is lost on a ketogenic diet.

### How to adjust insulin

Insulin dosages usually need to be reduced after starting a ketogenic diet; in type 1 diabetes, this usually entails decreasing the amount of insulin received per gram of carbohydrate. The following strategy can be used:

- If a patient's HbA1c is near target, the daily dosage of basal insulin may need to be decreased by 10% to 20%
- If the HbA1c is elevated, no adjustments may be required
- It is often safest to adjust insulin with the aim of reducing the risk of hypoglycemia; the patient can be instructed to take additional correction doses of short-acting insulin to address hyperglycemia
- Insulin dosages often need to be adjusted weekly in the initial stages as weight loss and adherence to the ketogenic diet will impact the necessary insulin adjustments, and these factors are highly individual.

### Other diabetes medications

Usually with the aim of weight loss, many patients with type 1 diabetes also take medications off-label that are approved by the US Food and Drug Administration for type 2 diabetes, including metformin, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists.

SGLT-2 inhibitors are associated with an increased risk of euglycemic DKA, particularly in type 1 diabetes. This may occur through multiple mechanisms, including reduction in insulin-mediated suppression of lipolysis and ketogenesis, volume contraction, promotion of glucagon secretion, and decrease in renal clearance of ketone bodies.<sup>19</sup> Accordingly, SGLT-2 inhibitors should be stopped before starting a ketogenic diet owing to the risk of DKA that often presents as euglycemic, making it difficult to recognize.<sup>20</sup>

GLP-1 receptor agonists, when used in type 1 diabetes, may increase the risk of hypoglycemia and DKA.<sup>21,22</sup> They can be continued with close monitoring in patients following a ketogenic diet, although some providers prefer to stop them.

Metformin is generally considered safe to continue.<sup>23</sup>

### ■ BLOOD GLUCOSE CONTROL: A BALANCING ACT

Optimizing glycemic control in type 1 diabetes can be extremely challenging but is essential to prevent life-threatening, short-term complications such as DKA. Long-term glycemic control is also important to reduce the risk of microvascular complications (neuropathy, retinopathy, and nephropathy) and perhaps macrovascular complications (stroke, coronary artery disease, and peripheral vascular disease). However, preventing hyperglycemia comes with the risk of inducing frequent or severe hypoglycemia, which can lead to lower quality of life, hospitalization, coma, and death.

Much of the challenge in maintaining euglycemia in patients with diabetes lies in the difficulty in matching carbohydrate intake with insulin administration, owing to errors in estimating the carbohydrate content in meals, variable insulin absorption, timing of insulin administration, and gastroparesis. Given these complicating factors, it is plausible that low carbohydrate intake and resulting lower prandial insulin bolus requirements may lead to better glycemic control, less blood glucose variability, and improved quality of life.<sup>24</sup>

### ■ EFFICACY AND SAFETY

Before the adoption of insulin as the gold standard treatment for type 1 diabetes, diet was one of the few therapy options available. In the early 20th century, the use of a very low-calorie, low-carbohydrate diet was used experimentally to manage it.<sup>9</sup>

The existing literature regarding the use of the ketogenic diet in type 1 diabetes is limited and has yielded mixed results. Many of the publications are case reports, and the majority are from the pediatric population for the treatment of medication-refractory epilepsy. The few studies are mostly observational and

**Monitoring ketones is important to identify and prevent diabetic ketoacidosis**

vary considerably in terms of the dietary macronutrient composition, making it difficult to generalize their results. Data on long-term cardiometabolic effects are also limited.

### Diet lowers blood glucose, sometimes dangerously

Leow et al<sup>25</sup> investigated the effects of a ketogenic diet (< 55 g of carbohydrates per day and fasting beta-hydroxybutyrate  $\geq$  0.4 mmol/L) in 11 adults with type 1 diabetes who self-initiated the diet before study recruitment. Mean HbA1c of study participants was excellent at 5.3%, and participants spent an impressive average of 74% of time within target range. However, many had a disproportionately high frequency and duration of hypoglycemic episodes.

Lennerz et al<sup>26</sup> evaluated the effect of a very low carbohydrate diet on 316 patients with type 1 diabetes, using an online survey of a social media group. Average carbohydrate intake was  $36 \pm 15$  g of carbohydrates per day for an average duration of  $2.2 \pm 2.9$  years. Patients achieved good glucose control (average HbA1c  $5.7\% \pm 0.66\%$ , average blood glucose by CGM  $104 \pm 16$  mg/dL) and reported high satisfaction. The rate of severe adverse events was low and included 7 patients (2%) with diabetes-related hospitalizations and 4 (1%) with DKA.

In their small, randomized crossover study, Ranjan et al<sup>15</sup> compared 1 week each on a low-carbohydrate diet ( $\leq$  50g carbohydrates per day) and a high-carbohydrate diet ( $\geq$  250g carbohydrates per day) in patients with type 1 diabetes using insulin pump therapy. The low-carbohydrate diet group had significantly lower average daily blood glucose levels (122 mg/dL vs 140 mg/dL,  $P = .02$ ), longer time in euglycemia (defined as 3.9–10.0 mmol/L [70–180 mg/dL]; 83% vs 72%,  $P = .004$ ), less glycemic variability ( $1.9$  vs  $2.6$  mmol/L,  $P = .02$ ), lower total daily insulin dose (22 vs 39 units,  $P = .0001$ ), and fewer daily units of bolus insulin administered ( $6.6$  vs  $23$ ,  $P = .0001$ ).<sup>15</sup>

### Weight loss possible but not well studied

Another potential benefit of the ketogenic diet is weight loss. Obesity in patients with type 1 diabetes is a common problem that has worsened in recent decades. This may be in part due to the use of long-term insulin, an

anabolic hormone that promotes weight gain. Obesity in type 1 diabetes can lead to metabolic syndrome and insulin resistance, as well as increased risk for microvascular complications.<sup>27–30</sup>

The ketogenic diet has been suggested as a tool for weight loss in overweight or obese patients with type 1 diabetes, although it has not been well studied in this population. In a well-designed crossover study, Rosenfalck et al<sup>31</sup> looked at insulin sensitivity and BMI and found no significant change in weight or BMI after 3 months of a ketogenic diet in 10 patients with type 1 diabetes.

### Animal studies have mixed results

A few animal studies have examined the effect of a ketogenic diet in type 1 diabetes, but their significance in humans is unclear. Poplawski et al<sup>32</sup> examined the effects of an 8-week ketogenic diet (5% carbohydrate, 8% protein, 87% fat) vs a high carbohydrate diet (64% carbohydrate, 23% protein, 11% fat) in rat models of type 1 diabetes with nephropathy. The ketogenic diet group had a drastically improved albumin-creatinine ratio, indicating reversal of diabetic nephropathy.

Al-Khalifa et al<sup>33</sup> placed 42 rats on either a normal diet, low carbohydrate diet, or high carbohydrate diet, all ad libitum, for 8 weeks. Half of each group was injected with streptozotocin to induce diabetes. Blood glucose levels and food and water intake increased with the normal and high-carbohydrate diets but not in the low-carbohydrate group ( $P < .01$ ). Weight gain was also significantly lower in the low-carbohydrate group ( $P < .05$ ). In the low-carbohydrate group, the number of beta cells did not differ between the control group and the group with the streptozotocin injection, while the other diet groups had a significant decrease in beta-cell mass in the streptozotocin groups vs controls. These results suggest that a low-carbohydrate diet may attenuate or prevent the development of diabetes.

However, other rodent studies suggest potential harm. Kanikarla-Marie and Jain<sup>34</sup> found that hyperketonemia in type 1 diabetes rat models induced macrophage-mediated damage and oxidative stress on hepatocytes, suggesting that a high ketone state may lead to liver damage. Grandl et al<sup>35</sup> reported that

**Differentiating diabetic ketoacidosis from desired nutritional ketosis poses a challenge**

mice fed a low-carbohydrate, high-fat ketogenic diet had a decrease in glucose tolerance due to blunted insulin-dependent hepatic glucose production during the fasting state.

### Effects on lipids mixed

Concerns have been raised regarding the ketogenic diet and adverse lipid profile changes, but the literature is inconsistent, and few publications have assessed the issue specifically in type 1 diabetes. Effects of ketogenic diets such as decreased total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels and increased high-density lipoprotein cholesterol levels have been reported.<sup>36-40</sup>

Yancy et al,<sup>41</sup> compared a low-carbohydrate diet to a low-fat diet in a randomized control trial of 120 overweight patients with hyperlipidemia. The low-carbohydrate diet led to greater decreases in serum triglyceride levels compared with patients on a low-fat diet (-74.2 vs -27.9 mg/dL,  $P = .004$ ) and greater increases in high-density lipoprotein levels (5.5 vs -1.6 mg/dL,  $P < .001$ ), but no significant differences were seen in low-density lipoprotein levels ( $P = .2$ ).

Using an online survey of a social media group for children and adults with type 1 diabetes who were following a very low carbohydrate diet, Lennerz et al<sup>26</sup> found that 51 of 316 respondents (16.1%) reported having a diagnosis of dyslipidemia (triglyceride level > 130 mg/dL, low-density lipoprotein level > 130 mg/dL, or high-density lipoprotein level < 35 mg/dL).

In a retrospective chart review of 30 patients with either type 1 or type 2 diabetes on a low-carbohydrate diet (< 30 g daily), O'Neill<sup>40</sup> reported that low-density lipoprotein levels decreased by 17%, from 155 to 130 mg/dL ( $P = .004$ ), and triglyceride levels decreased by 31%, from 107 to 74 mg/dL ( $P < .05$ ).

### Cardiac effects uncertain

Although multiple studies have examined the effect of a ketogenic diet on clinical markers of cardiovascular risk (eg, BMI, blood pressure, lipids), the literature is limited and inconclusive regarding direct impacts on cardiac health. A ketogenic diet is known to cause electrolyte disturbances, increasing the risk of cardiac arrhythmias, and some studies have suggested that it may increase risk for a

prolonged QT interval, atrial fibrillation, and other arrhythmias.<sup>42</sup> A case series reported the de novo development of a long QT interval in 3 of 20 children following a ketogenic diet for seizure disorder.<sup>43</sup> Long-term data of cardiac risk in the adult population are lacking.

### Blood pressure evidence scant

Data regarding the impact of a ketogenic diet on blood pressure have been inconsistent, and little exists specifically in the setting of type 1 diabetes. Several studies demonstrated no significant reduction in blood pressure with a ketogenic diet, while others suggested a mild benefit.<sup>37,44-46</sup> A long-term study on the cardiovascular impact of a ketogenic diet on 10 children with glut-1 deficiency over the course of 10 years found no change in systolic or diastolic blood pressures compared with healthy controls ( $P = .11$  and  $P = .37$ , respectively).<sup>36</sup>

### Possible microvascular benefit

Very little research has been conducted on the impact of a ketogenic diet on microvascular complications in patients with diabetes. Studies on rats have found that a ketogenic diet improved or reversed diabetic nephropathy<sup>32</sup> and reduced reactive oxygen species in peripheral nerve mitochondria, suggesting a positive impact on peripheral neuropathy.<sup>47</sup>

## SAFETY IN PEDIATRIC PATIENTS

There is a lack of observational and prospective studies in children following a ketogenic diet, but several case reports have discussed its benefits in children with type 1 diabetes.<sup>2,3,48-52</sup> They have found reductions in glycemia and glycemic variability and improvements in HbA1c level, growth rate, and lipid profiles, and many have been without severe adverse effects, like DKA and hypoglycemia.

Henwood et al<sup>48</sup> described a 4-year-old girl with pyruvate dehydrogenase deficiency, seizure disorder, and type 1 diabetes who was treated with a ketogenic diet. During 28 months follow-up, she had improved activity, better glycemic control, significant developmental advances, and an increase in linear growth from less than 5th percentile to 50th percentile. However, the diet was discontinued when she developed severe DKA.

**Patients should be educated regarding symptoms of diabetic ketoacidosis**

Other case reports have revealed concerns about the diet's safety in children with and without diabetes. de Bock et al<sup>38</sup> described 6 children with type 1 diabetes who were treated with carbohydrate-restrictive diets for epilepsy (diets varied from 20–90 grams per day in some, with others using a percentage-based formula ranging from 6% to 40% of the total daily calorie intake). Some children experienced weight loss and growth delay. Commonly observed effects were fatigue, reduced enjoyment in physical sports, and eating disorders. Ultimately, most families opted to return to a more liberal carbohydrate-containing diet.

Other reported long-term adverse effects are hyperlipidemia, kidney stones, vitamin and mineral deficiencies, electrolyte abnormalities, hypertriglyceridemia, gallstones, and elevated liver function tests.<sup>53,54</sup> Short-term risks, including hypoglycemia, DKA, dehydration, anorexia, gastroesophageal reflux disease, vomiting, diarrhea, and abdominal pain have also been reported. However, many of the complications seen in children have not been well described in adults.

### ■ CASE CONCLUSION

Two years after starting the ketogenic diet, the patient reported that his blood glucose control remained significantly improved. His HbA1c level has remained in the desired range for the past 2 years; most recently it was 5.5%. He lost 35 lbs with BMI improved from 30.4 to 25.5 kg/m<sup>2</sup>. His total average daily basal insulin requirement decreased from 48 to 30 units per day, and he reported that he rarely requires prandial or correctional insulin boluses (before the diet, he averaged 33 units

per day). According to his pump and CGM download, his bolus insulin requirements comprised only 3% of his total daily insulin dose (average of 1 unit per day). His blood glucose level remained within the goal range (3.9–10.0 mmol/L [70–180 mg/dL]) 98% of the time. He reported episodes of hypoglycemia 2 to 3 times every 2 weeks, but these have been mild and easily manageable. He has not had any episodes of DKA or severe hypoglycemia since starting the diet, but also admitted he would not feel safe following the diet without the safety afforded by CGM. He experienced an increase in low-density lipoprotein level up to 221 mg/dL, requiring starting high-dose atorvastatin, which may be due to a high proportion of saturated animal fats in his diet. He responded well to statin therapy and his low-density lipoprotein level decreased to 104 mg/dL, which has been maintained on the therapy.

### ■ THE BOTTOM LINE

Further research is needed on the efficacy and safety of the ketogenic diet in patients with type 1 diabetes. The diet may be appropriate for select patients, but only after a thorough discussion between patient and care team about the risks and benefits. A registered dietitian and specialists in diabetes care, education, endocrinology, and pharmacy should be part of any discussion. For patients on the diet, extra monitoring is critical, preferably with a CGM.

**A continuous glucose monitor can be useful for reducing hypoglycemia**

### ■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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