Brief Literature Review: Glycemic Control With Ketogenic Diet in People With Diabetes

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Evidence does not support a clear preference for a specific eating pattern for people with diabetes, yet recommendations should be evidence-based, standardized, and individualized. Current nutrition guidelines focus on whole foods and dietary patterns rather than specific nutrients (1). The ketogenic eating pattern was initially used as adjunctive therapy for epilepsy (2). However, recent evidence suggests that a ketogenic eating pattern may improve glycemic control in people with type 2 diabetes (2).

The macronutrient intake of people on a ketogenic diet predominantly consists of 55–60% fat, 30–35% protein, and <26% carbohydrates, with daily carbohydrate intake ranging from 20 to 50 g based on total caloric intake of 2,000 kcal/day (1–3). The key aspect of the ketogenic eating pattern is the restriction of carbohydrates, which limits the body's energy intake from glucose. To compensate for the lack of energy derived from glucose, the body produces ketone bodies from fatty acid oxidation to provide an alternative source of energy. The ketone bodies synthesized from fatty acid oxidation include β-hydroxybutyrate, acetoacetate, and acetone. These specific molecules are all able to cross the blood-brain barrier and provide energy to the brain. Additional use of these ketone bodies for energy production can be seen in the kidneys, heart, and muscle tissue (2).

The success of the ketogenic eating pattern in people with epilepsy (4,5) has garnered attention for people with other disease states such as type 2 diabetes. Interestingly, ketogenic diets were being developed for treatment of diabetes in the 1910s, at the same time as they were being developed as a treatment for epilepsy (6). Studies have shown patients experiencing rapid weight loss, as well as reductions in A1C and fasting blood glucose (FBG) levels (2).

Because of the popular interest in the ketogenic eating pattern among clinicians and people with diabetes, we performed a literature review seeking to identify primary literature on the ketogenic eating pattern and its effects on glycemic management. Our secondary objective was to evaluate the effect of a ketogenic diet on A1C, FBG, and postprandial glucose (PPG) levels in people with type 2 diabetes. Studies involving people with type 1 diabetes were excluded from this brief review because the physiology of these two diabetes classifications differs in ways that are especially relevant when considering an eating pattern with a goal of achieving nutritional ketosis. In addition, information on the efficacy of low-carbohydrate diets, including ketogenic eating patterns, in type 1 diabetes has already been published (7).

Research Design and Methods

Studies published between 1 January 2000 and 30 April 2019 were identified through searches of the PubMed and EBSCO Host databases using specific key terms, including "ketogenic diet," "glycemic control," and "diabetes mellitus." All randomized controlled trials (RCTs) with a population consisting of people with type 2 diabetes and glycemic control as an end point were included regardless of study duration. Studies were excluded if no control group was identified, the study population was people with type 2 diabetes, or the ketogenic eating pattern was not an intervention (Figure 1).

The ketogenic eating pattern was defined as daily consumption of <26% of total calories from carbohydrates and was commonly referred to as "low-carbohydrate diet," "very-low-carbohydrate diet," or "low-carbohydrate/high-fat diet." The effect of the ketogenic eating pattern on glycemic control parameters was determined based on change in A1C, FBG, and PPG levels. Statistical analysis could not be performed because of heterogeneity in study duration and comparator arms.

Results

The literature searches generated 34 results. However, only eight studies were eligible for inclusion for the purpose of this brief review. Initially, 10 studies were retrieved, but two

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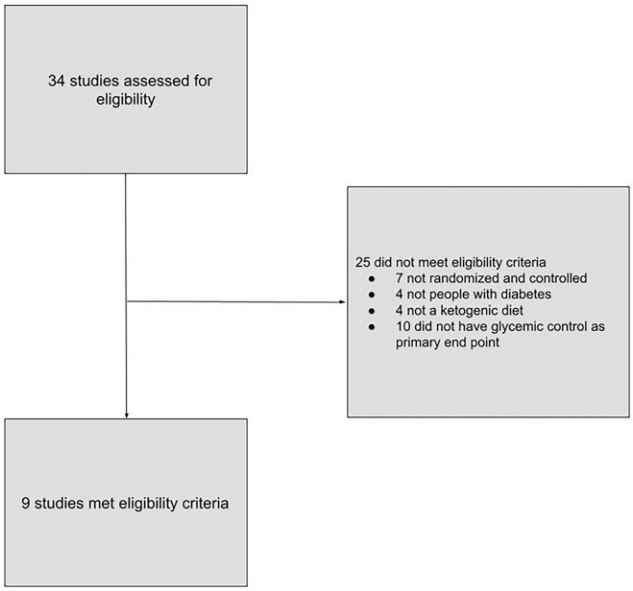

FIGURE 1 Flowchart of literature searches.

were discarded because they were not conducted as RCTs, leaving a total of eight studies eligible for review (8–15). Table 1 summarizes key details of these articles.

In all of the eight trials, participants in the ketogenic eating pattern group were found to have a greater reduction in A1C than those in the comparator diet groups. Study durations differed, but all studies showed that ketogenic eating patterns were associated with greater A1C reductions than other diet interventions regardless of whether they were followed for a short or longer term. However, the most noticeable reduction in A1C was found to be within a short-term duration of 3–6 months for both the ketogenic diet and comparator groups. After 6 months, A1C increased regardless of diet intervention.

Participants in the ketogenic eating pattern groups appeared to have greater reductions in FBG than those in the comparator groups. As with A1C, there appeared to be a more noticeable reduction in FBG over the short term than over a longer term. No definitive claim can be made on the effects of a ketogenic eating pattern on PPG levels because of a lack of data presented in the studies.

Discussion

This literature review has summarized evidence for the ketogenic eating pattern as a nonpharmacological intervention for people with type 2 diabetes. The available evidence suggests that patients who have been initiated on a ketogenic eating pattern may have improved glycemic control, specifically A1C levels. There is also some evidence indicating a similar trend for improved FBG levels. Overall, dietary intervention is an important nonpharmacological method to help people with type 2 diabetes attain glycemic control, and multiple eating patterns can be tailored to meet individual needs and preferences.

Additional information gleaned from the trials in this literature review could be relevant to applicable to clinical practice, particularly insights about other factors in these studies that may have contributed to improvements in glycemic control with a clinician-directed ketogenic diet.

Specifically, for weight changes, Saslow et al. (13) examined the effects on A1C in participants randomized to receive either a ketogenic eating pattern or the American Diabetes Association "Create Your Plate" intervention. This intervention included lean protein and green vegetables and limited the number of starch and carbohydrate servings. Twenty-five participants were enrolled in the 8-month trial, with 12 participants in the ketogenic eating pattern arm and 13 in the control group. At baseline, A1C was 7.1% in the intervention group and 7.2% in the control group. The intervention group saw a decrease of 0.8% after 8 months compared with a decrease of 0.3% (95% CI −0.6% to 0.0%) in the control group. These results were determined to be statistically significant. The difference in weight loss between groups was an exploratory outcome in this study, with the difference of 9.6 kg favoring the ketogenic eating pattern. It should be noted that this group had a higher baseline weight than the control group (109.7 vs. 90.9 kg).

In an RCT by Tay et al. (15), the ketogenic eating pattern was compared with a high-carbohydrate, low-fat eating pattern. The trial was conducted for 24 months, and the investigators did not detect a difference in weight loss or A1C between the 58 participants in the ketogenic eating pattern group and 57 participants in the comparator group. The ketogenic eating pattern led to a weight reduction of 6.8 kg, which was comparable to a 6.6-kg reduction in the comparator group.

A systematic review and meta-analysis by Franz et al. (16) found that following a specific eating pattern with activity, behavioral modifications, and thorough education promoted weight loss among people with type 2 diabetes who were overweight or have obesity. However, setting a primary goal of weight loss through the use of a specific eating pattern may not be an ideal strategy in people with type 2 diabetes, as it is common for A1C to increase after 6 months of following a specific eating pattern (16). Although not fully evaluated in this brief literature review, adherence to eating patterns, including reduction in daily caloric intake, should be assessed in clinical practice to determine the efficacy of a

TABLE 1 Summary of Studies Included in the Brief Review

Article	*N*	Mean Age, years	Sex	Duration, months	Interventions	Pre-Intervention A1C, %	Post-Intervention A1C, %	Pre-Intervention FBG, mg/dL	Post-Intervention FBG, mg/dL	Pre-Intervention PPG, mg/dL	Post-Intervention PPG, mg/dL
Samaha et al., 2003 (8)	64	54	109 male, 23 female	6	LCD	7.80	7.20	128.0	100.0	NA	NA
	68				LFD	7.40	7.40	124.0	104.0		
Westman et al., 2008 (9)	38	52	18 male, 66 female	6	LCKD	8.80	7.20 at 3 months; 7.30 at 6 months	178.1	156.4 at 3 months; 158.2 at 6 months	NA	NA
	46				LGRCD	8.30	7.50 at 3 months; 7.80 at 6 months	166.8	140.7 at 3 months; 150.8 at 6 months		
Davis et al., 2009 (10)	55	54	23 male, 82 female	9	LCD	7.50	6.86 at 3 months; 7.21 at 6 months; 7.48 at 9 months	NA	NA	NA	NA
	50				LFD	7.40	7.14 at 3 months; 7.25 at 6 months; 7.64 at 9 months				
Iqbal et al., 2010 (11)	70	60	130 male, 14 female	24	LCD	7.90	7.40 at 6 months; 7.80 at 12 months; 7.80 at 24 months	157.9	148.4 at 6 months; 143.7 at 12 months; 156.1 at 24 months	NA	NA
	74				LFD	7.60	7.50 at 6 months; 7.30 at 12 months; 7.40 at 24 months	145.3	138.0 at 6 months; 132.4 at 12 months; 141.0 at 24 months		
Goday et al., 2016 (12)	45	54	31 male, 58 female	4	VLCKD	6.90	6.00	136.9	108.9	NA	NA
	44				LD	6.90	6.40	142.8	123.3		
Saslow et al., 2017 (13)	12	56	10 male, 15 female	8	VLCD	7.10	6.20 at 4 months; 6.30 at 8 months	NA	NA	NA	NA
	13				CYPD	7.20	6.70 at 4 months; 6.90 at 8 months				
Saslow et al., 2017 (14)	16	60	9 male, 25 female	12	LCKD	6.60	6.00 at 6 months; 6.10 at 12 months	NA	NA	NA	NA
	18				MCLFD	6.90	6.70 at 6 months; 6.70 at 12 months				
Tay et al., 2018 (15)	58	58	66 male, 49 female	24	LCHFD	7.30	6.70	140.4	145.8	NA	NA
	57				HCLFD	7.40	6.50	151.2	144.0		

CYPD, Create Your Plate diet; HCLFD, high-carbohydrate, low-fat diet; LCD, low-carbohydrate diet; LCHFD, low-carbohydrate, high-fat diet; LCKD, low-carbohydrate ketogenic diet; LD, low-calorie diet; LFD, low-fat diet; LFLGD, low-fat, low-glycemic diet; LGRCD, low-glycemic, reduced-calorie diet; MCLFD, moderate-carbohydrate, low-fat diet; NA, not applicable; VLCD, very-low-carbohydrate diet; VLCKD, very-low-calorie ketogenic diet.

specific eating pattern in promoting glycemic control and weight loss in people with type 2 diabetes.

Finally, the ketogenic eating pattern may have both short- and long-term effects. Individuals following such a diet could experience illness, fatigue, nausea, and headache during the first few days or weeks, with these symptoms possibly resolving after about 2 weeks. However, the longer-term effects remain unknown. Although glucose levels may improve for some individuals, monitoring for any renal, hepatic, or lipid issues should be undertaken in clinical practice because of the high fat intake associated with this eating pattern.

Although not the focus of this review, medication changes may need to be considered for people with type 2 diabetes who initiate a ketogenic eating pattern for glycemic control. In the study by Westman et al. (9), insulin was reduced by 12.5–90% or discontinued by 6 months for participants, whose blood glucose levels were evaluated weekly for the first 3 months and then every other week for 3 months. Although medication adjustment was only noted in a single study in this review, people with type 2 diabetes may be taking oral medications, noninsulin injectable agents, and/or insulin therapy. It would be appropriate to prescribe and continue metformin, glucagon-like peptide-1 receptor agonists, and/or dipeptidyl peptidase-4 inhibitors for people with type 2 diabetes who are following the ketogenic eating pattern (17). Adjustments (e.g., 50% reduction in dose) or discontinuation would be considered due to concerns of hypoglycemia or euglycemic diabetic ketoacidosis, respectively, with insulin and/or sulfonylureas or sodium–glucose cotransporter 2 inhibitors (17). Thiazolidinediones would be discontinued because of the adverse effect of weight gain, as people with type 2 diabetes who institute a ketogenic eating pattern would most likely be trying it to promote weight loss. In clinical practice, the glucose levels of people with type 2 diabetes should be monitored periodically to determine whether medication adjustments are needed at clinical assessments and visits while following the ketogenic eating plan. Use of a continuous glucose monitoring system may be beneficial in obtaining more glycemic data points and trends.

Several limitations need to be addressed regarding the pool of literature included in this review. The low number of available studies could have resulted in incomplete or uncertain conclusions. Studies involving individuals with type 1 diabetes were excluded, as a ketogenic eating pattern is contraindicated for this patient population in that it increases production of ketone bodies, which can aggravate diabetic ketoacidosis. In addition, there were methodological differences among the included trials. The lack of a consistent comparator eating patterns, variations in population size, lack of certain laboratory data, and varying durations of the studies would affect statistical analysis, which was not performed for that reason. Thus, we were unable to prove the statistical significance of any findings. Overall, there is sparse literature reporting on RCTs for eating patterns because of the high degree of variability, high dropout rates, and low adherence to the single eating pattern as an intervention (18). These RCTs each used a single comparison eating pattern, but there were different primary end points, which affected our ability to identify the most relevant eating pattern for comparison in future goals. Finally, the effects of the ketogenic eating pattern on other outcomes (e.g., lipid parameters) were not evaluated in this review. It would be essential to educate people with diabetes to consume fruits and vegetables because of the high fat intake from the ketogenic eating pattern and to monitor them for changes in renal, hepatic, and lipid parameters.

However, this review did have some noteworthy strengths. The included trials had somewhat consistent primary end points and data allowing for the identification of general trends in A1C and FBG levels. In addition, a general trend could be noted toward improved glycemic control among participants randomized to a ketogenic eating pattern.

In summary, there is some evidence that the ketogenic eating pattern improves glycemic control, and particularly A1C and FBG levels in people with type 2 diabetes. Implementation should be clinician-directed, with adequate follow-up for monitoring of efficacy and safety parameters. Many variables can influence weight reduction (3). It is also important to note that, in some studies, A1C slightly increased for participants in both the intervention and comparator groups. Thus, it may be hypothesized that participants may have challenges adhering to a strict eating pattern. Further research is warranted to address this issue and some of the limitations of nutrition studies.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

P.M.G. contributed to the conception and design of the brief review, acquisition of data, and analysis and interpretation of data and drafted the manuscript. J.N.C. contributed to the conception and design of the brief review, revised/edited the manuscript, and submitted the manuscript for publication. Both authors are guarantors of this work and, as such, had full access to all the data reported and take responsibility for the integrity and interpretation of the data in this review.

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