

Efficacy of a low-carbohydrate or ketogenic diet in preventing patient morbidity and mortality

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Clinical Inquiries question

What is the efficacy of a low-carbohydrate or ketogenic diet in the prevention of patient morbidity and mortality?

Evidence-based answer

Ketogenic diets can reduce seizure incidence in refractory epilepsy (strength of recommendation [SOR] A: based on randomized controlled trials [RCTs] and systematic review). Low-carbohydrate diets are associated with weight loss in obese patients, although long-term evidence of weight-loss maintenance is not available (SOR A: based on meta-analysis of RCTs). Treatment of type 2 diabetes mellitus with low-carbohydrate diets demonstrated a decrease in hemoglobin A_{1c} (HbA_{1c}) levels (SOR C: disease-oriented evidence based on meta-analysis or RCTs). Low-carbohydrate diets paired with animal-based proteins are associated with increased mortality compared with moderate-carbohydrate diets, whereas low-carbohydrate diets with plant-based protein are associated with decreased mortality (SOR B: based on meta-analysis of prospective cohort studies).

Evidence summary

Low-carbohydrate diets are broadly defined as a carbohydrate intake of less than 40% of the total daily energy intake. Ketogenic diets are defined as high-fat and very low-carbohydrate (typically less than 30% to 40% of total daily energy intake) diets, with the goal of inducing nutritional ketosis.

Use of a ketogenic diet in refractory epilepsy. A 2018 Cochrane review analyzed 11 RCTs of patients (N=712 patients 18 years of age or younger; N=66 aged 18 or older) with drug-resistant epilepsy (ie, epilepsy despite use of medications [typically 2 to 3 medications]) and reported up to an 85% seizure reduction (50% or greater reduction in seizures) and 55% seizure elimination in the ketogenic diet group (diet of 3:1 or 4:1 ratio of energy from fats to energy from carbohydrates plus protein) compared with the control group after 3 months.¹ Side effects included vomiting, constipation, and diarrhea.

Most studies looking at ketogenic diets in epilepsy have been done with pediatric populations, but a 2014 systematic review of 5 open-label, noncontrolled studies ranging in duration from 3 to 26 months (N=47) evaluating dietary treatment (3:1 or 4:1 ketogenic diet)

in adults with refractory epilepsy demonstrated similar findings.² Overall, 32% of patients following a ketogenic diet achieved at least a 50% reduction in seizure frequency—with 9% having more than a 90% reduction. The dropout rate for the ketogenic diet was 51% owing to diet restrictiveness, complexity, and social and culinary restrictions.

Ketogenic diet used in reduction of weight. A 2016 meta-analysis of 11 unblinded RCTs (N=1369) with 6 to 24 months of follow-up compared dietary counseling and either a low-carbohydrate diet (20 to 40 g of daily carbohydrate intake) or a low-fat diet (10% to 30% of total energy intake as fat) in previously healthy, obese adults (body mass index of 30.6 to 36.1 kg/m²).³ The mean difference in weight was 2.17 kg (95% CI -3.36 to -0.99 kg) lower for low-carbohydrate versus low-fat diets; this difference was maintained even when excluding studies with less than 12 months of follow-up and those with unclear or high risk of bias, and with an all-female experimental population.

Low-carbohydrate diet and diabetes. A 2017 meta-analysis of 10 RCTs with 3 to 24 months of follow-up (N=1376 patients with type 2 diabetes from 7 countries) found a low- to moderate-carbohydrate diet (<45% of total daily energy intake) resulted in a 0.34% (95% CI 0.06% to 0.63%) lower HbA_{1c} level compared with a high-carbohydrate diet (45% to 60% of total daily energy intake) for the first year of dietary change; however, this effect did not persist at follow-up of 1 year or later.⁴ The measure of carbohydrate restriction correlated to the decrease in glucose level ($R=-0.85$, $P<.01$).

Notably, a 2018 non-randomized controlled before-and-after study (N=349) allowed study participants with type 2 diabetes to choose between a ketogenic diet, with continuous remote serum ketone monitoring and lifestyle coaching, and usual diabetes care, with medications and nurse education support. In the group choosing the ketogenic diet, HbA_{1c} levels decreased 17% from an average of 7.6% to 6.3% ($P<.0017$), participants experienced a 12% body weight loss ($P<.001$), and there was a decreased need for diabetes medications.⁵ Sixty percent of those following the ketogenic diet were able to achieve a normal HbA_{1c} level while discontinuing all diabetes medications or remaining on metformin alone, while only 10% of those receiving usual diabetes care were able to achieve this outcome. Cessation of

insulin was noted in 94% of patients in the ketogenic diet group ($P < .001$). Laboratory results also showed fasting glucose level decreased by 22% ($P < .001$), fasting insulin level by 43% ($P < .001$), and high-sensitivity C-reactive protein level by 39% ($P < .001$). Results also demonstrated high-density lipoprotein levels increased by 18% ($P < .001$) and low-density lipoprotein by 10% ($P < .001$).⁵ The usual-care control group had no reported significant changes to weight, medication use, or HbA_{1c} levels or other biomarkers.

Low-carbohydrate diet and mortality. A 2018 meta-analysis of 8 prospective cohort studies (N=432 179) including overweight patients from 21 different countries with between 7 and 26 years of follow-up showed the lowest mortality with mid-range carbohydrate dietary consumption at 50% to 55% of total daily energy consumption, compared with a low-carbohydrate diet (<40% of total daily energy intake; hazard ratio [HR] of 1.20, 95% CI 1.09 to 1.32) or a high-carbohydrate diet (>60% of total daily energy intake; HR=1.23, 95% CI 1.11 to 1.36).⁶ Notably, in a low-carbohydrate diet, if energy from carbohydrates was replaced with animal-based protein or fat sources, it was associated with increased mortality with an HR of 1.18 (95% CI 1.09 to 1.29), compared with decreased mortality if the energy was replaced with plant-based protein (HR=0.82, 95% CI 0.78 to 0.87).

Side effects. In a retrospective study (N=158) reviewing children (average age 4.6 years) admitted for ketogenic diet initiation for intractable epilepsy, the most common side effects (50% of patients) upon initiation of a ketogenic diet were gastrointestinal, including gastroesophageal reflux, nausea, vomiting, diarrhea, and constipation.⁷ Some other effects include hypoglycemia with associated lethargy and irritability, dyslipidemia typically not requiring medication intervention owing to overall weight loss and improved cardiovascular profile, increased incidence of nephrolithiasis, and headaches. The most common intervention was juice intake for a single episode of hypoglycemia in 24% of patients, followed by treatment for constipation in 6% and nausea medication administration in 3%.

Recommendations from others

The 2013 American Heart Association, American College of Cardiology, and Obesity Society "Guideline for the Management of Overweight and Obesity in Adults" updated consensus statement graded the following as having a high strength of evidence for producing weight loss in overweight and obese patients⁸:

- a higher-protein diet (25% protein, 30% fat, 45% carbohydrate), with a total energy deficit;
- a higher-protein Zone-type diet (5 meals a day; 40% carbohydrate, 30% protein, 30% fat) without formal prescribed energy restriction but with a total energy deficit;
- a low-carbohydrate diet (initially <20 g/d of carbohydrates) without formal prescribed energy restriction but with a realized energy deficit; and
- a low-glycemic-load diet, either with or without formal prescribed energy restriction, but with a realized energy deficit.

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Competing interests

None declared

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