Cochrane for Clinicians

Putting Evidence into Practice

Ketogenic Diets for Drug-Resistant Epilepsy

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Clinical Question

Are ketogenic diets safe and effective at reducing seizure frequency in patients with drug-resistant epilepsy?

Evidence-Based Answer

In children with drug-resistant epilepsy, a ketogenic diet decreases the risk of seizures by 50% after three to four months (absolute risk reduction [ARR] = 37.5%; 95% CI, 19.4% to 67.6%; number needed to treat [NNT] = 3; 95% CI, 1 to 5). (Strength of Recommendation [SOR]: B, based on inconsistent or limited-quality patient-oriented evidence.) Adverse effects such as gastrointestinal symptoms do not occur more often than in children who follow their usual diet. In adults, it is unclear whether ketogenic diets are beneficial, and adverse gastrointestinal effects are common.[1] (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

In 2015, approximately 3 million U.S. adults and 470,000 children were diagnosed with epilepsy.[2] Worldwide, approximately 30% of people taking two or more antiepileptic medications continue to have seizures; this is termed drug-resistant epilepsy.[3] Ketogenic diets have been suggested to reduce seizure frequency in people with epilepsy. Although the exact mechanism is unknown, historically, patients who fasted had less frequent seizures. Ketogenic diets mimic this fasting state by using fat as the primary fuel source. The classic ketogenic diet provides energy in a ratio of four calories of fat to every one calorie of carbohydrate or protein. The authors of this Cochrane review assessed the effectiveness of ketogenic diets, compared with usual diet, at reducing seizure frequency in children and adults with drug-resistant epilepsy.

This Cochrane review included 13 randomized controlled trials (three conducted in the United States, none in Canada; two trials included adults) and 932 participants (221 adults and 711 children).[1] The follow-up time ranged from two to 16 months. Results were reported separately for children and adults, and seizure frequency was assessed via self-report. Exclusion criteria in the majority of trials involved persons with known metabolic or neurodegenerative disorders, pregnancy, hyperlipidemia, and renal disease. Primary outcomes were seizure freedom (i.e., being declared seizure-free), seizure reduction (50% or greater reduction in frequency), and adverse effects.

Children who followed a ketogenic diet had higher rates of seizure freedom (ARR = 4.5%; 95% CI, 0.4% to 15.3%; NNT = 22; 95% CI, 7 to 250) and seizure reduction (ARR = 37.5%; 95% CI, 19.4% to 67.6%; NNT = 3; 95% CI, 1 to 5) at three to four months. Adults who followed a ketogenic diet had improved seizure reduction, although the results were not statistically significant. No adult participant experienced seizure freedom.

In children, the most common adverse effects reported were vomiting, constipation, and diarrhea, but these were no more likely with ketogenic diets than with usual diets. Both adult studies demonstrated that these adverse effects were more likely in the ketogenic diet group, but this was also not statistically significant. It is notable that the two adult studies used a modified Atkins diet, which allows for more carbohydrate and protein intake than a traditional ketogenic diet. These studies had conflicting results, with one showing significant decrease in seizure frequency and the other showing no effect.

Limitations of this review include the lack of blinding, which significantly increased performance and detection bias, and small sample size. Given the exclusion criteria, results may not be generalizable.

These are summaries of reviews from the Cochrane Library.

This series is coordinated by Corey D. Fogleman, MD, assistant medical editor.

A collection of Cochrane for Clinicians published in *AFP* is available at https://www.aafp.org/afp/cochrane.

CME **This clinical content** conforms to AAFP criteria for CME. See CME Quiz on page 521.

SUMMARY TABLE

Ketogenic Diets vs. Usual Care for Drug-Resistant Epilepsy

Outcomes at 3 to 6 months	Probable outcome with normal diet	Probable outcome with ketogenic diet (95% CI)	NNT or NNH (95% CI)	Participants (studies)	Quality of evidence
Seizure freedom					
Children	21 per 1,000	66 per 1,000 (25 to 174)	22 (7 to 250)	385 (4)	Very low
Adults	NA	NA	NA	141 (2)	Very low
Seizure reduction*					
Children	78 per 1,000	453 per 1,000 (272 to 754)	3 (1 to 5)	385 (4)	Low
Adults	29 per 1,000	144 per 1,000 (7 to 1,000)	NA	141 (2)	Very low
Adverse effects (gastrointestinal complaints)					
Children	NA	NA	NA	425 (5)	Low
Treatment withdrawal					
Adults	86 per 1,000	461 per 1,000 (36 to 1,000)	NA	141 (2)	Very low

NA = not applicable (no statistical difference in outcomes); NNH = number needed to harm; NNT = number needed to treat.

*—50% or greater reduction in frequency.

National Institute for Health and Care Excellence guidelines for management of epilepsy in children recommend referral to a tertiary specialist and consideration of ketogenic diet for those with drug-resistant seizures.[4] Family physicians working with patients who have epilepsy, especially children with drug-resistant epilepsy, should be able to discuss the risks and benefits of ketogenic diets with patients.

The practice recommendations in this activity are available at https://www.cochrane.org/CD001903.

Editor's Note: The ARRs, CIs, and NNTs reported in this Cochrane for Clinicians were calculated by the author based on raw data provided in the original Cochrane review.

The opinions herein are those of the author. They do not represent official policy of the Department of Defense or any of its components.

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Exercise for Dysmenorrhea

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Clinical Question

Is exercise a safe and effective treatment for primary dysmenorrhea?

Evidence-Based Answer

Low-intensity exercise, such as stretching or core strengthening, and high-intensity exercise, such as Zumba or aerobic training, improve menstrual pain intensity compared with no exercise (standardized mean difference [SMD] = −1.86; 95% CI, −2.06 to −1.66; nine randomized controlled trials [RCTs]; n = 632).[1] (Strength of Recommendation [SOR]: B, based on inconsistent or limited-quality patient-oriented evidence.) It is unclear whether any one type of exercise is superior to another at improving overall menstrual symptoms, mental quality of life, or physical quality of life. (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) The evidence is insufficient to draw any conclusions about adverse effects. Also, there is not enough evidence to determine the benefit or harm of exercise compared with nonsteroidal anti-inflammatory drugs

(NSAIDs) or oral contraceptives. (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Primary dysmenorrhea is defined as menstrual pain without known pelvic pathology. It is the most commonly reported menstrual symptom among young women, occurring in about 71% of those younger than 25 years, typically beginning six to 12 months following menarche.[1,2] Allopathic treatment options include NSAIDs, none of which have been shown to be superior to another. Combined hormonal, implantable, injectable, or hormone-releasing intrauterine contraceptives are also effective options. Exercise has long been recommended as a low-risk adjunct, and this review evaluated the effectiveness of exercise for treating primary dysmenorrhea.[3]

This Cochrane review included 12 trials with 854 patients in the subjective review and 10 trials with 754 women in the meta-analysis; participants had regular menses and a diagnosis of primary dysmenorrhea.[1] Women 18 to 43 years of age (mean age = 25 years) participated. Nine RCTs evaluated exercise compared with no exercise. Studies were varied and included either low-intensity exercise (e.g., yoga, stretching, core exercises) or high-intensity exercise (e.g., Zumba, aerobic training). Studies were performed in the United States, India, Iran, New Zealand, Egypt, and Korea. They lasted eight or 12 weeks, with the exception of one study that lasted seven months, and included both supervised and unsupervised training programs. Resistance training was not examined in any of the studies. Limitations included risk of performance bias and detection bias as well as lack of blinding and limited generalizability. Eight studies included in the meta-analysis used a visual analog scale (VAS); the McGill Pain Questionnaire and a numeric rating scale were each used in one study, necessitating the use of the SMD as a primary outcome. A VAS is used to subjectively measure a participant's level of agreement with a statement on a continuous line between two points. Previous studies comparing changes on a VAS have determined 10 mm to be a clinically significant change in pain after surgery.[4]

Results from this review suggest a clinically significant reduction in menstrual pain intensity (SMD = –1.86; 95% CI, –2.06 to –1.66; nine RCTs; n = 632) corresponding to a 25-mm decrease on a 100-mm VAS. Data on the effect of exercise on overall menstrual symptoms, mental quality of life, or physical quality of life were inconclusive. Only one RCT compared abdominal stretching plus mefenamic acid vs. mefenamic acid alone and found an additional VAS reduction in the abdominal stretching plus mefenamic acid group (mean difference = –7.40; 95% CI, –8.36 to –6.44; n = 122).

Adverse effects and safety of exercise were not reported well enough in the reviewed studies to draw conclusions, although exercise can be considered safe provided adequate consideration is made for recovery, nutritional support, and surveillance for injury. None of the studies compared exercise with any type of contraceptive.

These results are consistent with another 2019 systematic review that concluded that exercise is an effective and safe form of lifestyle intervention to decrease symptoms of dysmenorrhea.[5] Clinical guidelines from the American College of Obstetricians and Gynecologists recommend encouraging patients to exercise for the treatment of dysmenorrhea.[2]

The practice recommendations in this activity are available at http://www.cochrane.org/CD004142.

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