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The ketogenic diet in the treatment of refractory epilepsy

English summary

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SUMMARY

The ketogenic diet in the treatment of refractory epilepsy

Introduction

Epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures, which manifest as the transient presence of signs and/or symptoms due to excessive or abnormal synchronous neuronal activity in the brain. Two-thirds of people with epilepsy can control their seizures with an anticonvulsant medication. Those for whom two medications fail to control their seizures have what is referred to as refractory or drug-resistant epilepsy and have to turn to other treatment options, such as surgery, neuromodulation or ketogenic nutritional therapy. The latter consists of a high-fat, adequate-protein and low-carbohydrate diet, the original classic version of which was developed a century ago to treat epilepsy, although different versions of it (e.g., the modified Atkins diet and the medium-chain triglyceride diet) have subsequently been developed to improve its palatability, tolerability and acceptability. The ketogenic diet requires close medical follow-up because it is not without adverse effects, but also a follow-up by a nutritionist because meal preparation is complex and laborious. Some ketogenic formulas are commercially available in Canada and elsewhere in the world. With their predetermined fat-to-nonfat ratios, they make it easier to provide a ketogenic diet, particularly to infants and parenterally fed individuals, thereby improving safety and adherence to the diet.

To support the deliberation when assessing whether or not to include ketogenic nutritional formulas in the List of Medications for the public prescription drug insurance plan so that they would be covered for children with refractory epilepsy, the Institut national d'excellence en santé et services sociaux (INESSS) conducted a systematic review of the scientific literature on the efficacy and safety of the ketogenic diet as a complement to pharmacological therapy, and on ketogenic diet adherence and persistence, and a systematic review of the clinical practice guidelines.

Methodology

A systematic review was performed, in line with INESSS's standards, to obtain a more accurate picture of the efficacy, safety and adherence associated with the ketogenic diet compared to the usual treatment with no special diet. Since the request concerned commercial formulas with fat-to-nonfat ratios of 4:1 and 3:1 typical of the classic ketogenic diet, data on the classic version of this diet compared with data on other versions of it were gathered as well. This was supplemented with a systematic review of guidance documents and best clinical practice recommendations. The scientific literature search was conducted in the MEDLINE (Ovid), Embase (Ovid) and Evidence-Based Medical Reviews (Ovid) databases and covered the period from their date of inception to October 2019. The bibliographies in the selected articles were searched for other relevant publications.

Results

The analysis of the scientific data showed that, when used as a complement to antiepileptic therapy, the ketogenic diet reduces the frequency and severity of epileptic seizures to a greater degree than usual care with no special diet, both in the pediatric and adult population. However, the results of studies that compared the classic ketogenic diet with other versions are mixed and cannot be used as the basis to rule on the efficacy of the classic version compared to a less strict diet, such as the modified Atkins diet or the medium-chain triglyceride diet, all three diets being effective in reducing seizure frequency. Furthermore, the available data do not seem to indicate that the classic 4:1 ketogenic diet is more effective relative to lower fat-to-nonfat ratios. As for the efficacy of commercial ketogenic formulas, there are not enough studies to compare them with that of the other ketogenic diets.

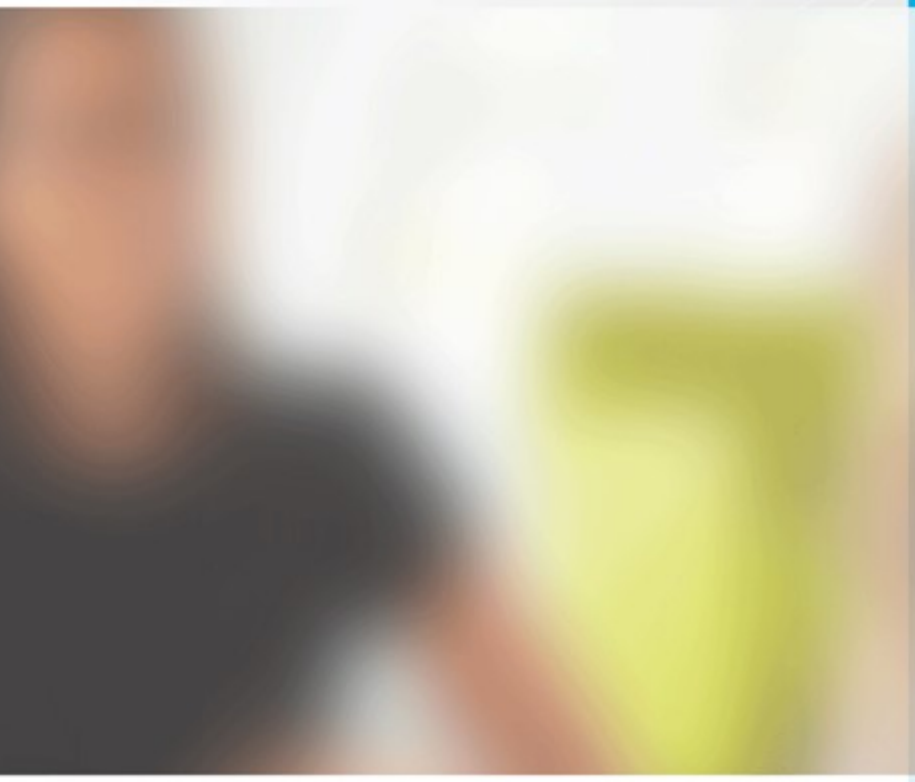
The safety data on the ketogenic diet indicate that gastrointestinal disorders, including constipation, diarrhea, vomiting and feeding problems, are the most common adverse effects. However, because the studies were not designed to have the statistical power to detect a difference in the frequency of adverse effects, safety could not be compared between the different versions of the ketogenic diet. Some components of the lipid profile, such as total cholesterol and the LDL level, appear to be affected by a ketogenic diet, possibly transiently, but the clinical impact of these changes has not been studied.

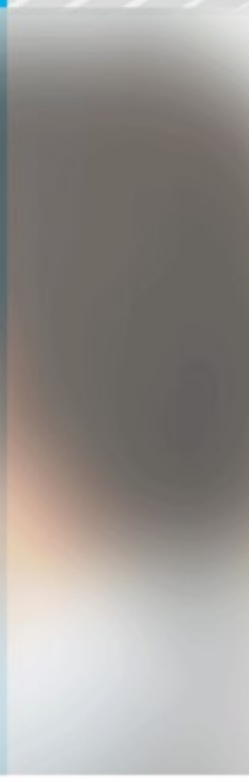
Ketogenic diet adherence rates appear to decrease over time and indicate that there is an issue here. Commercial nutritional formulas could improve adherence to this diet.

According to the selected clinical practice guidelines on the management of patients with refractory epilepsy, using the ketogenic diet in those who are ineligible for or waiting for neurosurgical treatment should be a recommended approach, regardless of the patient's age. The only absolute contraindications to adopting a ketogenic diet are mitochondrial fatty acid transport and oxidation disorders, whereas the relative contraindications are many and varied and require numerous clinical examinations, laboratory tests and evaluations to determine the patient's eligibility for ketogenic diet therapy. It is recommended that the nutritional composition of the diet be individualized and that the various principles of the modified Atkins diet, low-glycemic-index therapy and the medium-chain triglyceride diet be applied to make the nutritional therapy less costly and more pleasant and to thus foster adherence, persistence and even its efficacy. Indeed, the evidence of a correlation between the ketosis level and the efficacy of this diet is very limited. According to the selected clinical practice guidelines, a 3-month trial with fine-tuning should be done before considering discontinuing the diet if it has not been objectively found to be effective. When clinical benefits are observed, it is emphasized that the diet should be continued for at least two years, during which time the anticonvulsant doses can be cautiously reduced, if desired.

Conclusions

Our work has put into perspective the efficacy and safety data on the ketogenic diet in the context of treating refractory epilepsy and the level of adherence to and persistence with the diet as a determining factor in deriving clinical benefit from it. Although we cannot rule on the superiority of any of the versions of the ketogenic diet on the basis of the current data, the analysis confirms the benefits of this type of diet as a complement to pharmacological therapy in reducing seizure frequency compared to a standard diet. In addition to the methodological limitations of the clinical studies, the diversity in the composition of the ketogenic diet used in the trials and the multitude of types of epileptic seizures and symptoms studied make for considerable heterogeneity, which prevented us from conducting meta-analyses. This state-of-knowledge report has nevertheless enlightened INESSS's Comité scientifique permanent de l'évaluation des médicaments aux fins d'inscription on the value of the ketogenic diet in this disorder so that it can make recommendations to the Minister regarding the listing of nutritional formulas consistent with this diet.





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