Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy

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Authors' objectives
To systematically review and synthesise the available evidence on the efficacy of the ketogenic diet, in reducing seizure frequency for children with refractory epilepsy.

Searching
MEDLINE was searched using the keywords 'epilepsy/therapy', 'ketogenic diet', 'dietary therapy' and 'epilepsy'. The World Wide Web (via the Alta Vista search engine) and the Cochrane Controlled Trials Register on the Cochrane Library were also searched using the term 'ketogenic diet'. Current Contents, and the bibliographies of recent review articles and relevant primary research reports, were reviewed for additional citations. The review was limited to those studies published since 1970. No language restrictions were reported.

Study selection
Study designs of evaluations included in the review
The authors did not report any inclusion criteria relating to the study design. All the studies were uncontrolled.

Specific interventions included in the review
The interventions were either the classic ketogenic diet or a modification of the diet.

Participants included in the review
Children with refractory epilepsy were included in the review. The children included in the study were all refractory to new anti-epileptic drugs (AEDs), and in general, had failed or were intolerant of treatments with multiple drug regimes.

Outcomes assessed in the review
The studies had to report relevant health outcomes after treatment. The main outcome measure evaluated was a reduction in seizure frequency. The optimal outcome was the complete elimination of seizures. A 50% or greater reduction in seizures was considered clinically significant.

The studies also reported the percentage of patients achieving near complete elimination of seizures, i.e. greater than 90% reduction. Studies containing only subjective outcomes were excluded.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The studies were assessed on the basis of the following quality-related items: prospective versus retrospective design; and patient population, in terms of the mean age, type of seizures, mean pre-treatment seizure frequency, mean number of pre-treatment AEDs, development stage or IQ, and completeness of reporting the inclusion criteria. Each of the quality items studied were scored from 0 to 2.

The authors do not state how the papers were assessed for quality, or how many of the reviewers performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the
Methods of synthesis
How were the studies combined?
A random-effects model was used to pool the percentage of patients achieving each outcome measure. Sensitivity analyses were conducted on prospective studies, and on those studies achieving the highest rating on the specific elements of the quality assessment.

How were differences between studies investigated?
A test of homogeneity was performed for each outcome measure.

Results of the review
Eleven studies were included: 9 retrospective clinical series (n=281), 1 prospective uncontrolled trial (n=51), and 1 prospective study of consecutive patients (n=150).

The percentage of children who became seizure free ranged from 7 to 33% (9 studies). The pooled percentage was 15.3% (95% confidence interval, CI: 11.0, 21.7).

The percentage of children with a greater than 90% reduction in seizures ranged from 22 to 56% (6 studies). The pooled percentage was 32.2% (95% CI: 25.3, 39.8).

The percentage of children with a greater than 50% reduction in seizures ranged from 29 to 100% (9 studies). The pooled percentage was 55.8% (95% CI: 41.2, 69.7).

A sensitivity analysis limited to prospective studies showed a slight reduction in the percentage response rates. This result was also found in a separate analysis limited to high-quality studies.

There was inconsistent reporting of compliance with the diet and adverse effects. The range of reported non-compliance was 3 to 32%. The adverse effects reported included mild gastrointestinal symptoms, which occurred in one-third to one-half of the treated children, and kidney stones and metabolic abnormalities, which occurred in less than 5% of the treated children.

Authors' conclusions
The results of this analysis suggested that approximately half of those children with refractory epilepsy will have a clinically meaningful improvement after treatment with the ketogenic diet. However, since the results are based on uncontrolled studies, it is possible they could be explained by the placebo effect, spontaneous remission, and/or random variation. It is, however, unlikely that these factors could account for the degree of seizure reduction seen in these trials.

CRD commentary
This was a reasonable review of the area although it was limited by the poor quality of the studies included. The literature search could have been more extensive and included other databases. No specific attempts to locate unpublished studies were reported, although one unpublished report was included in the review. It is possible that the review may be subject to publication bias.

The inclusion criteria, except in relation to study design, were clearly stated. Extensive study details were presented in tabular format. However, very few details of the review methods were presented. A quality assessment was conducted, but this focused on the characteristics of the participants included in the studies rather than those factors which may have biased the results.

The studies were pooled using a random-effects model. However, significant heterogeneity was present for all but one of the outcomes investigated; for this outcome it was of borderline significance. It could be considered inappropriate to pool the results when heterogeneity is present; the results of the pooling should therefore be interpreted with caution.
The authors’ conclusions do follow on from the results presented, but should be interpreted with caution due to the limitations highlighted. It is particularly important to remember that the review is based on uncontrolled studies, which are likely to be subject to bias.

Implications of the review for practice and research
Practice: The authors state that ‘treatment with the ketogenic diet should be considered a valid therapeutic option for children with refractory epilepsy’.

Research: The authors state that controlled studies are needed in this area.

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