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Original article

# Effectiveness of the ketogenic diet used to treat resistant childhood epilepsy in Scandinavia

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ABSTRACT

*Background:* This Scandinavian collaborative retrospective study of children treated with ketogenic diet (KD) highlights indications and effectiveness over two years follow-up.
*Methods:* Five centres specialised in KD collected data retrospectively on 315 patients started on KD from 1999 to 2009. Twenty-five patients who stopped the diet within four weeks because of compliance-problems and minor side-effects were excluded. Seizure-type(s), seizure-frequency, anti-epileptic drugs and other treatments, mental retardation, autism-spectrum disorder and motor-dysfunction were identified and treatment-response was evaluated.
*Results:* An intention-to-treat analysis was used. Responders (>50% seizure-frequency reduction) at 6, 12 and 24 months were 50%, 46% and 28% respectively, seizure-free were 16%, 13% and 10%. Still on the diet were 80%, 64% and 41% after 6, 12 and 24 months. No child had an increased seizure-frequency.

The best seizure outcome was seen in the group with not-daily seizures at baseline ($n = 22$), where 45%, 41% and 32% became seizure-free at 6, 12 and 24 months A significant improvement in seizure-frequency was seen in atonic seizures at three months and secondary generalised seizures at three and six months. Side-effects were noted in 29 subjects; most could be treated and only two stopped due to hyperlipidaemia and two due to kidney-stones. In 167 patients treated with potassium-citrate, one developed kidney-stones, compared with six of 123 without potassium-citrate treatment (relative risk = 8.1).
*Conclusions:* As the first study of implementing KD in children in the Scandinavian countries, our survey of 290 children showed that KD is effective and well tolerated, even in such severe patients with therapy-resistant epilepsy, more than daily seizures and intellectual disability in the majority of patients. Long-term efficacy of KD was comparable or

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even better than reported in newer AEDs. Addition of potassium citrate reduced risk of kidney-stones. Our data indicate that the response might be predicted by seizure-frequency before initiation of the diet but not by age, seizure-type or aetiology.



## 1. Introduction

The ketogenic diet (KD) is a well-established treatment for drug-resistant childhood epilepsy with expanding indications, especially in the neurometabolic field. Although the underlying mechanisms of action remain partly unclear, recent work indicates that several mechanisms of action may exist for the ketogenic diet, including the disruption of glutamatergic synaptic transmission, the inhibition of glycolysis and the activation of ATP-sensitive potassium channels.[1–4] KD has been used since the first reports of beneficial effects on seizure control in the 1920s.[5] The diet has been shown to be effective in retrospective and prospective observational studies and more than 50% of treated children have achieved seizure reductions of more than 50%. Some children became seizure free within several months.[5–8] In a randomised controlled study performed in 2008, 28 children (38%) on the diet experienced a seizure reduction of more than 50% as compared to 4 (6%) controls ($p < 0.0001$), while five children (7%) in the diet group experienced a seizure reduction greater than 90% compared with no controls ($p = 0.0582$).[9] The diet is associated with mild side-effects and its long-term effectiveness is not yet fully explored.[10–14] However a retrospective evaluation found favourable results on seizure control and side effects long time after discontinuation of the diet.[15] The aim of this collaborative study in the three Scandinavian countries was to highlight the spectrum of indications, effects and adverse events in 315 children with therapy-resistant epilepsy treated with the diet and followed for two years.

## 2. Methods

In the three Scandinavian countries, Denmark, Norway and Sweden, all children (≤18 years) started on the ketogenic diet between 1999 and 2009 were enrolled in a large retrospective study. In Sweden though with the exception of 22 children from the northern diet centre from which patients were not included and in Norway only patients started between 2005 and 2007 were included. In all, 315 patients were collected. The children were referred from all parts of Denmark, Norway and Sweden to the centres specialising in the ketogenic diet. The included centres in Sweden were the Skane University Hospital in Lund, Queen Silvia Children's Hospital in Gothenburg, Astrid Lindgren Children's Hospital in Stockholm. In Denmark, Epilepsihospitalet Dianalund, and in Norway Epilepsisenteret, SSE, were included. Contraindications for the diet, such as disorders of carnitine metabolism, beta-oxidation defects and pyruvate carboxylase deficiency, were ruled out and porphyria was asked for. The children were assessed with regard to age at epilepsy onset and ketogenic diet initiation, epilepsy type and aetiology. Electroclinical syndromes were defined, when possible, in accordance with the International League Against Epilepsy (ILAE). Seizure type(s) were defined as absence, myoclonic, atonic, tonic, tonic-clonic, focal and infantile spasms in accordance with the ILAE.[16] Seizure frequency and concurrent anti-epileptic drugs and other treatments during a three-month steady state before diet were monitored. In addition clinical data and test-results on mental retardation, motor dysfunction and autism spectrum disorders (ASD) (asked for but not extensively tested for in Norway) were collected.

The ketogenic diets were started at a 3:1 or 4:1 ratio (fat:-protein and carbohydrate) and the protein content was generally kept at World Health Organisation (WHO) minimum requirements for age. All ketogenic diets were calculated on an individual basis by a dietitian with regard to the child's current food preferences. The initial calorie prescription for the ketogenic diets was based on an average of the subjects' pre-diet intake and 75–80% of the recommended energy requirements. Diets were fully supplemented with vitamins and minerals. In Sweden, potassium citrate was used. In Denmark and Norway, potassium was not supplemented during the early years of the KD but was then added. At each centre, one or two senior neuropediatricians were responsible for the follow-up of the diet treatment. In most cases, the individual child at a centre was evaluated and followed by one neuropediatrician. The primary outcome in this descriptive study was efficacy, which was defined as a decrease in seizure frequency (>50% reduction was defined as responder). This was assessed by the parents or a caregiver in seizure records, together with the clinician at 3, 6, 12 and 24-month follow-ups. The parents or caregiver filled in a protocol on seizure frequency and were questioned by the neuropediatrician about the nature and timing of any seizures occurring during the previous three months. The average seizure frequency per month before the start of the diet was compared with the frequency during the month before each follow-up visit. Seizure outcome was compared between the groups with "not daily", "daily, but less than 10 a day", "10–50 a day" and "more than 50 a day". In addition to seizure frequency reduction changes in the severity of the seizures, QoL and parents' perception of the children's general behaviour were scored by a senior neuropediatrician. The scoring was based on structured questions to the parents at each visit, every 3rd month, whether QoL, behaviour and seizure severity was improved, unchanged or worse. Side-effects and reason for stopping the diet before two years of treatment were also assessed. Cholesterol levels in plasma were taken after overnight fasting and determined by a well-