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Universitair Medisch Centrum Rotterdam

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Ketogenic diet therapy in paediatric epilepsy

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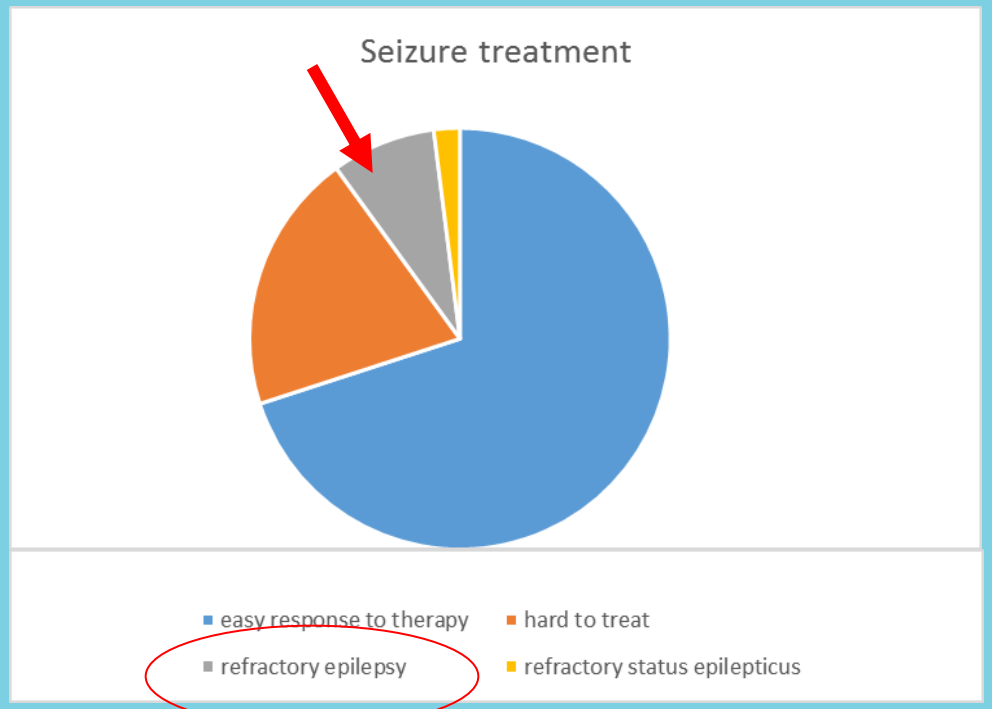
Teaching course Budapest 2016

Refractary epilepsy

- 20-40% of the children with epilepsy will have seizures despite treatment with 2-3 first line antiepileptic drugs
  - (valproic acid, levetiracetam, carbamazepine, lamotrigine, topiramate, diazepines)



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And in children severe epilepsy syndromes are common

- Ohtahara syndrome
- West syndrome
- Lennox Gastaut syndrome
- Dravet syndrome and other gene related epilepsy syndromes (CDKL5, 4p-, STXBP1 etc)
- Myoclonic astatic epilepsy (Doose)
- Progressive myoclonus epilepsy
- Malignant epilepsy with a migrating focus
- Mitochondrial diseases
- Asssociated with disorders of cerebral migration
- Etc……

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Alternatives in case of refractory epilepsy

- 4 alternatives:
  - Epilepsy surgery
  - New generation Anti-epileptic drugs
  - Vagus nerve stimulation
  - Ketogenic therapy (diet)
    - Fasting / hunger diet (1900's)
    - Classic ketogenic diet (ratio Fat: Carbohydrates = 4:1)
    - Medium Chain Triglicerides / MCT diet

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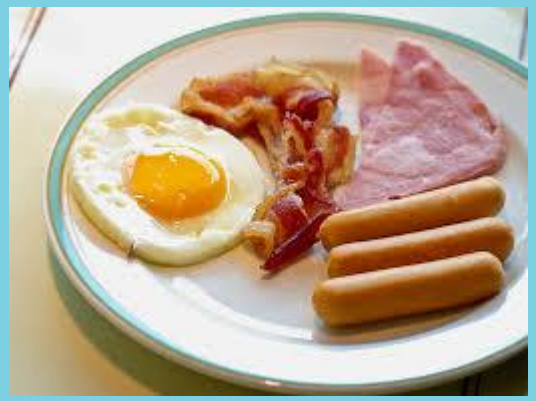
Alternatives in case of refractory epilepsy

- 4 alternatives:
  - Epilepsy surgery
  - New generation Anti-epileptic drugs
  - Vagus nerve Stimulation
  - Ketogenic therapy (diet)



Challenge to make the ketogenic diet palatable

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Alternatives in case of refractory epilepsy

- 4 alternatives:
  - Epilepsy surgery
  - New generation Anti-epileptic drugs
  - Vagus nerve Stimulation
  - Ketogenic therapy (diet)

Challenge to make the ketogenic diet palatable

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Ketogenic diet

High fat, low carbohydrate and adequate protein diet

Ketones serve as alternative source of energy for the brain

Carbohydrate metabolism → *Fat metabolism*

= Metabolic way of fast in an anabolic situation

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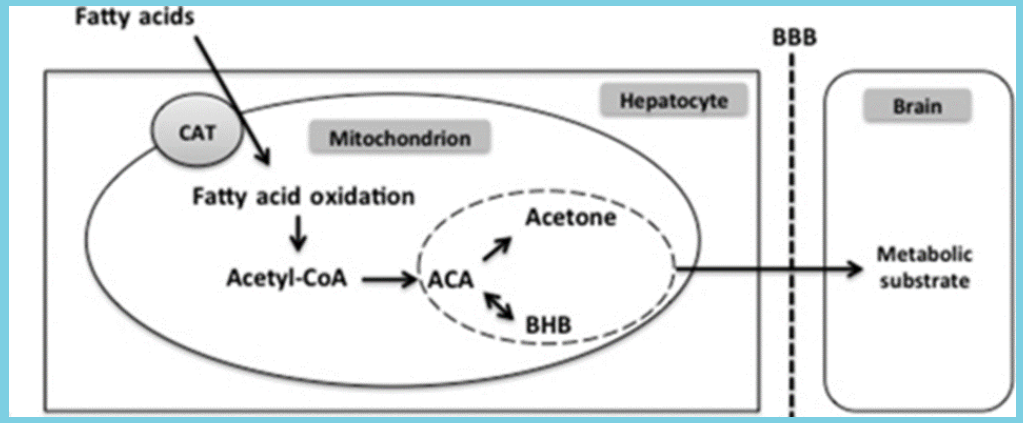
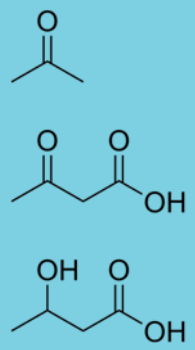
How does a ketogenic diet wotk

High fat, low carbohydrate and adequate protein diet

Ketones serve as alternative source of energy for the brain

Carbohydrate metabolism → *Fat metabolism*





aceton

acetoacetaat (ACA)

β-hydroxyboterzuur (BHB)

- **Production of ketones in liver because of increase availability of fatty acids and decreased availability of carbohydrates**
- **Metabolic switch most likely by way of inhibition of TORC1 (target of rapamycin complex 1)**

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Accepted indications

- **Refractory epilepsy**

- **selected metabolic conditions**
  - Glucose Transporter Deficiency (Glut 1)
  - Pyruvate Dehydrogenase Deficiency

-

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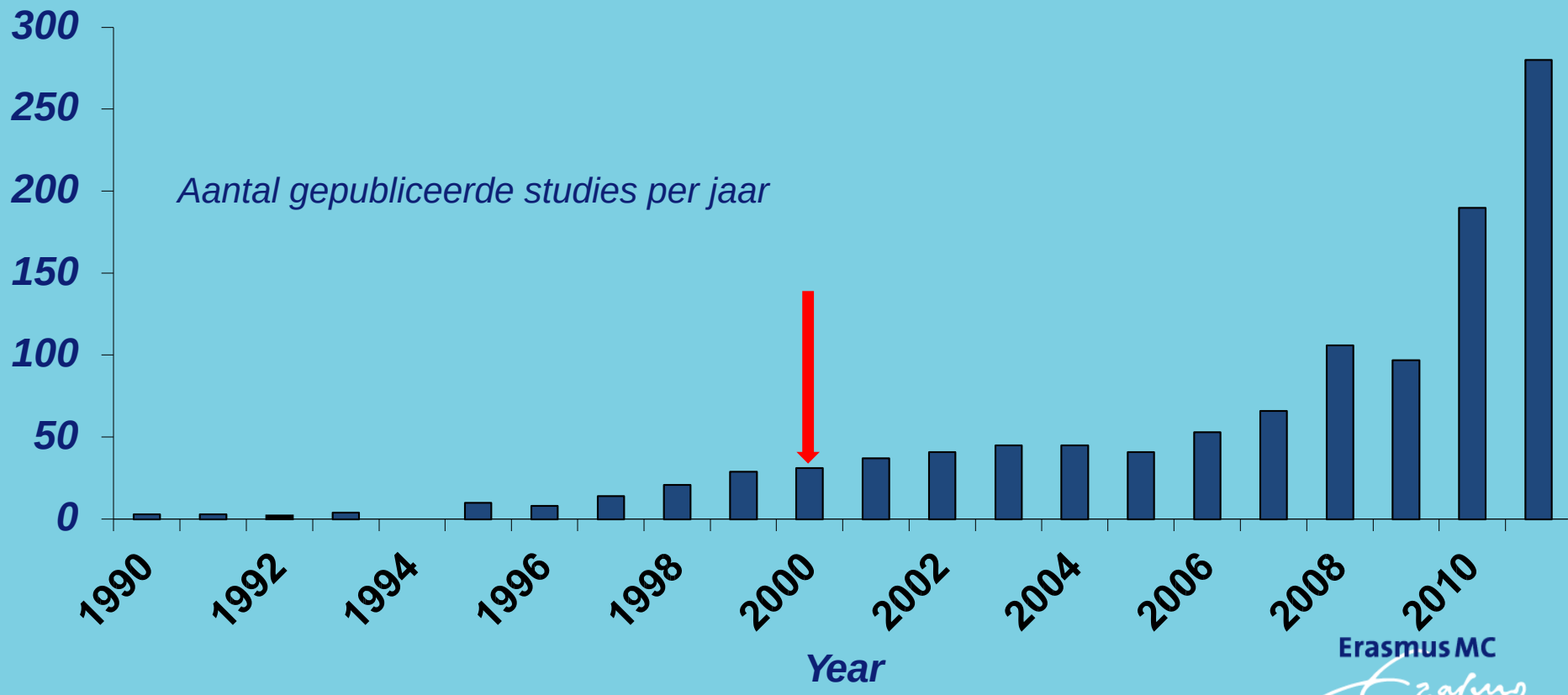
Available data

Lefevre and Aronson 2000

Systematic review of 11 studies

All observational; only 2 prospective



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Is a Ketogenic Diet effective??

- **Levy & Cooper: Cochrane Database Syst Rev 2012**
  - 4 RCT; 5 publications Kossoff 2007, Bergqvist 2005, Seo 2007, Neal 2008, Neal 2009

- Total number of children described in these studies: **289**
  - heterogenic types of epilepsy/ syndromes
  - in all studies 38% of patients 50% seizure reduction at 3 months follow up
  - response was still present after a year

- **Vehmeijer et al EJPN 2015:**
  - **Retrospective study of 59 children treated with KD**
    - After 3 months 49% > 50% reduction of seizures
    - After 12 months 36% > 50% reduction of seizures

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In which children should the KD be used ??

Syndrome specific effectivity?

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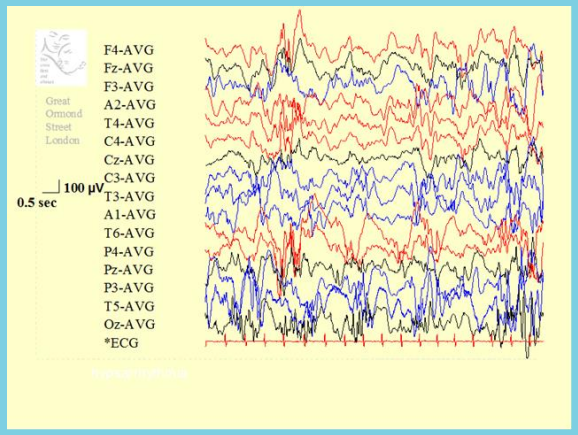
Ketogenic diet and epilepsy syndromes



- **West syndrome:**
- Kossoff et al. Epilepsia 2008;49:1504-1509
  - Retrospective study in new onset spasms
  - seizure free 8/13 KD - 18/20 ACTH
- Numis et al Epilepsy Res 2011;96:172-5
  - 26 refractory patients,
  - 46% >90% seizure reduction after 6 months KD
- Pires et al Epilepsy Res 2013 epub Jan 25
  - 17 infants treated with steroids and vigabatrin,
  - 65 % seizure free after 3 months
- **Vehmeijer et al EJPN 2015: 13 / 52 patients with West syndrome**
  - 46% > 50% seizure reduction after 3 months KD
  - 31% > 50% seizure reduction after 12 months KD

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Ketogenic diet and epilepsy syndromes

- **Lennox Gastaut syndrome**

- Lemmon et al. Dev. Med. Child Neurol. 2012;54:464-8.
  - 71 children 18 months-18 years (median 3 y 6 m),
  - onset < 10 years
  - Different seizure types o.a. tonic, atonic and atypical seizures
- after 6 months ketogenic diet:
  - **51% >50%** seizure reduction
  - **23% >90%** seizure reduction

- Literature review: **47%** of children **> 50%** seizure reduction after 3-36 months KD

- **Vehmeijer et al. EJPN 2015: 6/52 patients with Lennox Gastaut syndrome**
  - **50%** seizure free after 3 and 12 months !!

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Ketogenic diet and epilepsy syndromes

- **Dravet syndrome**
- Caraballo et al Epilepsia 2005;46:1539-44
  - 52 children with Dravet; 20 start KD
  - At 12 months only 13 on KD
  - 2 (15%) seizure free
  - 8 (61.7%) 75-99% seizure reduction
  - 3 (23%) 50-74% seizure reduction
- Nabbout et al Epilepsia 2011;52:e54-7
  - 15 children with Dravet syndrome and insufficient response to Stiripentol
  - >75% reduction 10 (1m), 8 (6m), 6 (9m). After 12m only 5 children on KD
  - **KD has a favourable influence on behaviour. Alertess , ADDH symptoms !**

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Ketogenic diet and epilepsy syndromes

- Myoclonic Astatic Epilepsy (MAE, Doose syndrome)

Study	*N*	*Outcome*
Oguni et al 2002	***26/81***	***15 (58%) 'excellent'***
Fejerman et al 2005	***11***	***6 (55%) >50% reduction***
Caraballo et al 2006	***11/30***	***6 (55%) > 50% reduction***
Kirau & Bergqvist 2007	***10/23***	***5 (50%) seizure freedom***

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Epilepsia, 51(10):2033–2037, 2010
doi: 10.1111/j.1528-1167.2010.02703.x

FULL-LENGTH ORIGINAL RESEARCH

Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES)

*†Rima Nabbout, *Michel Mazzuca, ‡Philippe Hubert, §Sylviane Peudennier, ¶Catherine Allaire, **Vincent Flurin, ††Marina Aberastury, ‡‡Walter Silva, and *†Olivier Dulac

*Department of Neuropediatrics, Centre de Référence Épilepsies Rares, Hôpital Necker-Enfants Malades, Paris, France; †Inserm U663, University Paris Descartes, Hôpital Necker-Enfants Malades, Paris, France; ‡Pediatric Intensive Care Unit, Hôpital Necker-Enfants Malades, Paris, France; §Department of Pediatrics, Hôpital Morvan, CHU Brest, France; ¶Department of Pediatrics, Hôpital Morvan, CHU Brest, France; **Department of Pediatrics, Hôpital Anne de Bretagne, CHU Rennes, France; ††Department of Pediatrics, Hôpital Le Mans, France; and ‡‡Department of Child Neurology, Hospital Italiano de Buenos Aires, Argentine

9 patients with FIRES treated with ketogenic diet over 12 years

7 responders – within 2-4 days ketonuria, 4-6 days of diet initiation

One relapsed and died

Others continued with seizures at a later date

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DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

The ketogenic diet improves recently worsened focal epilepsy

NATHALIE VILLENEUVE MD[1] | FLORENCE PINTON MD[2] | NADIA BAHI-BUISSON MD PHD[3] | OLIVIER DULAC MD[3] | CATHERINE CHIRON MD PHD[3] | RIMA NABBOUT MD PHD[3]

AIM We observed a dramatic response to the ketogenic diet in several patients with highly refractory epilepsy whose seizure frequency had recently worsened. This study aimed to identify whether this characteristic was a useful indication for the ketogenic diet.

METHOD From the 70 patients who received the ketogenic diet during a 3-year period at our institution, we retrospectively selected patients with focal epilepsy. There were 22 children, 13 females and nine males, aged from 5 months to 18 years 6 months (mean 6y 9mo, SD 5y 11mo). Fifteen had symptomatic and seven had cryptogenic focal epilepsy. Seizure frequency 1 week before initiating the ketogenic diet was compared with that at 1 month and at the last visit on the diet.

RESULTS Eleven patients were responders (defined as reduction of seizures by more than 50%) at 1 month. Responders were higher (p=0.046) in the group with a recent worsening of seizures than in those with stable seizure frequency. Seven patients were still seizure-free at 6 months on the diet. Tolerability was excellent in 10 patients. Five patients stopped the diet because of early side effects.

INTERPRETATION The ketogenic diet may be a valuable therapeutic option for children with pharmacoresistant focal epilepsy, particularly those with a recent deterioration of seizure control and neurological status. Because of its rapid effect, the ketogenic diet may be a useful support to intravenous emergency drugs in such a situation.

Dev Med Child Neurol 2009; 51: 276-281

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Factors that may predict response to Ketogenic Diet

- Efficacy in syndromes is approximately the same

- Similar results were found in respect to all other epilepsy causes or seizure types!!

Schoeler et al. Epilepsy research 2013;106:1-16

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Factors that may predict response to Ketogenic Diet

- **Weak evidence**
- for an effect on response to ketogenic diet (reported in less than half of the reported cases)

  - Age at diet initiaton
  - Age at seizure onset
  - Response to, type or number antiepileptic drugs previously used
  - BMI
  - Diet ratio
  - EEG patterns
  - Ketosis
  - Pre-diet seizure frequency
  - Time between seizure onset and initiation of KD

Schoeler et al. Epilepsy research 2013;106:1-16

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Factors that may predict response to Ketogenic Diet

- **Strong** evidence to **NO effect** of response to KD
  - gender
  - intellectual status

Schoeler et al. Epilepsy research 2013;106:1-16

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Factors that may predict response to Ketogenic Diet

- Also **mixed findings**: effect on response only found in half of the reported cases

  - Plasma phospholipid fatty acids
  - HVA/5HIAA levels
  - Carnitene
  - Amino acids
  - Organic acids
  - Linoleic acids
  - Octanic acid
  - Decanoid acid

Schoeler et al. Epilepsy research 2013;106:1-16

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Factors that may predict response to Ketogenic Diet

- on:
  - **Limited data**

  - Blood glucose
  - Single genetic syndromes
  - MRI abnormalities
  - Ethnicity

Schoeler et al. Epilepsy research 2013;106:1-16

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Types of ketogenic diet

Classic Ketogenic dieet:

- 90 en% LCT fat
- 5 en% carbohydrates
- 5 en% protein

MCT dieet:

- 71 en% fat of which
  - 60 en% MCT
  - 11 en% LCT
- 19 en% carbohydrates
- 10 en% protein

Combinations are also possible

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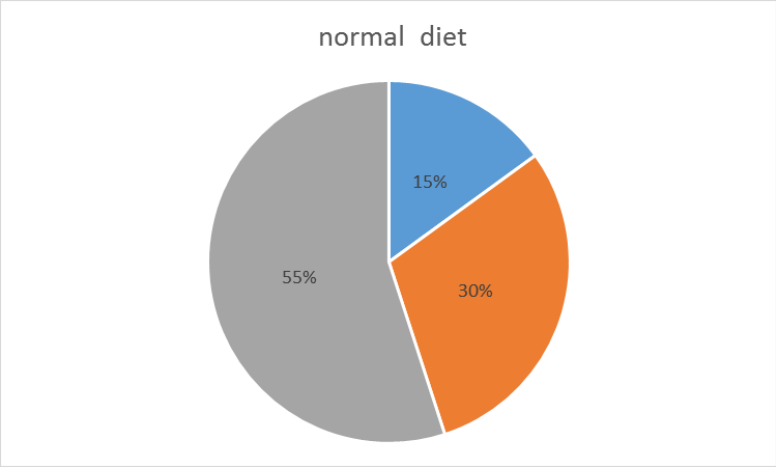
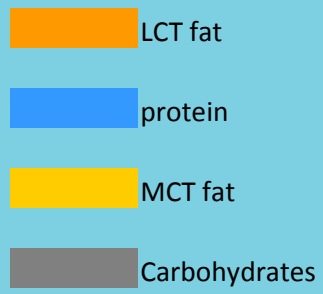
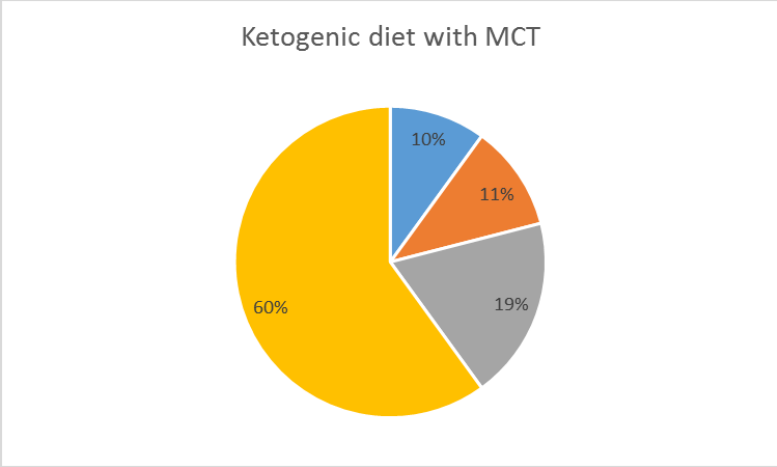
Diet constitution







Side effects

- Feeling hungry!
- Hypoglycemia
- Nausea
- Food refusal
- Tired, no energy

- Effort to continue diet
- Social burden
- Growth retardation (especially infans and toddlers)
- Kidney stones (in combi with anhydrase inhibitors)

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Remaining questions

- When is optimal timing for use?
- Is there advantage over AEDs?
- How long for?
- Can we simplify application?
- Better choice of candidates?

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alternative diets?

Modified Atkins Dieet

- High fat – low Carb (20 gram/day)
- Eating as much as one wants
- No protein restriction
- Possibly also effective in children with epilepsy
  - **Miranda et al Seizure 2011;20:151-5,**
  - **Kim et al Brain Dev 2012;34:570-5,**
  - **Chen & Kossoff J Child Neurol 2012;27:754-8**

- Especially effective and easy for older children and adults
  - **Smith et al Epilepsia 2011;52:775-80,**
  - **Cervenko et al Epilepsia 2012;53:728-732,**
- When there is a response, KD in such a patient even more effective
  - **Kossoff et al Epilepsia 2010;51: 2496-9**

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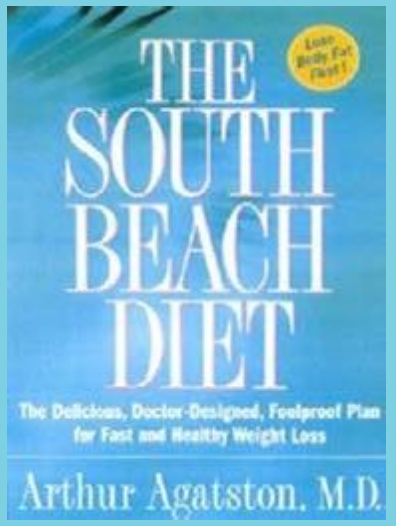
Low Glycaemic Index Therapy

- Glycaemic index:
  - represents the patients increase of blood glucose after consumption of food
  - Varies between 50 (no glucose load) and 100 (glucose ingestion)

- Muzykewicz et al Epilepsia 2009;50:1118-1126
  - 6 children; 50% >50% seizure reduction after 3 months

- Coppola et al Seizure 2011;20:526-8
  - 15 patients 11-22 years,
  - Follow up 14.5 +/- 6.5 months
  - 40% had 75-90% seizure reduction
  - No side effects



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Dietary therapy of epilepsy

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Tour de France 2015; ketogenic is NEWS, HOT, ACCEPTED

University of Oxford develops new super-expensive ketone energy drink that provides body with an alternative source of energy. Ketones have already been used by pro riders to win 'significant internationally famous events'

image: http://keyassets.timeincuk.net/inspirewp/live/wp-content/uploads/sites/2/2015/01/handing-up-bottle-630x420.jpg

The Difference Between Sports Champs and Sports Chumps? Ketones…

Published Mon, Feb 3, 2014 | Tech Research
TeamShare on facebook Share

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Important for succes is te multidisciplinary approach!

TEAM EFFORT

paediatric neurologist, paediatrician,
farmacist, dietician, specialised nurse

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Sophia Kinderziekenhuis

Ketogenic diet practical issues

different types of fat used

Long chain fatty acids (LCT)

Medium chain fatty acids (MCT)

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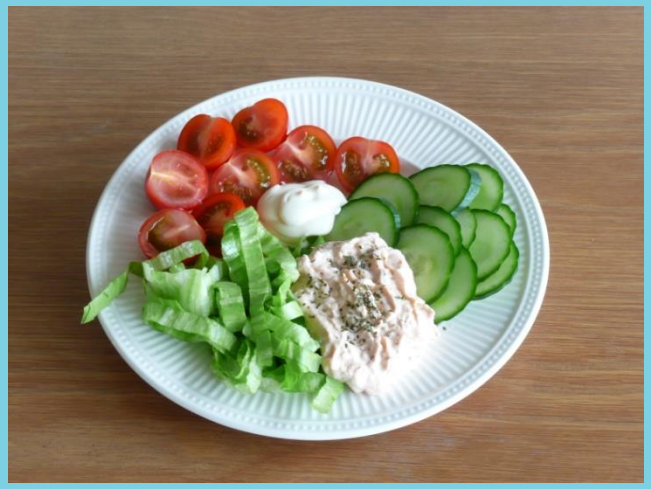
Classic ketogenic diet



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Helpful for a classic ketogenic diet

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INFANT (800 kcal)

Example day menu for a 9 month old child

4 x 200ml bottle (or tube!!) feeding made from Ketocal 3:1

1 serving of vegetables;

- 75 g broccoli
- 10 ml oil
- 12 g crème fraiche

(in case half of it is not eaten give100ml ketocal bottle extra)

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Ketogenic diet with MCT

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Ketogenic diet with MCT appraches a ‘normal’ diet and is easier to follow for an older child

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Initiating the ketogenic diet

Cheque contraindications: absolute

- Fatty acid oxidation disorders (VLCAD, LCHAD, MCAD, OCTN2, CPT1, CPT2)
- Pyruvate carboxylase deficiency and other dsorders of gluconeogenesis (fructose 1,6 difosfatase deficiency)
- Glycogen storage diseases (m.u.v. GSD type 2)
- Deficits of ketolysis defecten
- Porfyria
- Long QTc syndrome cardiac arrythmia's
- Sever chronic disease of liver, kidney, pancreas

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Initiating the ketogenic diet

Cheque contraindications: relative

- Parents not motivated or not able to calculate the diet
- Dyslipidemia (despite adequate treatment
- Secundary carnitine deficiency
- Renal tubular acidosis
- Co-treatment with Topiramate, Acetazolamide, Zonisamide or other risk factors to develop kidney stones
- Steroïd treatment
- Diuretics
- Diabetes Mellitus or hyperinsulinism
- Weight < -2SD

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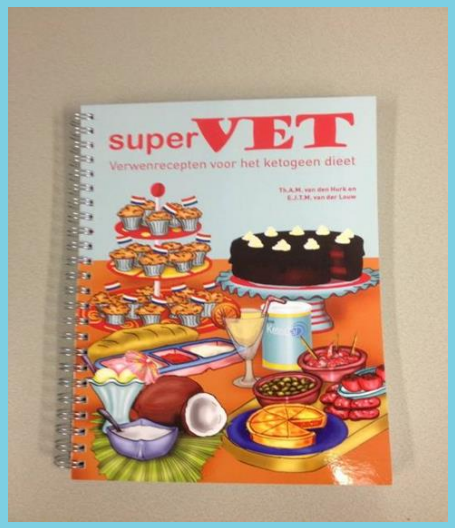
Initiating the ketogenic diet

- ✓ Prepare the parents; the diet can only be succesful when they are motivated and understand what is asked from them!!

- ✓ Self-sustainability of parents is the key to succes!!



Cook book

Websites

Parent groups

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Initiating the ketogenic diet

- ✓ Prepare the parents; the diet can only be succcesful when they are motivated and understand what is asked from them!!

- ✓ < 2 years: admit to hospital. CAVE: hypoglycemia!!! Older children can be initiated on the diet in an outpatient

- ✓ Choose the diet type dependent from the situation of the child

- ✓ -MCT diet is easier to follow for an older child

Initiating the ketogenic diet

- Measure blood ketones every day: target 2-4 +
  - (range 1.5-6.5 is acceptable)

- Monitor:

- - length and weight
- - **blood glucose**
- - self-sustainability parents for measuring glucose and ketones as well as the calculating program for the diet

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Inititiating the diet

- KD is an unhealthy diet
- Add:
  - Vitamines
  - Calcium

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Monitoring glucose and ketosis

-

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Preparations before diet initiation

- Calculation the daily caloric need of patiënt + food diary
- Measure energy metabolism with the help of indirect calorimetry (delta trac)
- **Medication** : 24 hour carbohydrate content; pharmacist can calculate this and advice on changes in type of administration

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This list of medication is not an exception!!

- * Domperidon tabl 10 mg: 3dd 1tabl
  * lamotrigine disp tabl 25mg: 2dd 3 tabl
  * Baclofen tabl 5mg: 4dd 1tabl
  * Oxcarbazepine tabl 300mg: 1dd 1 tabl + 1dd 1,5 tabl
  * Acetazolamide suspension 10mg /ml: 2dd 5ml
- * Dantrolene 15mg caps: 4dd 1caps holds:

    0,3 st dantrolene caps 50mg

    0,12gr lactose monohydric 100m

    1 st caps cards 3-50 hel 153075

  * Ferrofumarate suspension 20mg/ml: 3dd 10 ml
  * Klyx clysma flac 120ml: 3x per week 1
  * Movicolon jr nat pdr : 1 dd 1 sach
  * Esomeprazol gran msr v susp 10mg: 1dd 2 sachets
  * Vit d in oil drupp: 1 dd 10 drops

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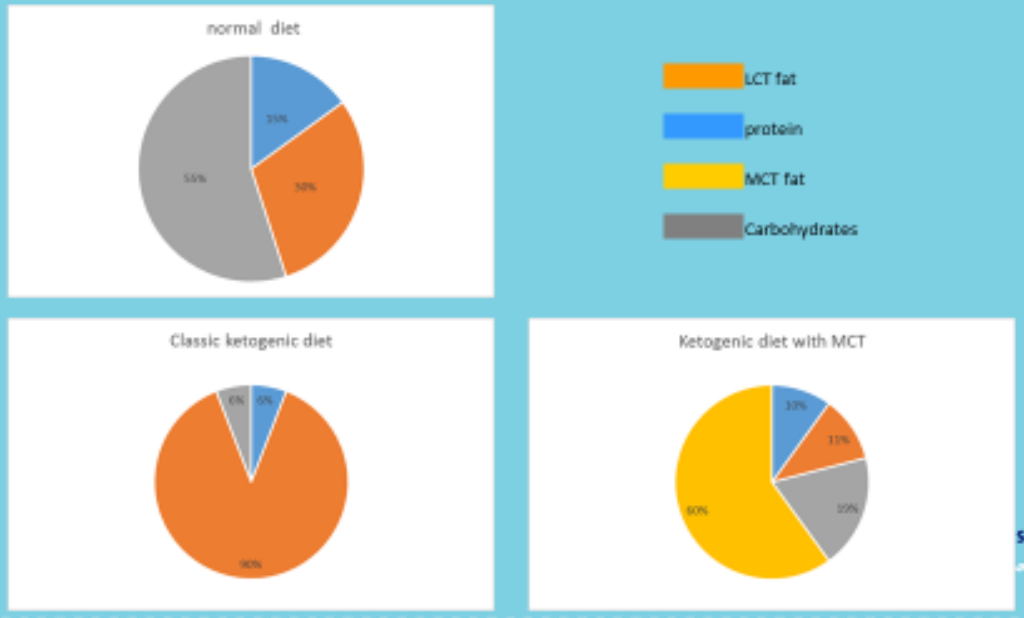
AIM: max 1 gram carbohydrates in medication / 24 hour!!

(in classic ketogenic diet even less!)

Diet constitution



Carbohydrates that are permitted during KD therapy:

1. cellulose, limited amount of lactose

2. Maltitol en mannitol

3. (natrium)saccharine, aspartaam, Asulfaam K

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Carbohydrates that are NOT permitted during KD therapy:

1. Fructose
2. Saccharose
3. Glucose
4. Xylitol
5. Sorbitol

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EXAMPLE

Patient, 8 years old

Dravet syndrome

R/ levetiracetam, topiramate, clobazam and KD

Admitted to ICU with status epilepticus

Complicated with aspiration pneumonia

Policy:

- Tube feeding, antibiotics etc
- Artificial ventilation
- IV midazolam up to 0,5 mg/kg/h

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EXAMPLE

Ketosis in next 5 dagen >3 +, seizures diminish

On day 6 ketosis 0.6, seizures recur!!

What could be the reason ??

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EXAMPLE

Ketosis in next 5 dagen >3 +, seizures diminish

On day 6 ketosis 0.6, seizures recur!!

Midazolam is dissolved in glucose 5% (instead of NaCl) – medication contains > 4 gram saccharose!!!!

Policy: 24h fasting and introduce the diet again in 2 days

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Dietary treatment for epilepsy

- **Thank you for your attention**

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World Congres Paediatric Neurology