Specific needs of patients with chronic disease

Ketogenic diets for cancer patients: paradigm shift?

N. Erickson (DE)
KETOGENIC DIETS FOR CANCER PATIENTS: PARADIGM SHIFT?

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In compliance with COI policy, ESPEN requires the following disclosures to the session audience:

<table>
<thead>
<tr>
<th>Category</th>
<th>Disclosures</th>
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<tbody>
<tr>
<td>Shareholder</td>
<td>No relevant conflicts of interest to declare</td>
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Presentation includes discussion of the following off-label use of a drug or medical device: <N/A>
LEARNING OBJECTIVES

• Know the definition and indications of a ketogenic diet

• Know the approved and borderline indications of a ketogenic diet

• Know the benefits and risks of a ketogenic diet

• Know how to conduct and monitor a ketogenic diet
KETOGENIC DIET

✓ Very low Carbohydrate Intake
(2%–15% TEE)

✓ High in Fat
(60%–90% TEE)

✓ Many different versions exist
  ✓ Classic ketogenic Diet; Middle Chain Triglyceride-Diet, Modified Atkins-Diet & Low-Glycemic Index-Therapy (LGIT)
  ✓ Lesser known Variations: Mediterranean Ketogenic Diet, Paleolithic Ketogenic Diet

✓ Goal: imitate the metabolic effects of fasting while still on an iso-caloric diet

Erickson & Boscheri, AEM CME 2017
Gesellschaft für Neuropädiatrie S1-Leitline 022/021: Ketogene Diäten; 2014
4 MAJOR KETOGENIC DIETS
(STUDIED UTILIZING CONSISTENT PROTOCOLS)

Figure 2: Macronutrient Breakdown of the four major variations of ketogenic diet presented as percentage of total individual estimated energy requirements

Modified after 5, 8, 10, 34-36

CLASSICAL KETOGENIC DIET 4:1
- 4% Carbohydrate
- 6% Protein
- 90% Fat

MIDDLE CHAIN TRIGLYCERIDE (MCT) DIET
- 10% Protein
- 10-35% Carbohydrate
- 71-80% Fat

MODIFIED AKTINS DIET
- 30% Protein evenly spread throughout the day
- 10% Carbohydrate
- 60-66% Fat

LOW GLYCEMIC INDEX DIET (LGIT)
- 20-30 % Protein evenly spread throughout the day
- 40-60g/day Carbohydrate with a glycemic index < 50
- 60-70% Fat

Erickson et al. Med Oncol (2017) 34:72
IMPLEMENTATION

- **Ketogenic Diets** *(International Consensus Statement on clinical implementation of the ketogenic diet)*

- Carried out in Team: Physician, specialized Dietitian, Family

- Necessary to select high-fat foods as well as additional sources of fat at every meal in order to achieve the recommended fat content

- All forms of the KD are considered nutritionally inadequate
  - international KD consensus statement and the S1 guidelines require a carbohydrate-free multivitamin with trace minerals (including selenium) & Calcium
  - Vitamin D is strongly recommended

*Kossoff EH. Epilepsia. 2008; 49(Suppl 8):11–3.*

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Established Indications:

✓ **First line Therapy for:**

- **Glucose transporter type 1 (Glut1) deficiency syndrome**
  
  rare genetic metabolic disorder characterized by deficiency of a protein that is required for glucose (a simple sugar) to cross the blood-brain barrier

- **Pyruvate dehydrogenase complex deficiency (PDCD)**
  
  (formerly known as PDH deficiency) is an inherited inborn error of metabolism

✓ **Second line therapy for:**

  **children and young people with epilepsy** whose seizures have not responded to appropriate oral anti-epileptic drugs AEDs

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*Gesellschaft für Neuropädiatrie S1-Leitline 022/021: Ketogene Diäten; 2014*
Ketogenic Diet Benefits and Efficacy Data from Epilepsy

- Generally efficacy: ≥50% improvement in seizure frequency
  - Comparable to pharmaceutical interventions for epilepsy

After 3 months dietary adherence in children:
- Classic KD: Seizure freedom = ≤55% & ≤85% reduction
- MAD: Seizure freedom = ≤10% & ≤60% reduction

After 3 months dietary adherence in adults:
- Classic KD: ≤52% & MAD: ≤34% seizure reduction
  
  (Roehl et al. J Acad Nutr Diet. 2017; 117: 1279)

- Most patients, even those with 75–100% seizure frequency reduction, eventually stop the diet due to restrictiveness, complexity of the diet & social restrictions
  
### Ketogenic Diet

**Absolute Contraindication:**

<table>
<thead>
<tr>
<th>Absolute Contraindication</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatty Acid oxidation disorders</strong></td>
<td>Ketone production prevented</td>
</tr>
<tr>
<td><strong>Ketolyse deficiency</strong></td>
<td>Disturbance in metabolism of ketone bodies</td>
</tr>
<tr>
<td><strong>Non compliance</strong></td>
<td>No basis for treatment</td>
</tr>
<tr>
<td><strong>Hyperinsulismus</strong></td>
<td>Interferes with ketone metabolism</td>
</tr>
<tr>
<td><strong>Pyruvatecarboxlase deficit</strong></td>
<td>Interferes with gluconeogenesis</td>
</tr>
</tbody>
</table>

*Gesellschaft für Neuropädiatrie S1-Leitline 022/021: Ketogene Diäten; 2014*
## Ketogenic Diet

### Relative Contraindications:

<table>
<thead>
<tr>
<th>Relative Contra-indication</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbances in ATP synthesis</td>
<td>Increases lactic acidosis</td>
</tr>
<tr>
<td>Kidney Stones</td>
<td>↓ PH in Urine = ↑ risk of kidney stones</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td></td>
</tr>
<tr>
<td>Liver, Kidney, Pancreas disease</td>
<td>↑ risk of complications</td>
</tr>
<tr>
<td>Intermittent Porphyria</td>
<td>↓ CHO can cause flares</td>
</tr>
<tr>
<td><strong>Cardio-myopathy, Arrhythmia, Long-QT-Syndrome</strong></td>
<td>Known complications of KD</td>
</tr>
<tr>
<td>Disturbances in Lipid metabolism</td>
<td>↑ fat diet = ↑ Lipid metabolism</td>
</tr>
<tr>
<td>Use of Carboanhydrase Inhibitor</td>
<td>↑ Acidosis</td>
</tr>
</tbody>
</table>

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*Gesellschaft für Neuropädiatrie S1-Leitline 022/021: Ketogene Diäten; 2014*
Ketogenic Diet for Cancer: Clinical Data

- Clinical Data studying iso-caloric KD-Programs among cancer patients is limited

- Systematic Review (2017) (Methods: Cochrane Effective Practice and Organization of Care (EPOC))
  - 15 clinical studies and case reports mined from our search
    - 5 case reports
    - 8 prospective studies
      - (6 single-arm studies, 1 single-arm crossover study, & 1 three-arm study utilizing TPN)
    - 2 retrospective studies

Erickson et al, Med Oncol. Med Oncol 2017; 34:72
METHODOLOGICAL LIMITATIONS

- Small numbers of participants **N= 330**
  - 11 out of 15 studies less than 15 Participants
    - (5 had N= ≤ 5; 6 had N= ≤15)
- **177 (53%)** followed a ketogenic diet at any point during the studies
  - 67/177 (**37%**) of the patients following the KD—or 20% of all patients included in the studies managed to adhere to the dietary recommendations for the duration of the study

- **Largest Studies**
  - N = 53: **N= 6 followed a ketogenic regime**
  - N= 78: **N= 7 followed a ketogenic regime**

*Erickson et al, Med Oncol. Med Oncol 2017; 34:72*
METHODOLOGICAL LIMITATIONS

- Variations in duration, administration, & type of KD
  - Duration and type of intervention
  - single 3-h glucose-based or lipid-based TPN regime
  - oral diets with ranging from 4 days to 5 years (1 case)
  - 6/15 studies looked at dietary interventions ≥ 3 months

- Lack in homogeneity of type, location and cancer stage
  - Results cannot be compared

- No consistent standardized dietary and monitoring protocols
  - No two studies utilized same protocol
  - Some studies used PN which cannot be compared to oral diets
  - Oral diets administered without dietitian
  - Some monitored ketones in blood samples while others measured ketones in the urine—or compared both

Erickson et al, Med Oncol. Med Oncol 2017; 34:72
METHODOLOGICAL LIMITATIONS

- Majority of studies looked at feasibility, dietary adherence and Effect on QOL
- None were able to demonstrate an effect on survival and/or tumor growth
  - Rieger et al. reported antitumor observations, non-statistical significance could be derived \((Int\ J\ Oncol.\ 2014;44(6):1843)\)
  - Tan & Shalaby observed no correlations between clinical response and ketosis or glycaemia \((Nutr\ Metab\ (Lond).\ 2016;13:5)\)
  - In Rossi et al.’s three-arm trial, 9 of the 27 patients received the KD delivered through TPN. For all 27 patients, including the 9 receiving the KD, there was no significant difference in tumor growth between the three arms \((Clin\ Nutr.\ 1991;10(4):228–3)\)

\[\text{Erickson\ et\ al,\ Med\ Oncol.\ Med\ Oncol\ 2017;\ 34:72}\]
SIDE EFFECTS PROBLEMATIC FOR CANCER PATIENTS

- Reported Adverse Side Effects:

- Total of over 30 known side effects e.g.:
  - Dehydration
  - Cardiac abnormalities
  - Shifts in blood parameters:
    - $\uparrow$ Ca$^+$; $\uparrow(\text{or})\downarrow$ K$^+$; $\uparrow$ Blood Lipids, $\downarrow$ Mg
  - Various Gastro-intestinal symptoms:
    - constipation, diarrhoea, nausea, vomiting,
  - Pancreatitis
  - Pedal edema
  - Renal Calculi
  - Weight loss

Erickson et al, Med Oncol. Med Oncol 2017; 34:72
“The causes for impaired intake are complex and multifactorial. Reduced food intake is caused by primary anorexia (i.e. central nervous system level) and may be compounded by secondary impairments to oral intake, some of which are reversible with suitable medical management. Key secondary causes of reduced intake include oral ulceration, xerostomia, poor dentition, intestinal obstruction, malabsorption, constipation, diarrhoea, nausea, vomiting, reduced intestinal motility, chemosensory alteration, uncontrolled pain, and side effects of drugs.”

SIDE EFFECTS MOST PROBLEMATIC FOR CANCER PATIENTS

WEIGHT LOSS

- 73% lost Weight (7.5 ± 5.8 kgs)
  

- 4% observed weight loss (± 6.1 kgs)
  

ESPEN LL:
- Weight loss = unfavorable prognosis, increased toxicity of anticancer treatments & reduced quality of life
  
KETOGENIC DIETS VS. ESPEN GUIDELINES

- “The optimal ratio of carbohydrates and fat in feeding cancer patients has not been determined but may be derived from pathophysiologic arguments.”

  - **Fat to CHO not defined. Individual energy dense nutrition regimes stressed**

  - “Due to their low palatability, ketogenic diets may lead to insufficient energy intake and weight loss”

  - “Theoretical arguments that nutrients “feed the tumor” are not supported by evidence related to clinical outcome and should not be used to refuse, diminish, or stop feeding.”

  - **What does the patient hope to achieve from restrictive diet?**

THE CHALLENGE: PATIENTS WHO WANT THE KETOGENIC DIET

PRACTITIONERS

Fine Balancing Act

“Keep your feet firmly planted in conventional medicine and the scientific method, and yet reach out to people with very different perspectives from your own remaining compassionate and open-minded.”

Shattuck, JADA 97:12, 1997
Table III. *Ten steps as a guideline for discussing complementary and alternative medicine (CAM) with patients.* (9).

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Elicit the person’s understanding of their situation</td>
</tr>
<tr>
<td>2</td>
<td>Offer alternatives!</td>
</tr>
<tr>
<td>3</td>
<td>Discuss relevant concerns while respecting the person’s beliefs</td>
</tr>
<tr>
<td>4</td>
<td>Provide balanced, evidence-based advice</td>
</tr>
<tr>
<td>5</td>
<td>Summarize discussions</td>
</tr>
<tr>
<td>6</td>
<td>Document the discussion</td>
</tr>
<tr>
<td>7</td>
<td>Monitor and follow-up</td>
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TAKE HOME POINTS

- Not enough clinical evidence to support Ketogenic diets for cancer patients

ESPEN Guidelines: „Due to their low palatability, ketogenic diets may lead to insufficient energy intake and weight loss”

- Patients should be informed about indications and contraindications

- Patients should be informed about risks and side effects

- Alternatives can be offered
RECOMMENDED FURTHER READING


THANK YOU FOR YOUR ATTENTION

QUESTIONS?

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