Is there a role for ketogenic therapies in the clinical management of neurodegenerative disease? A systematic review

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Aim
To examine the current evidence available for the clinical utility of ketogenic therapies in people with neurodegenerative disease.

Background and Rationale
• Neurodegenerative diseases (NDD) are increasingly prevalent health issues lacking effective therapies[1].
• NDD present with similar aetiopathological pathways; mitochondrial dysfunction, cerebral hypo-metabolism, protein aggregation and misfolding, neuro-inflammation, excitotoxicity and oxidative stress[2].
• The ketogenic diet has been efficaciously used to reduce epileptic seizures since the 1920’s[3].
• Serum ketones (i.e. beta-hydroxybutyrate) become elevated during periods of starvation, fasting, exercise or carbohydrate restriction.
• Ketone bodies provide an alternative fuel source for the brain; to bridge the ‘energy gap’ resulting from reduced glucose utilisation.
• Induction of ketosis; via exogenous supplementation, dietary modification, or fasting.
• Pre-clinically, the ketogenic metabolic state can improve cellular metabolism, enhance neurotrophic factors, increase antioxidant capacity, and reduce inflammation[1].
• Ketogenic therapies may represent a viable clinical management tool for persons with NDD, however little is known of its efficacy within a clinical context.

Method
Population: People with a neurodegenerative disease.
Intervention: Induction of ketosis; via exogenous supplementation, dietary modification, or fasting.
Comparisons: A control group.
Outcome: Disease-specific outcomes relevant to clinical care.

Inclusion Criteria
• Neurodegenerative disease (excl. epilepsy).
• Controlled clinical trials only.
• Trial must have control group.
• Chronic intervention (≥ 4 weeks).
• Intervention must induce ketosis.
• Clinically relevant outcomes must be assessed.

Results

Table 1. Effects of Ketogenic Therapies on Primary Outcome Measures

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Studies (N)</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td>5</td>
<td>Improvement in one or more cognitive domain was observed in all 5 studies using ADAS-Cog, V-PAL. No changes observed in TMT or DST[4-9].</td>
</tr>
<tr>
<td>Brain ketone metabolism</td>
<td>1</td>
<td>Brain ketone metabolism ↑ by 230% with MCT treatment as evidenced by FDG-PET; improved measures of episodic memory, executive function and processing speed[10].</td>
</tr>
<tr>
<td>Alzheimer’s disease biomarkers</td>
<td>1</td>
<td>KD ↑ faecal butyrate, which negatively correlate with presence of amyloid-beta 42[11].</td>
</tr>
<tr>
<td>Eicosanoid expression</td>
<td>1</td>
<td>KD significantly ↓ expression of pro-inflammatory eicosanoid ALOX5- and controls (p &lt; 0.005)[12].</td>
</tr>
<tr>
<td>Regional cerebral blood flow (rCBF)</td>
<td>1</td>
<td>APOE4 (-) participants had significantly elevated rCBF after 45 days of Capryliden. No effect observed for APOE4(-) participants[13].</td>
</tr>
<tr>
<td>Microbiome composition</td>
<td>1</td>
<td>KD temporarily reduced microbial abundance and diversity; however, at endpoint, microbial abundance and diversity exceeded baseline values, comparable to that of healthy controls[14].</td>
</tr>
<tr>
<td>Motor function</td>
<td>1</td>
<td>KD ↑ non-motor daily living experience (Part 1 MDS-UPDRS) of controls[15].</td>
</tr>
<tr>
<td>Disease relapse (MS)</td>
<td>1</td>
<td>Fasting (Ramadan) had no unfavourable effect on disease relapse in MS(RR)[16].</td>
</tr>
<tr>
<td>Safety &amp; feasibility</td>
<td>1</td>
<td>KD safe, feasible and well-tolerated[17].</td>
</tr>
</tbody>
</table>

Conclusions and Future Research Directions
• This is an emerging and rapidly moving field of research. This review summarises and critically appraises the available evidence in the context of safety, efficacy and feasibility and provides recommendations for future research.
• Significant heterogeneity in study design, intervention and outcome measures assessed across trials.
• Dietary interventions tended to have higher attrition rates, lower adherence and less rigorous study design.
• Studies using exogenous ketogenic agents (i.e. MCT) tended to produce superior outcomes, however tolerability was an issue.
• Further studies are required to determine disease-specific dosing protocols and minimal effective dose for specific clinical outcomes.
• Future research should compare exogenous ketones, a ketogenic diet, and a combination of the two to determine whether dietary changes are necessary, or if similar clinical outcomes can be achieved with exogenous ketones alone.
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References:

Key:

AD Alzheimer’s Disease
ADAS-Cog Alzheimer’s Disease Assessment Scale-Cognitive Subscale
AFO5 Arachidonate 5-lipoxygenase
APoE Apolipoprotein E
DST Digital Symbol Test
FDG-PET Fluorodeoxyglucose – Positron Emission Tomography
KD Ketogenic diet
MCI Mild cognitive impairment
MCT Medium chain triglycerides
MDS-UPDRS Movement Disorders Society-Unified Parkinson Disease Rating Scale
MS Multiple sclerosis
NDD Neurodegenerative disease
PD Parkinson’s disease
PD-MCI Mild cognitive impairment secondary to Parkinson’s disease
RCBF Regional cerebral blood flow
RR Relapse-remitting
TMT Trail Making Test
V-PAL Verbal Paired Association Learning Test

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