

## Topic Brief: Ketogenic Diet

**Date:** 8/6/2019

**Nomination Number:** 857

**Purpose:** This document summarizes the information addressing a nomination submitted on 5/12/2019 through the Effective Health Care Website. This information was used to inform the EPC Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

**Issue:** Lifestyle changes, including diet, is frequently recommended for the prevention and treatment of chronic diseases, including hypertension, atherosclerotic disease, and diabetes mellitus. There is uncertainty about the optimal diet that would lead to most benefit while limiting harms or unintended consequences. One such diet is the ketogenic diet, which promotes a very low carbohydrate intake with most energy intake from fat. There are concerns about whether this diet is sustainable long-term, and whether it has negative effects on cardiovascular health.

**Program Decision:** The EPC Program will not develop a new systematic review because we did not find enough primary studies addressing the concerns of this nomination

### Key findings

- We found completed and in-process systematic reviews that addressed the use of a ketogenic diet in people with diabetes, obesity, and intractable seizures.
- Too few studies were identified that focused on healthy adults, people with cardiovascular disease, and metabolic syndrome.

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### Background

- A ketogenic diet primarily consists of high-fats, moderate-proteins, and very-low-carbohydrates. A very low carbohydrate ketogenic diet has <50 grams of carbohydrates per day. Instead of carbohydrates, more calories come from fat, which may supply as much as 90% of daily calories.<sup>1</sup> The intent is to cause the body to release ketones into the bloodstream and use ketones as an energy source.
- There has been increased interest in the ketogenic diet for weight loss.
- A ketogenic diet has been proposed for a variety of conditions including obesity and overweight, intractable seizures, diabetes, metabolic syndrome and certain cancers. Collectively these conditions affect a significant number of Americans.<sup>2</sup>
- There are concerns about the effect of the ketogenic diet because of the potential effects on liver function, nutrient intake, and kidney function.<sup>1</sup>

### Nomination Summary

- The nominator is interested in the benefits and harms of a ketogenic diet for a variety of conditions including disease prevention, health promotion and for specific conditions,

including cardiovascular disease, intractable seizures, diabetes, obesity, and metabolic syndrome. The nominator states that most robust evidence is in obesity, type 2 diabetes, metabolic syndrome and intractable seizures.

- The nominator plans to use the report to inform the development of clinical guidance, tools, and instructional materials.
- Scope clarification with the nominator
  - The nominator indicated that narrowing the focus to cardiovascular disease and adults was acceptable if the scope was large.
  - The nominator had preferred restricting studies to those that had confirmation of nutritional ketosis through urine, blood, or breath testing.
  - The nominator recommended restricting the literature to studies that defined the ketogenic diet as 0-10% carbohydrates of daily calories/day. She stated that 20-50 grams carbohydrates/day was also acceptable but preferred using % carbohydrates definition.
  - The nominator recommended excluding studies that included ketone supplements.
- In this brief, the ketogenic diet was defined as 20-50 grams carbohydrates/day or less than or equal to 10% carbohydrates of daily calories/day. We excluded studies of ketone supplements. We did not require testing for nutritional ketosis for inclusion because this may not be specified in abstracts.

### Scope

1. What is the effectiveness and harms of a ketogenic diet on cardiovascular risk factors in adults without a diagnosed health condition?
2. What is the effectiveness and harms of a ketogenic diet in adults with atherosclerotic heart disease?
3. What is the effectiveness and harms of a ketogenic diet in adults with type 2 diabetes?
4. What is the effectiveness and harms of a ketogenic diet in adults with obesity and overweight?
5. What is the effectiveness and harms of a ketogenic diet in adults with metabolic syndrome?
6. What is the effectiveness and harms of a ketogenic diet in adults with intractable seizures?

**Table 1.** Questions and PICOTS (population, intervention, comparator, outcome, timing and setting)

Questions	1. Ketogenic diet in adults	2. Ketogenic diet, atherosclerotic heart disease	3. Ketogenic diet, diabetes types 2	4. Ketogenic diet, obesity and overweight	5. Ketogenic diet, metabolic syndrome	6. Ketogenic diet, intractable seizures
<b>Population</b>	Adults 18 years and older without diagnosed health conditions	Adults 18 years and older with atherosclerotic heart disease	Adults 18 years and older with diabetes mellitus type 2	Adults 18 years and older with obesity and overweight	Adults 18 years and older with metabolic syndrome	Adults 18 years and older with intractable seizures
<b>Interventions</b>	Ketogenic diet (0-10% total calories/day or 20-50 grams)	Ketogenic diet (0-10% total calories/day or 20-50 grams)	Ketogenic diet (0-10% total calories/day or 20-50 grams)	Ketogenic diet (0-10% total calories/day or 20-50 grams)	Ketogenic diet (0-10% total calories/day or 20-50 grams)	Ketogenic diet (0-10% total calories/day or 20-50 grams)
<b>Comparators</b>	Usual care Other type of diet	Usual care Other type of diet	Usual care Other type of diet	Usual care Other type of diet	Usual care Other type of diet	Usual care Other type of diet

Questions	1. Ketogenic diet in adults	2. Ketogenic diet, atherosclerotic heart disease	3. Ketogenic diet, diabetes types 2	4. Ketogenic diet, obesity and overweight	5. Ketogenic diet, metabolic syndrome	6. Ketogenic diet, intractable seizures
Outcomes	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Morbidity</li> <li>• Lipid levels</li> <li>• Blood pressure</li> <li>• Weight/BMI</li> <li>• Blood sugar</li> <li>• Other cardiovascular risk factors</li> </ul>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Cardiac event (MI)</li> <li>• Weight/BMI</li> <li>• Blood pressure</li> <li>• Lipid levels</li> <li>• Reduction in medication use</li> </ul>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Hemoglobin A1C</li> <li>• Hypoglycemia</li> <li>• Weight/BMI</li> <li>• Lipids</li> <li>• Reduction in medication use</li> </ul>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Weight/BMI</li> <li>• Reduction in medication use</li> </ul>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Weight/BMI</li> <li>• Blood pressure</li> <li>• Reduction in medication use</li> </ul>	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Seizure frequency</li> <li>• Quality of life</li> <li>• Reduction in medication use</li> </ul>

Abbreviations: BMI=body mass index; MI=myocardial infarction;

## Assessment Methods

See Appendix A.

## Summary of Literature Findings

We found recent and in-process systematic reviews that addressed the use of ketogenic diet in people with diabetes (question 3)<sup>3-10</sup>, obesity (question 4)<sup>3, 11</sup>, and intractable seizures (question 6)<sup>12</sup>. We found systematic reviews related to healthy adults (question 1)<sup>3, 13, 14</sup> and metabolic syndrome (question 5)<sup>15</sup>. We did not consider these reviews to be duplicative because of lack of detail about how the low carbohydrate diet was defined; the population was not restricted solely to those without any cardiovascular risk factors; or the search dates were too old to be relevant. We did not identify any reviews on people with atherosclerotic disease (question 2).

We found few studies in our targeted literature search related to the remaining questions focused on healthy people (question 1)<sup>16-23</sup>, people with atherosclerotic heart disease (question 2), and people with metabolic syndrome (question 5)<sup>24</sup>. Most of the studies in healthy people looked at BMI or other weight measures. None studied other outcomes, such as blood sugar, lipid levels, and blood pressure.

**Table 2.** Literature identified for each Question

Question	Systematic reviews (6/2016-7/2019)	Primary studies (7/2014-7/2019)
1. Healthy adults	Total: 3 <ul style="list-style-type: none"> <li>• VA/DoD-1<sup>3</sup></li> <li>• Other-2<sup>13, 14</sup></li> </ul>	Total: 8 <ul style="list-style-type: none"> <li>• RCT-4<sup>17, 19, 21, 23</sup></li> <li>• Pre-post-2<sup>18, 22</sup></li> <li>• Cross-sectional-1<sup>16</sup></li> <li>• Case-control-1<sup>20</sup></li> </ul>
2. Atherosclerotic heart disease	Total: 0	Total: 0
3. Diabetes	Total: 9 <ul style="list-style-type: none"> <li>• VA/DoD-1<sup>3</sup></li> <li>• Other<sup>4-11</sup></li> </ul>	Not done
4. Obesity	Total: 2 <ul style="list-style-type: none"> <li>• VA/DoD-1<sup>3</sup></li> <li>• Other-1<sup>11</sup></li> </ul>	Not done
5. Metabolic syndrome	Total: 1 <ul style="list-style-type: none"> <li>• Other<sup>15</sup></li> </ul>	Total: 1 <ul style="list-style-type: none"> <li>• RCT<sup>24</sup></li> </ul>
6. Intractable seizures	Total: 1 <ul style="list-style-type: none"> <li>• Cochrane-1<sup>12</sup></li> </ul>	Not done

## Summary of Selection Criteria Assessment

The ketogenic diet has been proposed for use for a variety of conditions. While single type of diet is not recommended for treating some conditions, such as atherosclerotic disease, diabetes, and metabolic syndrome, for these conditions a “heart healthy” low-fat diet has been generally recommended. A new review could address questions around whether a ketogenic diet could be a reasonable alternative to recommended diets. However the nomination scope was partly covered by existing systematic reviews, and the remaining scope had too few studies for a systematic review.

Few studies indicated whether there was confirmation of nutritional ketosis by urine or blood testing. Most studies of healthy adults were in elite athletes and did not assess outcomes related to cardiovascular risk factors.

It is not surprising to find an absence of studies in people with atherosclerotic disease and metabolic syndrome. The lack of studies in people with atherosclerotic disease may be related to the prevailing guidance that a diet that is low in fat is recommended. Few studies may be performed in people with metabolic syndrome because this group overlaps significantly with populations in the other questions in this nomination, such as people with obesity and diabetes.

Please see Appendix B for detailed assessments of the EPC Program selection criteria.

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**Conflict of Interest:** None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Lionel Banez, MD

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## Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

### Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

### Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years July 2016 to July 2019 on the key questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
  - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
  - AHRQ EHC Program <https://effectivehealthcare.ahrq.gov/>
  - US Preventive Services Task Force <https://www.uspreventiveservicestaskforce.org/>
  - AHRQ Technology Assessment Program <https://www.ahrq.gov/research/findings/ta/index.html>
- US Department of Veterans Affairs Products publications
  - Evidence Synthesis Program <https://www.hsrd.research.va.gov/publications/esp/>
  - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospero/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>

### Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

### Feasibility of New Evidence Review

We conducted a limited literature search in PubMed from the last five years 2014-2019 on parts of the nomination scope not addressed by earlier identified systematic reviews. We reviewed all identified titles and abstracts for inclusion and classified identified studies by key question and study design to estimate the size and scope of a potential evidence review.

### Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to July 11, 2019

Date searched: July 12, 2019

Searched by: Robin Paynter, MLIS

#	Searches	Results
1	Diet, Ketogenic/	1093
2	(ketogenic* or ketosis).ti,ab,kf.	5930



#	Searches	Results
3	or/1-2	6024
4	Exp Coronary Artery Disease/ or exp Arteriosclerosis/	113221
5	arterioscler*.ti,ab,kf.	21142
6	or/4-5	122044
<b>7</b>	<b>and/3,6</b>	<b>KQ2 8</b>
8	Obesity/ or Obesity, Abdominal/ or Obesity, Metabolically Benign/ or Obesity, Morbid/ or Pediatric Obesity/ or Overweight/	204570
9	(obese or obesity or overweight or "BMI ≥ 35" or "BMI ≥ 40" or "BMI ≥ 50").ti,ab,kf.	296823
10	or/8-9	338299
<b>11</b>	<b>and/3,10</b>	<b>KQ4 459</b>
12	Metabolic Syndrome/	29507
13	("metabolic syndrome" or "syndrome x" or MetS).ti,ab,kf.	51358
14	or/12-13	56086
<b>15</b>	<b>and/3,14</b>	<b>KQ5 52</b>

### Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to July 15, 2019

Date searched: July 16, 2019

Searched by: Robin Paynter, MLIS

#	Searches	Results
1	Diet, Ketogenic/	1093
2	(ketogenic* or ketosis).ti,ab,kf.	5933
3	or/1-2	6027
4	3 not ((exp Animals/ not Humans/) or (bovine or cow or cows).ti,ab,kf.)	4183
5	exp Coronary Artery Disease/ or exp Arteriosclerosis/	168535
6	arterioscler*.ti,ab,kf.	21150
7	or/5-6	174527
8	Obesity/ or Obesity, Abdominal/ or Obesity, Metabolically Benign/ or Obesity, Morbid/ or Pediatric Obesity/ or Overweight/	204631
9	(obese or obesity or overweight or "BMI ≥ 35" or "BMI ≥ 40" or "BMI ≥ 50").ti,ab,kf.	297092
10	or/8-9	338578
11	Metabolic Syndrome/	29518
12	("metabolic syndrome" or "syndrome x" or MetS).ti,ab,kf.	51414

#	Searches	Results
13	or/11-12	56143
14	diabetes mellitus/ or diabetes mellitus, experimental/ or exp diabetes mellitus, type 1/ or exp diabetes mellitus, type 2/ or diabetes, gestational/ or diabetic ketoacidosis/ or donohue syndrome/ or latent autoimmune diabetes in adults/	336497
15	diabet*.ti,ab,kf.	594634
16	or/14-15	635616
17	seizures/ or exp status epilepticus/	58212
18	epilepsy/ or drug resistant epilepsy/ or exp epilepsies, partial/ or epilepsy, benign neonatal/ or exp epilepsy, generalized/ or epilepsy, post-traumatic/ or epilepsy, reflex/ or exp epileptic syndromes/	107411
19	((intract* adj3 seizur*) or epilep*).ti,ab,kf.	133435
20	or/17-19	189530
21	7 or 10 or 13 or 16 or 20	1242382
22	4 not 21	1311
23	limit 22 to (meta analysis or "systematic review")	8
24	limit 22 to (adaptive clinical trial or clinical trial, all or controlled clinical trial or equivalence trial or pragmatic clinical trial or randomized controlled trial)	63
25	limit 22 to observational study	1
26	(healthy adj5 (adult* or aged or elderly or male* or female* or middle-aged or men or women or individual* or participant* or patient* or senior* or subject*)).ti,ab,kf.	416076
27	4 and 26	132
28	limit 27 to (meta analysis or "systematic review")	1
29	limit 27 to (adaptive clinical trial or clinical trial, all or controlled clinical trial or equivalence trial or pragmatic clinical trial or randomized controlled trial)	22
30	limit 27 to observational study	0
31	23 or 28	9
32	24 or 29	75

<https://clinicaltrials.gov/ct2/results?cond=ketogenic+diet&term=&cntry=&state=&city=&dist=>

## Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
<b>1. Appropriateness</b>	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for an evidence report?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
<b>2. Importance</b>	
2a. Represents a significant disease burden; large proportion of the population	<p>Yes the conditions included in the nomination questions affect a significant number of people.</p> <ul style="list-style-type: none"> <li>• Coronary heart disease is the most common type of heart disease, killing over 370,000 people annually. About 375,000 Americans have a heart attack each year.<sup>25</sup></li> <li>• 30.3 million people have diabetes.<sup>26</sup></li> <li>• The prevalence of obesity was 39.8% and affected about 93.3 million of US adults in 2015–2016.<sup>27</sup></li> <li>• In 2015, 1.2% of the US population had active epilepsy. This is about 3.4 million people with epilepsy nationwide: 3 million adults and 470,000 children.<sup>28</sup></li> <li>• Among US adults aged 18 years or older, the prevalence of metabolic syndrome 34.2% in 2007–2012.<sup>29</sup></li> </ul>
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. Dietary changes are recommended for many of the conditions included in the nomination (diabetes, atherosclerotic disease, obesity, and metabolic syndrome). <sup>30-34</sup> However the choice of diet is unclear.
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	<p>Yes</p> <p>Heart disease costs the United States about \$200 billion each year. This total includes the cost of health care services, medications, and lost productivity.<sup>25</sup></p> <p>Average medical expenditures for people with diagnosed diabetes were about \$13,700 per year. About \$7,900 of this amount was attributed to diabetes.<sup>25</sup> After adjusting for age group and sex, average medical expenditures among people with diagnosed diabetes were about 2.3 times higher than expenditures for people without diabetes.<sup>26</sup></p> <p>The estimated annual medical cost of obesity in the United States was \$147 billion in 2008 US dollars; the medical cost for people who have obesity was \$1,429 higher than those of normal weight.<sup>27</sup></p>
<b>3. Desirability of a New Evidence Review/Absence of Duplication</b>	

<p>3. A recent high-quality systematic review or other evidence review is not available on this topic</p>	<p>A new review would be partly duplicative. Recent systematic reviews address: people with diabetes (question 3); people with obesity (question 4); and people with intractable seizures (question 6). The nominator agreed that these reviews would be useful, especially those by Kanaan<sup>8</sup>, Singh<sup>9</sup> and Ross<sup>11</sup>.</p> <p>We found three reviews potentially related to question 1; however they were not considered duplicative because the low carbohydrate diet was not defined and because the population was not restricted solely to those without any cardiovascular risk factors. We did not identify any reviews on people with atherosclerotic disease (question 2). We found one review related to people with metabolic syndrome<sup>15</sup> (question 5) but the search ended in 2014, and might be too old to be relevant.</p> <p>None of the reviews restricted inclusion to studies that had confirmation of nutritional ketosis by blood, breath, or urine testing.</p> <ol style="list-style-type: none"> <li>1. Adults without diagnosed health conditions <ul style="list-style-type: none"> <li>• Schwingshackl et al. Comparative effects of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: A systematic review and network meta-analysis.<sup>13</sup> <ul style="list-style-type: none"> <li>○ A low carbohydrate diet was defined as &lt;25% carbohydrates of total energy intake; high intake of animal and/ or plant protein; often high intake of fat. They did not look specifically at very low carbohydrate diets.</li> <li>○ In the network MA, the low carbohydrate diet was ranked 3<sup>rd</sup> in effectiveness in decreasing systolic blood pressure.</li> </ul> </li> <li>• In-process VA/DoD guideline on dyslipidemia. This guideline will include different diets and their impact on cholesterol and safety. The release date is not known.<sup>3</sup></li> <li>• Chawla et al. Evidence-based lifestyle medicine: a systematic review of effects of diet interventions on cardiovascular outcomes. <ul style="list-style-type: none"> <li>○ This in-process review will include different types of diets including ketogenic diet. Parameters for carbohydrate intake were not specified in the review protocol.</li> </ul> </li> </ul> </li> <li>2. Adults with atherosclerotic heart disease <ul style="list-style-type: none"> <li>• None</li> </ul> </li> <li>3. Adults with diabetes <ul style="list-style-type: none"> <li>• Huntriss et al. The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials<sup>4</sup> <ul style="list-style-type: none"> <li>○ This review was inclusive of low-carbohydrate diets.</li> <li>○ Six studies prescribed a very low carbohydrate diet (&lt;50 grams/day). Two studies looked at diets of &lt;20 grams carbohydrates/day; two studies of &lt;50 grams/day; on 3 study of 20-25 grams/day; and one study of 25-40 grams/day.</li> <li>○ Meta-analyses showed statistical significance in favour of a low-carbohydrate diet for HbA1c, HDL cholesterol, triglycerides, and systolic blood pressure.</li> </ul> </li> <li>• Snorgaard et al. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes.<sup>7</sup> <ul style="list-style-type: none"> <li>○ This review searched for any diet &lt;45% carbohydrates. It included 10 studies. The range of carbohydrate intake was 14-43%. None studied a diet with 10% or less carbohydrates.</li> <li>○ In the first year of intervention, low carbohydrate diet was followed by a 0.34% lower HbA1c compared with high carbohydrate diet. The greater the carbohydrate restriction, the greater the glucose-lowering effect. At 1 year or later, however, HbA1c was similar in the 2 diet groups. The effect of the 2 types of diet on BMI/body weight, LDL cholesterol, quality of life, and attrition rate was similar throughout interventions.</li> </ul> </li> <li>• Sainsbury et al. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: A systematic review and meta-analysis.<sup>5</sup> <ul style="list-style-type: none"> <li>○ This review compared carbohydrate restricted diets &lt;45% total energy compared to high carbohydrate diet &gt;45%. It found that those that restrict carbohydrate to &lt;26% had greater reductions in HbA1C.</li> <li>○ Studies were grouped by degree of carbohydrate restriction, with very low carbohydrate ketogenic diets defined as &lt;10% total energy or &lt;50 grams per day.</li> <li>○ Due to insufficient numbers of studies very low and low carbohydrate diet groups were combined into one group for meta-analysis.</li> <li>○ 5 studies were of very low carbohydrate ketogenic diets.</li> </ul> </li> </ul> </li> </ol>
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- Carbohydrate-restricted diets, in particular those that restrict carbohydrate to <26% of total energy, produced greater reductions in HbA1c at 3 months and 6 months, with no significant difference at 12 or 24 months. Although there are issues with the quality of the evidence, this review suggests that carbohydrate-restricted diets could be offered to people living with diabetes as part of an individualised management plan.
  - Schwingshackl et al. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus<sup>35</sup>
    - Low-carbohydrate diet was defined as <25% carbohydrates of total energy intake. Six of the 8 studies of low-carbohydrate diet aimed for intake of <50 grams carbohydrates/day
    - In the network meta-analysis the low-carbohydrate diet was ranked as the best dietary approach for lowering HbA1C.
  - VA/DoD Clinical Practice Guideline for the management of type 2 diabetes in primary care<sup>3</sup>
    - The guideline recommends reducing carbohydrates to 14-45%/day in patients who do not choose a Mediterranean diet.
    - They identified a SR of 20 RCTs and 2 RCTs. In the SR, carbohydrates ranged from 14-45% of total energy requirements.
    - Their review found that diets with a lower percent of energy coming from carbohydrates led to improved clinical surrogate markers (HbA1C, self-monitoring blood glucose, post-prandial blood glucose, weight, reduced medication requirements, improve lipids and improved blood pressure).
  - Kanaan et al. Conventionally recommended versus ketogenic diets in type 2 diabetes: a meta-analysis.<sup>8</sup>
    - This in-process review will focus on very low carbohydrate ketogenic diets, defined as 10% of total energy based on 2000 kcal diet, or 20-50g/day carbohydrates.
  - Turton et al. An evidence-based approach to formulating low-carbohydrate diets for type 2 diabetes management: a systematic review of methods and effect in pre-post intervention studies<sup>10</sup>
    - This in-process review will include low-carbohydrate diet interventions (any diet equal to or below 26% total energy intake or 130 grams per day from carbohydrate). It is unclear if subanalysis by different levels of carbohydrate intake will be performed.
  - Singh et al. Ketogenic diet for adults with type 2 diabetes: Systematic review.<sup>9</sup>
    - This in-process review did not define carbohydrate intake parameters for inclusion
  - Ross et al. Does a very low-carbohydrate, high-fat diet improve health outcomes compared to low-fat diets for the management of overweight/obesity and cardiovascular risk? A systematic review of randomised controlled trials.<sup>11</sup>
    - Very-low-carbohydrate intake (<26% energy from carbohydrates) and a high dietary fat intake (>35% energy from total fat)
    - Possible subgroup analyses may include CHO intake (<10%, 10-20%, 20-30%, >30%)
4. Adults with obesity
- VA DoD guideline on obesity is in the process of an update. We confirmed that the low carbohydrate diet will be included. Date for release of the guideline and evidence base is not yet determined.<sup>3</sup>
  - Ross et al. Does a very low-carbohydrate, high-fat diet improve health outcomes compared to low-fat diets for the management of overweight/obesity and cardiovascular risk? A systematic review of randomised controlled trials.<sup>11</sup>
    - Very-low-carbohydrate intake (<26% energy from carbohydrates) and a high dietary fat intake (>35% energy from total fat),
    - Possible subgroup analyses may include carbohydrate intake (<10%, 10-20%, 20-30%, >30%)
5. Adults with metabolic syndrome
- Steckhan et al. Effects of different dietary approaches on inflammatory markers in patients with metabolic syndrome: A systematic review and meta-analysis.<sup>15</sup>
    - Three of the 13 included studies compared a low-carbohydrate diet to other controls.
    - Low-carbohydrate diets (23 +/- 10% energy from carbohydrates) were able to induce significant weight loss. Low-carbohydrate diets were able to decrease insulin.
6. Adults with intractable seizures
- Martin-McGill. 2018. Ketogenic diets for drug-resistant epilepsy. Cochrane.<sup>12</sup>
    - This review included children and a range of ketogenic diet variations.

Selection Criteria	Assessment
	<ul style="list-style-type: none"> <li>○ One of the 11 studies in this SR included adults randomized to modified Atkins diet (MAD) or control. MAD was defined as 1 gram of carbohydrate/day or 4-6% carbohydrates.</li> <li>○ This study found that 35% of people on MAD had a 50% reduction in seizures, compared to none in the control group.</li> </ul>
<b>4. Impact of a New Evidence Review</b>	
<p>4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?</p>	<p>ACC/AHA guideline recommends plant-based and Mediterranean diets for primary prevention of atherosclerotic disease.<sup>31</sup></p> <p>ACC recommends that people with elevated lipids, metabolic syndrome and atherosclerotic disease should consume a diet that emphasizes intake of vegetables, fruits, whole grains, legumes, healthy protein sources, and nontropical vegetable oils; and limits intake of sweets, sugar-sweetened beverages, and red meats. Their guideline does not mention a low-carbohydrate diet.<sup>31, 32, 36</sup> The guideline on lipids was developed in collaboration with a number of other clinical societies such as the American Geriatric Society, American College of Preventive Medicine, and the American Association of Physicians Assistants.</p> <p>The ACC/AHA guideline on hypertension and prehypertension recommends a heart-healthy diet, such as the DASH diet.<sup>34</sup></p>
<p>4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?</p>	<p>Likely there is practice variation because a single diet is not recommended.</p>
<b>5. Primary Research</b>	
<p>5. Effectively utilizes existing research and knowledge by considering:</p> <ul style="list-style-type: none"> <li>- Adequacy (type and volume) of research for conducting a systematic review</li> <li>- Newly available evidence (particularly for updates or new technologies)</li> </ul>	<p>We did not find enough studies to recommend a systematic review by the EPC Program.</p> <p>Most of the studies on healthy adults looked at measures of weight. Some were in athletes, which may not be representative of a larger population. We found no studies on people with atherosclerotic disease; and one study on people with metabolic syndrome.</p> <p>The lack of studies in people with atherosclerotic disease may be related to the prevailing guidance that a low-fat diet is recommended. Few studies may be performed in people with metabolic syndrome because this group overlaps significantly with populations in the other questions in this nomination, such as people with obesity and diabetes.</p> <p>According to the abstracts, only three studies included confirmation of nutritional ketosis.<sup>22-24</sup></p> <p><b>KQ 1 (healthy adults)</b></p> <ul style="list-style-type: none"> <li>• Cicero et al. Middle and Long-Term Impact of a Very Low-Carbohydrate Ketogenic Diet on Cardiometabolic Factors: A Multi-Center, Cross-Sectional, Clinical Study.<sup>16</sup></li> <li>• Colica et al. Efficacy and safety of very-low-calorie ketogenic diet: a double blind randomized crossover study.<sup>17</sup></li> <li>• Greene et al. A Low-Carbohydrate Ketogenic Diet Reduces Body Mass Without Compromising Performance in Powerlifting and Olympic Weightlifting Athletes.<sup>18</sup></li> <li>• Iacovides et al. The effect of a ketogenic diet versus a high-carbohydrate, low-fat diet on sleep, cognition, thyroid function, and cardiovascular health independent of weight loss: study protocol for a randomized controlled trial.<sup>19</sup></li> <li>• Merra et al. Very-low-calorie ketogenic diet with amino acid supplement versus very low restricted-calorie diet for preserving muscle mass during weight loss: a pilot double-blind study.<sup>20</sup></li> <li>• Rubini et al. Effects of Twenty Days of the Ketogenic Diet on Metabolic and Respiratory Parameters in Healthy Subjects.<sup>21</sup></li> <li>• Urbain et al. Impact of a 6-week non-energy-restricted ketogenic diet on physical fitness, body composition and biochemical parameters in healthy adults.<sup>22</sup> <ul style="list-style-type: none"> <li>○ Confirmation of ketosis with urine testing</li> </ul> </li> <li>• Vargas et al. Efficacy of ketogenic diet on body composition during resistance training in trained men: a randomized controlled trial.<sup>23</sup> <ul style="list-style-type: none"> <li>○ Confirmation of ketosis with urine testing</li> </ul> </li> </ul> <p><b>KQ 2 (atherosclerotic disease): no studies</b></p> <p><b>KQ 5 (Metabolic syndrome)</b></p> <ul style="list-style-type: none"> <li>• Gibas et al.<sup>24</sup> Induced and controlled dietary ketosis as a regulator of obesity and metabolic syndrome pathologies. <ul style="list-style-type: none"> <li>○ Confirmation of ketosis with blood testing</li> </ul> </li> </ul>

**Abbreviations:** ACC=American College of Cardiology; AHA=American Heart Association; AHRQ=Agency for Healthcare Research and Quality; DASH=Dietary Approaches to Stop Hypertension; DoD=Department of Defense; EPC=Evidence-based Practice Center; HbA1C=hemoglobin A1C; MAD=modified Atkins diet; RCT=randomized controlled trial; SR=systematic review; VA=Veterans Affairs; KQ=Key Question