The Ketogenic Diet: Making a Comeback

Americans have embraced a large number of diets in an attempt to manage obesity, improve quality of life, and address specific health problems. Among diets developed to address health problems, the ketogenic diet has had a long and variable history. Developed in the 1920s by a faith healer to help children with epilepsy, this diet induces a state that mimics carbohydrate starvation. As medications became available and effectively addressed seizures, the diet fell out of favor. During the last few decades, researchers and clinicians have learned that it can be useful in children and adults with refractory epilepsy and a variety of other conditions. Once again, pharmacists may encounter patients who are employing dietary management of serious health problems. This very high-fat diet almost eliminates carbohydrates from the patient's food selection. The result is the substitution of ketone bodies as a source of energy. Today's ketogenic diet has been modified with scientifically proven adjustments to increase palatability and help with adherence. Effective for some forms of epilepsy, the ketogenic diet also seems to have some utility in Alzheimer's disease, Parkinson's disease, and glaucoma, and many Americans are using it to lose weight. Consultant pharmacists may field questions about this diet, its potential to correct or alleviate health conditions, and its limitations. The article discusses the ketogenic diet's strengths, limitations, potential mechanisms, and use in a number of conditions with an emphasis on the elderly.

ABBREVIATIONS: AD = Alzheimer's disease, ATP = Adenosine triphosphate, BBB = Blood-brain barrier, DKA = Diabetic ketoacidosis, g = Gram, KB = Ketone bodies, KD = Ketogenic diet, LCT = Long-chain triglyceride, LGIT = Low Glycemic Index Treatment, MAD = Modified Atkins Diet, MCT = Medium-chain triglyceride, MPTP = Neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, PD = Parkinson's disease, ROS = Reactive oxygen species, TG = Triglyceride, UPDRS = Unified Parkinson's Disease Rating Score.

KEY WORDS: Alzheimer's disease, Elderly, Epilepsy, Ketogenic diet, Ketone bodies, Parkinson's disease.

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Introduction

Roughly 37% of American adults are obese.[1] An entire weight-loss industry now promotes well-known diets such as the Atkins diet, Nutrisystem, and Weight Watchers. Fad diets are all the rage. Many are designed with weight loss in mind. Others have different goals. Fad diets, from juice cleanses that claim to rid your body of toxins to diets that require meticulous micronutrient tracking for maximal muscle gain, are common. Many diets boast outrageous claims and incorporate unsafe practices while others are reasonable from a nutritional standpoint.

Researchers have created diets to specifically target and combat disease states such as hypertension, inflammatory conditions, and hypercholesterolemia, among others. Treating disease by altering one's diet is not a new idea. Ancient Greek physicians treated disease states like epilepsy by altering their patients' diets.[2]

Backed by scientific evidence, the ketogenic diet (KD) stands out from the majority as having medical implications. Russell M. Wilder, MD, of the Mayo Clinic, first introduced the KD in the 1920s. He developed the KD to treat children with epilepsy after learning that

Hugh Conklin, an osteopath and faith healer, successfully treated children's epilepsy with a diet that induced starvation-like conditions.[2] As pharmaceutical firms developed new, effective anticonvulsant medications in the ensuing decades, the KD fell out of favor. It was easier to take a medication than track food intake diligently. In recent years, the KD has re-emerged as a therapeutic option in children with medication-refractory seizures, and has become the subject of much scientific study.

What Is the Ketogenic Diet?

The KD drastically limits carbohydrate intake, replacing lost calories with fat, while maintaining a normal protein intake. It consists of around 80% fat, 15% protein, and 5% carbohydrates.[3,4] Traditional KD involves the use of lipid:nonlipid ratios measured in grams (g).[3] Today, the KD's goal lipid:nonlipid ratio ranges from 4:1 to 2:1, with the higher ratio being more effective.[3,5]

Users of the KD read nutrition labels and count fat, protein, and carbohydrate intake in grams. Caregivers or clinicians can tally nutrients for patients who are unable to do so themselves. Many KDs aim to keep total daily intake of carbohydrates of less than 20 g. Ketogenic dieters often use the term "net carbs." To calculate net carbs, one needs to understand how dietary fiber is involved. Dietary fiber is lignin that is intrinsic to plants and is a type of nondigestible carbohydrate.[6] Since it is not digested, the carbohydrate content is unavailable as a fuel source and is often subtracted from the total carbohydrate content of the serving of food to reflect this. For example, if the total carbohydrate content of a serving of almonds amounts to 7 g and its fiber content is 4 g, the net carbohydrate calculation would be 7 g carbohydrate – 4 g dietary fiber = 3 g net carbs. Only net carbs are counted toward the total daily carbohydrate intake. Table 1 provides an example of net carb calculation and its incorporation into total daily carbohydrate intake.

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To keep fat intake high, dieters must incorporate many sources of fat into their food choices. Most fat in KDs are long-chain triglycerides (LCTs) found in meat, fish, dairy products, and eggs.[3] A variation to the traditional KD is incorporation of medium-chain triglycerides (MCTs). Dieters can purchase pure MCTs in bulk, or consume foods such as coconut oil, palm kernel oil, and cheeses, though these have lower MCT concentrations than the pure formulation. MCTs are more accessible to the liver than LCTs and can be used to generate more ketone bodies. Since MCTs are more ketogenic than LCTs, dieters who elevate their MCT intake can increase their carbohydrate and protein intake because extra MCTs increase the supply of ketone bodies.[3,7] Consequently, an MCT-based KD is more palatable and just as effective as the traditional KD.[7] An MCT-based KD employs caloric percentages instead of lipid:nonlipid ratios.[7] Table 2 depicts a modified LCT-based KD meal plan.

With modifications to ingredients, the KD is able to offer a variety of meals. Some recipes are ketogenic replicas of traditional foods. Often these recipes involve the use of

Table 1. Example of Net Carbohydrate Calculation and Incorporation into Daily Totals

Food	Carbohydrate (grams)	Dietary Fiber (grams)	Net Carbohydrate (grams)	Fat (grams)	Protein (grams)
Blackberries	14	8	6	0.7	2
Strawberries	8	2	6	0.3	0.7
Salmon	0	0	0	27	40
Daily Totals:			12	28	42.7

ketogenic-friendly ingredients like almond flour or cheeses, in place of traditional ingredients (e.g., flour). For example, for breakfast on Day 2, a cream cheese base is used for pancakes instead of flour. Others, like the cinnamon flax-meal porridge, take advantage of the net carb calculation. Dieters can access many resources and recipes complete with nutritional breakdowns on the Internet. No studies have been done on a vegetarian KD, but theoretically it is possible, and many online forums are dedicated to vegetarian KDs. Day 3 represents a vegetarian KD meal plan. Accurate logs of food eaten and nutrient breakdown are key to successful implementation of a KD. Figure 1 depicts a nutrient breakdown for Day 1 of Table 2.

Day 1's sample meal plan is roughly 2,000 calories, contains 18 g of carbohydrate, 173 g of fat, and 120 g of protein. KD proponents advise dieters to use food scales to measure food servings accurately. This KD meal plan relies on fatty foods such as cheese and almonds, and is protein rich. Protein sources that contain beneficial fats such as omega-3 fatty acids in fish are a plus. There are few fruits, but an abundance of leafy greens can be included. The sugar content in fruit and sweeter vegetables such as peppers and carrots may contain too much carbohydrate and must be used sparingly. Ketogenic-friendly fruits include berries with high dietary fiber content that offset the carbohydrate content (e.g., strawberries, blackberries, and raspberries). Avocados are another ketogenic-friendly fruit with high fat content. A ketogenic dieter must also consider the carbohydrates consumed in liquids. For example, instead of using sweeteners in their coffee, they opt for heavy cream, which has a high fat content and little carbohydrate.

Biochemistry Behind the KD

The KD's objective is to create a state of ketosis. Ketosis is ketone generation and accumulation as a result of excessive breakdown of fat because of inadequate carbohydrate use.[8] Essentially, the body shifts from using glucose as its main source of fuel to using ketone bodies (KB).

To comprehend the KD, one must understand some basics:

- The body relies on glucose for adenosine triphosphate (ATP) production in a normal diet.
- In starvation conditions, the body resorts to using its fat stores by fatty-acid oxidation. Fatty-acid oxidation generates KBs that are used as an alternate fuel source for ATP production.
- By reducing carbohydrate intake, the KD mimics this "starvation mode." This change in metabolic function causes a variety of downstream effects, such as increased mitochondrial efficiency and reduced production of reactive oxygen species (ROS).

Table 2. An Example of a Modified LCT Ketogenic Meal Plan

Meal	Day 1	Day 2	Day 3 (Vegetarian-friendly)
Breakfast	Scrambled eggs with cheese and bacon, side of spinach	Cream cheese pancakes	Cinnamon flax-meal porridge
Snack	Almonds	Hummus with celery	String cheese
Lunch	Mackerel fillet seared in olive oil	Low-carb chili	Spaghetti squash
Snack	Avocado	Greek yogurt	Pumpkin seeds
Dinner	Steak with a side of broccoli	Salmon with a side of asparagus	Black bean-stuffed portabella mushrooms
Dessert	Sugar-free gelatin with Cool Whip	Low-carb lemon poppy seed soufflé	Peanut butter fudge bars

Abbreviation: LCT = Long-chain triglycerides.

Figure 1. Nutritional Breakdown for Day 1

Breakfast: Scrambled Eggs with Cheese, Side of Bacon, Side of Spinach	•2 Eggs (50g/each): 1.2g net carbs, 10g fat, 12g protein •2 Slices of Bacon (8g/each): 1g net carbs, 9g fat, 5g protein •1 Slice American Cheese (28g): 0.2g carbs, 6.5g fat, 6g protein •1 Cup Spinach (30g): 0.4g net carbs, 0.1g fat, 0.9g protein
Snack: Almonds	•1 Ounce Serving Almonds (28g): 2.5g net carbs, 14g fat, 6g protein
Lunch: Mackerel Fillet Seared in Olive Oil	•1 Mackerel Fillet (100g): 0g carbs, 25g fat, 19g protein •2 Tablespoons Olive Oil (40g): 0g carbs, 28g fat, 0g protein
Snack: Avocado	•1 Avocado (200g): 4g net carbs, 29g fat, 4g protein
Dinner: Steak with a Side of Brocolli	• 8 Ounce Steak (224g): 0g carbs, 48g fat, 62g protein • 1 Serving Brocolli (148g): 6.2g net carbs, 0.5g fat, 4.2g protein
Dessert: Sugar-free Gelatin Dessert Cup	•1 Cup Sugar-free Gelatin (90g): 0g carbs, 0g fat, 1g protein •2 Tablespoons Cool-Whip (18g): 2g net carbs, 3g fat, 0g protein

After several days of following the KD, the carbohydrate-starved body depletes its glucose stores.[9] With an abundance of fatty acids and scarcity of carbohydrates, the body shifts to fatty-acid oxidation as its primary method of energy generation. Unlike glucose, fatty acids cannot be transported through the blood brain barrier (BBB).[9,10] The body must resort to other metabolic mechanisms to break down the fatty acids into components that can be transported through the BBB. To maintain normal blood glucose levels:

- The liver diverts oxaloacetate from normal energy production in the Krebs cycle (a sequence of chemical reactions that convert glucose, proteins, and fats into energy) to the process of gluconeogenesis.[10] Diverting oxaloacetate cripples the Krebs cycle, reduces its efficiency, and prevents processing of the extra acetyl-CoA.
- Fatty-acid oxidation generates high quantities of acetyl-CoA that would normally be processed by the hepatic Krebs cycle.[10]
- The hepatic mitochondrial matrix converts the excess acetyl-CoA units to acetoacetate.
- Acetoacetate is spontaneously decarboxylated into acetone and is also enzymatically converted to beta-hydroxybutyrate.[9,10]

Acetoacetate, acetone, and beta-hydroxybutyrate are all KBs that can pass through the BBB and are alternative fuel sources for the brain and other tissues. KB formation is referred to as ketogenesis, giving the KD its name.

Centrally, the brain's mitochondria take up the KBs and use multiple enzymes to convert them back into acetyl-CoA. ATP production follows.[10] A similar process occurs in other extrahepatic tissues' mitochondria. Ketogenesis increases blood and urine KB levels. One method to check whether ketosis is occurring involves the use of a urine dipstick that can detect the presence of ketone bodies. Most urine dipstick tests report a value of 0 to 4+, which correlates to a ketone concentration of 0 to > 16 mmol/L.[11] Diabetics often use dipsticks to monitor for a related but clinically different condition known as diabetic ketoacidosis (DKA).

In DKA, KBs and associated protons are produced very rapidly, overwhelming the body's acid-base buffering system.[12] DKA is a life-threatening medical emergency and must be treated. Dietary ketosis is a much more gradual process, thus safer. KB blood levels reach a maximum level of 7 to 8 mmol/L with minor alterations in pH, whereas in DKA the levels can reach 20 mmol/L and cause an acidic pH.[9] Patients with ketosis subsequent to the KD or undiagnosed diabetes share another clinical feature: sweet breath odor. This is the result of acetone's volatility and respiration from the lungs.[9]

Dieters use KBs as their main fuel source, but blood

sugar levels remain physiologically normal, though on the lower end of the spectrum.[9,13] This physiologically normal blood-glucose level originates from glucose production from glucogenic proteins and the liberation of glycerol during fatty-acid oxidation.[9,13] Through this process, cells that strictly require glucose, such as red blood cells (that lack mitochondria), are able to meet their metabolic demand.[12] Figure 2 depicts the chemical structure of the KBs.

Benefits in Neurologic Diseases

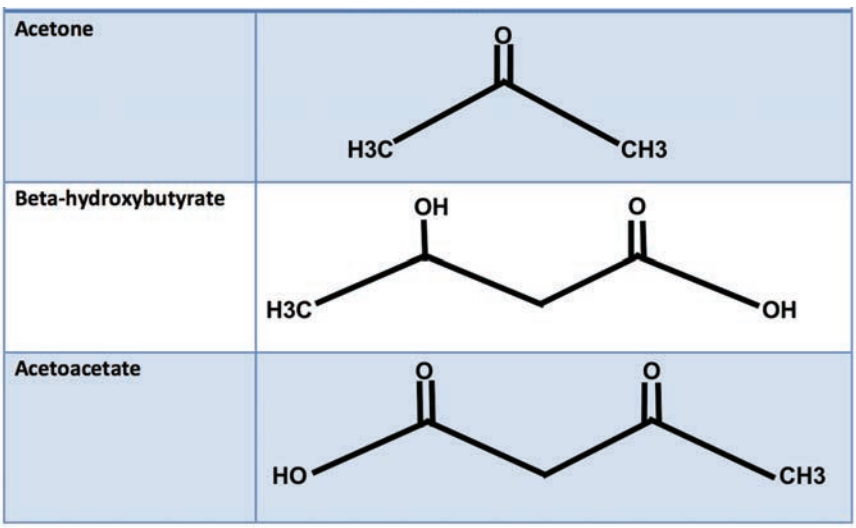
The KD first achieved scientific validity in the treatment of epilepsy. Clinical trials and systematic reviews have shown its efficacy in reducing seizure frequency in children with refractory epilepsy.[14-16] Additionally, children treated with the KD were able to remain seizure-free after halting the KD.[17] In children, the effects of the KD often last even after they stop the diet. The mechanism by which the KD protects against seizures is poorly understood and the subject of current research. A variety of hypotheses have been proposed. It is likely that interplay between many metabolic systems and the downstream effects of KBs, taken together, provide protection from seizures.

One hypothesis is that the KBs' beta-hydroxybutyrate and acetoacetate protect against oxidative stress in neuronal cells.[10,18] In animal models, Kim and colleagues found that KBs might prevent oxidative injury in neurons by decreasing mitochondrial ROS.[18] Other hypotheses suggest that KBs act as anticonvulsants or that metabolic systems that modulate other physiological functions are triggered with the KD.[13] For instance, glutamate, an excitatory neurotransmitter, was found to be decreased when beta-hydroxybutyrate (rather than glucose) was used for energy production.[19,20] Acetoacetate was found to inhibit vesicular glutamate transporters by inhibiting an anion regulatory site on presynaptic vesicles.[19,21] Leptin, the satiety hormone, is increased during the KD. Leptin also has a role in modulating and suppressing seizure activity.[19,22,23] Another hypothesis is that the KD brings about intracellular pH changes that have an inhibitory effect on excitatory neuronal signals. Decreased intracellular pH within neuronal and glial cells during neuronal excitability releases adenosine, which decreases excitatory neural transmissions during a seizure.[19,24]

Most clinical research conducted on the KD's effect on epilepsy has been conducted in children. The few studies on the KD's effect on adult epilepsy are open-label and uncontrolled, which necessitates a need for more and better-designed adult studies.[17,25] A recent review article examined the KD's efficacy in adults with epilepsy. Across the studies analyzed, 32% of adults following the KD experienced a seizure reduction of at least 50%, with 9% reporting seizure reduction of at least 90%.[25] In contrast to children, adults following the KD may not experience antiseizure effects outlasting treatment duration.[17,25,26]

Given the hypothesized neuroprotective effects, researchers have used the KD for neurological disorders besides epilepsy.

Figure 2. Ketone Bodies



A common theme in all neurological conditions is cellular energy and metabolic dysregulation, which contribute to pathogenesis. Of interest to consultant pharmacists is its application in neurological conditions such as Alzheimer's disease (AD) and Parkinson's disease.[13,27]

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Alzheimer's Disease

The KD might be a useful tool when treating AD. A clinical study found that MCT administration in AD patients improved memory performance. Additionally, they found that the degree of memory improvement directly correlated to beta-hydroxybutyrate plasma levels.[28,29] Besides having benefit on the cognitive impairments associated with AD, the KD shows promise in the pathological progression of the disease. Amyloid-beta proteins have been implicated in contributing to plaque deposition found in the brains of AD patients. In a mouse model of AD, KD administration for 43 days reduced soluble beta-amyloid proteins by 25%.[28,30] As AD progresses, glucose metabolism in specific brain regions slows.[31] A low glucose state is harmful to neurons and may contribute to AD's pathology.[31] The KBs produced in the KD diet can supplement the brain's need for energy, increase mitochondrial efficiency, and ameliorate negative effects of a low glucose state.[31] This approach has shown success in both animal and human models.[31-33] For example, when beta-hydroxybutyrate levels were increased through ketosis in mild-to-moderate probable AD patients, they did better on a paragraph recall test and achieved better scores on the Alzheimer's Disease Assessment Scale-Cognitive subscale.[31,33]

Parkinson's Disease

To date, many animal and *in vitro* models support the notion that the KD is partially protective in PD. PD is characterized by a severe reduction in dopamine secretion. Researchers often use neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in animal models to simulate PD.[28] Beta-hydroxybutyrate may be protective against degeneration of mesencephalic dopaminergic neurons. Kashiwaya and colleagues created an MPTP-based tissue culture model of PD and found that beta-hydroxybutyrate partially protected the neurons against the neurotoxin.[28,32] In mouse models, infusions of beta-hydroxybutyrate partially protect against MPTP toxicity in dopaminergic neurons.[28,34] A small uncontrolled study of seven PD patients tested looked for improvement in the Unified Parkinson's Disease Rating Score (UPDRS) after participants followed a KD for 28 days. Five participants successfully implemented the diet with concurrent improvements in their UPDRS.[28,35] Though this study was small and ignored placebo effects, the KD could be a major treatment option for PD patients. More studies are needed.

This very high-fat diet almost eliminates carbohydrates from the patient's food selection.

Glaucoma

With age, visual acuity declines and the likelihood of ophthalmological disorders increases. Glaucoma, a group of neuropathies that damage the optic nerve, is a leading cause of blindness.[38] More than three million Americans have glaucoma.[39] With no cure, current pharmaceuticals attempt to reduce intraocular pressure to prevent further progression. The KD's neuroprotective effect might benefit this patient population. Acetoacetate and beta-hydroxybutyrate produce a dose-dependent neuroprotective effect on retinal ganglionic cells in rat models of *N*-methyl-D-aspartate-induced neuronal damage.[40,41] Many neurodegenerative disorders including glaucoma share common mechanisms such as impaired energy metabolism, ROS production, neurotransmitter abnormalities, and inflammation.[40] A team of medical researchers based at the Medical University of Lublin, Poland, and at Drexel University, in Philadelphia, hypothesize that neurochemical changes brought on by the KD can be potentially beneficial in glaucoma patients, though clinical studies of the KD and glaucoma are lacking.[40] Further studies are needed.

Inflammation contributes to many neurological conditions.[28] For instance, in AD, neuronal degradation and insoluble beta-amyloid plaques stimulate inflammatory responses that may cause further disease progression.[36] A ketogenic state produces fewer ROS, which are pro-inflammatory.[37] As discussed above, a ketogenic state may cause intracellular pH changes that release adenosine. Adenosine—in addition to being protective against seizures—is also anti-inflammatory.[37] The KD's high fat content increases physiological free fatty acid levels. Increased levels of polyunsaturated fatty acid bind to peroxisome proliferator-activated receptors, which are involved in anti-inflammatory mechanisms.[37]

Today's ketogenic diet has been modified with scientifically proven adjustments to increase palatability and help with adherence.

Applicability and Safety Concerns

Increasingly, older adults are turning to low- or no-carbohydrate diets to lose weight. Thirty-seven percent of U.S. adults 60 years of age and older are obese.[1] The KD has stimulated weight loss, although an exact mechanism has not been found. The high protein and fat components of the KD likely promote satiety. (Who doesn't like bacon?) With a higher rate of satiety it is possible that a ketogenic dieter simply consumes fewer calories in a given day. Additionally, a ketotic state has an effect on ghrelin, a neuropeptide hormone that stimulates feeding behavior.[13] Dieting often promotes ghrelin release in response to less food intake. In a small study of 39 patients, the expected release of ghrelin and increase in appetite was mitigated when the subjects were in a state of ketosis.[42]

Many adults may find it hard to adhere to the traditional KD. The need to measure food, tempting (and ubiquitous) availability of carbohydrates, and social norms are adherence barriers. Several diets, however, can produce ketogenic effects.

The Modified Atkins Diet (MAD) consists of a lipid:nonlipid ratio of 1:1 in contrast to the 4:1 ratio in the traditional KD.[17] MAD does not require measurement of food items, allows up to 30 g of carbohydrate daily, and allows unrestricted protein intake.[17] MAD's palatability may increase patients' adherence rates. Another low-carbohydrate diet, called the Low Glycemic Index Treatment (LGIT), uses the glycemic index, which categorizes foods based on their ability to raise glucose levels. Low glycemic foods cause a slower release of glucose and corresponding insulin and vice versa. The LGIT allows up to 60 g of carbohydrates daily with a glycemic index of less than 50 relative to glucose.[17]

Many clinicians may express concern regarding the KD's potential to raise blood lipid levels (and cardiovascular risk) such as low-density-lipoprotein cholesterol and triglycerides (TGs).[9] Several studies show that low carbohydrate diets can reduce total cholesterol levels, increase high-density-lipoprotein cholesterol, and decrease TGs.[9,13,43] HMG-CoA-reductase, the enzyme responsible for producing cholesterol, is stimulated by insulin.[9] With KD-induced lower glucose levels and adequate dietary intake of fat, HMG-CoA may be less active, thus reducing cholesterol.[9]

With an ever-increasing population of elderly adults, the KD may be a beneficial treatment option in this population.

Another concern is that a KD may have negative effects on bone. A short-term KD in rat models impaired bone mass density and the mechanical properties of bone.[9,44] In children, long-term use of a KD may progressively reduce bone-mineral content.[9,45] A small case series examining the effects of the KD in three adult patients with glucose transporter 1 deficiency syndrome found that there were no major negative effects on body composition, bone-mineral content, or bone-mineral density after adhering to the KD for five years.[46] Adults who follow the KD should supplement with a multivitamin, a mineral and trace element supplement, calcium, magnesium, and vitamin D.[17]

Some supplements and medications may contain carbohydrates.[17] Consultant pharmacists should be wary of this and attempt to avoid sources of supplements and medications that include carbohydrates.

Conclusion and Future Directions

The KD and its variations are the subject of much exciting research. Its history of effectiveness in medication-resistant epilepsy in children is substantial, and its current applicability to a variety of neurological conditions in adults is promising. Future research will aim at fully elucidating the mechanisms by which the KD grants neuroprotective effects. Future directions can potentially include development of pharmacological agents that emulate these mechanisms. With an ever-increasing population of elderly adults, the KD may be a beneficial treatment option in this population.

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