A Comparative Review of Established Diets for Prevention of Cardiovascular Disease and Newer Dietary Strategies

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Abstract: As part of a population-based approach to combating obesity, the American Heart Association has published specific dietary guidelines for the management of obesity and cardiovascular disease prevention. These guidelines give a primary view of healthy dietary changes and goals which may reduce cardiovascular risk. The American Heart Association guideline on Cardiovascular Prevention focuses on the benefits of a Plant-Based Diet and the Mediterranean diet. In addition to these recommendations, several other diets exist with variable long-term cardiovascular outcomes. In recent years, the ketogenic and intermittent fasting diets have been emerging and have garnered their own respective followings as weight loss strategies, and we will include them in our discussion of the potential long-term benefits related to cardiovascular risks. As the guidelines emphasize, all of the diets we will cover throughout this review must be discussed at the level of the individual patient with their primary care provider, and cannot be exercised without informed consent regarding the potential outcomes. Further research is required, and caution is advised before prescribing any of these diets to patients in the

Conflict of Interest and HCA Disclaimer: The authors declare that there is no conflict of interest regarding the publication of this paper. This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.
Curr Probl Cardiol 2021;46:100582
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2020.100582

long-term, due to the potential to exacerbate cardiovascular risk factors. (Curr Probl Cardiol 2021;46:100582.)

Introduction

Despite increased awareness of the cardiovascular complications of the burgeoning obesity pandemic, the prevalence of obesity among US adults increased from 34% in 2007-2008 to 40% in 2015-2016.[1] In an effort to develop guidelines to combat obesity, the American College of Cardiology (ACC) and the American Heart Association (AHA) collaborated with the National Heart, Lung, and Blood Institute to develop clinical practice guidelines for the assessment of cardiovascular risk, lifestyle modifications to reduce cardiovascular risk, management of blood cholesterol in adults, and management of overweight and obesity in adults.[2] The authors point out that guidelines are meant to be evaluated with respect to the individualized patient; they are not a replacement for clinical judgment.[2] Therefore, the practitioner must assess the practicality of these guidelines in conjunction with their patient. These guidelines give a primary view of healthy dietary changes and goals which may reduce cardiovascular risk.

The AHA guidelines on the primary prevention of cardiovascular disease (CVD) emphasize that diets associated with CVD mortality typically consist of sugar, low-calorie sweeteners, high-carbohydrate diets, low-carbohydrate diets, refined grains, trans fat, saturated fat, sodium, red meat, and processed red meat (such as bacon, salami, ham, hot dogs, and sausage). These guidelines encourage a healthy plant-based or Mediterranean-like diet high in vegetables, fruits, nuts, whole grains, lean vegetable or animal protein (preferably fish), and vegetable fiber. . .shown to lower the risk of all-cause mortality.[3] The authors aptly point out that while these guidelines have been focused on medical practice in the United States, they are relevant to the global patient.

In addition to these recommendations, several other diets exist with variable long-term cardiovascular outcomes.[10,69,70] Additionally, newer dietary strategies including the ketogenic diet[71] and intermittent fasting[72] have gained popularity. The purpose of this review is to evaluate the clinical evidence of established dietary patterns with regards to reducing cardiovascular risk, as well as to discuss the existing literature regarding newer dietary strategies.

The Dietary Approaches to Stop Sodium Diet

The Dietary Approaches to Stop Sodium (DASH) diet was designed to incorporate dietary changes that would lower blood pressure, primarily by emphasizing fruits, vegetables, and low-fat dairy foods.[4] The DASH diet also includes whole grains, poultry, fish, and nuts, with a much lower content of red meat, sweets, and sugar-containing beverages. When the DASH diet is supplemented by dietary sodium reduction to 1150 mg daily, there was a significant 10 mm Hg reduction in systolic blood pressure compared to a non-DASH diet without sodium restriction.[5]

Postulated mechanisms for the BP-lowering effect of the DASH dietary pattern include effects on the natriuresis, renin-angiotensin-aldosterone system, reduced adrenergic tone, and increased vascular relaxation.[6] While researchers have begun investigating whether the DASH diet lowers blood pressure via natriuresis, there is room to develop this topic further. In the journal written by Lin et al, the researchers ran a randomized controlled trial testing the effects of 2 dietary patterns on sodium excretion, plasma renin activity, aldosterone, catecholamines, and markers of vascular endothelial function. Participants were separated into 2 groups; the typical American (control) diet, and the DASH diet. The same team conducted earlier research suggesting that the DASH diet shifts the pressure-natriuresis curve, and that potassium supplementation would promote natriuresis, though citing there is no clear evidence for this. During this respective trial, the researchers maintain that the rise in both plasma renin activity (PRA) and aldosterone suggests a natriuretic effect of DASH, supporting existing data suggesting that an increase in PRA is a response to a high intake of potassium, found widely in the DASH diet.

The research by Shin et al, further explores the different responses of renin and aldosterone in sodium sensitive and sodium resistant subjects based on dietary sodium intake, and whether or not the participants in this trial had hypertension. The researchers carried out a study during which participants were placed on either a low-sodium DASH diet, or a high-sodium DASH diet for 1 week. In this study, in normotensives, the level of PRA and aldosterone decreased only in sodium resistant participants after consuming the high sodium diet compared with the level in those who consumed the low sodium diet. In the hypertensives who were also sodium resistant, the study found significant decreases in PRA and aldosterone, but only PRA decreased meaningfully in sodium sensitive hypertensives based on salt intake. This particular research did not find significant correlations in sodium sensitive normotensive and hypertensive participants.[7]

In specific subpopulations, including hypertensives and type 2 diabetics, the DASH diet and increased walking were associated with clinically significant reductions in ambulatory blood pressure measurement values.[8] Shirani and authors further explored this by conducting a systematic review and meta-analysis on randomized controlled trials that examine the effects of DASH diet consumption on the indices of glycemic control such as fasting blood glucose, serum fasting insulin level, and Homeostatic Model Assessment insulin resistance. They concluded that the DASH dietary pattern may lead to an improvement in insulin sensitivity independent of weight loss. Furthermore, there can be a significant outcome in glycemic control in long-term interventions.[9]

Several meta-analyses of the DASH diet have demonstrated an improvement in lipid parameters, blood pressure and weight.[10] Schwingshackl et al[11] evaluated a meta-analysis of 18 prospective cohort studies on the DASH diet and noted a significant 20% reduced incidence of CVD.[10] Despite this, the diet's dairy content has been called into question. Song et al[12] found a significant 11% increase in cardiovascular mortality with a diet high in dairy consumption, when compared to a diet high in vegetable protein intake. While the consumption of saturated fat leads to increased low density lipoprotein (LDL) levels and subsequently increased risk of the development of CVD, this does not address that some food sources high in saturated fats contain both saturated and unsaturated fatty acids, which can distinctly affect lipoprotein metabolism.[13] Huth et al, noted that while saturated fat from whole milk and butter does increase LDL; they may also increase high density lipoprotein (HDL), having a more equivocal effect or even lowering the cholesterol:HDL ratio. Huth and team also found that cheese intake lowers LDL cholesterol compared with butter of equal milk fat content.[13] One systematic review of meta-analyses of prospective population studies associating dairy consumption with CVD, coronary artery disease, stroke, hypertension, metabolic syndrome, and type 2 diabetes found that the consumption of various forms of dairy products shows either favorable or neutral associations with cardiovascular-related clinical outcomes.[14] A separate meta-analysis supported an inverse association between dairy consumption and overall risk of CVD and stroke. Stroke risk was significantly reduced by consumption of low-fat dairy, and coronary heart disease risk was significantly lowered by cheese consumption, further supporting the potentially beneficial effect of dairy consumption on CVD. Low-fat dairy products and cheese may protect against stroke or coronary heart disease incidence.[15] Therefore, concerns regarding the dairy content may be re-evaluated.

Overall, while the DASH diet has been proven to reduce incident CVD, this dietary plan may be refined by lowering sodium and dairy intake to further reduce cardiovascular risk.

The Mediterranean Diet

The Mediterranean diet is one of the most popular dietary regimens for cardiovascular benefit. The Mediterranean diet is a generic term, as the American Heart Association points out, there's no one Mediterranean diet. This is likely attributed to the vast region where a Mediterranean diet is consumed, from parts of Europe, to the Middle East, and East Africa. Widely accepted in the Mediterranean diet is a high consumption of fruits, vegetables, bread and other cereals, potatoes, beans, nuts and seeds; olive oil; dairy products; fish and poultry are consumed in low to moderate amounts, and little red meat is eaten; eggs are consumed 0 to 4 times a week; and wine is consumed in low to moderate amounts.[16] There is not a particular list of which foods are to be included or left out, rather, the foods are more specific to the regions where they are consumed; they are influenced by the regional values, its respective culture, religion, and of course terrain. Specifically, the diet should include at least 2 of the following: high monounsaturated to saturated fat ratio, low to moderate red wine consumption, high consumption of legumes, high consumption of grains and cereals, high consumption of fruits and vegetables, low consumption of meat and meat products and increased consumption of fish, and moderate consumption of milk and dairy products.

The Seven Countries Study of Cardiovascular Diseases was started at the end of the 1950s and continued to run for decades. It enrolled, at entry, 16 population cohorts in 8 nations of 7 countries for a total of 12,763 middle-aged men. This was the tipping point for studies designed to investigate whether CVD was related to dietary patterns. Evidence found in this study pointed toward the Mediterranean diet, officially recognized in the 1960s, for its association with lower incidence and mortality from CVD, particularly in Italy and Greece, when compared to northern Europeans or Americans.[17,18] In a separate journal by Menotti, he addresses whether the study remains relevant today, and speaks its critics, suggesting that criticisms are not well established and were largely based off of misinterpretations.[19]

In 2010, a meta-analysis of 8 studies demonstrated that adherence to a Mediterranean diet was associated with a 10% reduced incidence of cardiovascular events.[20] This study also pointed to a reduction in other surrogates of CVD, such as waist-to-hip ratio, lipids, and markers of

inflammation. In a higher risk secondary prevention population studied in the Lyon Diet Heart Study,[21] the Mediterranean diet was associated with a significant 65% reduction in cardiac death or nonfatal myocardial infarction over a duration of 4 years post index myocardial infarction. One Israeli study used a short dietary screening survey to demonstrate that for every one-point increase in compliance with a Mediterranean diet, there was a 12% reduction in all-cause mortality.[22] As a result of these significant outcomes, the Mediterranean dietary strategy is widely recommended for the primary prevention of CVD by both the American Heart Association and the European Society of Cardiology.[23,24]

Per the 2015 Dietary Guidelines Advisory Committee report, red and processed meats are higher in the Mediterranean-style diets but lower in the DASH-style diet than is recommended by the USDA Food Patterns.[25] This might suggest that the DASH diet lags behind with recommended guidelines regarding meat consumption. However, the DGAC report concludes that they are in sync with the conclusions of the NEL Dietary Patterns Systematic Review Project and AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk, that strong and consistent evidence demonstrates that dietary patterns associated with decreased risk of CVD are characterized by higher consumption of vegetables, fruits, whole grains, low-fat dairy, and seafood, and lower consumption of red and processed meat.[25]

The Prevention with Mediterranean Diet (PREDIMED) trial evaluated the cardiovascular benefit of 2 principal components of the Mediterranean diet; extra-virgin olive oil, and nuts.[26] The PREDIMED trial studied 7447 participants at high cardiovascular risk but without prior diagnosed CVD, randomizing to a Mediterranean diet supplemented with either extra-virgin olive oil or mixed nuts, or a control diet involving dietary advice to reduce fat intake. After a median of 4.8 years, participants in the extra-virgin olive oil and nuts groups had significant 31% and 28% reductions respectively in the primary endpoint of cardiovascular death, myocardial infarction or stroke, compared to the control diet.

In the study conducted by Downer et al, the researchers sought to address concerns with respect to the PREDIMED diet, specifically targeting the concern that the mercury content in fish may increase CVD risk. The researchers evaluated associations between mercury exposure, fish consumption and CVD, and did not find evidence that mercury exposure from regular fish consumption increases CVD risk in the population studied. This particular study would suggest that this one concern related to the PREDIMED diet does not necessarily lessen the established cardiovascular benefits of fish consumption.[27] In 2018, the New England

Journal of Medicine retracted the 2013 study, "Primary Prevention of Cardiovascular Diseases with a Mediterranean Diet," as a result of error in randomization procedures affecting a portion of participants in the PREDIMED (Prevención con Dieta Mediterránea) trial. There is a corrected version of the study currently in publication, entitled, "Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts." The authors do point out that while there were errors regarding randomization in the PREDIMED trial, the overall conclusion remains largely unchanged, in that individuals with high cardiovascular risk have a lower incidence of major cardiovascular events when following a Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to a reduced-fat diet.[28]

There remains a robust body of evidence supporting the utility of the Mediterranean diet in primary and secondary prevention of CVD. The PREDIMED study highlighted the specific benefit of additional supplementation with nuts and extra-virgin olive oil.

Plant-Based Diet

Meat consumptions remains a debated topic. Many researchers point out the benefits of meat consumption. As Ekmekcioglu et al, point out, meat is an important food for human nutrition, providing high-quality protein and also some essential micronutrients, including iron, zinc, and vitamin B_{12}.[29] A meta-analysis of randomized controlled trials found that total red meat intake of $\geq$0.5 servings/day does not negatively influence CVD risk factors.[30] Specifically, the consumption of $\geq$0.5 servings of total red meat/day does not influence blood lipids and lipoproteins or blood pressures.[31] Going further, some researchers suggest there is evidence that supports the role of lean red meat as a positive moderator of lipid profiles, as well as a dietary source of the anti-inflammatory long chain n-3 PUFAs and conjugated linoleic acid. These studies suggest that moderate consumption of lean red meat as part of a balanced diet is unlikely to increase risk for CVD or colon cancer, but may positively influence nutrient intakes and fatty acid profiles, thereby impacting positively on long-term health.[73]

But there are other studies which show evidence that meat consumption has been associated with an increased cardiovascular risk,[32] while supplementation of dietary protein from plant-based rather than animal-based sources has been associated with a reduction in mortality.[33] A combined analysis of 5 prospective studies, including more than 76,000 participants followed for a median of 10.6 years, showed a 24% reduction in cardiovascular mortality for vegetarians compared to nonvegetarians.[33]

A large combined cohort of more than 131,000 participants from the Nurses' Health Study and the Health Professionals Follow-up study was studied for the effect of plant-based versus animal-based protein on all-cause and cardiovascular mortality.[34] This showed that while animal-based protein intake was associated with a borderline increased cardiovascular risk, plant-based protein intake was associated with a markedly lower risk of cardiovascular death. Furthermore, dietary supplementation with plant-based protein instead of animal-based protein led to a markedly reduced all-cause mortality risk.

Per the 2015-2020 Dietary Guidelines, there is strong evidence that a lower intake of meats as well as processed meats and processed poultry are associated with reduced risk of CVD in adults. Only moderate evidence suggests a reduced risk of obesity, type 2 diabetes, and some types of cancer in adults. They suggest limiting intake to 26 ounce-equivalents per week.[35] The 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk suggests advising patients who would benefit from LDL reduction, and blood pressure reduction, to consume a diet low in red meat. They go further to state that the adult population should be encouraged to practice heart-healthy lifestyle behaviors, including (but not limited to) lowering red meat intake.[36]

There is evidence that suggests an association between long term low-carbohydrate and high-protein diets and a higher all-cause mortality risk, and an inverse association between plant protein and cardiovascular mortality.[37] Specifically, monounsaturated fatty acids obtained through plant consumption, as opposed to animal consumption, are preferred with respect to CVD prevention.[38] Substituting almonds for a carbohydrate-rich snack within a lower-saturated-fat diet can help maintain a favorable HDL and improve cholesterol efflux in normal-weight individuals with elevated LDL cholesterol.[39] Eating cashews daily, when substituted for a high-carbohydrate snack, may be a simple dietary strategy to help manage total cholesterol and LDL cholesterol.[40] This effect has been noted with respect to triglycerides as well; the addition of cinnamon, cacao products and isocaloric substitution of 1 serving of nuts may contribute another 5%-15% lowering of triglyceride. This can be particularly beneficial in patients with hypertriglyceridemia who are at increased risk of CVD.[41]

The Adventist Health Study-2 followed 81,337 participants for a median of 9.4 years and noted 2276 cardiovascular deaths during the study period.[42] This study stratified dietary protein intake into quintiles of animal-based and plant-based protein. Those in the highest quintile of animal-based protein intake had a significant 61% increased risk of cardiovascular mortality. In contrast, the highest quintile of plant-based protein intake was associated with a 40% reduction in cardiovascular mortality risk.

In addition to the longitudinal, population-based studies referenced, the PREDIMED trial randomized patients to a Mediterranean diet versus a control diet. A secondary analysis of PREDIMED trial data[43] showed that a provegetarian diet was associated with a significant reduction in all-cause mortality.

A vegetarian diet is well established in the literature, however, it is not without its weaknesses. Some researchers suggest that negative changes associated with vegetarianism include hyperhomocysteinemia, protein deficiency, anemia, decreased creatinine content in muscles, and menstrual disruption in women who undertake increased physical activity. It is further suggested by these authors that these types of effects can decrease the ability for performing activities that require physical effort.[44]

These recent studies have demonstrated the potential role of a plant-based diet in reducing CVD. While supplementation with animal-based protein has yielded conflicting results (borderline statistically significant increased risk in the Nurses' Health Study/Health Professionals Follow-up Study versus significant 61% increased risk in the Adventist Health Study-2), there is unequivocal cardiovascular benefit for supplementation with plant-based protein.

The Ketogenic Diet

The classic ketogenic diet refers to a diet high in fat and low in carbohydrates. It differs from the Atkins diet mainly because there is a cap on protein intake, and carbohydrates are restricted from the very beginning. Of note, the medium-chain triglyceride ketogenic diet allows more carbohydrate and protein food, which makes the diet more easily tolerated than the classic ketogenic diet. The medium-chain triglyceride ketogenic diet D is not based on diet ratios as is the ketogenic diet, but uses a percentage of calories from medium-chain triglyceride oil to create ketones.[45] In the classic ketogenic diet, the dietary macronutrients are divided into approximately 55%-60% fat, 30%-35% protein, and 5%-10% carbohydrates.

In a 2000 kcal per day diet, carbohydrates account for up to 20-50 grams per day. By reducing carbohydrate intake, insulin secretion is in turn reduced, and the body enters a catabolic state; thus, gluconeogenesis and ketogenesis ensue.[46] Gluconeogenesis refers to the endogenous production of glucose in the body; once glucose depletes even further, ketogenesis begins in order to provide an alternate source of fuel, ketone bodies. During ketogenesis, there is little stimulus for insulin to be secreted, this reduces the stimulus for fat and glucose storage. Fatty acids are also metabolized to substrates of ketone bodies. During low-

carbohydrate intake, the body remains in the ketotic state, considered safe, as this does not alter blood pH (versus ketoacidosis, which does alter blood pH and can be life threatening). Ketone bodies are readily available for energy production in the heart, muscles, kidneys, and brain. One hundred grams of acetoacetate generates 9400 grams of ATP, and 100 grams of beta-hydroxybutyrate yields 10,500 grams of ATP; whereas, 100 grams of glucose produces only 8700 grams of ATP. This allows the body to maintain efficient fuel production even during a caloric deficit.

The 2013 AHA/ACC/TOS Guideline for Management of Overweight and Obesity in Adults points out that weight loss in the obese and overweight subpopulations can be achieved with a higher-protein diet (25% of total calories from protein, 30% of total calories from fat, and 45% of total calories from carbohydrate), with provision of foods that realize an energy deficit.[2] The meta-analysis by Bueno et al, researched randomized controlled trails which assigned adults to a very low carbohydrate ketogenic diet versus a low fat diet with 12 months or more of follow-up, with a primary outcome of bodyweight. The meta-analysis suggested that individuals assigned to a very low carbohydrate ketogenic diet achieve a greater weight loss than those assigned to a low fat diet in the long term; hence, supporting that a ketogenic diet is effective against weight loss, which can in turn help reduce CVD risk factors.[47]

The ketogenic diet was first recognized in the literature in the 1920s, as a therapy for epilepsy. However, from the 1960s to present day it has been more commonly used to treat obesity. There is evidence that suggests that the ketogenic diet may have beneficial effects with respect to diabetes, polycystic ovary syndrome, acne, neurological diseases, cancer ,and the amelioration of respiratory and cardiovascular disease risk factors.[48]

The dietary review by Soldati et al, supports the evidence that dietary patterns can enhance the immune response against cancer; specifically the Mediterranean, and the very low ketogenic diet are among the patterns listed which have been suggested by the authors to lower the risk of developing several cancers and reduce the mortality associated with them.[49] With respect to prostate cancer, Kaiser and team found evidence that supports the association between insulin resistance and prostate cancer. Specifically, periprostatic adipocytes promote extracapsular extension of prostate cancer through chemokines, which would make the association between obesity and high-grade cancer plausible. Among these patients, low carbohydrate/ketogenic diets can be encouraged because of their superior impact on weight loss and metabolic parameters and encouraging clinical data.[50]

Much of the current research supporting the ketogenic diet is from studies which have mainly tested the diet in a patient population of children with drug-resistant epilepsy. Such studies have suggested that a ketogenic diet can lead to a gradual decrease in carotid distensibility and an increase in LDL-C, apoB and the TC:LDL-C and LDL-C:HDL-C ratios at 3 and 12 months of ketogenic diet-treatment, though these differences were not significant at 24 months.[51] The retrospective study by Wibisono et al, evaluated children with epilepsy who consumed a ketogenic diet from 2003 to 2012, to evaluate the efficacy, tolerability, and compliance of the classical ketogenic diet, medium-chain triglyceride, and modified Atkins diet.[52] Among the children enrolled in the study, constipation was reported. Lower rates of side effects were reported for the modified Atkins diet. The least tolerated diet was the medium-chain triglyceride diet, but the researchers point out that this may have been due to adequate seizure control, suggesting that the patients stopped the diet once their seizures were under control. Nephrolithiasis was reported in 1 patient before potassium citrate was used and 2 patients noncompliant with potassium citrate supplementation developed hypercalciuria. The researchers concluded that overall, these 3 forms of ketogenic diet were well tolerated, and they encouraged potassium citrate supplementation for the prevention of nephrolithiasis.[52]

There is evidence to support the positive health outcomes with respect to both the Mediterranean and the ketogenic diets, and as such, some researchers have gone further and investigated a combined diet. These authors make mention of combined ketogenic and Mediterranean diets, combining the beneficial outcomes from each, respectively. One such study was undertaken by Paoli et al, and analyzed overweight males between the ages of 25 and 65 years of age, with no reported health problems other than obesity, and how their bodies responded to a ketogenic Mediterranean diet with phytoextracts combined with ω-3 supplementation. All subjects experienced a significant loss of body weight and body fat. There were also significant decreases in total cholesterol, LDL-c, glucose levels, triglycerides, insulin levels, and inflammatory cytokines (IL-1β, IL-6, TNF-α). The authors suggested that ω-3 supplementation improved the positive effects of a ketogenic Mediterranean diet with phytoextracts on some cardiovascular/metabolic risk factors and inflammatory state.[53]

This concept was similarly studied in a group of Spanish individuals by Perez-Guisado et al, to determine the effectiveness of a protein ketogenic diet rich in olive oil, salad, fish and red wine (ie, Mediterranean diet). This Ketogenic diet was called the Spanish Ketogenic Mediterranean Diet. Results were statistically significant, and included reduction in

body weight, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, and glucose. Specifically there was a significant reduction in LDL and an extremely significant increase in HDL. The researchers point out that the most affected parameter was the triglycerides.[54]

Paoli continued to investigate this topic in 2011, with the modified ketogenic diet based on green vegetables, olive oil, fish, and meat plus dishes composed of high quality protein and virtually zero carbohydrate, with the addition of some herbal extracts (KEMEPHY ketogenic Mediterranean with phytoextracts). Again Paoli found that this type of combined diet can yield weight reduction, improvements in cardiovascular risk markers, reduction in waist circumference and showed good compliance.[55]

Some research has suggested that markers of atherosclerosis may be increased with the ketogenic diet. However, we cannot state that the ketogenic diet is without support. While more research is needed to suggest long-term outcomes, there have been studies with encouraging support that this diet can lead to effective weight loss along with improvement in several cardiovascular risk parameters.[56]

The Atkins Diet

The Atkins diet is a variant of the original ketogenic diet. Key differences between the ketogenic diet and the Akins diet include that the former requires a protein cap and strict early limitation of carbohydrates. The Atkins diet is a less restrictive interpretation of the ketogenic diet. It is started without a fast and without any restrictions on calories, fluids, or protein. This "Modified Atkins Diet" restricts carbohydrates to 10 g/day (15 g/day in adults) while encouraging high fat foods.[57]

The Modified Atkins Diet was created at the Johns Hopkins Hospital to offer a better alternative to patients struggling to adopt a purely ketogenic diet, such as children with epilepsy. The MAD was similar in fat composition to a 0.9:1 ketogenic ratio (fat:carbohydrate and protein) diet, with approximately 65% of the calories from fat sources. The diet is “modified” from the Atkins diet as the induction phase of the diet limiting carbohydrates is maintained indefinitely, fat is encouraged (not just allowed), and weight loss is not the goal (unless nutritionally indicated).[57]

There is evidence that the Atkins diet can result in a statistically significant increase in total cholesterol, specifically LDL cholesterol,[57] while triglyceride levels were significantly reduced.[58] However, timing is significant when it comes to the Atkins diet. While total cholesterol and LDL increased over the first 3 months of the diet, these values normalized within a year of

treatment, including in patients treated with MAD for more than 3 years.[59] Therefore, it is worth researching further in longer clinical trials to see whether long-term implementation of the MAD has any long-term effect on cholesterol levels and hard cardiovascular end-points.

Intermittent Fasting

Intermittent fasting is defined as 60% energy restriction on either 2 days per week, every other day, period fasting (consumption of 750-1100 calories daily for 5 days,) and time-restricted feeding is limiting the daily period of food intake to 8 hours or less, respectively. The concept behind intermittent fasting is for a subject to undergo ad libitum feeding, determined to be 16-48 hours with little energy intake, with intervening periods of normal food intake, in a repetitive cycle. Animals can function optimally when food-deprived, or fasting. Humans typically consume at least 3 times a day. When compared to animal populations (who typically feed only as needed), humans are found to develop comorbidities associated with over-eating, such as insulin resistance, excessive accumulation of visceral fat, etc.[60]

Preliminary studies have shown a reduction in insulin resistance, and risk factors for CVD.[60] Specifically, findings support a reduction in blood pressure, cardiovascular stress adaptation improvement, heart rate variability increases, and increased resistance of heart and brain cells to ischemic injury.[61] Additional studies suggest an extended lifespan.[62] Other confirmed benefits of intermittent fasting include the inhibition of the development of atherosclerotic plaques by reducing the concentration of inflammatory markers, such as IL-6, homocysteine, and C-reactive protein.[63] Regarding the prevention of hypertension, the intermittent fasting diet causes an increase of brain-derived neurotrophic factor (BDNF) factor, which results in lowering the systolic and diastolic blood pressure by activating the parasympathetic system. BDNF causes acetylcholine to be released by the vagus nerve, which reduces the frequency of heart contractions.[63] There is evidence to suggest a protective effect on the heart against ischemic injury, which attenuates post-myocardial infarction cardiac remodeling, likely via antiapoptotic and anti-inflammatory mechanisms. Further research suggests that intermittent fasting works at the level of adaptive cellular stress response signaling pathways that enhance mitochondrial health, DNA repair, and autophagy. Period fasting promotes stem-cell regeneration, and can have long-lasting metabolic effects. Collectively, the beneficial effects of intermittent fasting on the cardiovascular system are similar to those of regular physical exercise.[64]

Specific subpopulations studied have included the fasting population in Muslim nations during Ramadan, specifically those with prosthetic valves. This population underwent beneficial changes including significantly elevated HDL levels 20 days post-Ramadan.[65] However, randomized, long-term trials are required to determine whether intermittent fasting can be a feasible life-style change and beneficial for the population at large.

This diet is not without controversy, as some researchers have found evidence that would argue against prolonged fasting in high-risk cardiovascular patients.[66] Fasting at the start can cause bad mood, fatigue, or dizziness, as the body accustoms itself to using ketones instead of glucose. Fasting can provoke and aggravate certain baseline conditions, and incite cardiovascular events.[66] Specific populations that should be cautious include the elderly, diabetics, pregnant women, and those people performing heavy physical work. In the elderly, intermittent fasting is associated with an increased risk of CVD, arrhythmia, and stroke.[63] In diabetics, caloric restriction with the simultaneous use of antidiabetic drugs may lead to severe hypoglycemia and even death. Furthermore, fasting can lead to dysregulation of hormone management, causing menstrual cycle disorders in women and reduced testosterone in men. Intermittent fasting should not be used by children, pregnant women, and people performing heavy physical work.[63]

It is worth mentioning that research is underway to study how intermittent fasting can enhance treatment with both chemotherapy and radiation therapy. Calorie restriction and fasting elicit different responses in normal and cancer cells, and reduce certain side effects of cytotoxic therapy.[67] The authors make clear that further research is needed.

A discussion of intermittent fasting would not be complete without mentioning the fasting mimicking diet, broadly defined as one that is low in calories, sugars, and protein but high in unsaturated fats.[68] Wei and team carried out a trial with subjects divided into an unrestricted diet arm, and a fasting mimicking diet arm for a period of 3 months. Their findings included a post hoc analysis of subjects, which showed that body mass index, blood pressure, fasting glucose, IGF-1, triglycerides, total and LDL-C, and C-reactive protein showed improvement in participants at risk for disease versus those who were not at risk. No serious adverse effects were reported in this study.[68]

Future Directions

While the DASH, plant-based, and Mediterranean diets have well-established roles in the reduction of cardiovascular events, and are

TABLE 1. Comparison of established and newer dietary strategies

Diet	Description	Benefits	Adverse effects
DASH diet	Fruits, vegetables, low-fat dairy foods, whole grains, poultry, fish, and nuts, with a much lower content of red meat, sweets, and sugar-containing beverages Sodium reduction to 1150 mg daily	Significant 10 mm Hg reduction in SBP Improvement in lipid parameters Weight loss	Not identified
Mediterranean diet	At least 2 from below: High monounsaturated/saturated fat ratio Low-moderate red wine consumption High consumption of legumes High consumption of grains and cereals High consumption of fruits and vegetables Low consumption of meat and meat products Increased consumption of fish Moderate consumption of milk and dairy products	10% reduced incidence of cardiovascular event Decrease in waist-to-hip ratio, lipids, and markers of inflammation 65% reduction in cardiac death or nonfatal MI 4 years postindex MI Reduced stroke risk	Not identified
Plant based diet	Plant-based dietary protein No animal products	24% reduction in cardiovascular mortality Markedly reduced all-cause mortality risk	Hyperhomocysteinemia, protein deficiency, anemia, decreased creatinine content in muscles, and menstrual disruption in women who undertake increased physical activity
Ketogenic diet	High in fat and low in carbohydrates 55%-60% fat 30%-35% protein 5%-10% carbohydrates.	Lowered blood glucose, triglyceride, and insulin levels Enhance the immune response against cancer Weight loss	Decrease in carotid distensibility and an increase in LDL-C, apoB and the TC:LDL-C and LDL-C:HDL-C
Atkins diet	0.9:1 ketogenic ratio (fat:carbohydrate and	Triglyceride levels were significantly reduced	

(*continued*)

TABLE 1. (*continued*)

Diet	Description	Benefits	Adverse effects
	protein) diet, with approximately 65% of the calories from fat sources		Significant increase in total cholesterol, specifically LDL
Intermittent fasting	60% energy restriction on two days per week, every other day, period fasting is consumption of 750-1100 calories daily for five days, and time-restricted feeding is limiting the daily period of food intake to 8 hours or less, respectively	Improved functional outcome with respect to diabetes, cardiovascular disease, cancers, dementia, Parkinson's disease, and stroke, as well as extended lifespan Lessens post-MI cardiac remodeling Promotes stem cell regeneration Increased HDL Inhibition of the development of atherosclerotic plaques Prevents hypertension Weight loss Enhance treatment with both chemotherapy and radiation therapy	Can provoke and aggravate cardiovascular events in the elderly Bad mood, fatigue, or dizziness

guideline-supported, there is evidence to support further investigation into recent dietary trends. While there are suggestions from small observational studies,[52] that the ketogenic diet and intermittent fasting diet may incur an increased cardiovascular risk, further research in these areas is required to more definitively evaluate the roles of these dietary strategies, if any, in the prevention of CVD. Table shows a description, benefits, and possible adverse effects of each of the diets described above.

The 2015-2020 Dietary Guidelines emphasize that everyone has a role in helping to create and support healthy eating patterns in multiple settings nationwide, from home to school to work to communities.[35] The guidelines specifically discuss a social-ecological model for food and physical activity decisions. The social-ecological model takes into account how social and cultural norms and values, sectors, settings, and individual factors ultimately influence food and beverage intake, physical activity patterns, and ultimately health outcomes.[35] While the above factors take place on the individual level,

they can collaboratively be targeted at the community, and ultimately the population level. Through educating individuals and helping guide them toward better dietary options, we can promote better health on a small scale, which can spark a movement on a larger scale, and ultimately work toward reducing cardiovascular risk factors. This is what these guidelines ultimately seek to achieve; they emphasize that the individual's goals must be the focus of their healthcare provider, but that there is a more primary global goal at stake.

Conclusions

The plant-based and Mediterranean diets have been emphasized in the most recent American Heart Association guideline for the Prevention of Heart Disease,[23] largely due to the wealth of prevailing evidence from large population-based studies demonstrating cardiovascular benefit. Conversely, there are less clear guidelines regarding implementation of the ketogenic and intermittent fasting diets, and their potential long-term benefits or cardiovascular risks. Our team of researchers has found evidenced-based medicine which would suggest that there are potential health benefits to the ketogenic, and intermittent fasting diets. Further research is required, and caution is advised before prescribing these diets to patients in the long-term, due to the potential to exacerbate cardiovascular risk factors.

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