Low-Carbohydrate/Ketogenic Diet and Coronary Artery Disease

A Brief Review of the Limited Evidence Between Them

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Abstract: Nowadays there is a lot of interest among the general population regarding the ketogenic diet (KD) and its health benefits. Most people following this diet have a reduced intake of carbohydrates which gets replaced by calories coming from fat and protein. Even though KD has shown some limited health benefits, there is no consensus on long-term effects and cardiovascular safety profile, especially the relation of KD to coronary artery disease (CAD). This concern comes predominantly from increased fat intake in KD and other similar diets with decreased carbohydrate intake. One study has shown a link between type 1 diabetes and increased coronary artery calcium scores but, in addition to many other limitations, after adjusting for other cardiovascular risk factors, the association was not significant. Results from a subanalysis of the CARDIA prospective study found that progression of CAD measured by coronary artery calcium was more pronounced in people with low-carbohydrate intake, especially when the compensatory calorie intake was from animal sources as compared to plant-based sources. In addition, other studies have tried to find a link between this type of diet and other traditional cardiovascular risk factors that have been traditionally associated with CAD, especially comparing low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride (TAG) levels without clear clinical significance. Other studies found an association between KD and all-cause mortality, but no association with cardiovascular mortality. Lastly, there is an association between animal-based KD and all-cause mortality in patients who have already suffered a myocardial infarction. These findings are modified when accounting for saturated fat intake, which may give us an insight into possible mechanisms to explain these differences.

Key Words: ketogenic diet, low-carbohydrate diet, coronary artery disease, calcium score

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The ketogenic diet (KD) consists of limiting the number of calories originating from carbohydrate intake and replacing it with calories from increased fat and protein intake. The usual goal for carbohydrate intake is less than 50 grams a day with 1 to 1.5 grams of protein per kilogram of body weight, while the rest of the calories come from fat.[1] Initially developed to treat epilepsy in children,[2] the KD has now shown some limited benefits in glucose metabolism for diabetic patients and weight loss for obese patients.[3] Currently there is an increased interest among the general population in this type of diet. It is widely discussed in pop culture, health magazines, and social media. In 2020, the KD garnered significant attention in the United States with 25.4 million Google searches, indicating a rising interest that helped its global market reach a value of 9.57 billion dollars in 2019.[4] With a very limited body of evidence to argue for or against it in respect to coronary artery disease (CAD), we lack the proper information to advise our patients who are interested in following this dietary trend. Our aim is to review the latest evidence linking KD and CAD to elucidate a better answer to our patients' questions.

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DEVELOPMENT AND PROGRESSION OF CORONARY ARTERY DISEASE AND KETOGENIC DIET

A 2009 study by Snell-Bergeon et al[5] explored the variations in self-reported dietary carbohydrate and fat intake among individuals with Type 1 Diabetes Mellitus (T1DM) and those without the condition. This investigation further involved a comparison of their respective coronary artery calcium (CAC) scores. The study found that those with T1DM eat more fat and less carbohydrates than the control. However, the study found that after adjusting for other known CAD risk factors, such as high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol, hypertension, body mass index (BMI), physical activity, and insulin sensitivity, there was no significant association between high-fat diet and coronary artery calcifications. This suggests that the association between higher dietary fat intake and coronary artery calcifications is mediated through the already-known risk factors for CAD. However, this study had many limitations. For one, it sought to compare patients with T1DM to patients without T1DM. Patients with diabetes with poor glycemic control have been shown to have an increased risk of developing CAC.[6] Furthermore, this study uses data that was self-reported and retrospective, leaving the possibility of bias. Furthermore, a significant portion of their controls were the spouse or live-in partner of a patient in the experimental group, making this less randomized, since couples who live together may eat a similar diet. Finally, this study only involved 571 participants with T1DM and 696 controls.

Another study published by Gao et al. in 2020[7] (Table 1) reported on the CARDIA study, which was a prospective multicenter cohort study. This study examined the evolution of CAD risk by evaluating CAC over a long period of time, after noting dietary history in young adulthood. The study found that the most significant CAC progression was in participants with the lowest carbohydrate intake. This association held true even after controlling for other risk factors like age, BMI, and hypertension. Interestingly, the study found that animal-based low-carbohydrate diets (LCDs) were significantly associated with more severe CAC progression compared to plant-based LCDs. This study also had some limitations. For one, diet was measured by a questionnaire, which can produce systematic errors. Furthermore, the study only measures the diet in the first 7 years of the study, but does not account for changes in diet in the years following, when they would only check for CAC.

While both studies show an association between LCD and progression of CAD, they fail to prove a causative link, due to the nature of the studies. Since CAC takes a long time to develop, a more controlled study with stricter control of diet would be more useful, but probably unfeasible.

TABLE 1. Comparison of Different Meta-Analysis on Cardiovascular Risk Factors and Ketogenic Diets

Meta-Analysis (Ref. No.)	Year	Types of Diets Compared	Study Duration	Population Studied	Body Weight/ BMI Changes	HDL Changes	LDL Changes	Other CV Risk Factors Noted
Santos et al[8]	2012	Low-carbohydrate diet (LCD) vs baseline	Variable	1141 obese patients	↓	↑	↔	Abdominal circumference: ↓, SBP: ↓, DBP: ↓, Triglycerides: ↓, Fasting plasma glucose: ↓, HbA1C: ↓, Plasma insulin: ↓, CRP: ↓
Bueno et al[9]	2013	Very-low-carbohydrate ketogenic diet (VLCKD) vs low-fat diet (LFD)	≥12 months	1415 patients (VLCKD) for body weight, varying for others	↓	↑	↑	TAG: ↓, Diastolic blood pressure: ↓, Fasting blood glucose: ↔, Insulin: ↔, HbA1c: ↔, C-reactive protein: ↔
Mansoor et al[10]	2015	Low-carbohydrate (LC) vs low-fat (LF)	≥6 months	1369 participants in 11 RCTs	↓	↑	↑	TAG: ↓, SBP: ↔, DBP: ↔, Fasting glucose: ↔, Insulin concentrations: ↔
Nordmann et al[11]	2006	Low-carbohydrate (LC) vs low-fat (LF)	≥6 months	447 individuals in 5 trials	↓ (at 6 months) ↔ (at 12 months)	↑ (at 6 months)	↑ (at 6 months)	Triglycerides: ↓ (at 6 months) Blood pressure: ↔

KETOGENIC DIET AND CARDIOVASCULAR RISK FACTORS

A 2012 meta-analysis by Santos et al[8] examined the effect of a LCD on patients with obesity in terms of weight loss and cardiovascular risk factors. They examined a total of 23 reports which correspond to 17 clinical investigations. Patients with diabetes, as well as any patients with other endocrinological conditions were excluded. This meta-analysis did not have a low-fat diet (LFD) control and instead compared subjects to their baseline. While their primary outcome was change in body weight, they also examined changes in cardiovascular risk factors. They found that LCDs are associated with lower body weight, BMI, abdominal circumference, systolic blood pressure, and diastolic blood pressure. Statistically significant decreased lab values include triglycerides, fasting plasma glucose and HbA1C, and fasting plasma insulin. They found that LCD increased HDL-C. For LDL-C, their data show a small statically significant increase in LDL-C in studies that report data for LCD within 6 months, but show an insignificant effect on LDL-C levels between 6 months and 11 months compared to baseline. For studies reporting between 12 months and 23 months as well as studies reporting data from 24 months, an LCD is associated with a statistically significant reduction in LDL-C. However, they state that overall, the change in LDL-C is insignificant. Some limitations they mention in their study include having varied criteria for what is meant by an LCD in each study. Such variations might explain differences in results between individual studies. Finally, they advocate for studies that evaluate the long-term effects of LCDs, past the 24-month checkpoint of studies done thus far.

A 2013 meta-analysis by Bueno et al[9] delved into the effects of a very-low-carbohydrate ketogenic diet (VLCKD) on overweight and obese individuals, focusing on weight loss and cardiovascular risk factors. The study incorporated 13 studies, representing a total of 1577 participants, 787 of whom were randomized to the LFD group and 790 of whom were randomized to the VLCKD group. The research specifically compared the VLCKD to a conventional LFD over a long-term period (defined as 12 months or more postintervention). The analysis did not directly compare either diet's effectiveness compared to the participant's baseline, but only compared the 2 diets to each other. It found that the VLCKD had a greater decrease in body weight and triglycerides. They reported a greater increase in both HDL-C and LDL-C in the VLCKD group than in the LFD group. They did not find any statistically significant difference between fasting blood glucose, plasma insulin, HbA1C, and C-reactive protein between the 2 diets. Interestingly, when comparing the diets in studies that kept track of these benchmarks for 24 months, they found no statistically significant difference between them except for a higher HDL-C in the VLCKD group. When discussing the increased LDL-C in the VLFKD group, they quote a study by Krauss et al. that showed that high-fat intake combined with carbohydrate restriction raises the levels of larger-sized LDL-C specifically, which are known to be less harmful than small, dense LDL-C. The limitations of this study include the use of aggregate data instead of direct patient data and that they did not take adherence to the diets into account for their analysis.

A 2015 meta-analysis by Mansoor et al[10] also evaluated studies that compared LFD and LCD. The study included 11 randomized controlled trials (RCTs) with a total of 1369 participants who were followed between 6 and 24 months. They found, once again, that participants in LCDs lost more weight and had lower triglyceride levels compared to LFDs, and had higher HDL-C, however, they found that the LCD groups had higher levels of LDL-C. They also did not directly compare either diet's effectiveness compared to the participants' baselines. They only included healthy participants, without comorbidities such as severe obesity (classified as BMI ≥35 kg/m^2)

or diabetes. Once again, the studies included in this meta-analysis had weight change as their primary endpoint, and cardiovascular risk factors were a secondary endpoint. They also note that in most of their included studies, the LFD group was imposed an energy restriction, while the LCD group was not imposed a formal calorie restriction. They note that in many RCTs the LCD group self-imposed a calorie restriction, often up to 30% of their baseline energy intake, even though it was not required or encouraged at the outset. They emphasize that the benefits of increased weight loss and triglyceride level reduction in a LCD must be weighed against the drawback of higher LDL-C, which is a cardiovascular risk factor. One limitation mentioned by the authors is the high dropout rate in these RCTs. They finish by highlighting that no RCT has examined the effects of LCDs versus LFDs on hard endpoints, such as mortality. A 2006 meta-analysis[11] also reached similar conclusions using a subset of the RCTs included in the Mansoor meta-analysis, with the additional finding that after 12 months there was no statistical significance between body weight change between the LFD and LCD groups.

More recently, at the 2023 ACC conference a paper was presented on "Association of a Low-carbohydrate High-fat (Ketogenic) Diet with Plasma Lipid Levels and Cardiovascular Risk in a Population-based Cohort."[12] It presented a cross-sectional study comparing a group of 305 participants who self-reported a low-carbohydrate, high-fat diet, consisting of <25% of daily calories from carbohydrates and >45% of daily calories from fat to a control group of 1220 participants who reported a standard diet. They found that those who self-reported a low-carbohydrate diet had a higher mean BMI, higher LDL-C, triglycerides, and apolipoprotein-B (apo-B) compared to the standard diet group. They also reported that major adverse cardiac event incidence was more than double in the low-carbohydrate high-fat group compared to the standard diet group (9.8% and 4.3%, respectively). They note some limitations of this study, including that groups were divided based on self-reported dietary data which was provided only at 1 point in time, and there was no standardization for specific dietary intake in either group.

MORTALITY DATA ASSOCIATED WITH KETOGENIC DIET

A prospective study published in 2014 by Li et al[13] examined the long-term outcomes of a LCD after an initial myocardial infarction (MI) in 2 large existing cohort studies, 1 of female nurses (2258 women) between the ages of 30 and 55 and the other of male healthcare professionals (1840 men) between the ages of 40 and 75.

A validated food frequency questionnaire was filled out at least once pre-MI and post-MI in addition to every 4 years of follow-up. The percentage of calories originating from carbohydrates, fats, and protein was calculated for each participant. In addition, food sources for those calories (animal and plant) were also calculated. They were then given a score from 0 (more carbohydrates consumed) to 30 (more fats and protein consumed) and divided into quintiles. Most of the comparisons were made between the extreme quintiles.

Interestingly, participants increased their carbohydrate consumption after the initial MI, but the participants who kept a LCD had a higher baseline prevalence of diabetes. This study found that a LCD was associated with a higher all-cause mortality for women but not for men after adjusting for time since MI, age, and calendar year. This was also true for participants (men and women pooled together) who had a higher animal-based LCD compared to participants who had a higher plant-based LCD. In addition to all-cause mortality, the animal-based LCD group had an increased cardiovascular mortality [hazard ratio was 1.30 with 95% confidence interval (CI) 1.03 to 1.65 for all-cause mortality, and 1.53 with 95% CI 1.10 to 2.13 for cardiovascular mortality]. These findings were attenuated when adjusting for saturated fat intake, hinting at a possible cause or mechanism for the increased mortality. The group who adhered to a plant-based LCD did not have a mortality benefit.

It is important to note that this study was based on questionnaires that were very far apart and recall bias is always a possibility. In addition, it may have lacked sufficient power in a post-MI survivor population and some residual and unmeasured confounding factors were not considered such as clinical characteristics and prognosis of the initial MI (survival bias).

A previous meta-analysis in 2013 by Noto et al[14] included 4 studies that provided carbohydrate intake by caloric density with a total study population of 272,216 individuals. The study showed that being part of the LCD cohort had a higher risk of all-cause mortality [relative risk (RR) 1.31 with 95% CI, (1.07–1.59); $P = 0.007$] but did not increase the risk of cardiovascular death or cardiovascular events. Similar results were seen in groups with low-carbohydrate/high-protein diets [RR 1.30 (1.01–1.68); $P = 0.04$]. Differences in follow-up time also showed a difference, but the reason is unclear. In the studies where follow-up time was less than 10 years, there was a marked increase in RR for all-cause mortality for the LCD compared to the studies with follow-up longer than 10 years [RR 1.40 (1.12–1.74) vs 1.27 (0.88–1.84)]. There was also a difference in all-cause mortality for men following a LCD as compared to women [RR 1.19 (1.08–1.31) vs 1.34 (0.96–1.87)]. Overall heterogeneity was moderate for this meta-analysis. Some studies were observational and the relationship may not be causal and confounding factors may be present. More so, studies with long follow-up periods may involve changes in dietary patterns that were not accounted for in all studies.

CONCLUSIONS

There seems to be limited data that supports an association between LCDs and CAD using CAC as a surrogate but there is insufficient evidence to prove causation. There is a need for better studies given the multiple drawbacks in the existing ones including possible confounding factors. Using traditional risk factors as another surrogate marker has yielded contradicting results. There could be a significant difference in LCDs that supplement the loss of carbohydrate calories with fats and proteins from animal sources as compared to those where most fats and proteins come from plant-based sources. The macronutrient composition of the diet may be as important as its source, but more studies are needed to clarify and describe this difference in regard to CAD and should include long-term outcomes.

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