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Invited Review Article

Ketogenic diet and cardiovascular risk – state of the art review

Joanna Popiolek-Kalisz, MD PhD [a,b,*]

[a] Clinical Dietetics Unit, Department of Bioanalytics, Medical University of Lublin, ul. Chodzki 7, 20-059, Lublin, Poland
[b] Department of Cardiology, Cardinal Wyszynski Spaceship in Lublin, Poland

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ABSTRACT

The ketogenic diet is based on extreme carbohydrate intake reduction and replacing the remaining with fat and has become a popular dietary pattern used for weight loss. The relationship between the ketogenic diet and cardiovascular risk is a controversial topic. This publication aimed to present evidence on the ketogenic diet and cardiovascular risk factors and mortality.

The ketogenic diet does not fulfill the criteria of a healthy diet. It presents the potential for rapid short-term reduction of body mass, triglycerides level, Hb1Ac, and blood pressure. Its ef-ficacy for weight loss and the above-mentioned metabolic changes is not significant in long-term observations. In terms of cardiovascular mortality, the low-carb pattern is more beneficial than very low-carbohydrate (including the ketogenic diet). There is still scarce evidence comparing ketogenic to the Mediterranean diet. Other safety concerns in cardiovascular patients such as adverse events related to ketosis, fat-free mass loss, or potential pharmacological interactions should be also taken into consideration in future research.

Introduction

Cardiovascular diseases have become the leading global cause of death.[1] That is why counteracting cardiovascular risk factors such as dyslipidemia, hypertension, diabetes, and obesity is the priority for public health in cardiovascular disease primary prevention.[2] Lifestyle, including diet, is the most important factor determining metabolic health status.[3] Mediterranean diet emerged as the most universal dietary pattern for cardiovascular prevention[2], but there are still new concepts under investigation. The ketogenic diet has become a popular dietary pattern used for weight loss. The foundation of this diet is extreme carbohydrate intake reduction (to 5-10 % of total daily dietary requirements) and replacing the remaining with dietary fat.[4] The ketogenic diet is used in epilepsy treatment[4], however, there are debates about its metabolic effects in terms of weight loss. On the other hand, the possibility of such a carbohydrate intake reduction is introduced by extreme limitation of wholegrain products, fruits, and vegetable consumption, which can result in insufficient fiber, vitamins, and antioxidants intake. Moreover, the proportional higher consumption of fat often carries along a higher intake of saturated fatty acids and high-processed animal-based products. That is why, the relationship between the ketogenic diet and cardiovascular risk is a controversial topic that is still deeply investigated.

The current European Society of Cardiology guidelines on cardiovascular disease prevention were published in 2021.[2] They mention the role of diet in cardiovascular prevention and suggest the Mediterranean diet as the most beneficial in long-term outcomes. However, they mention the application of very low carbohydrate diets as a possible approach for weight loss, however, they underline

* Corresponding author at: Medical University of Lublin, ul. Chodzki 7, 20-059, Lublin, Poland.
E-mail address: joanna.popiolek-kalisz@umlub.pl.

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that this model brings only short-term effects, and afterward the effects of this dietary model tend to diminish. Moreover, the guidelines emphasize that the long-term health benefits are determined by the quality of nutrients, such as low levels of saturated fatty acids, and high intake of vegetables, fruits, and dietary fiber. The ketogenic diet usually does not fulfill these criteria, as already mentioned above. What is more, the European Society of Cardiology guidelines indicate that low carbohydrate diets can be ketogenic, thus they should be supervised by a professional. There are mentioned possible advantages of low carbohydrate diets including tri-glyceride level reduction, diabetes medication demand reduction, and appetite decrease which are based on the publication by Kirkpatrick et al. from 2019. Since that time, during the last 4 years, the state of knowledge about ketogenic diets improved.

This publication aimed to present the latest evidence regarding ketogenic diet and cardiovascular risk published as meta-analyses after 2019. The search was made in the PubMed database and included meta-analyses published between 2020 and 2023 which referred to the topic of the ketogenic diet and cardiovascular risk, cardiovascular mortality, lipid profile, blood pressure, glycemic control, and weight loss.

Body mass

Excessive body mass is the main lifestyle factor that leads to metabolic complications such as dyslipidemia, diabetes, and hypertension. It is estimated that 42.8% of adults are obese.[5] Central obesity together with its complications is acknowledged as a metabolic syndrome.[6] That is why proper body mass management is crucial in terms of cardiovascular prevention.

The meta-analysis which compared the ketogenic diet to a balanced diet in obese individuals showed no significant differences in body mass index (BMI) between them.[7] The included studies covered the observation from 3 to 24 months. On the other hand, when the ketogenic diet was analyzed in terms of weight loss it led to significant weight loss depending on the ketogenic phase length.[8] It also led to a significant loss in fat mass and lean body mass as well.[8] However, this meta-analysis included 12 studies among which only 4 used low carbohydrate diets as the comparator and 9 were not compared to other diets. Moreover, they covered the mixed periods of 3 to 104 weeks of follow-up with up to 12 weeks of ketosis phase.[8] Another meta-analysis of 18 trials revealed a significant reduction in body mass, BMI, fat mass, percentage body fat, visceral adipose tissue, fat-free mass, lean body mass, and waist circumference in mixed (6 to 96 weeks) observations of a ketogenic diet compared to mixed group of diets (e.g. low calorie, high carbohydrate, or regular diets).[9] This analysis did not include any comparison to the Mediterranean pattern.

Diabetic patients represent a group at particularly high cardiovascular risk. The meta-analysis of 8 studies, published in 2022 showed that diabetic patients present higher body mass and waist circumference reduction on ketogenic diets compared to moderate carbohydrate or hypocaloric diets.[10] However, there were no significant differences in BMI reduction in these studies.[10] The length of these interventions was between 3 months to 2 years. It is worth noting that the ketogenic diet was not compared to the Mediterranean diet which is a recognized standard. The meta-analysis by Yuan et al. also suggested a positive impact of the ketogenic diet in diabetic patients on body mass enlargement, however, the included studies covered different follow-up periods (1 to 56 weeks), and in most of them, the ketogenic diet was not compared to any control, so this meta-analysis does not bring information about the current position of ketogenic diet compared to recommended standards as well.[11] On the other hand, in the meta-analysis by Rafiullah et al. the ketogenic diet resulted in greater weight loss compared to diabetes-recommended diets after 3 and 6 months, however, the ketogenic diet was not better than the recommended diet after 12 months.[12]

Moreover, the dose-response meta-analysis showed a linear relationship between body mass reduction and the decrease in carbohydrate intake at the short-term follow-up (up to 6 months) in diabetic patients.[13] On the other hand, at the longer follow-up (12 months) there was a U-shaped relationship between carbohydrate intake decrease and the body mass reduction with the greatest reduction at the 35 % carbohydrate intake.[13] Furthermore, there was no significant relationship between carbohydrate intake and body mass reduction at longer follow-ups in diabetic patients.[13]

A dietary approach is often a part of broader lifestyle modification, which usually includes physical activity introduction as well. When the ketogenic diet was combined with physical activity there was a significant decrease in waist circumference compared to the control, while there were no significant differences in BMI, fat mass, and lean body mass in short-term observations (4 to 24 weeks).[14] The combination of the ketogenic diet with resistance training compared to nonketogenic diets (normal or other unspecified diets) presented significantly decreased body mass, BMI, fat mass percentage, and fat-free mass which was not ameliorated by the addition of the resistance training after 3 to 12 weeks in mixed observation of obese individuals and athletes.[15]

Relatively rapid effects in terms of weight loss made the ketogenic diet popular for this purpose. That is why the Italian Society of Endocrinology recommends a 12-week ketogenic diet as part of the approach for obese patients who need to lose weight rapidly due to clinical reasons.[16] However, multiple mechanisms are suggested to be the reasons for the ketogenic diet's effectivity in body mass reduction including the modulation of resting energy expenditure[17], appetite suppression[18], but also increased diuresis due to ketosis[19], glycogenolysis[20], and fat-free mass loss.[20] There is scarce evidence for the long-term positive effects of the ketogenic diet for weight loss.

Lipid profile

Atherosclerosis is the main cause of cardiovascular diseases. Among other factors, it results mainly from lipid profile disorders, i.e. elevated low-density lipoprotein cholesterol (LDL) and triglycerides levels, and decreased high-density lipoprotein cholesterol (HDL) levels. The ketogenic diet is based on high-fat intake which is against the healthy diet recommendations.[2] However, lipid profile depends also on carbohydrate intake which leads to discussion about this dietary pattern's impact on lipid profile.

In normal-weight individuals, the ketogenic diet significantly increased total cholesterol, LDL, apolipoprotein B, and HDL, while

triglyceride levels were not significantly different between the ketogenic diet and diets containing 45-65 % carbohydrates.[21] The umbrella review of meta-analyses regarding multiple health outcomes of the ketogenic diet showed that this dietary pattern may lead to a significant increase in LDL and total cholesterol levels in individuals without diabetes but with excessive body mass (overweight or obese) as well.[22] On the other hand, the meta-analysis that compared the ketogenic diet to a balanced diet in obese individuals showed no significant differences in total cholesterol, LDL, HDL, and triglyceride levels between them.[7] The included studies covered the observations from 3 to 24 months. Interestingly, in the meta-analysis by Castellana et al. the ketogenic diet led to a significant decrease in total cholesterol and triglycerides levels without significant changes in HDL and LDL levels.[8] However, this meta-analysis included 12 studies among which only 4 used low carbohydrate diets as the comparator and 9 were not compared to other diets. Moreover, as already mentioned, they covered the mixed periods of 3 to 104 weeks of follow-ups with up to 12 weeks of ketosis phase.[8] This meta-analysis also revealed that liver function parameters such as alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase were also significantly lower after the ketogenic diet.[8]

The dose-response meta-analysis by Jayedi et al. showed at the 6-month follow-up the linear relationship between the decrease in carbohydrate intake and triglyceride levels reduction, however, the lowest noted carbohydrate intake was 15 %, while ketogenic diet is based on carbohydrate intake reduction to 10 % or lower.[13] This relationship was also confirmed at the 12-month follow-up, but it was not present at longer follow-ups.[13] For LDL and total cholesterol levels, there was a U-shaped relationship with the greatest reduction at the 40 % carbohydrate intake at the 6 and 12-month follow-ups, but it was not present at longer follow-ups. The changes in HDL were not significant in diabetic patients at the 6-, 12-month, or longer follow-up.[13]

When the ketogenic diet was compared to diets containing 40-60 % carbohydrates in diabetic patients there were no significant differences between total cholesterol, HDL, and LDL levels after 3, 6, and 12 months.[23] Triglyceride levels decreased after the ketogenic diet compared to 40 - 60 % carbohydrate intake after 3 months, but there were no significant differences after 6 and 12 months.[23]

Moreover, the meta-analysis by Yuan et al. suggested a positive impact of the ketogenic diet on the lipid profile in diabetic pa-tients.[11] However, as already noted, the studies included in this meta-analysis covered different follow-up periods (1 to 56 weeks), and in most of them, the ketogenic diet was not compared to any control, which is why this meta-analysis does not bring information about the current position of ketogenic diet compared to recommended standards.[23] On the other hand, when the ketogenic diet was compared to diabetes-recommended diets it showed greater triglycerides reduction and HDL level increase after 3, 6, and 12 months.[12] For LDL it did not show significant changes at the 3 and 6-month follow-up, but then at 12-month follow-up, it showed a significant increase of LDL level in the ketogenic diet group.[12]

When the ketogenic diet was combined with exercise in overweight/obese individuals, it led to a significant reduction in tri-glyceride levels compared to control in short-term observations (4 to 24 weeks), with no significant differences in total cholesterol, LDL, or HDL.[14] In diabetic patients with excessive body mass, a ketogenic diet combined with physical activity led to an increase in HDL level and a decrease in triglycerides level.[22] It is important to note that physical activity itself can also impact lipid profile, including triglyceride and HDL levels. However, this observation was also shown when the ketogenic diet was compared to moderate carbohydrate or hypocaloric diets in the meta-analysis by Zhou et al.[10]

Lower intake of carbohydrates in ketogenic diets can lead to triglyceride levels reduction, however, significantly increased levels of LDL were also noted. What is more, the positive effects of the ketogenic diet on triglyceride levels seem to diminish in longer observations.

Glucose metabolism

In short-term observations (4 to 24 weeks) in overweight/obese individuals, fasting glucose did not change significantly after the intervention of a combined ketogenic diet with physical activity compared to control in 4 trials included in the meta-analysis by Lee at al. from 2021.[14] These results were confirmed for diabetic patients with excessive body mass in the meta-analysis from 2022, in which there were no significant differences between ketogenic and other investigated diets (moderate carbohydrate or hypocaloric) in terms of glucose level, fasting insulin, or HOMA-IR.[10] In the dose-response meta-analysis by Jayedi et al. each 10 % of carbohydrate reduction led to fasting glucose reduction at the up to 6-month follow-up, but this relationship was not then observed at the 12-month and longer follow-ups in diabetic patients.[13]

For HbA1c, Zhou et al. observed a higher decrease in the course of the ketogenic compared to other mentioned diets.[10] A dose-response meta-analysis in diabetic patients also showed a linear relationship between carbohydrate intake reduction and HbA1c decrease, with a maximum reduction at the level of 10 % carbohydrate intake at the up to 6-month follow-up.[13] This relationship was also confirmed for 12-month follow-ups and longer however the studies included in longer observations investigated the lowest level of carbohydrate intake at 15 % while ketosis requires carbohydrate intake reduction to unless 10 %.[13] Similar observations were made in the meta-analysis by Rafiullah et al. in which the ketogenic diet resulted in greater HbA1c reduction compared to diabetes-recommended diets after 3 and 6 months, however, the ketogenic diet was not better than the recommended diet after 12 months.[12]

The meta-analysis by Yuan et al. suggested a positive impact of the ketogenic diet in diabetic patients also on the level of fasting blood glucose and HbA1c, however, as highlighted above the included studies covered mixed follow-up periods (1 to 56 weeks), and in the majority of them, the ketogenic diet was not compared to any control.[11] Analogically, in the meta-analysis by Castellana et al. the ketogenic diet led to a significant decrease in Hb1Ac.[8] However, this meta-analysis included 12 studies among which only 4 used low carbohydrate diets as the comparator and 9 were not compared to other diets. Moreover, they covered the mixed periods of 3 to 104 weeks of follow-ups with up to 12 weeks of ketosis phase.[8]

The only meta-analysis that compared the ketogenic diet to 10 other dietary approaches including the Mediterranean diet showed

that the ketogenic along with the low-carbohydrate and low-fat diet significantly and effectively reduced HbA1c, while the moderate-carbohydrate, low glycemic index, Mediterranean, high-protein, and low-fat diet significantly and effectively reduced fasting glucose compared to a control diet in diabetic patients.[24] The follow-up period was between 6 to 60 months, and the ketogenic diet was represented by only one study which included 49 participants for 6 months of observation compared to the low glycemic index diet.[25] This study was also characterized by a high drop-out rate (41.7 %).[25]

The reduced carbohydrate intake in the course of ketogenic diets seems to result in a short-term HbA1c level decrease, however, this effect fades in longer observations.

Blood pressure

Elevated blood pressure is another cardiovascular risk factor. The recommended diet for arterial hypertension treatment and prevention is the Dietary Approach Against Hypertension (DASH) model which is similar to the Mediterranean pattern.[26]

In the meta-analysis by Castellana et al. the ketogenic diet led to a significant decrease in systolic and diastolic blood pressure with a significant increase in sodium levels without significant changes in potassium levels.[8] However, as already mentioned, among 12 studies included in this meta-analysis, only 4 used the comparator (low carbohydrate diets) and 9 were not control-compared. Moreover, the included studies covered the mixed periods of 3 to 104 weeks follow-ups with up to 12 weeks of ketosis phase.[8]

The dose-response meta-analysis by Jayedi et al. showed at the 6-month follow-up the linear relationship between the decrease in carbohydrate intake and systolic blood pressure reduction in diabetic patients.[13] However, this relationship was not present at the 12-month follow-up and longer follow-ups.

One of the possible reasons for the short-term effect of the ketogenic diet on blood pressure can be increased diuresis as a result of ketosis and rapid weight loss.[19]

Cardiovascular disease mortality

There is not much new evidence available in terms of ketogenic diet and cardiovascular mortality. The results of the high-versus- low meta-analysis published in 2023 revealed that cardiovascular disease mortality was not linearly associated with a low carbohy-drate diet score, no matter if the pattern was plant-based or animal-based.[27] The further dose-response analysis revealed the U-shaped relationship between a low carbohydrate diet score and the risk of cardiovascular disease mortality, with the lowest cardiovascular disease mortality at the level of low carbohydrate diet score at 14-15 points (within the range of 0 to 30 points available).[27] It suggests that the low-carb pattern seems more beneficial than very low-carbohydrate (including ketogenic) in terms of cardiovascular mor-tality.[27] The dose-response analysis of the subgroups regarding animal or plant-based models did not confirm such a trend in the separate subgroups.[27] The ketogenic diet does not seem to be an optimal approach in terms of cardiovascular mortality according to the newly published meta-analysis.

Other concerns

Apart from inconsistency regarding the impact of the ketogenic diet on selected cardiovascular risk factors, there are other concerns in terms of ketogenic diet introduction in cardiovascular patients. As already mentioned, high fat intake usually results in a higher intake of saturated fatty acids, red meat, and processed food, while the European Society of Cardiology recommendations indicate that saturated fatty acid intake should not exceed 10 % of the total daily energy intake.[2] Moreover, as already mentioned, extreme car-bohydrate intake reduction is executed by limitation in wholegrain products, fruits, and vegetable consumption. This approach is not in line with the healthy diet model which is based on high fruit (unless 200 g daily), vegetables (unless 200 g daily), and wholegrain products consumption.[2] It can also lead to insufficient dietary fiber intake which is normally advised as 30-45 g daily.[2]

Better vegetables and fiber intake in the course of the ketogenic diet can be achieved by high consumption of leafy products, such as lettuce, cabbage, spinach, etc. However, they are also high in vitamin K. Numerous cardiovascular patients suffer from conditions that require oral anticoagulation, such as atrial fibrillation, thromboembolic episodes, or valve replacements. If the patient is treated with old-generation anticoagulants, i.e. vitamin K antagonists (warfarin, acenocumarol), the sudden increase in leafy products' con-sumption can potentially interact with pharmacological treatment and make it less sufficient.

Another pharmacological aspect in cardiovascular patients is heart failure patients, who according to European Society of Car-diology guidelines, should receive SGLT-2 inhibitors as part of heart failure treatment.[28] At the same time according to practical guidelines published by Westman et al. if a diabetic patient is about to start a ketogenic diet, the SGLT-2 inhibitors should be dis-continued due to the risk of normoglycemic ketoacidosis.[29] This aspect could also potentially impact the heart failure pharmaco-therapy efficacy.

The nutritional issue that should be also addressed is that ketogenic diets present also higher fat-free mass loss compared to other diets. This aspect can potentially threaten the nutritional status, especially in elderly or chronic disease patients prone to malnutrition or sarcopenia including cardiovascular patients. The last concern also important for elderly patients is initial dehydration due to elevated diuresis resulting from ketosis.[19] In elderly patients, this could lead to orthostatic hypotonia, which should be also taken into consideration.

These safety concerns should be addressed in future studies focused on the ketogenic diet.

Conclusions

To sum up, the ketogenic diet does not fulfill the criteria of a healthy diet proposed by the European Society of Cardiology. Its efficacy in long-term weight loss and metabolic changes is still unevaluated enough, however, the available evidence suggests that it is not better for long-term effects compared to current dietary standards. Moreover, other safety concerns regarding cardiovascular patients such as adverse events or potential pharmacological interactions should be also taken into consideration when conducting future research on this topic.

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Declaration of competing interest

The authors declaire that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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