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Review Article

The Ketogenic Diet: The Ke(y) - to Success? A Review of Weight Loss, Lipids, and Cardiovascular Risk

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Abstract

Background: Obesity remains a global epidemic with over 2.8 million people dying due to complications of being overweight or obese every year. The low-carbohydrate and high-fat ketogenic diet has a rising popularity for its rapid weight loss potential. However, most studies have a maximal 2-year follow-up, and therefore long-term adverse events remain unclear including the risk of Atherosclerotic Cardiovascular Disease (ASCVD).

Results: Based on current evidence on PubMed and Google Scholar, there is no strong indication ketogenic diet is advantageous for weight loss, lipid profile, and mortality. When comparing a hypocaloric ketogenic diet with a low-fat diet, there may be faster weight loss until 6 months, however, this then appears equivalent. Ketogenic diets have shown inconsistent Low-Density Lipoprotein (LDL) changes; perhaps from different saturated fat intake, dietary adherence, and genetics. Case reports have shown a 2-4-fold elevation in LDL in Familial hypercholesterolaemic patients which has mostly reversed upon dietary discontinuation. There is also concern about possible increased ASCVD and mortality: low (< 40%) carbohydrate intake has been associated with increased mortality, high LDL from saturated fats, high animal product consumption can increase trimethylamine N-oxide, and cardioprotective foods are likely minimally ingested.

Conclusion: Ketogenic diets have been associated with short-term positive effects including larger weight reductions. However, by 2 years there appears no significant differences for most cardiometabolic risk markers. Therefore, this raises the question, excluding those who have a critical need to lose weight fast, is this diet worth the potentially higher risks of ASCVD and mortality while further long-term studies are awaited?

More Information

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Introduction

Obesity remains a global epidemic with over 2.8 million people dying due to complications of being overweight (body mass index (BMI) 25 - 29.9 kg/m2) or obese (BMI > = 30 kg/m2) every year [1]. Despite public health strategies to combat obesity, the worldwide prevalence has tripled between 1975 and 2016 and not only is there an increasing number of adults becoming obese but also 39 million children under the age of five were reported as BMI > = 25 in 2020 [1]. It is well known that obesity is not only a major risk factor for multiple chronic diseases including ischaemic heart disease, stroke, diabetes mellitus [2], and certain cancers including breast, colorectal, and liver [3] but can also be a debilitating condition in isolation.

In the Obesity Society 2018 Position Statement, they describe obesity as a "multi-causal chronic disease… distinguished by multiple phenotypes, clinical presentations, and treatment responses" [4]. Various approaches to managing obesity have been implemented over the years including different dietary modifications, exercise regimes, emerging pharmacological treatments, and in severe cases, bariatric surgery. Different proposed diets have often been subject to scrutiny with a limited evidence base of concept or safety profile, often leading to polarising opinions about their appropriateness.

The low-carbohydrate (CHO) and the high-fat ketogenic diet have been utilized for over one hundred years; however, we still require further evidence of long-term safety. There are several contraindications including liver failure, pancreatitis, and rarer conditions such as porphyria, disorders of fat metabolism, primary carnitine deficiency, and pyruvate kinase deficiency. A common short-term side effect is "keto

flu" including symptoms such as fatigue, headache, nausea, vomiting, and low exercise tolerance which are usually mild and self-limiting. However long-term adverse effects may include hepatic steatosis, nutritional deficiencies, and renal stones. As most studies have only followed up with patients for a maximum of 2 years, long-term adverse events and safety profiles remain unclear including the risk of atherosclerotic cardiovascular disease (ASCVD) [5].

Methodology

To identify relevant studies and reviews, we used electronic databases including PubMed and Google Scholar and manually searched reference lists to reduce missing records up until 1 February 2024. We used the keywords "keto" and "ketogenic" diet to identify papers in the English language and reviewed guidelines of relevant societies. While there may be an individual set point for where patients become ketotic, we focussed on studies that prescribed reduced CHO intake to < 50 g/day. However clearly with dietary intervention, it can be hard to assure complete adherence.

The basis of the ketogenic diet

The Ketogenic diet was first introduced in 1921 in France as an adjunct treatment for refractory epilepsy in children [6]. During severe CHO restriction, the body's glucose reserves become insufficient to fuel the central nervous system after approximately 3 days - 4 days. As fatty acids do not cross the blood-brain barrier, the brain requires an alternative source of energy. Low insulin levels promote lipolysis and fatty acids undergo beta oxidation to form ketone bodies largely in the mitochondrial matrix in the liver, which can then be utilized by the brain as energy. The diet gained mainstream popularity in the 1970s and has recently received more public attention likely due to its rapid short-term weight loss potential [7-9]. In a 2023 survey of 1022 American adults aged 18 to 80 years old, 10% of those following a diet described this as low in CHO [10]. There are now different types of ketogenic diets characterized by their macronutrient content to try and improve adherence to this dietary plan. These include long-chain triglyceride, medium-chain triglyceride, and modified Atkins [5].

Typically, the fat content in ketogenic diets is over 70-80% of total intake with very low CHO intake of ~20 - 50 g/ day or 5% - 10% total intake [11-13] with moderate protein intake (1.2 - 1.5 g/kg/day) [11,13]. This is almost the opposite of recommendations by the World Health Organisation and the European Societies of Cardiology (ESC) and Atherosclerosis (EAS) which advise total fat should not exceed 30% of total energy with saturated < 10% [14,15]. This advice is also echoed in the Public Health England, United Kingdom Government Dietary Recommendation - the Eatwell Guide [16].

While not focussed in this paper, the European Association of Obesity recently recommended A Very Low-Calorie Ketogenic Diet (VLCKD) as a possible treatment option for obesity. However, they stipulated this was a short-term intervention usually lasting 8 weeks - 12 weeks (or a weight loss target of 80%) under medical supervision in select patients needing immediate and substantial weight loss. Examples of potential patients include those with severe obesity and/or comorbidities such as preoperative period of bariatric surgery and cardiovascular and metabolic diseases. The diet which is split into 3 phases starts with initially a VLCKD characterized by daily 500 - 800 calories, 15 g - 30 g fat, < 50g CHOs, and 1 g - 1.5 g protein/kg of ideal body weight, which is a lower amount of fat consumed than in other ketogenic diets. This is then followed by a low-calorie diet (1200 - 1500 calories/day) where CHOs are reintroduced to the maintenance stage (1500 - 2000 calories/ day). Their meta-analysis of fourteen studies showed VLCKD was advantageous for faster weight loss for up to 1 year, but they expressed concern about possible adverse effects that may be found in the future [17].

Ketogenic diet and lipid profile

Ketogenic diets have shown an increase in High-Density Lipoprotein (HDL), reduction in triglycerides, and inconsistent changes in Low-Density Lipoprotein (LDL) cholesterol in patients with BMI > = 25 in short-term studies [8,12,18-20].

There are many possible explanations for these changes in lipid levels. The variation in LDL results may reflect variations in the CHO and fat quantity, variable dietary adherence, genetics, and different diet macronutrient prescriptions. As ketogenic diets require a high fat intake, they may be rich in saturated fat and/or trans fatty acids and animal protein which can in turn raise LDL [21]. Conversely, weight loss from any method can reduce LDL and triglycerides while increasing HDL [22]. Triglycerides may also be reduced due to low insulin levels as low quantities of CHO are consumed [12]. In addition, gene-nutrient interaction studies have demonstrated that genetics contribute to different responses in blood cholesterol to dietary intervention, however further studies are required to allow this to be applied to personalized nutrition [23]. For example, carriers of APOE4 have been found to have higher serum cholesterol levels after consuming a high-cholesterol diet compared to APOE2 carriers [24].

While dietary studies are usually performed in those with raised BMI, a meta-analysis of 3 randomized control studies investigating ketogenic diet in 42 participants with BMI < 25 kg/m2 was carried out by Joo, et al. While low sample size, results suggest increased total cholesterol, LDL, and HDL. Triglyceride levels were not significantly different with commencing the ketogenic diet; however, the 3 studies had varied results (mean difference -0.29 to 0.13 mmol/L) [25] and as baseline triglyceride levels were 0.6 - 0.86 mmol/L, triglyceride changes in any of these studies likely did not represent a strong clinically significant difference.

While there is evidence ketogenic diets can increase LDL, there is limited information about the morphology and density of these particles. It is well known that small dense LDL cholesterol particles are significantly more atherogenic than larger particles [26] and therefore we cannot ascertain if there will be a direct elevated ASCVD risk even if LDL is increased.

Ketogenic diet and genetic disorders of lipid metabolism

It is well known that patients with genetic dyslipidaemias are at a higher risk of CVD and prematurely [15]. The basis of treatment for these patients is usually pharmacological and lifestyle management. However, as mentioned above there is further work required to establish if personalized nutrition plans would be indicated in relation to genetic profiles [23]. Currently, dietary advice for non-hyperchylomicronaemic genetic dyslipidaemic patients is similar to the general population with a recommendation for a Mediterranean-style diet, and in the presence of hypercholesterolemia, saturated fat intake should be reduced to < 7% of total energy [15].

The National Lipid Association has expressed considerable concern about the ketogenic diet in patients with hypercholesterolemia, especially Familial Hypercholesterolaemia (FH) as they may be predisposed to increased LDL. They also state ketogenic diets are contraindicated in patients with hyperchylomicronaemia as they must adhere to a very low-fat diet (< 15 – 20 g/ day or 10% - 15% total daily intake) due to their increased risk of acute pancreatitis [21].

Familial hypercholesterolaemia: Heterozygous Familial Hypercholesterolaemia (FH) is a common monogenic dyslipidaemia with a prevalence of at least 1 in 200 - 250 [27], caused by loss-of-function mutations in LDLR (95%) or APOB gene or gain-of-function in PCSK9. Patients have an up to ten-fold increased risk of coronary heart disease, many of whom develop premature disease. Therefore, early diagnosis and appropriate management are paramount to reduce this risk. Commonly used criteria to help identify patients with probable FH include the Simone Broome criteria and Dutch Lipid Clinic Network diagnostic criteria [15].

While there are few case reports of known FH patients consuming a ketogenic diet, there are a few showing dramatic elevations in LDL cholesterol ranging from 2-4-fold which returned to near baseline upon discontinuing their diet. Omar, et al. described an over 2-fold increase in LDL in a 45-year-old APOB missense mutation female upon starting a ketogenic diet with LDL rising from 211 mg/dL to 454 mg/dL. Interestingly upon following a "less strict" ketogenic diet, her LDL reduced to 276 mg/dL with no additional intervention [28]. A similar case has been described by Khovidhundkit, et al. with a 49-year-old lady with probable FH who experienced an almost 4-fold increase in LDL: LDL 133 mg/dL rising to 530 mg/dL which again reversed with the implementation of low saturated fat diet and also Ezetimibe [29]. Finally, Houttu, et al. described a 41-year-old APOB mutation male having their stable LDL rise from 2.9 mmol/L to 8.39 mmol/L which reversed to baseline upon discontinuation of this diet [30].

Familial dysbetalipoproteinaemia: Familial dysbetalipoproteinaemia (i.e.type III hyperlipoproteinaemia) is a rare autosomal recessive disorder characterized by raised total cholesterol and triglycerides, usually both approximately 7 - 10 mmol/L. Clinical signs such as tuberoeruptive xanthomas or palmar xanthomata can develop in severe cases and patients can be diagnosed by APOE genotyping [15]. Patients are known to be at an increased risk of Coronary Artery Disease (CAD) and it is known that there is a strongly increased risk of premature familial CAD with elevating triglycerides [31].

Case reports have shown a ketogenic diet in these patients may also exaggerate an increase in LDL levels [28, 32]. Omar, et al. described 2 patients with the ApoE3/4 variant, a 58-year-old male who had an over 3-fold increase in LDL with a baseline 132 mg/dL rising to > 455 mg/dL, and a 53-year-old male whose LDL increased approximately 1.5 fold despite losing 100 pounds on a ketogenic diet: 212 mg/dL to 317 mg/dL [28]. Goldberg, et al. described a 69-year-old female with APOE2 homozygosity who after consuming < 20 grams CHO/ day for 6 weeks, developed marked dyslipidaemia with total cholesterol 947 mg/dL, triglycerides 1109 mg/dL and LDL 683 mg/dL [32]. While the patient's baseline lipid profile was not stated, the patient was only referred for genetic testing with these results and she developed palmar xanthomas upon commencing her diet, and therefore we can assume her baseline lipids were much less severely deranged. It is well known the majority of APOE2/2 subjects are either normolipidaemic or hypocholesterolaemic and it is thought a genetic, hormonal, or environmental factor can precipitate the dyslipidaemia [33] for which the patient already had many baseline risk factors including sex, obesity and insulin resistance.

Ketogenic diet and weight loss

The National Lipid Association Nutrition and Lifestyle Task Force has stated that personal preference should be considered when selecting a weight loss diet after being presented with the different options [21]. This is mostly due to the wide variation in weight loss achieved in different trials.

When comparing low CHO ketogenic to low-fat diets, studies have suggested low CHO diets may result in faster weight loss in the first 6 months, however, longer-term the weight loss effects appear equivalent in both normoglycaemic [8,12,18] and impaired glycaemic control/ type 2 diabetics patients [12,19,20]. It seems likely the initial weight loss is primarily due to body water loss [5,34,35] which may be due to increased renal sodium and water loss secondary to ketosis and glycogen depletion [35]. Ketogenic diets also cause larger

lean body mass loss which may be reduced by an increase in protein intake [12,36,37].

It is well known that adherence to diets can be challenging, especially very low/ low CHO diets [12,18-20]. Rafiullah, et al. performed a meta-analysis of 10 studies encompassing 320 patients on a very low CHO ketogenic diet. However, in only 2 of the studies, patients were able to achieve the desired dietary cut-off for a ketogenic diet [20]. Mansoor, et al. also noted that in their meta-analysis, 7 studies that reported macronutrients at the study end date had varied CHO intake ranging from 9% - 40% of total energy also showing a lack of adherence [18]. Clearly given variable dietary adherence, data should be interpreted with caution and possibly limits its generalisability.

Ketogenic diet and atherosclerotic cardiovascular risk

The 2013 Joint American Heart Association/ American College of Cardiology/ The Obesity Society Guideline for management of overweight and obese adults felt there was insufficient evidence to comment on the cardiovascular risk factor effects of these diets, and there remain gaps in the evidence today due to lack of long-term studies [22].

As previously described, the ESC/EAS recommends a Mediterranean-style diet with CHO intake between 45% - 55% [15]. Siedelmann, et al. performed a meta-analysis of 432,179 participants which showed a U-shaped curve with CHO intake and mortality. They noted marked increases in mortality with low CHO (< 40% of total intake) and high CHO (> 70%) diets. However, they noted food type modified this, with plant-derived protein and fat such as vegetables, nuts, and whole-grain breads associated with lower mortality compared to animal-derived products [38]. There is a potentially increased ASCVD risk and mortality by increased trimethylamine N-oxide exposure (TMAO) in animal products [39] which can be seen in patients consuming ketogenic diets both acutely postprandially and chronically [40].

In addition, typically there is limited emphasis on the type of fat consumed in ketogenic diets. This may result in high saturated fat intake, higher LDL cholesterol, and increased ASCVD risk [15,21]. There also will likely be a reduction in cardioprotective food intake such as fiber-rich fruits, vegetables, and whole grains [15]. The EAS/ESC promotes low saturated fat intake [15] and the American Heart Association supports omega 6 polyunsaturated intake of at least 5% - 10% of energy intake to help reduce CHD risk [41].

By approximately 2 years, there are no differences in most cardiometabolic risk factors, and therefore with the potential increase in ASCVD and mortality, there is no evidence to routinely recommend this diet [21].

Conclusion

Ketogenic diets have been associated with a positive reduction in multiple cardiovascular risk factors including triglycerides, weight, and an increase in HDL in the short term. However, by 2 years there are no significant differences in most cardiometabolic risk factors and low carbohydrate intake (< 40%) has been associated with increased mortality. Moreover, there has been noted concern regarding the potential increased LDL, especially in those with genetic disorders of lipid metabolism who already have an increased premature ASCVD risk. While it is unclear if the LDL is directly atherogenic given its wide heterogeneous composition, the National Lipid Association and EAS/ESC are not recommending the ketogenic diet for routine use currently.

Long-term studies are required to understand the true effects of a ketogenic diet, especially on ASCVD and mortality, as well as look at patients' quality of life and adherence. While patient preference is important, currently there is no evidence this diet should be preferentially adopted routinely by the public. However, a short-term ketogenic diet could be an important tool utilized by medical professionals in specific clinical scenarios, but they must weigh up the potential benefits and risks.

References

1. World Health Organisation. Obesity and overweight. 2020. Accessed February 2024. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

2. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: The Framingham experience. Arch Intern Med. 2002 Sep 9;162(16):1867-72. doi: 10.1001/archinte.162.16.1867. PMID: 12196085.

3. Pati S, Irfan W, Jameel A, Ahmed S, Shahid RK. Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management. Cancers (Basel). 2023 Jan 12;15(2):485. doi: 10.3390/cancers15020485. PMID: 36672434; PMCID: PMC9857053.

4. Jastreboff AM, Kotz CM, Kahan S, Kelly AS, Heymsfield SB. Obesity as a Disease: The Obesity Society 2018 Position Statement. Obesity (Silver Spring). 2019 Jan;27(1):7-9. doi: 10.1002/oby.22378. PMID: 30569641.

5. Masood W, Annamaraju P, Khan Suheb MZ, Uppaluri KR. Ketogenic Diet. 2023 Jun 16. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29763005.

6. Höhn S, Dozières-Puyravel B, Auvin S. History of dietary treatment from Wilder's hypothesis to the first open studies in the 1920s. Epilepsy Behav. 2019 Dec;101(Pt A):106588. doi: 10.1016/j.yebeh.2019.106588. Epub 2019 Oct 30. PMID: 31677579.

7. Evans M. Keto diets: good, bad or ugly? J Physiol. 2018 Oct;596(19):4561. doi: 10.1113/JP276703. Epub 2018 Aug 31. PMID: 30106483; PMCID: PMC6166066.

8. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr. 2013 Oct;110(7):1178-87. doi: 10.1017/S0007114513000548. Epub 2013 May 7. PMID: 23651522.

9. Choi YJ, Jeon SM, Shin S. Impact of a Ketogenic Diet on Metabolic Parameters in Patients with Obesity or Overweight and with or without Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. Nutrients. 2020; 12(7):2005.

10. International Food Information Council. Food and Health Survey. 2023. Accessed February 2024. https://foodinsight.org/wp-content/uploads/2023/05/IFIC-2023-Food-Health-Report.pdf.

11. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, Accurso A, Frassetto L, Gower BA, McFarlane SI, Nielsen JV, Krarup T, Saslow L, Roth KS, Vernon MC, Volek JS, Wilshire GB, Dahlqvist A, Sundberg R, Childers A, Morrison K, Manninen AH, Dashti HM, Wood RJ, Wortman J, Worm N. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition. 2015 Jan;31(1):1-13. doi: 10.1016/j.nut.2014.06.011. Epub 2014 Jul 16. Erratum in: Nutrition. 2019 Jun;62:213. PMID: 25287761.

12. Patikorn C, Saidoung P, Pham T, Phisalprapa P, Lee YY, Varady KA, Veettil SK, Chaiyakunapruk N. Effects of ketogenic diet on health outcomes: an umbrella review of meta-analyses of randomized clinical trials. BMC Med. 2023 May 25;21(1):196. doi: 10.1186/s12916-023-02874-y. PMID: 37231411; PMCID: PMC10210275.

13. Miller VJ, Villamena FA, Volek JS. Nutritional Ketosis and Mitohormesis: Potential Implications for Mitochondrial Function and Human Health. J Nutr Metab. 2018 Feb 11;2018:5157645. doi: 10.1155/2018/5157645. PMID: 29607218; PMCID: PMC5828461.

14. World Health Organisation. Healthy Diet. 2020. Accessed February 2024. https://www.who.int/news-room/fact-sheets/detail/healthy-diet.

15. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis. 2019 Nov;290:140-205. doi: 10.1016/j.atherosclerosis.2019.08.014. Epub 2019 Aug 31. Erratum in: Atherosclerosis. 2020 Jan;292:160-162. Erratum in: Atherosclerosis. 2020 Feb;294:80-82. PMID: 31591002.

16. Public Health England. Eatwell Guide 2016. Accessed February 2024. https://assets.publishing.service.gov.uk/media/5bbb790de5274a22415d7fee/Eatwell_guide_colour_edition.pdf.

17. Muscogiuri G, El Ghoch M, Colao A, Hassapidou M, Yumuk V, Busetto L; Obesity Management Task Force (OMTF) of the European Association for the Study of Obesity (EASO). European Guidelines for Obesity Management in Adults with a Very Low-Calorie Ketogenic Diet: A Systematic Review and Meta-Analysis. Obes Facts. 2021;14(2):222-245. doi: 10.1159/000515381. Epub 2021 Apr 21. PMID: 33882506; PMCID: PMC8138199.

18. Mansoor N, Vinknes KJ, Veierød MB, Retterstøl K. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. Br J Nutr. 2016 Feb 14;115(3):466-79. doi: 10.1017/S0007114515004699. PMID: 26768850.

19. Huntriss R, Campbell M, Bedwell C. The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Eur J Clin Nutr. 2018 Mar;72(3):311-325. doi: 10.1038/s41430-017-0019-4. Epub 2017 Dec 21. PMID: 29269890.

20. Rafiullah M, Musambil M, David SK. Effect of a very low-carbohydrate ketogenic diet vs recommended diets in patients with type 2 diabetes: a meta-analysis. Nutr Rev. 2022 Feb 10;80(3):488-502. doi: 10.1093/nutrit/nuab040. PMID: 34338787.

21. Kirkpatrick CF, Bolick JP, Kris-Etherton PM, Sikand G, Aspry KE, Soffer DE, Willard KE, Maki KC. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: A scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. J Clin Lipidol. 2019 Sep-Oct;13(5):689-711.e1. doi: 10.1016/j.jacl.2019.08.003. Epub 2019 Sep 13. PMID: 31611148.

22. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, Jordan HS, Kendall KA, Lux LJ, Mentor-Marcel R, Morgan LC, Trisolini MG, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014 Jun 24;129(25 Suppl 2):S102-38. doi: 10.1161/01.cir.0000437739.71477.ee. Epub 2013 Nov 12. Erratum in: Circulation. 2014 Jun 24;129(25 Suppl 2):S139-40. PMID: 24222017; PMCID: PMC5819889.

23. Vazquez-Vidal I, Desmarchelier C, Jones PJH. Nutrigenetics of Blood Cholesterol Concentrations: Towards Personalized Nutrition. Curr Cardiol Rep. 2019 Mar 29;21(5):38. doi: 10.1007/s11886-019-1124-x. PMID: 30927095.

24. Jones PJ, Main BF, Frohlich JJ. Response of cholesterol synthesis to cholesterol feeding in men with different apolipoprotein E genotypes. Metabolism. 1993 Aug;42(8):1065-71. doi: 10.1016/0026-0495(93)90024-i. PMID: 8345812.

25. Joo M, Moon S, Lee YS, Kim MG. Effects of very low-carbohydrate ketogenic diets on lipid profiles in normal-weight (body mass index < 25 kg/m2) adults: a meta-analysis. Nutr Rev. 2023 Oct 10;81(11):1393-1401. doi: 10.1093/nutrit/nuad017. PMID: 36931263.

26. Lamarche B, Tchernof A, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, Després JP. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Québec Cardiovascular Study. Circulation. 1997 Jan 7;95(1):69-75. doi: 10.1161/01.cir.95.1.69. PMID: 8994419.

27. Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, Tu JV. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open. 2017 Sep 1;7(9):e016461. doi: 10.1136/bmjopen-2017-016461. PMID: 28864697; PMCID: PMC5588988.

28. Omar A, Fishberg R, Alam L. Ketogenic diets exacerbating hypercholesterolaemia in APOE variants and APOB mutations – potential role for measuring intestinal absorption of lipids. J Clin Lipidol. 2022;16(3)e60-e61.

29. Khovidhunkit W, Hanvivadhanakul P. Hypercholesterolemia exacerbated by a ketogenic diet. J Clin Lipidol. 2021 May-Jun;15(3):523-524. doi: 10.1016/j.jacl.2021.04.009. Epub 2021 May 7. PMID: 34030982.

30. Houttu V, Grefhorst A, Cohn DM, Levels JHM, Roeters van Lennep J, Stroes ESG, Groen AK, Tromp TR. Severe Dyslipidemia Mimicking Familial Hypercholesterolemia Induced by High-Fat, Low-Carbohydrate Diets: A Critical Review. Nutrients. 2023 Feb 15;15(4):962. doi: 10.3390/nu15040962. PMID: 36839320; PMCID: PMC9964047.

31. Hopkins PN, Wu LL, Hunt SC, Brinton EA. Plasma triglycerides and type III hyperlipidemia are independently associated with premature familial coronary artery disease. J Am Coll Cardiol. 2005 Apr 5;45(7):1003-12. doi: 10.1016/j.jacc.2004.11.062. PMID: 15808755.

32. Goldberg IJ, Ibrahim N, Bredefeld C, Foo S, Lim V, Gutman D, Huggins LA, Hegele RA. Ketogenic diets, not for everyone. J Clin Lipidol. 2021 Jan-Feb;15(1):61-67. doi: 10.1016/j.jacl.2020.10.005. Epub 2020 Oct 31. PMID: 33191194; PMCID: PMC7887024.

33. Mahley RW, Huang Y, Rall SC Jr. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia). Questions, quandaries, and paradoxes. J Lipid Res. 1999 Nov;40(11):1933-49. PMID: 10552997.

34. Yang MU, Van Itallie TB. Composition of weight lost during short-term weight reduction. Metabolic responses of obese subjects to starvation and low-calorie ketogenic and nonketogenic diets. J Clin Invest. 1976 Sep;58(3):722-30. doi: 10.1172/JCI108519. PMID: 956398; PMCID: PMC333231.

35. Gomez-Arbelaez D, Bellido D, Castro AI, Ordoñez-Mayan L, Carreira J, Galban C, Martinez-Olmos MA, Crujeiras AB, Sajoux I, Casanueva FF. Body Composition Changes After Very-Low-Calorie Ketogenic Diet in Obesity Evaluated by 3 Standardized Methods. J Clin Endocrinol Metab. 2017 Feb 1;102(2):488-498. doi: 10.1210/jc.2016-2385. PMID: 27754807.

36. Krieger JW, Sitren HS, Daniels MJ, Langkamp-Henken B. Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: a meta-regression 1. Am J Clin Nutr. 2006 Feb;83(2):260-74. doi: 10.1093/ajcn/83.2.260. PMID: 16469983.

37. Adam-Perrot A, Clifton P, Brouns F. Low-carbohydrate diets: nutritional and physiological aspects. Obes Rev. 2006 Feb;7(1):49-58. doi: 10.1111/j.1467-789X.2006.00222.x. PMID: 16436102.

38. Seidelmann SB, Claggett B, Cheng S, Henglin M, Shah A, Steffen LM, Folsom AR, Rimm EB, Willett WC, Solomon SD. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. Lancet Public Health. 2018 Sep;3(9):e419-e428. doi: 10.1016/S2468-2667(18)30135-X. Epub 2018 Aug 17. PMID: 30122560; PMCID: PMC6339822.

39. Heianza Y, Ma W, Manson JE, Rexrode KM, Qi L. Gut Microbiota Metabolites and Risk of Major Adverse Cardiovascular Disease Events and Death: A Systematic Review and Meta-Analysis of Prospective Studies. J Am Heart Assoc. 2017 Jun 29;6(7):e004947. doi: 10.1161/JAHA.116.004947. PMID: 28663251; PMCID: PMC5586261.

40. Tacconi E, Palma G, De Biase D, Luciano A, Barbieri M, de Nigris F, Bruzzese F. Microbiota Effect on Trimethylamine N-Oxide Production: From Cancer to Fitness-A Practical Preventing Recommendation and Therapies. Nutrients. 2023 Jan 21;15(3):563. doi: 10.3390/nu15030563. PMID: 36771270; PMCID: PMC9920414.

41. Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ, Engler MM, Engler MB, Sacks F. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. Circulation. 2009 Feb 17;119(6):902-7. doi: 10.1161/CIRCULATIONAHA.108.191627. Epub 2009 Jan 26. PMID: 19171857.