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ABSTRACT

Introduction The ketogenic diet is a very low carbohydrate diet known for its ability to reduce weight and counteract hyperglycaemia. However, ketogenic diets recommend an increased intake of fats, raising concerns about cardiometabolic risk in adults. Due to the higher intake of fats in the ketogenic diet, there is significant variability in outcomes of lipid metabolism in the population. Interventions have reported improvements in lipid profile while other studies did not find changes, and there are reports of increased low density lipoprotein (LDL) and triglyceride values. Hence, this is a protocol for a systematic review of the published literature and a summary of the effect of ketogenic diets on lipid metabolism in adults.

Methods and analysis Five databases (PubMed, Embase, Scopus, Cochrane Library and Web of Science) will be searched for studies on ketogenic diets in adult populations. Studies will be included if they report results from ketogenic diet interventions among adults. Exclusion is populations with diagnosed neurological disorders. Two reviewers will independently screen retrieved citations, extract data and appraise the risk of bias. Quantitative estimates (eg, standardised mean difference) measuring the change in the total cholesterol, LDL and triglyceride concentration will be pooled using random effects meta-analysis to produce one summarised weighted estimate. Sources of heterogeneity will be explored using subgroup analysis. This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols (PRISMA), and the final review will be reported following the PRISMA 2020 guidelines.

Ethics and dissemination The present protocol and the systematic review to be carried out do not require ethics clearance. The data source will be published studies. This review will provide estimates to inform the public about the effect of ketogenic diets on lipid metabolism and the possible peril of increasing cardiometabolic risk. The results will be published in a peer-reviewed journal.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The evidence will be extracted through a comprehensive and systematic search in five biomedical databases.
⇒ Two authors will independently select and extract data from studies, reducing bias and improving the accuracy and reliability of data extraction.
⇒ The Covidence systematic review software will be used for screening, conflict resolution, extraction and quality assessment by three independent reviewers.
⇒ Limitations include an English language bias and the exclusion of grey, non-peer-reviewed studies.

INTRODUCTION

The increasing prevalence of obesity in industrialised nations has led to a corresponding rise in cardiovascular diseases.[1 2] Additionally, obesity is a primary risk factor for insulin resistance and type 2 diabetes.[3] Insulin resistance frequently results in ectopic lipid accumulation, particularly in the liver and skeletal muscle, which can cause non-alcoholic fatty liver disease (NAFLD).[4] NAFLD is a standalone predictor of cardiovascular disease and is characterised by steatosis that does not stem from excess alcohol consumption, viral or autoimmune causes, or iron overload.[5] Because NAFLD is present in nearly 90% of obese patients, weight loss is one of the primary treatments supported by other interventions such as physical activity.[6] NAFLD also increases the risk of developing insulin resistance and type 2 diabetes, which may coincide with other cardiovascular risk factors, including dyslipidaemia and hypertension. Hence, one of the most significant and challenging issues is the management of obesity. Weight loss is recommended as a therapeutic approach to managing metabolic syndrome components.[6]

Diets that contain high levels of carbohydrates are linked to metabolic syndrome. Various diets have been suggested to achieve weight loss, with carbohydrate restriction being the most effective intervention for reducing all metabolic syndrome features. The ketogenic diet was first described as a

dietary treatment for epilepsy in the 1920s.[7] However, with the advancement of antiepileptic drugs and their widespread use, the clinical use of the ketogenic diet for epilepsy has significantly diminished. Ketogenic diets are typically low in carbohydrates but high in fats and/or proteins.[8 9] Practically, ketogenic diets involve reducing carbohydrate intake to less than 50 g/day and increasing the proportion of proteins and fats. Some variations of the ketogenic diet, such as very low-carbohydrate diets, are even more restrictive, with less than 30 g of carbohydrates per day.[9]

Numerous studies have found that ketogenic diets effectively manage obesity by reducing human food intake and producing a higher metabolic burn than high-carb diets.[10–13] In humans, ketogenic diets result in weight loss from fat and lean mass. However, evidence from animal studies suggests that ketogenic diets increase the fat mass percentage compared with regular-chow diets, with decreased or no effect on lean mass.[14 15] Ketogenic diets are considered to be beneficial for type 2 diabetes, a chronic condition closely linked to obesity and NAFLD, despite reports that ketogenic diets, due to high-fat content, can cause insulin resistance. Studies have found that ketogenic diets induce insulin resistance and glucose intolerance in animal models despite reducing glucose and insulin levels.[16 17] In humans with type 1 diabetes mellitus, the ketogenic diet is associated with dyslipidaemia[18 19] and hypoglycaemic episodes,[20] despite excellent glycated hemoglobin (HbA1c) levels[21] and minimal glycaemic variability.[22]

Many studies have investigated the impact of ketogenic diets on serum lipid profiles. In a study of 20 normal-weight men with normal lipid profiles, a 6-week ketogenic diet significantly reduced fasting serum triglycerides, postprandial lipidaemia and fasting serum insulin concentrations while increasing high density lipoprotein (HDL).[23] However, the diet did not affect fasting serum total and low density lipoprotein (LDL) or oxidised LDL. These findings suggest that a short-term ketogenic diet does not worsen cardiovascular disease risk profiles and may improve dyslipidaemia. Another report found that a higher proportion of protein to carbohydrate in the ketogenic diet could also benefit serum lipids and promote weight loss.[24] However, reports that prescribing a ketogenic diet for at least 12 months significantly increased serum total and LDL cholesterol and triglyceride[25 26] levels muddy the waters.

Furthermore, another study found that a 6-month ketogenic diet significantly increased median triglycerides, total cholesterol, LDL and HDL, indicating that it may also lead to hypercholesterolaemia and hypertriglyceridaemia.[27] Given that ketogenic diets are high in lipids, concerns regarding the potential risk of elevated levels of lipids, including serum total and LDL cholesterol and triglycerides, are reasonable. While some studies suggest that ketogenic diets benefit lipid profiles, others indicate the opposite, possibly due to differences in diet composition between animal and human studies. Therefore, while the ketogenic diet is an ideal approach to managing cardiometabolic risk factors associated with obesity, caution should be exercised regarding the potential safety concerns related to the diet, given the conflicting evidence. A comprehensive analysis of the available evidence is needed to address these concerns. Therefore, this systematic review and meta-analysis aims to examine the current evidence on the effects of ketogenic diets on lipid metabolism. By assessing the current evidence on ketogenic diets in modulating lipid profiles, this review seeks to provide clearer insights into the safety and efficacy of this dietary approach in managing cardiometabolic risk factors associated with obesity.

OBJECTIVES

This systematic review aims to answer the question: 'What is the effect of ketogenic diets on adult lipid metabolism? Does it increase the risk of cardiometabolic risk? Does it increase circulating lipid profile?' and if so, 'What subgroup of adults are more likely to be negatively affected by ketogenic diet interventions?'.

METHODS AND ANALYSIS

This study protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines[28] and is registered in the International Prospective Register of Systematic Reviews. The reporting checklist for PRISMA-P is provided as online supplemental file 1. Any changes made to this protocol will be documented in the PROSPERO registration. The study is scheduled to commence in June 2023 and conclude by May 2024. An online supplemental file contains a copy of the PRISMA-P checklist. The Cochrane Handbook for Systematic Reviews of Interventions will inform the final review, which will be reported according to the latest PRISMA 2020 statement.[29]

Eligibility criteria

Population

Adult population aged 18 years or older. Participants may be healthy or presenting with cardiometabolic factors such as obesity, type-2 diabetes, dyslipidaemia or hypertension. Studies primarily focused on participants with neurological disorders or athletes will be excluded.

Intervention

Ketogenic diet interventions or diets with very low carbohydrates (≤10% carbohydrate composition). Interventions with exogenous ketones and exercise will be excluded.

Comparison

Control diets or baseline data from the same intervention.

Outcomes

Primary outcomes

Changes in the mean serum biochemical markers of study subjects exposed to a ketogenic diet compared with those who were not exposed to the diet. The serum biochemical markers of interest include HDL, LDL, total cholesterol, triglycerides, apolipoprotein B, lipoprotein A, lipoprotein lipase, hormone-sensitive lipase, leptin and adiponectin.

Secondary outcomes

Changes in anthropometric indices such as body weight, alterations in blood pressure and other serum biochemical markers such as glucose and insulin.

Type of studies

Peer-reviewed randomised controlled trials, non-randomised controlled trials, pre–post intervention studies and non-randomised studies of the intervention. Studies to be included should provide quantified or quantifiable data on the difference in lipid metabolism between the two comparison groups, that is, those exposed to the ketogenic diet and those who are not. Non-peer-reviewed studies (conference papers, letters, editorials, opinions, conference abstracts and preprints), animal studies, in vitro studies, preclinical studies, case reports, cohort studies and cross-sectional studies will be excluded.

Information sources

Our literature search will cover the electronic databases PubMed (NLM), Embase (Elsevier), Scopus (Elsevier), Cochrane Library (Cochrane Collaboration) and Web of Science (Clarivate). We will search all databases from their inception to June 2023. Before the manuscript submission, we will conduct a full search update to ensure that the most current and relevant studies are included.

Search strategy

A comprehensive and systematic search strategy was developed by a medical librarian (LÖ) and reviewed by subject specialists (SH, CP and LS) to identify relevant studies for the review. As outlined previously, the search terms were based on population, intervention, comparison and outcome (PICO) and the study's inclusion and exclusion criteria. The search strategy was refined using PubMed and PubMed's MeSH during the presearch phase from June 2022 to April 2023. The search strategy developed in PubMed will be used in all selected databases without filters for publication year, species or language. The search terms will be searched in a combination of fields such as 'Title,' 'Abstract' and 'Keywords,' as well as in the MeSH/Thesaurus (if available). To ensure transparency and reproducibility, a search log containing all search technical details, search term inclusion, results, dates and notes for all searches will be appended to the review. The search strategy developed through presearches in PubMed can be found in online supplemental file 2. In addition, the final review will include a search log containing notes, results and details for the searches in all included databases and a[29] flow diagram outlining the details of the search and screening process.[29] Finally, a search update in all databases will be conducted before finalising the manuscript to ensure the inclusion of relevant studies published after the initial search. In all cases, Cabell's predatory report will be consulted to ensure the academic status of the finally selected papers published in open-access journals.[30]

Study records

Data management

All records identified in the database search will be uploaded to the Covidence systematic review software for automatic deduplication, blinded screening, conflict resolution, study selection and data extraction. On identifying studies for inclusion in the review, they will be exported to the reference management tool, EndNote.

Selection process

The selection process in Covidence will adhere to the PRISMA workflow. Initially, four independent reviewers (OA, FA, SH and CP) will screen the titles and abstracts of all identified papers based on the predetermined inclusion and exclusion criteria. Any conflicts identified by the software will be resolved by a third reviewer (LS). Following this, SH and CP will independently review the full texts of papers identified as potentially eligible during the title and abstract screening. Any reasons for exclusion will be documented based on the preset study exclusion criteria imported to Covidence. LS will resolve any conflicting exclusion reasons or paper inclusion/exclusion with the assistance of the software. Only studies that meet the inclusion criteria will undergo a thorough screening for data extraction. The screening and selection process results will be recorded in a PRISMA flow diagram.

Data extraction (selection and coding)

The Covidence extraction module will be used to ensure the study objectives are met. Two independent reviewers (SH and CP) will extract data from the final studies that meet the eligibility criteria for inclusion in the review. Discrepancies between the reviewers will be resolved by a third reviewer (LS) through discussion until a consensus is reached. The extracted data will include basic publication characteristics such as authors, year of publication, journal, country, study design, population and intervention duration. Primary variables of interest will be collected, including HDL, LDL, total cholesterol, triglycerides, lipoprotein lipase, hormone-sensitive lipase, apolipoprotein B and lipoprotein A. Population characteristics such as age, gender, smoking habits, body composition, weight, body mass index, serum glucose

and insulin data, blood pressure, physical activity and dietary parameters will also be extracted for analysis. If additional data are needed, the corresponding author of the included papers will be contacted via email.

Risk of bias in individual studies

Two independent reviewers (SH and CP) will evaluate the risk of bias and quality of evidence in the studies included in this review. The methodology of each study will be critically assessed to identify potential biases related to attrition, publication, outcome or conclusion. The quality of evidence for each outcome will be appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. The assessment process will use appropriate tools for the study design (eg, RoB 1 for non-randomised controlled trials and RoB 2 for randomised controlled trials). The reviewers will base their evaluation on the rigour of the research methodology implemented in each study. In the case of disagreements or discrepancies, a third reviewer (LS) will be consulted until a consensus is reached. Any systematic differences in baseline characteristics between the groups compared in a study will be discussed in the review's conclusion.

Data synthesis

We will create a comprehensive table to summarise the PICO characteristics of each study, including all relevant interventions and outcomes.

Meta-analysis

Using the random-effect meta-analysis, the extracted standardised mean differences in the outcomes of interest between the exposed and non-exposed population or baseline to end of intervention will be combined to produce one weighted summarised estimate. Heterogeneity between studies will be measured via I^2 statistics and Cochran's Q test. An I^2 greater than 50% will indicate substantial heterogeneity or a p value of 0.10 or less for the Q test.

Subgroup and sensitivity meta-analyses

We will provide a narrative summary of the findings for outcomes that cannot be pooled. Subgroup analyses will be conducted on the study population based on diet characteristics and cardiometabolic factors, including age, gender, smoking, type-2 diabetes, insulin resistance, obesity, hypertension and physical activity. The robustness of the pooled results will be explored after removing trials with high and moderate risk of bias.

Publication bias

Potential publication bias will be assessed using funnel plots and by conducting Egger's test. Review Manager software, V.5.3, or Stata software, V.16.0, will be used for quantitative data syntheses.

Strength of evidence

We will use the GRADE tool to determine the strength of evidence, including publication bias, indirectness, inconsistencies, imprecision and risk of bias. The quality of each study will be assessed by two independent reviewers (SH and CP), and any potential conflicts will be resolved by a third independent reviewer (LS).

Patient and public involvement

No patient or members of the public will be included in the performance of this study.

DISCUSSION

Metabolic syndrome is a growing health concern, strongly associated with cardiovascular disease and mortality. Weight management is a primary recommendation for managing this condition, and ketogenic diets have emerged as a potential dietary intervention to manage obesity-related cardiometabolic risks. However, due to the uncertainty of dietary interventions, there is an ongoing debate regarding the safety and drawbacks of employing ketogenic diets. While some studies have shown promising results, the clarity on how ketogenic diets influence human lipid metabolism remains unclear. This systematic review aims to identify the potential cardiometabolic risks that arise due to the modulation of lipid metabolism associated with ketogenic diet intervention in adult populations. Specifically, we will evaluate the effect of ketogenic diets on lipid metabolism, including HDL, LDL, total cholesterol, triglycerides, lipoprotein lipase, hormone-sensitive lipase, apolipoprotein B and lipoprotein A. This systematic review is underpinned by several methodological strengths, including a comprehensive literature search across multiple medical databases without restrictions on publication year, ensuring a thorough and inclusive review of available literature. The review process is further bolstered by a rigorous study selection and data extraction procedure conducted independently by two authors, which minimises bias and enhances the reliability of the findings. Adherence to the PRISMA guidelines for the review's protocol and reporting phases ensures high methodological rigour and transparency. However, the methodology is not without limitations. The language restriction of published literature to English excludes relevant evidence in other languages.

However, including other languages poses significant challenges for the team in accurately interpreting studies in unfamiliar languages. In addition, by excluding studies involving populations with diagnosed epilepsy, the review may overlook the potentially significant effects of the ketogenic diet in these groups. Since ketogenic diets have been studied extensively for this condition, this exclusion could limit the understanding of the diet's broader applicability. To address the effect of the ketogenic diet on lipid metabolism, excluding this population was considered the better strategy because the overall outcomes

of ketogenic diet intervention in this population are not aligned with our review's purpose. Additionally, the wide-ranging inclusion criteria for the adult population may lead to significant heterogeneity among the studies, potentially complicating the synthesis of findings and drawing generalised conclusions. This limitation can be addressed through subgroup analysis, which can help understand sources of heterogeneity. In conclusion, this review will summarise existing findings to synthesise their data to answer whether ketogenic diets increase cardiometabolic risk in adult populations, which is strongly associated with increased mortality. The results of this review will inform clinical practice and guide future research in this area.

Ethics and dissemination

Ethics approval is not typically required as systematic reviews involve analysing and synthesising data from already published studies. Our review will follow established ethical principles, including the use of published data. We intend to publish our review in a peer-reviewed journal, ensuring the findings are available to the scientific community and the public.

Potential amendments

We do not plan to make any changes to the protocol. However, if minor amendments are made during the research process, those will be transparently recorded in the online PROSPERO registration to avoid publication bias.

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Contributors SH, CP and LS were involved in all study aspects, from conceptualisation, protocol development and the preliminary search strategy. LÖ developed the preliminary search strategy, contributed with text for the methods part of the manuscript and will conduct the final literature search and the reference management in Covidence. OA, FA, SH, CP, HIA, LCI and ASAD will carry out further literature screening and data extraction, and data will be validated by LS. The protocol manuscript was written by OA, FA, SH, CP and LÖ. LS, HIA, LCI, RHA-R and ASAD revised the draft for intellectual content and will assist with drafting and revising content in the final project. RHA-R will oversee the data extraction process and complete all aspects of the data analysis.

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