



**ΔΗΜΟΚΡΙΤΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΡΑΚΗΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ**

«Κετογονικές δίαιτες και ο αντίκτυπός τους στην καρδιαγγειακή υγεία»

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Αλεξανδρούπολη, 2025



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**ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ:
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MASTER DISSERTATION

«Ketogenic diets and their impact on cardiovascular health»

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A thesis submitted in partial fulfilment of the requirements for the degree of Master in Health Sciences, Department of Medicine, Democritus University of Thrace

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Abbreviations

BHB	Beta-Hydroxybutyrate
BMI	Body Mass Index
BP	Blood Pressure
WC	Waist Circumference
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
CVR	Cardiovascular Risk
DBP	Diastolic Blood Pressure
FBS	Fasting Blood Sugar
GABA	Gamma-Aminobutyric Acid
HDL	High-Density Lipoprotein
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
IHD	Ischemic Heart Disease
IR	Insulin Resistance
KD	Ketogenic Diet
LDL	Low-Density Lipoprotein
NIH	National Institutes of Health
PICO	Population, Intervention, Comparator, Outcome
WHR	Waist-to-Hip Ratio
SBP	Systolic Blood Pressure
TC	Total Cholesterol
TG	Triglycerides
TNF-α	Tumor Necrosis Factor-alpha

Abstract

Objective: The aim of this study is to investigate the potential association of ketogenic dietary patterns and their effects on cardiovascular risk factors.

Methods: Following the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, a systematic review of the literature from 2014 to 2024 was conducted in the Pubmed and Scopus search databases. Eligible studies included Randomized Controlled Trials (RCTs) and Cross-over trials examining the effects of ketogenic diet interventions in adults (≥ 18 years), either healthy or with metabolic syndrome components, compared to control populations adhering to other dietary models. Specifically, biomarkers related to lipid and glycemic profiles, as well as secondary factors such as body composition and blood pressure, were evaluated.

Results: A total of 843 studies were screened, from which 26 RCTs were selected for final evaluation, encompassing 1584 individuals. These studies examined the effect of the ketogenic diet on cardiovascular risk factors. The majority ($>80\%$) demonstrated beneficial outcomes, showing significant improvements in cardiovascular risk parameters compared to control groups. In addition, most studies associated ketogenic diet with beneficial changes in body composition. However, the diet was also linked to increases in certain cardiovascular risk factors (such as low-density lipoprotein cholesterol). Furthermore, the ketogenic diet was also associated with a higher incidence of adverse effects and challenges in adherence compared to other dietary interventions.

Conclusions: Ketogenic diet showed beneficial results in improving cardiovascular risk factors and body composition when compared to alternative dietary approaches. However, in some cases, the ketogenic diet had the opposite effect, worsening cardiovascular risk factors or causing adverse effects. Further research is needed to clarify the long-term impact of the ketogenic diet.

Keywords: Ketogenic diet; cardiovascular risk; lipid profile; blood pressure; metabolic syndrome; randomized controlled trial; systematic review.

Περίληψη

Σκοπός: Σκοπός αυτής της μελέτης είναι να διερευνήσει τη πιθανή συσχέτιση των κετογονικών διατροφικών προτύπων και τις επιπτώσεις τους στους παράγοντες καρδιαγγειακού κινδύνου.

Μέθοδοι: Ακολουθώντας τις κατευθυντήριες γραμμές PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), πραγματοποιήθηκε μια συστηματική ανασκόπηση της βιβλιογραφίας από το 2014 έως το 2024 στις βάσεις δεδομένων αναζήτησης Pubmed και Scopus. Οι επιλέξιμες μελέτες περιελάμβαναν Τυχαιοποιημένες Ελεγχόμενες Δοκιμές (RCTs) και διασταυρούμενες δοκιμές που εξέταζαν τα αποτελέσματα των παρεμβάσεων κετογονικής διαίτας σε ενήλικες (≥ 18 ετών), είτε υγιείς είτε με χαρακτηριστικά μεταβολικού συνδρόμου, σε σύγκριση με πληθυσμούς ελέγχου που συμμορφώνονται με άλλα διατροφικά μοντέλα. Συγκεκριμένα, αξιολογήθηκαν βιοδείκτες που σχετίζονται με τα λιπιδικά και γλυκαιμικά προφίλ, καθώς και δευτερογενείς παράγοντες όπως η σύσταση του σώματος και η αρτηριακή πίεση.

Αποτελέσματα: Ελέγχθηκαν συνολικά 843 μελέτες, από τις οποίες επιλέχθηκαν 26 RCTs για τελική αξιολόγηση. Αυτές οι μελέτες, περιελάμβαναν 1584 άτομα και εξέτασαν την επίδραση της κετογονικής διαίτας στους παράγοντες καρδιαγγειακού κινδύνου. Η πλειοψηφία ($>80\%$) έδειξε ευεργετικά αποτελέσματα, παρουσιάζοντας σημαντικές βελτιώσεις στις παραμέτρους καρδιαγγειακού κινδύνου σε σύγκριση με τις ομάδες ελέγχου. Επιπλέον, η κετογονική διαίτα συσχετίστηκε με ευεργετικές αλλαγές στη σύσταση του σώματος στις περισσότερες μελέτες. Ωστόσο, η διαίτα συνδέθηκε επίσης με αυξήσεις ορισμένων παραγόντων καρδιαγγειακού κινδύνου, όπως η χαμηλής πυκνότητας λιποπρωτεΐνη χοληστερόλη (LDL). Επιπλέον, η κετογονική διαίτα συσχετίστηκε με υψηλότερη συχνότητα εμφάνισης ανεπιθύμητων ενεργειών και προκλήσεων στην συμμόρφωση με την διατροφική παρέμβαση, σε σύγκριση με άλλες διατροφικές παρεμβάσεις.

Συμπεράσματα: Η κετογονική διαίτα έδειξε ευεργετικά αποτελέσματα στη βελτίωση των παραγόντων καρδιαγγειακού κινδύνου και της σύστασης του σώματος σε σύγκριση με εναλλακτικές διατροφικές προσεγγίσεις. Ωστόσο, σε ορισμένες περιπτώσεις, η κετογονική διαίτα είχε το αντίθετο αποτέλεσμα, επιδεινώνοντας τους καρδιαγγειακούς παράγοντες κινδύνου ή προκαλώντας δυσμενείς επιπτώσεις. Απαιτείται περαιτέρω έρευνα για να αποσαφηνιστεί ο μακροπρόθεσμος αντίκτυπος της κετογονικής διαίτας.

Λέξεις-κλειδιά: Κετογονική διαίτα; καρδιαγγειακός κίνδυνος; λιπιδαιμικό προφίλ; αρτηριακή πίεση; μεταβολικό σύνδρομο; τυχαιοποιημένη κλινική δοκιμή; συστηματική ανασκόπηση.

Introduction

Mediterranean Diet declaration by UNESCO as a Cultural Heritage

The declaration of the Mediterranean diet by UNESCO as "UNESCO's Intangible Cultural Heritage of Humanity" in 2010 was a significant event of crucial importance (Trichopoulou, 2021). The diet followed in places such as Greece, Cyprus, Italy, Morocco, Croatia and Portugal (UNESCO, 2013) has been studied more extensively since the 1960s and has been linked to good health, longevity, and good cardiovascular function (Bloomfield et al., 2016; Martinez-Gonzalez & Martín-Calvo, 2016). Since the declaration by UNESCO, research and commercial interest regarding this dietary model has increased exponentially (Ingrassia et al., 2023). More specifically, of the 13.001 peer-reviewed publications reporting on the Mediterranean Diet, 9.409 occurred after its recognition by UNESCO (Trichopoulou, 2021). This extensive research activity has resulted in a multidimensional and more extensive understanding of this diet, and its health benefits which largely seem to stem from its antioxidants (Gualtieri et al., 2023; Kapciak et al., 2024) and anti-inflammatory effects (Quetglas-Llabrés et al., 2023).

The example of the Mediterranean diet demonstrates how a dietary model can gain particular recognition and research interest in terms of its clinical benefits even many years after its initial period of application and research. Therefore, not only the KD, which is the dietary model under investigation in this study, but any dietary model that appears to have positive effects on health and disease prevention is particularly important to be extensively studied and researched, because, through the research conducted, the foundations are laid for holistic and efficient data collection, which may contribute to the future identification of dietary models with remarkable human health outcomes.

Dietary Patterns and Diet Plans

In the context of the analysis of the Mediterranean diet, it is important to note that dietary patterns, such as the Mediterranean diet, the Japanese diet, etc., have been associated not only with the consumption of specific food categories, but also with cultural heritage, social factors and, in general, a complex of habits and general lifestyle (De Cosmi et al., 2022). A short-term eating plan or diet usually refers to a diet plan with a specific goal (e.g. weight loss, cholesterol reduction) for a limited period of time. In contrast, a dietary pattern is a way of eating that can be followed in the long term and is based on a specific metabolic mechanism. Both influence health, but dietary patterns are broader and shaped by various social and individual factors (Skeaff, 2023).

Mediterranean and Ketogenic Diet

The ketogenic diet (KD) comprises several distinct types that will be analyzed in detail later. (Barzegar et al., 2021; Mohammadifard et al., 2022). The basic principle of this dietary model involves the consumption of low carbohydrates with moderate consumption of protein and high consumption of fat (Malhotra & Sawal, 2023). In this context, the KD, as a nutritional model, is not restrictive and can be combined with the principles and staple foods of the Mediterranean diet. In a related study conducted with

a sample of 40 subjects, the combination of ketogenic and Mediterranean diet yielded positive results in terms of weight loss, promoting non-atherogenic lipid profiles, lowering blood pressure, and improving fasting blood glucose levels (Pérez-Guisado et al., 2008). This study used the principles of the KD in terms of reduced carbohydrate intake and four staple foods of the Mediterranean diet (olive oil, wine, fish, and vegetables). Thus, the combination of the two dietary models, when applied, maintains the low-carbohydrate consumption principle of the KD, while ensuring that fat intake is derived from high-quality sources of polyunsaturated fatty acids, the hallmark of the Mediterranean diet, along with its numerous antioxidant-anti-inflammatory benefits (Gualtieri et al., 2023; Kapciak et al., 2024; Quetglas-Llabrés et al., 2023).

1.1. Ketogenic Diet

Historical Overview

The term “*ketogenic diet*” was coined by Russell Morse Wilder, who observed that ketones (a class of organic compounds containing the characteristic carbonyl group in their chain) were produced in epileptic children, to whom he had previously suggested the administration of this form of diet. This particular diet was designed to mimic the biochemical effects of fasting, through the production of ketones by the liver, with one of its most frequent compositions being suggested by Peterman in 1925 (Peterman, 1925): 1 g of protein per kg (of body weight in children), 10-15 g of carbohydrate, and the remaining calories to be obtained from fat. As a therapeutic intervention for the treatment of epilepsy, fasting was used according to reports from 500 BC, and this knowledge led to the formulation of the KD as a model that patients could follow for longer periods. Around the 1920s, the frequent use of this dietary pattern led to a large decrease in the use of anti-epileptic drugs in the coming decades (Wheless, 2008). Subsequently, advances in anti-epileptic drugs led to a gradual reduction in the use of ketogenic diets in the last decades.

Different variations of this dietary pattern are administered to patients with epilepsy, including children, with potentially significant results in drug-tolerant epilepsies (Karoń et al., 2024). The KD, which, as already mentioned, mimics the metabolic state of fasting, is linked to a reduction in seizure occurrence through several proposed mechanisms, such as alterations in neurotransmitter levels and improved energy metabolism (McDonald & Cervenka, 2018). This particular dietary pattern also increases ketone bodies and polyunsaturated fatty acids, enhancing brain energy and reducing neuronal excitability. Consequently, it stimulates the production of inhibitory neurotransmitters like gamma-aminobutyric acid (GABA), stabilizes synaptic function, and provides neuroprotection by safeguarding nerve cells from damage (Verrotti et al., 2020). A systematic review that included eight studies involving 1330 children with refractory epilepsy revealed that 54% experienced seizure reduction and 17% became seizure-free within one month of starting a KD, demonstrating its efficacy in managing epilepsy (Araya-Quintanilla et al., 2016). However, the same study found minimal differences between the different types of KD, highlighting that the choice of the KD type should heed individual factors and patient needs.

In this setting, a systematic review and meta-analysis investigating the efficiency of this diet plan on the management of epilepsy in infants showed that 69% of infants with epilepsy experienced a $\geq 50\%$ reduction in seizure frequency after three months, while 36% were seizure-free. Treatment duration ranged from 84% at 3 months to 27% at 24 months. It is worth noting that the most common adverse events observed in this analysis included dyslipidemia (12%), vomiting (6%), constipation (4%), and gastroesophageal reflux (4%) (Lyons et al., 2020). Such findings, underline that this dietary pattern is often difficult for patients to follow, and can lead to serious adverse effects, deficiencies, or even an increase in harmful health factors (such as triglycerides and LDL-cholesterol) (Batch et al., 2020; Karoń et al., 2024) Therefore, in contrast to what may be a popular belief, it is advised that the KD should only be adopted for its therapeutic benefits following thorough medical consultation and supervision.

Given its documented benefits, the KD has also been examined in the setting of other neurological diseases such as Alzheimer's disease and Parkinson's disease (Gasior et al., 2006; VanItallie et al., 2005), while current investigations target a multitude of other aspects of health such as the effect on the microbiome, the epigenome, diabetes, weight loss, cardiovascular health, and cancer (Dowis & Banga, 2021).

Mechanism of Action

The ketogenic diet (KD) is characterized by high fat intake, low carbohydrate consumption, and moderate protein intake (Malhotra & Sawal, 2023). As opposed to what a carbohydrate-based diet would lead to, i.e. glycolysis, the primary aim of this plan is to induce a metabolic state called ketosis. Ketosis is a metabolic state in which the body, due to reduced carbohydrate intake and hence the low availability of glucose (the main source of energy), shifts to using fat as the primary source of energy (Masino & Rho, 2012) (Zhu et al., 2022). As such, KD functions by reducing the intake of carbohydrates and therefore glucose levels (availability). A significant reduction of carbohydrates in the diet causes blood glucose and insulin levels to decline (Williams et al., 2024). This induced hypoglycemic state triggers the activation of lipolysis (the process by which stored fat is broken down to meet the body's energy demands), while fatty acids released from fat are converted into ketone bodies in the liver through ketogenesis. Through this mechanism, ketone bodies are produced as byproducts.

The main ketone bodies (Figure 1: Structure of ketone bodies) are β -hydroxybutyrate (BHB), acetoacetate (AcAc), and acetone. These molecules can serve as an alternative energy source for the brain and other tissues, replacing glucose effectively (Masino & Rho, 2012; Tyminski, 2024).

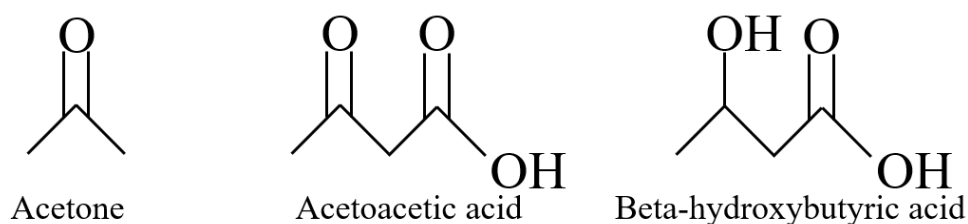


Figure 1: Structure of ketone bodies

The process consists of the stages described, in a simplified form, below:

- **Reduced carbohydrate intake:** Reduction of carbohydrates in the diet induces blood glucose levels to decrease. This consequently leads to decreased levels of insulin, a hormone responsible for storing glucose and using it as an energy source.
- **Fat degradation:** In the absence of sufficient glucose and low levels of insulin, lipolysis (the process of breaking down stored fat to produce energy) is triggered. The fatty acids released from this process are transported to the liver.
- **Production of ketone bodies:** In the liver, fatty acids are broken down through beta-oxidation to produce ketone bodies:
 - B-hydroxybutyrate (BHB): The primary ketone body circulating in the blood.
 - Acetoacetate (AcAc): another ketone body that can be converted to BHB or degraded to acetone.
 - Acetone: Formed through the spontaneous breakdown of acetoacetate and excreted primarily via respiration and urine.

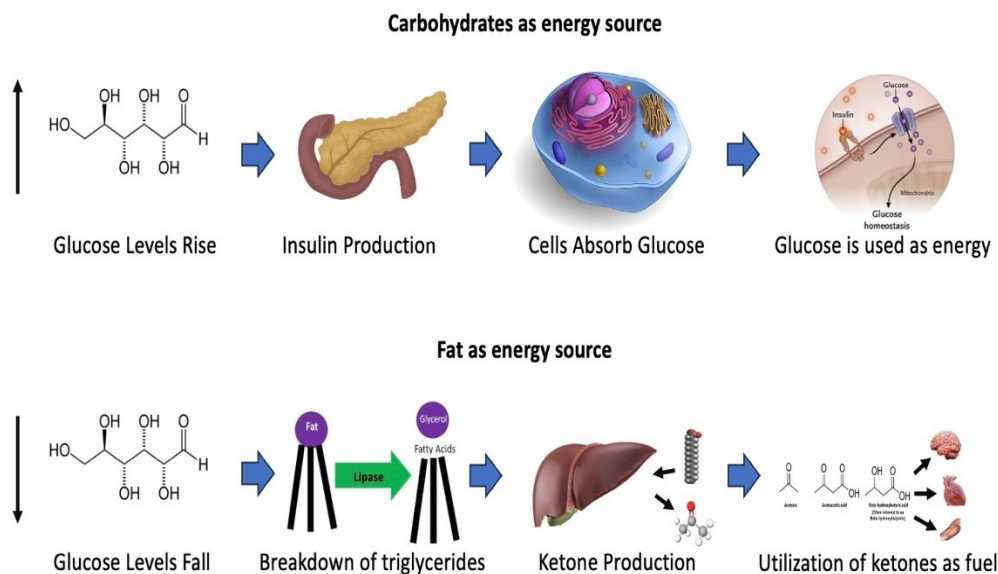


Figure 2 Fat as an energy source

Among the key features of the KD is the utilization of ketone bodies as an alternative fuel source. Ketone bodies are transported through the bloodstream to various tissues, such as muscles and the brain, where they are used as an alternative energy source, replacing glucose. BHB, for example, can cross the blood-brain barrier and be utilized as an energy source for brain cells (Jensen et al., 2020). The reduction in glucose and glycogen stores during ketosis further promotes the production of ketone bodies, as glycogen depletion triggers lipolysis and, consequently, ketogenesis (Masino & Rho, 2012). Under physiological conditions, the plasma concentration of ketone bodies remains low but can be significantly increased by KD, providing an efficient energy source without compromising mitochondrial function (Branco et al., 2016).

Ketogenic diet Types

The KD encompasses several variations, distinguished by the distribution of the macronutrients that define each dietary pattern. The percentage of carbohydrates, which are generally low, protein, and fats, determines the type of KD. (Barzegar et al., 2021; Mohammadifard et al., 2022)

Table 1 Different types of ketogenic diet (KD)

KD Type	Carbohydrate	Protein	Fat
	Macronutrient Proportion (% of Total Energy)		
Classic	4	6	90
Low Glycemic Index Treatment	28	28	43
Very Low-Calorie Ketogenic Diet	13	43	44
Medium-Chain-Triglyceride	13	10	73
The Modified Atkins Diet	5	30	65

It has been well-established that the effects of KD might vary by its composition and type of macronutrients (Dhamija et al., 2013). This dietary pattern has demonstrated beneficial results for numerous health conditions such as seizures, cancer, and cardiovascular disease (CVD). KD composition plays a major role in its therapeutic potential (Kayode et al., 2020). However, increased saturated fat consumption could raise health-related concerns, particularly related to the elevation of LDL cholesterol levels (Crosby et al., 2021).

Classic Ketogenic Diet

As mentioned in Historical Overview the classic ketogenic diet (KD) was first described by Russell Morse Wilder in 1921 as a therapeutic diet for drug-resistant epilepsy in which 80-90% of calories come from fat, mainly long-chain triglycerides (LCTs). The typical ratio of fat to carbohydrate + protein is 4:1, but this can be reduced to 3.5:1 or 3:1 in children with increased protein requirements (Barzegar et al., 2021).

Low Glycemic Index Treatment

The Low Glycemic Index Treatment (LGIT), introduced in 2005, is an alternative dietary approach to drug-resistant epilepsy (Pfeifer & Thiele, 2005) that restricts carbohydrates to foods with a low glycemic index (<50), such as meat, dairy products, certain fruits, and whole grains. The literature suggests that it is easier to implement and more palatable than the classic ketogenic diet, with similar efficacy (Barzegar et al., 2021; Pfeifer et al., 2008).

Very Low-Calorie Ketogenic Diet

The Very Low-Calorie Ketogenic Diet (VLCKD) is a hypocaloric ketogenic diet used to treat obesity, typically providing 600-800 kcal/day. It is characterized by a very low carbohydrate intake (<50g/day), high protein and moderate fat, which promotes weight loss and improves metabolic parameters (Gorini et al., 2023). The very low percentage of calories and carbohydrates makes them difficult to follow and increases the need for monitoring by health professionals, recording of micronutrient intake and frequent monitoring.

Medium-Chain-Triglyceride

The medium-chain triglyceride diet (MCTD), introduced in the 1950s, is an alternative ketogenic diet for drug-resistant epilepsy in children. It is based on medium-chain triglycerides (MCTs), mainly octanoic (C8) and decanoic (C10) acids, which produce more ketones per kcal and are more rapidly absorbed by the liver (Barzegar et al., 2021). Due to its high ketogenic potential, it allows for more carbohydrate and protein intake, making it more palatable than traditional KD. Its efficacy is similar to classic KD (Neal et al., 2009), although its acceptability is limited due to possible gastrointestinal discomfort (Khabbush et al., 2017).

The Modified Atkins Diet

The Modified Atkins Diet (MAD) is a less restrictive ketogenic diet used as an alternative to the standard KD as an effective treatment for resistant epilepsy (Barzegar et al., 2021). Approximately 65% of calories come from fat (Sharma et al., 2016), making it more palatable and suitable for adolescents and adults, with similar (or slightly less efficient) results (Auvin, 2012) and greater tolerance compared to the standard KD with fewer reported side effects. MAD is characterized by a lower fat-to-carbohydrate and protein ratio, allowing greater protein and fat intake.

1.2. Cardiovascular disease

Noncommunicable diseases (NCDs) are the leading cause of mortality worldwide, accounting for approximately 70% of all deaths annually. According to the World Health Organization (WHO), “ischemic heart disease” is the leading cause of death worldwide, responsible for 13% of total global deaths (Kareva, 2024). These statistics identify ischemic heart disease and stroke as the most common contributors to global mortality; thus, CVDs are classified among the leading causes of death in low-, middle-, and high-income countries (WHO, 2024). Furthermore, compared to the previous decade, the prevalence of CVDs seems to have increased by 17.1% and is projected to continue rising in the coming years (Kale et al., 2023). The global burden of CVD has increased significantly from 1990 to 2019. During this period, the prevalence of CVD cases almost doubled, from 271 million to 523 million, while CVD-related deaths increased from 12.1 million to 18.6 million. Similarly, disability-adjusted life years (DALYs) have doubled due to CVD and ischemic heart disease (IHD) alone accounted for 182 million DALYs, 9.14 million deaths, and 197 million cases in 2019. Stroke contributed to 143 million DALYs, 6.55 million deaths, and 101 million cases in the same year, highlighting the growing global impact of these conditions (Roth et al., 2020).

CVD is a broad term that includes a variety of conditions that affect the cardiovascular system. According to the Centers for Disease Control and Prevention (CDC), “*The term cardiovascular disease refers to a variety of conditions that affect the heart and blood vessels. The most common forms include coronary artery disease, stroke, and heart failure*” (CDC, 2024). CVD is a multifaceted condition with a wide array of contributing factors, reflecting its complex and multifactorial nature. The events leading to a cardiovascular episode are seldom attributable to a single cause, as

numerous genetic, environmental, socioeconomic, and behavioral elements often interplay to increase CVR. Additionally, genetic predispositions, such as a family history of hypertension or early-onset cardiovascular events, can significantly heighten susceptibility to CVD. It is worth noting that socioeconomic determinants, including limited access to healthcare, low income, and inadequate health literacy, also play a critical role in influencing lifestyle choices and the ability to manage predisposing conditions. Behavioral factors are particularly prominent in elevating CVR, with physical inactivity, tobacco use, and harmful dietary patterns, such as high intake of saturated fats, sugar, and sodium, being major contributors. Additionally, obesity and excessive alcohol consumption exacerbate metabolic imbalances, further predisposing individuals to conditions such as hypertension, dyslipidemia, and Type 2 Diabetes Mellitus (T2DM), which are directly linked to cardiovascular morbidity and mortality (Hussain et al., 2024). These factors, either independently or in combination, underscore the importance of a comprehensive approach to understanding and mitigating CVR.

Relevant parameters

For the purposes of this study, it is also essential to introduce the term biomarkers as they will be further investigated in the setting of CVD. According to the National Institutes of Health (NIH), a biomarker is defined as “*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention*” (Strimbu & Tavel, 2010). This definition highlights the importance of biomarkers for understanding physiological and pathological conditions, as well as for assessing responses to therapeutic interventions. An overview of the parameters of interest in the setting of CVD is presented in the table below (Table Table 2)

Table 2 Correlation of primary/ secondary parameters to cardiovascular risk

Parameter	Correlation to Cardiovascular Risk
LDL (Low-Density Lipoprotein)	Strongly associated with atherosclerosis and increased risk of CVDs.
HDL (High-Density Lipoprotein)	Linked to a lower risk of cardiovascular events, HDL has a protective, anti-atherogenic role.
Triglycerides	Associated with metabolic syndrome and an increased risk of heart attack.
Fasting blood glucose	Indicates prediabetes or T2DM, both of which increase CVR.
Fasting insulin	Suggest insulin resistance, which is a key factor in CVR.
HOMA-IR (Homeostasis Model Assessment of Insulin Resistance)	Indicates insulin resistance, which is linked to metabolic syndrome and CVDs.
HbA1c (Glycated Hemoglobin)	Reflects chronic hyperglycemia and is associated with a higher risk of heart attacks and strokes.
Weight	Increases the risk of hypertension, dyslipidemia, and CVDs.

Waist circumference	Marker of visceral fat and a strong predictor of CVR.
Systolic blood pressure	Increases the risk of heart attack, stroke, and heart failure.
Diastolic blood pressure	Linked to CVR, (especially in younger individuals).

Blood pressure

Hypertension (BP) is associated with significant health risks, including heart disease and stroke. It is often asymptomatic or undiagnosed and can lead to serious complications if left untreated. Management of hypertension typically involves both lifestyle modifications and pharmacological interventions. Data from large cohort studies have identified high BP as a crucial risk factor for numerous conditions, including heart failure, atrial fibrillation, chronic kidney disease, valvular heart disease, aortic syndromes, dementia, coronary artery disease, and stroke (Fuchs & Whelton, 2020). A systematic review that included 123 studies with 613,815 participants concluded that lowering blood pressure can significantly reduce vascular risk, regardless of initial blood pressure levels and the presence of comorbidities (Ettehad et al., 2016). These findings highlight the need to reduce systolic blood pressure to levels below 130 mm Hg (which is the global guideline) and the importance of early diagnosis and preventive screening of hypertension to reduce its associated risks.

Blood lipid biomarkers

Blood lipid biomarkers, including total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides, are crucial for assessing CVR. Dyslipidemia, for instance, is causally associated with atherosclerotic CVD, highlighting the need for lipid profiling at baseline assessments and ongoing follow-up (Couderc et al., 2017). A cohort study that involved over four thousand participants (conducted from May 2009 to July 2020), showed that maintaining optimal lipid levels can help prevent CVD and reduce mortality rates. Specifically, the study revealed that elevated triglyceride levels were associated with the development of CVD, but also very low triglyceride levels were associated with an increased risk of death from any cause (Dong et al., 2021), highlighting that blood lipid parameters are essential to be maintained at ranges within the recommended limits.

Low-density lipoprotein (LDL)

Low-density lipoprotein (LDL) is directly associated with atherosclerosis, CVD, and increased mortality. LDL serves as a critical marker of cardiovascular health, and it is crucial that its levels remain within the recommended range (<100 mg/dL) for individuals considered to be at “typical risk”, as defined by the European Society of Cardiology (Guasti & Lupi, 2024). High LDL cholesterol levels are strongly associated with an increased risk of CVD. A recent study found that patients with LDL levels greater than 130 mg/dL had a higher risk of CVD compared to those with LDL levels ≤ 130 mg/dL (Dianat & Zahraei, 2023). Furthermore, hypercholesterolemia, defined as elevated blood cholesterol levels, is epidemiologically associated with the development of CVD (Ormiston et al., 2021).

High-density lipoprotein (HDL)

High-density lipoprotein (HDL) is associated with improved cardiovascular health and a more favorable epidemiological profile of CVD when maintained at desirable high levels. The beneficial effects of HDL cholesterol on cardiovascular health are mainly linked to its anti-atherogenic properties, which inhibit the progression of atherosclerosis (Ormiston et al., 2021). However, recent insights from randomized clinical trials and studies in human genetics suggest that the relationship between HDL levels and cardiovascular health may be more complex than previously understood (Kjeldsen et al., 2022).

Total cholesterol (TC)

Total cholesterol represents the sum of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels. TC concentration is largely influenced by genetic and dietary factors (Ormiston et al., 2021). Although elevated TC levels may not always be a cause for concern, it is necessary to investigate the underlying causes of its elevation, as total cholesterol can, under certain circumstances, be an important marker of CVR. Furthermore, elevated total cholesterol has been correlated with an increased risk of stroke, as highlighted in a 2016 meta-analysis (Peters et al., 2016).

Triglycerides (TG)

Elevated triglyceride levels are also a critical biomarker and a well-established risk factor for CVD. They are specifically associated with coronary artery disease, increased risk of myocardial infarction, and all-cause mortality. Large-scale epidemiological studies, such as the Emerging Risk Factors Collaboration, which analyzed data from more than 300,000 individuals, have documented the relationship between high triglyceride levels and increased risk of cardiovascular events (Emerging Risk Factors Collaboration et al., 2009). Specifically, elevated triglyceride concentrations are associated with a higher risk of coronary artery disease and ischemic stroke. This association is explained through multiple mechanisms, including the promotion of inflammation and foam cell formation, with evidence supported by both genetic and epidemiological data (Nordestgaard & Varbo, 2014).

Blood Glucose biomarkers

Blood glucose biomarkers play a critical role in the assessment of cardiovascular risk, particularly in patients with diabetes. Epidemiological evidence highlights a strong association between diabetes and CVD, while diabetes is strongly associated with a significantly increasing risk of coronary heart disease and stroke (Leon & Maddox, 2015). A 2018 systematic review demonstrated that, during the study period, CVD was responsible for one in two cases (50%) among diabetic patients (Einarson et al., 2018).

Glycosylated hemoglobin (HbA1c)

Glycosylated hemoglobin is a diagnostic process that reflects the average blood glucose levels over the past 2-3 months. It is considered to be a vital biomarker for the diagnosis and monitoring of diabetes and is also linked with the assessment of cardiovascular mortality risk (Ormiston et al., 2021). According to data provided by the American Heart Association, HbA1c levels above recommended standards are associated with an

increased risk of CVD and mortality outcomes, regardless of gender (Butalia et al., 2024). These findings emphasize the critical need for systematic monitoring and preventive strategies, particularly in individuals with diabetes and prediabetes, to achieve improvements in glycemic control to reduce CVR.

Insulin resistance

Insulin resistance is the reduced responsiveness of insulin-sensitive tissues to insulin signaling, leading to reduced biological activity of insulin. This means that insulin is less effective in facilitating the entry of glucose into cells, where it would otherwise serve as a primary energy substrate. As a result, excess glucose remains in the bloodstream, leading to hyperglycemia. This metabolic disorder is strongly associated with the promotion of CVD, as it can trigger pathophysiological mechanisms such as obesity, inflammation, and the development of dyslipidemia. This process contributes to the occurrence of CVDs, including atherosclerosis, hypertension, and other related disorders (Kosmas et al., 2023).

Fasting glucose (FBS)

One of the most common and effective biomarkers used in the diagnosis of diabetes and prediabetes is fasting plasma glucose. Elevated levels of fasting plasma glucose have been associated with an increased risk of CVD (Chen et al., 2023). Risk, including ischemic heart disease, myocardial infarction, and thrombotic stroke, increases significantly when fasting plasma glucose levels exceed 100 mg/dL. On the contrary, particularly low fasting glucose should also be considered a potential risk factor for stroke and coronary heart disease risk (Park et al., 2013).

Body composition

Body Mass Index (BMI), fat mass, waist circumference (WC), waist-to-hip ratio (WHR), total body fat percentage, and fat-to-muscle ratio have been identified as key factors with potentially detrimental effects on cardiovascular health. The correlation between body composition factors and cardiovascular risk (CVR) has been researched in numerous studies, with the results often highlighting a direct correlation between body composition and cardiovascular risk, including the deterioration of relevant biomarkers. For instance, a study of 2,867 healthy individuals (men and women) by (Chuang et al., 2012) concluded that body fat percentage (BF%) was associated with risk factors for CVD and metabolic syndrome in both sexes. More precisely, body fat percentage constituted a particularly valuable predictor of risk in metabolically obese normal-weight individuals. The findings of this study highlight the importance of body composition measurements for the evaluation of cardiovascular risk. The correlation between CVR and body composition was also demonstrated in a 2023 study examining multiple ethnic groups (Carter et al., 2023). Furthermore, research focusing on body fat percentage (BF%) revealed that higher BF% is significantly associated with increased CVR (Kistan et al., 2024).

Body mass index (BMI)

Body Mass Index (BMI) is a measurement based on height and weight that can be applied to adults. Obesity is defined as a BMI ≥ 30 and is a well-established indicator of body composition, highlighting a potentially important risk factor for dyslipidemia, hypertension, diabetes, cardiometabolic syndrome, CVD, and even certain types of cancer (Ormiston et al., 2021). Obese individuals have an increased risk of cardiovascular morbidity and mortality compared to individuals with a normal BMI. It is important to note that while slightly overweight individuals have a similar life expectancy to those with a normal BMI, they have a significantly higher probability of developing CVD at a young age, leading to a higher incidence of CV-related morbidity (Khan et al., 2018). Although BMI is a critical indicator, other factors, such as body fat percentage, WC, etc., should also be considered for a more detailed and reliable assessment of body composition and, by extension, the associated risk for CVD.

Waist Circumference

Another important indicator of CVR in adults is WC, and the waist-to-height ratio (WHtR). British Heart Foundation suggests that CVR increases exponentially when the WHtR exceeds 0.5 (British Heart Foundation, 2024). Furthermore, individuals with a WC over 100 cm appear to have significantly higher levels of total cholesterol, LDL-C, and triglycerides, compared to individuals with normal WC, findings that potentially suggest an increased risk of cardiovascular events (Hernández-Reyes et al., 2020). WC has also been associated with mortality across all BMI categories (from 20 kg/m² to 50 kg/m²). This was concluded because of a meta-analysis that examined data from 11 prospective cohort studies, which included 650,386 white adults aged 20–83 years from the USA, Australia, and Sweden (Ross et al., 2020). Furthermore, WC seems to be directly associated with morbidity and mortality, regardless of age, gender, or ethnicity, highlighting the relevance of this factor to the overall health of diverse populations (Cerhan et al., 2014).

Body fat and body fat to muscle ratio

Among the critical body composition factors directly associated with CVR are body fat and body fat to body mass ratio. Elevated levels of body fat percentage (visceral fat included) are directly associated with various cardiometabolic abnormalities. Individuals with increased levels of visceral fat are more likely to develop metabolic disorders, such as insulin resistance, hyperinsulinemia, glucose intolerance, and dyslipidemia (characterized by high TG and low HDL). These conditions increase the risk of developing CVD. For instance, increased levels of hepatic fat, which are often associated with visceral obesity, can contribute to hyperglycemia and insulin resistance, factors critical for the pathogenesis of T2DM and CVD (Després, 2012).

Regarding muscle-to-fat ratio, it has also been found to be a critical and determining factor for cardiovascular health. In a study involving 6,451 participants between 1999 and 2006, the group with the highest muscle-to-fat ratio appeared to have a significantly lower risk of developmental and cardiovascular mortality than the group with the lowest relative rates (Srikanthan et al., 2016). In a recent study with 468,885 participants from the UK Biobank, who did not have any CVDs at baseline, it was found that high total

and regional fat accumulations were associated with increased risks of developing CVD. One possible mechanism for this association is the correlation between obesity and cardiometabolic and inflammatory cells, which are known to be involved in the pathogenesis of CVDs (Zhou et al., 2023).

1.3. Ketogenic diet and Cardiovascular health

The association between KD and cardiovascular health has been extensively researched in recent years. High-fat and low-carbohydrate diets are widely used nowadays due to their efficiency in reducing body weight, improving CVR, and exerting anti-inflammatory effects (Norwitz & Loh, 2020). However, clinical research highlights the need for careful blood lipid monitoring due to the high-fat content of this diet plan. Moreover, given the limited evidence of long-term safety and efficiency, the need for further research remains critical to better understand its long-term implications. Although several studies have evaluated the potential risks and possible associations between ketogenic diets and cardiovascular health, the epidemiological evidence will possibly be better established in the following years (Mohammadifard et al., 2022).

As current literature indicates, one of the primary mechanisms linking the KD to CVD is its anti-inflammatory potential (Dyńska et al., 2023; Mohammadifard et al., 2022). Factors such as ketosis, restriction of simple sugars, and consumption of omega-3 fatty acids, among others, seem to contribute to the reduction of inflammation, which is a key factor in the pathogenesis of CVD. Additionally, ketogenic diets may exert indirect beneficial effects through mechanisms like body weight reduction – i.e. significant weight loss (Dyńska et al., 2023; Marinescu et al., 2024) and overall improvement in body composition parameters, associated with improvement in CVR markers (Malhotra & Sawal, 2023; Xing et al., 2024). In addition, recent studies underscore the significance of ketone bodies for the function of the affected heart, highlighting the potential therapeutic benefits of this dietary pattern (Mohammadifard et al., 2022).

At the same time, there is evidence, although conflicting, indicating that KD may help reduce blood pressure. On the contrary, some studies suggest that high-fat diets could potentially elevate the risk of stroke through an increase in LDL and triglycerides (Joo et al., 2024). Notably, KDs vary significantly between individuals with CVD and healthy individuals (Dyńska et al., 2023), highlighting the need for a better understanding of the mechanisms of action. Despite the controversy on the association of KD and the cardiovascular system, many studies have revealed a potential role of KD in CVD prevention, treatment, and disease reversal through improvements in energy metabolism, endothelial and mitochondrial function, inflammation reduction, and antioxidant effect (Dyńska et al., 2023; Mohammadifard et al., 2022).

One other aspect to be taken into consideration, according to the research in this field, is that adherence to KD is difficult, especially for children and even for adults over long periods (Lopes Neri et al., 2024). The most common reasons for low adherence were associated with ineffectiveness in seizure control, adverse effects, food refusal, difficulty in preparing KD meals or restrictiveness of the diet, lack of motivation, poor parental compliance, or the financial cost of the diet.

2. Scope

Research Question

The aim of this review was to summarize current knowledge on how ketogenic diets impact cardiometabolic risk factors based on their effects on cardiovascular biomarkers.

POPULATION	ADULT INDIVIDUALS FOLLOWING KETOGENIC DIET
INTERVENTIONS	KETOGENIC DIET (KD)
COMPARATORS	INDIVIDUALS ON CONVENTIONAL DIET OR NO DIET
OUTCOMES	CORRELATION BETWEEN KETOGENIC DIET AND CARDIOVASCULAR RISK FACTORS AND BIOMARKERS INCLUDING BLOOD LIPID PROFILE, BLOOD GLUCOSE PROFILE, BLOOD PRESSURE LEVELS AND BODY COMPOSITION

Figure 3 PICO framework

Research rationale and objectives

It is well-documented that diet plays a critical role in the regulation of lipids and glycemic biomarkers, thus directly influencing cardiovascular health (CDC, 2024; Khan et al., 2018; Liao et al., 2024). For instance, the Mediterranean diet, characterized by its high content of dietary fiber, monounsaturated fats, and phytosterols, has been proven to reduce LDL cholesterol levels and increase HDL cholesterol levels, while also exerting anti-inflammatory effects and reducing the risk of atherosclerosis (Bloomfield et al., 2016; Kapciak et al., 2024; Quetglas-Llabrés et al., 2023). Furthermore, increased consumption of foods rich in complex carbohydrates and dietary fiber, such as legumes and whole grains, contributes to reducing fasting glucose and glycosylated hemoglobin (HbA1c) levels, thereby improving glycemic control in people with T2DM. In contrast, diets high in saturated fat or added sugars increase LDL cholesterol and triglyceride levels, promote insulin resistance, and detrimentally influence CVR markers (Ormiston et al., 2021). Consequently, the assessment of relevant biomarkers provides a non-invasive, cost-effective, and flexible tool for clinicians to quantify patient responses to dietary interventions and their impact on cardiovascular health.

KD has gained increasing recognition as a dietary model, especially in recent decades, with potentially beneficial or detrimental effects on cardiovascular and metabolic health (Dyńska et al., 2023; Marinescu et al., 2024; Mohammadifard et al., 2022). However, given the conflicting evidence in the literature regarding its effect on cardiovascular health, it is critical to conduct a systematic review. This review aims to assess whether the KD is associated with positive or negative effects on CVR markers, focusing on factors such as lipid profile, glycemic profile, blood pressure levels, and body composition. In addition, particular emphasis is placed on assessing the quality and adequacy of the existing literature and identifying potential gaps to provide a

comprehensive understanding of the relationship between this dietary approach and cardiovascular health.

This systematic review focuses on biomarkers linked to blood lipid and glycemic profiles, both of which are associated with an increased CVR. Concerning lipid profile markers, this study examined Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C), Total Cholesterol, and Triglycerides. For glycemic indices, the biomarkers analyzed included Fasting Blood Glucose Levels and Glycated Hemoglobin (HbA1c). These biomarkers were selected due to their established roles in predicting cardiovascular and metabolic risk. Primary results will be further analyzed in the methodology section.

For this study, additional data were collected as secondary outcomes. These data were oriented on body composition, blood pressure, and any adverse events associated with the diet investigated. Specifically, changes in body composition were analyzed, including factors such as Body Mass Index (BMI), fat mass, WC, waist-to-hip ratio (WHR) or central obesity, total body fat percentage, and fat-to-muscle mass ratio. In addition, data were collected regarding systolic and diastolic blood pressure, diet adherence, participant dropout rates, and any adverse events resulting from dietary interventions.

Overall, this systematic review will provide a relative analysis of the correlation of the above cardiovascular risk parameters (biomarkers and body composition factors, blood pressure) and whether the administration of KD is a factor in their modification.

3. Methodology

Materials and methods

This systematic review follows the recommendations of the PRISMA 2020 Declaration and the Cochrane Handbook for systematic reviews of interventions (Version 6.3). In the following systematic review, randomized clinical trials (RCTs) and crossover trials that were examined compared the intervention of the KD in adults (≥ 18 years), whether healthy or with metabolic syndrome factors, against control populations following other dietary models in terms of cardiovascular health risk outcomes and relative biomarkers.

Search strategy

The systematic review was conducted by searching two databases, PubMed and Scopus. The search focused on studies published in the English language over the past decade, from 2014 to July 2024, the last search was conducted on 27 July 2024.

Keywords used for the search included the terms: Ketogenic diet, keto, very low carbohydrate diet, Ketosis, Ketone Bodies, Low Carbohydrate High Fat Diet, Diet, Ketogenic/adverse effects [Mesh], Diet, Ketogenic [Mesh], cvd, cardiovascular disease, cardiovascular risk, Heart Disease, Atherosclerosis, Hypertension, Blood Pressure, Triglycerides, Lipid Profile, Cardiovascular Risk Factors, Myocardial Infarction, diabetes, Heart Disease Risk Factors [Mesh], Cardiovascular Diseases/diet therapy [Mesh], Randomised control trial, clinical trial, controlled clinical trial, rct, Randomized Controlled Trial [Publication Type]. The exact search strategy for each database is presented in detail in the Appendix (1).

Inclusion and exclusion criteria

Inclusion Criteria:

- **Language and Publication Date:** Studies published in English from July 2014 to July 2024.
- **Population:** Studies involving exclusively adults (aged 18 years and older).
- **Study Type:** Randomized controlled trials (RCTs) and case-control studies.
- **Dietary Intervention:** Studies examining the effects of the ketogenic diet without the combination of pharmacological treatment.
- **Assessment of Biomarkers and Clinical Outcomes:** Studies assessing the impact of the KD on biomarkers of CVD risk factors such as blood lipid profile, blood glucose profile, body composition, blood pressure, and adverse effects that occurred from following the KD,

Exclusion Criteria:

- **Language:** Studies published in languages other than English.
- **Population:** Studies involving children or adolescents (under 18 years of age).
- **Pharmacological Interventions:** Studies that include pharmacological treatments as part of the intervention.
- **Use of Exogenous Ketones:** Studies examining the administration of exogenous ketones as the primary intervention.
- **Combination with Exercise:** Studies that include exercise as the sole intervention factor in combination with the KD.
- Non- human trials
- Review articles, case reports and case series, letters to the editor, conference abstracts

Primary Outcomes

- Low-Density Lipoprotein Cholesterol (LDL-C)
- High-Density Lipoprotein Cholesterol (HDL-C)
- Total Cholesterol
- Triglycerides
- Fasting Blood Glucose Levels
- Glycated Hemoglobin (HbA1c)
- Insulin Resistance

Secondary Outcomes

- Changes in Body Composition
- Systolic Blood Pressure
- Diastolic Blood Pressure
- Adherence to the Diet or Dropout
- Any Adverse Effects from the Diets
- Differences that May Arise Depending on Age, Gender, or Ethnicity

Data extraction and analysis

Data were abstracted from each identified study by using a standardized extraction form. The following information was collected:

- 1) Study Information** (Authors, title, trial number, journal, year, country)
- 2) Study Design** (study type, duration, arms),
- 3) Methodology** (Randomization, Allocation Concealment, Blinding, Outcomes Assessment)
- 4) Ketogenic diet type** (keto type, Keto macros%)
- 5) Participants** (Age, sex, Sample Size, Inclusion Criteria, Exclusion Criteria, Baseline Characteristics (Comorbidities), exercise, medication)
- 6) Intervention** (intervention (dietary), Duration of intervention, Other interventions, adherence/adverse effects)
- 7) Comparator** (comparator (dietary), Duration of intervention, Other intervention, adherence/adverse effects)
- 8) Outcomes** (Primary, secondary, comments)
- 9) Results** (results, statistical significance, odds ratio)
- 10) Additional information** (Study limitations, Missed information).

For studies with intervention and control groups, the weighted mean changes were determined using both sample size and intervention duration as weighting factors. Confidence intervals (95% CI) were calculated based on standard error estimates.

Table 3: Studies Characteristics

Study Country	Study Type	Duration	Sample Size	Intervention 1	Intervention 2	Comorbidities
New Zealand (Zinn et al., 2017)	RCT	12 Weeks	41	LCHF ¹	HCLF ²	Overweight/Obese
Australia (Tay et al., 2015)	RCT	24 Weeks	115	LCD ³	HCD ⁴	Overweight/Obese With T2DM
Spain (Goday et al., 2016)	RCT	16 Weeks	89	VLCKD ⁵	LCD ⁶	Overweight/Obese With T2DM
USA (Saslow et al., 2023)	RCT	16 Weeks	94	VLCD ⁷	DASH ⁸	Overweight/Obese
Korea (Choi et al., 2018)	RCT	2 Weeks	46	KD 4:1 (Drink) ⁹	BND ¹⁰	Healthy Adults
USA (Aronica et al., 2023)	RCT	12 Weeks	39	LCHF	ULF ¹¹	Overweight/Obese
Spain (Vargas-Molina et al., 2021)	RCT	8 Weeks	21	LCHF	RSD ¹²	Healthy Adults
Australia (Turton et al., 2023)	Non-Randomized Single/Arm Clinical Trial	16 Weeks	20	LCD	-	≥ 1 Metabolic Syndrome Factors
Finland (Tragni et al., 2021)	Multi-Center, Prospective, Uncontrolled Trial	24 Weeks	33	VLCKD	-	≥ 1 Metabolic Syndrome Factors
Canada (Cipryan et al., 2022)	RCT	12 Weeks	91	VLCHF ¹³	TD ¹⁴	Overweight/Obese
USA (Goss et al., 2020)	RCT	8 Weeks	34	VLCD	LFD ¹⁵	Obesity
New Zealand (Harvey et al., 2019)	RCT	12 Weeks	77	VLCKD	LCD	Healthy Adults
China (Li et al., 2022)	RCT	12 Weeks	60	KD	DD ¹⁶	Overweight/Obese with Newly Diagnosed T2DM

Poland (Michalczyk et al., 2020)	RCT	12 Weeks	91	LCKD ¹⁷	TD	Overweight/Obese
USA (Saslow et al., 2017)	RCT	48 Weeks	34	VLCD	MCCR ¹⁸	Overweight/Obese with T2DM or Prediabetes
Italy (Di Rosa et al., 2022)	RCT	12 Weeks	268	VLCKD	MD ¹⁹	Overweight/Obese
Norway (Retterstøl et al., 2018)	RCT	3 Weeks	30	LCHF	TD	Healthy Adults
Italy (Merra et al., 2017)	RCT	3 Weeks	60	VLCKD1 (Lower Carbs)	VLCKD2 (Higher Carbs)	Obesity
Spain (de Luis et al., 2016)	RCT	24 Weeks	29	VLCK	VLCK (+Dha Supplumentation)	Obesity
Denmark (Hansen et al., 2023)	RCT	26 Weeks	165	LCHF	HCLF	T2DM
Sweden (Burén et al., 2021)	RCT	23 Weeks	17	LCHF	SNC ²⁰	Healthy Adults
USA (Gardner et al., 2022)	RCT	24 Weeks	40	KD	MD	Prediabetes
Iran (Rajaie et al., 2014)	RCT	6 Weeks	30	MRC ²¹	IUD ²²	Overweight/Obese Women With Mets
USA (Buga et al., 2022)	RCT	12 Weeks	7	LCHF	LCHF	Healthy Adults
Finland (Luong et al., 2024)	RCT	3 Weeks	11	KD	TD	Overweight/Obese
Italy (Colica et al., 2017)	RCT	3 Weeks	42	VLCKD 50% Of Protein Replaced With Synthetic Amino Acids	VLCKD With Placebo.	Overweight/Obese

1 = LCHF: Low Carb High Fat (moderate-to-strict carb restriction), **2 = HCLF:** High Carbohydrate Low Fat, **3 = LCD:** Low Carb Diet, **4 = HCD:** High Carb Diet, **5 = VLCKD:** Very Low Calorie Ketogenic Diet, **6= LCD:** Low Calorie Diet (calorie-restricted, non-keto), **7 = VLCD:** Very Low Carb Diet, **8 = DASH:** Dietary Approaches to Stop Hypertension (heart-healthy, low-sodium), **9 = KD:** Ketogenic Drink 4:1 (high-fat formula), **10 = BND:** Balanced Nutrition Drink (standardized nutrient mix), **11 = ULF:** Ultra Low Fat Diet (fat <10% energy), **12 = RSD:** Regular Spanish Diet (moderate, Mediterranean-inspired), **13 = VLCHF:** Very Low Carb High Fat (≤ 15% carbs), **14 = TD:** Typical Diet (habitual), **15 = LFD:** Low Fat Diet (high-carb, low-fat), **16 = DD:** Diabetes Diet (carb-controlled, not restrictive), **17 = LCKD:** Low Carb Ketogenic Diet, **18 = MCCR:** Moderate Carb Calorie Restricted (moderate carb, low-fat), **19 = MD:** Mediterranean Diet (plant-rich, olive oil), **20 = SNC:** Swedish National Control Diet (high-carb), **21 = MRC:** Moderately Restricted Carbs (carbs 43–47%), **22 = IU:** Iranian Usual Diet (high-carb-65%, low fat)

* Keto drink (KD 4:1) every 4 grams of fat, there is a combined total of 1 gram of carbohydrates and protein

4. Results

4.1. Study Selection Process

The above-mentioned search strategy identified a total of 845 studies. These studies were screened for duplicate entries using the Zotero citation management system. Following this process, 143 duplicate studies were identified and removed, leaving 702 unique studies for further evaluation.

The next phase involved screening the titles and abstracts of the 702 remaining studies to assess their relevance to this systematic review. This screening process was carried out independently by two researchers (E.D. and S.E.) to ensure objectivity and reduce bias. Where the title and abstract showed relevance to the focus of the study - i.e. the effects of the KD on key outcomes such as lipid profile (triglyceride, total cholesterol, HDL, LDL), glycemic profile (insulin, HbA1C, HOMA-IR), body composition (BMI, Waist to hip ratio, Fat percentage, Fat to muscle ratio, W. C), blood pressure or diet-related adverse effects; studies were advanced to the next stage of the full-text review. Upon completing the first screening procedure, 645 studies were excluded (mainly referring to animal models, studies with pharmacological interventions, or not reporting the target outcomes of this review), and a total of 57 studies were identified as potentially eligible and retrieved for detailed full-text review. During this phase, each study was carefully reviewed to determine its suitability for inclusion based on predefined eligibility criteria. As a result of this in-depth assessment, 26 studies were deemed eligible and included in the final analysis.

The remaining 30 studies were excluded for the following reasons:

- Twenty-four studies did not report primary or secondary outcomes relevant to the research question (e.g., no data on lipid profile, glycemic profile, body composition, blood pressure, or diet-related side effects).
- Three studies involved significant comorbidities that could influence the interpretation of the results.
- Three studies were classified as pilot studies and, therefore, did not meet the criteria for inclusion in this systematic review.

This rigorous selection process ensured that only high-quality studies directly relevant to the research question were included, thus enhancing the validity and reliability of the findings.

The process is illustrated in the diagram below (Figure 4)

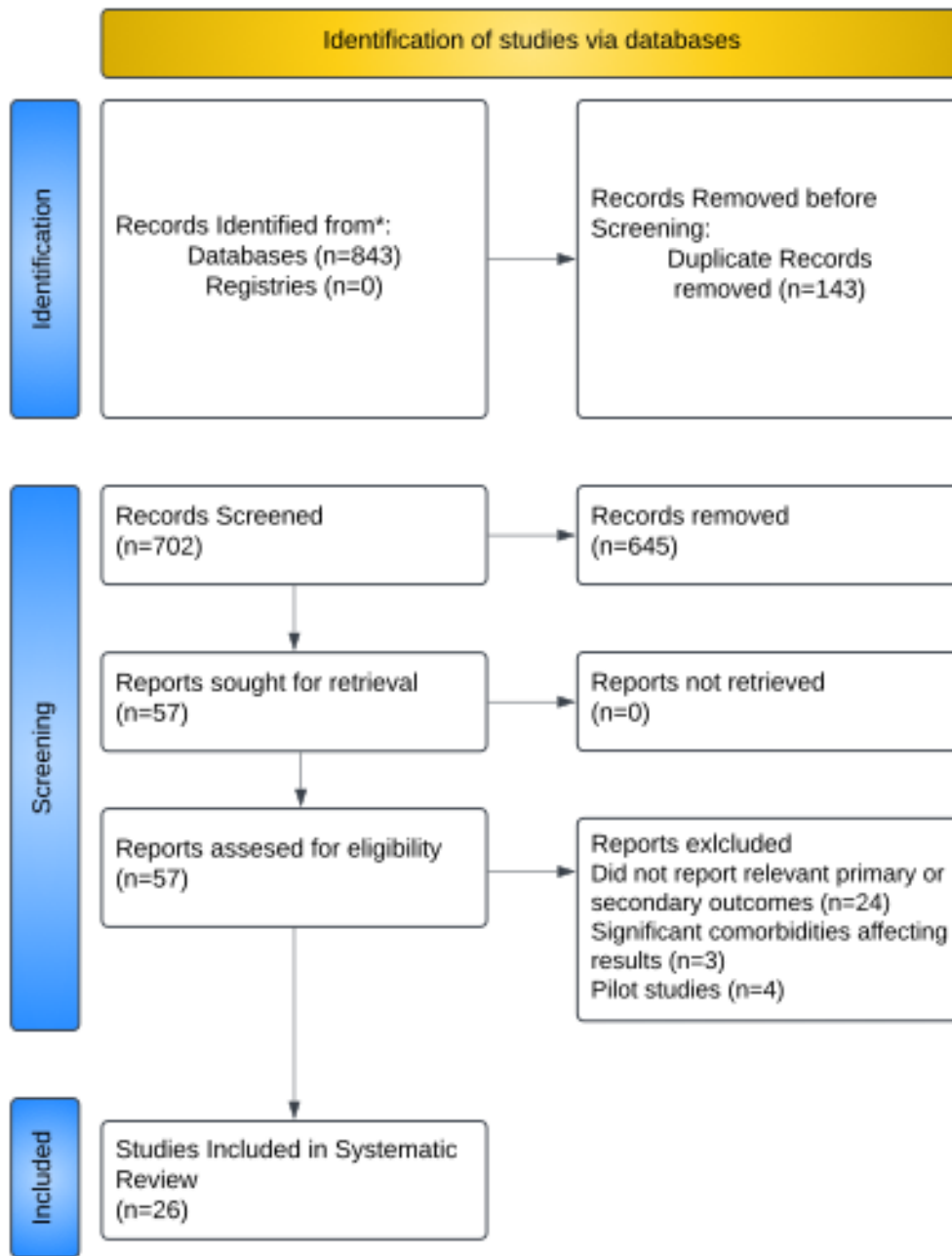


Figure 4 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (2020) of search process for studies.

Study characteristics

Twenty-six studies with a total of 1584 participants were included in the systematic review, with the number of participants per study ranging from 7 to 268. These studies were published between 2014 and 2024. Of the included studies, 6 took place in the USA (Aronica et al., 2023; Buga et al., 2022, 2022; Gardner et al., 2022; Goss et al., 2020; Saslow et al., 2017, 2023), 1 in Iran (Rajaie et al., 2014), 1 in Sweden (Burén et al., 2021), 2 in Australia (Tay et al., 2015; Turton et al., 2023), 2 in New Zealand (Harvey et al., 2019; Zinn et al., 2017), 2 in Finland (Luong et al., 2024; Tragni et al., 2021), 1 in Korea (Choi et al., 2018), 1 in Canada (Cipryan et al., 2022), 1 in China (Li et al., 2022), 1 in Poland (Michalczyk et al., 2020), 1 in Norway (Retterstøl et al., 2018), 3 in Spain (de Luis et al., 2016; Goday et al., 2016; Vargas-Molina et al., 2021), 1 in Denmark (Hansen et al., 2023), and 3 in Italy (Colica et al., 2017; Di Rosa et al., 2022, p. 5; Merra et al., 2017).

They consisted of 24 randomized clinical trials (6 studies of which had a cross-over design) and 2 single-arm studies, of which 1 was a multi-center, prospective trial. In 10 of the included trials, patients were overweight or obese, 6 of the trials included normal weight subjects, and the remaining 10 included subjects with coexisting diabetes or metabolic disease factors with obesity or overweight. The duration of the intervention ranged from 2 weeks to 26 weeks. Of the studies, 5 included only women, 1 included only men, and the remaining 20 included both sexes.

4.2. Analysis of Outcomes

Blood lipid parameters

LDL-Cholesterol

This systematic review included 21 studies that examined the change in LDL-Cholesterol after KD intervention, with the weighted mean being **4,69 md/dL (4,33, 5,06 CI 95%)**, after adjusting for the mean change, sample size, and duration of intervention. Of the studies that assessed Low-Density Lipoprotein (LDL), some showed an increase, while others showed a decrease. More specifically, an increase in LDL was recorded in 13 studies, of which 8 had statistically significant results ($p < 0.05$). Conversely, of the 8 that showed a decrease in the LDL levels, 4 had statistically significant results ($p < 0.05$).

However, the change in LDL between studies was not directly linked with any participant characteristics (e.g., gender, age, or the presence of obesity or metabolic risk factors), nor with the amount of carbohydrates in the individual dietary plan or the duration of the intervention.

Compared with the results of studies that examined another dietary model (control groups), 14 studies examined the change in LDL cholesterol, with 11 studies showing a decrease (6 with statistically significant results, $p < 0.05$), 2 showing an increase (1 with statistically significant results, $p < 0.05$) and 1 showing no change (no statistically significant results, $p > 0.05$). The weighted mean change in LDL value in studies that tested intervention with control groups was calculated as **-8,04 mg/dL (-8,16, -7,92 CI 95%)** after calculating the mean change, sample size, and duration of intervention.

HDL- Cholesterol

Twenty-two studies examining HDL-cholesterol were included. The weighted mean change in HDL-cholesterol after the KD intervention was **4,85 mg/dL (4,76, 4,93 CI 95%)** after calculating the mean change, sample size, and duration of the intervention. Of the studies that examined the change in the above biomarker, 18 identified a relative increase, with 11 of them showing statistically significant results ($p < 0.05$). Additionally, a decrease in HDL-cholesterol was identified in 3 of the included studies, with 1 of them showing statistically significant results ($p < 0.05$).

In studies with an exclusively female patient sample (four in total), an increase in HDL cholesterol was observed in the KD intervention. In contrast, in the respective control groups, where applicable, a relative decrease was noted. However, the small sample size of studies with exclusively female participants (4 studies) limits the ability to draw conclusions regarding causality and only suggests a potential area for future research. Furthermore, there was no other linked association in the change of the above parameter with respect to the duration of intervention or the morbidity of the population under study. In addition, the composition of the KD intervention in terms of grams of carbohydrates did not seem to have any direct correlation with the change in the HDL biomarker.

Compared to the respective control groups that examined another dietary model, the change in HDL-Cholesterol was examined in 16 studies with 7, studies showing an increase in relative value (4 with statistically significant results, $p < 0.05$), 8 a decrease in value (with 2 having statistically significant results $p < 0.05$) and one study not detecting any change. The weighted mean change of the control groups was **1,06 mg/dL (1,02, 1,09 CI 95%)** after calculating the mean change, sample size, and duration of intervention.

Triglycerides

Triglycerides were examined in a total of 22 studies, 20 of which recorded a decrease in triglyceride levels after the intervention period using a KD. More specifically, the weighted mean changes in triglycerides in the 22 studies under review was **-35,46 mg/dL (-35,84, -35,08 CI 95%)** after adjusting for the mean change, sample size, and duration of the intervention. Of the 22 studies that showed a decrease in triglycerides after the intervention period, 11 had statistically significant results ($p < 0.05$). In addition, one study showed an increase and one did not detect a change after the intervention period, but without statistically significant results for either of them.

The KD appears to have had an effect on reducing triglyceride levels in almost all groups of participants regardless of the state of weight, health, or morbidity within the study period. In addition, there did not appear to be a specific correlation regarding triglyceride reduction with respect to the intervention interval or the percentage of carbohydrates in the dietary regimen.

All of the studies that examined a sample of exclusively female patients demonstrated a relatively high reduction in triglycerides. However, this was a sample of four (4)

studies (with three of them having statistically significant results), and therefore, no conclusions regarding causality should be drawn without further investigation.

Compared to different dietary models examined (control groups), the change in triglyceride levels was examined in 16 studies in total, of which a decrease in the relevant parameter was found in 13 (4 with statistically significant results $p < 0.05$), while an increase was detected in 2 studies, with no statistically significant results ($p > 0.05$) and 1 additional study detected no change. The weighted mean change was **-12,44 mg/dL (-12,62, -12,26 CI 95%)** after calculating the mean change, sample size, and duration of the intervention.

Blood glucose parameters

Fasting blood glucose

Change in fasting glucose was examined in a total of 17 studies, 16 of which noted a decrease in this value after the administration of a KD for a defined period of time, while 6 of them had statistically significant results ($p < 0.05$). More specifically, the weighted mean change in fasting glucose was **-20,63 mg/dL (-20,83, -20,43 CI 95%)** after adjusting to the mean change, sample size, and duration of intervention. Regarding the studies that examined KD intervention, one study identified an increase in glucose (without statistically significant results, $p > 0.05$).

Changes in fasting glucose seem to have been smaller in studies with shorter intervention periods. In particular, the reduction in fasting glucose in studies with an intervention period of 3 to 8 weeks appears to have been smaller compared to studies with an intervention period of more than 12 weeks.

Additionally, it appears that in studies where participants had diabetes or pre-diabetes, there was a greater reduction in fasting glucose levels after the intervention compared to studies that compared healthy and/or obese patients without diabetes or pre-diabetes as comorbidities.

The effect of studies that tested different dietary models (control groups) on fasting glucose reduction had an overall weighted mean of **-13,56 mg/dL (-13,78, -13,33 CI 95%)** after adjusting to the mean change, sample size, and duration of the intervention. More specifically, the glucose biomarker was examined in 11 studies, with 10 identifying a decrease (3 with statistically significant results, $p < 0.05$) and one study identifying no change in value (no statistically significant results, $p > 0.05$).

Fasting insulin

Fasting insulin levels change after KD intervention was examined in a total of 12 of the included studies. A decrease was found in 11 studies, with 5 having statistically significant results ($p < 0.05$). Overall, the weighted mean was **-30,48 pmol/mol (-30,93, -30,04 CI 95%)** after adjusting for the mean change, sample size, and duration of intervention. One study, with no statistically significant results ($p > 0.05$), noted an increase in glucose levels after the intervention period through the KD.

Additionally, the change in insulin seems to be greater in terms of its reduction in obese participants compared to normal-weight participants.

The KD appears to have had a greater effect on reducing fasting insulin in obese participants compared to the different dietary approaches of the control groups. Namely, the effect of different dietary patterns on insulin reduction in control groups was examined in 7 studies with 5 detecting a decrease (1 with statistically significant results, $p < 0.05$) and 2 detecting an increase, with no statistically significant results ($p > 0.05$); the weighted mean change was **-16,27 pmol/mol (-16,95, 15,58 CI 95%)** after adjusting for the mean change, sample size and duration of intervention

HOMA-IR

Insulin resistance (HOMA-IR) was measured in 12 of the studies included in the final phase of the systematic review. Twelve recorded a decrease in HOMA-IR, 7 of which had statistically significant results ($p < 0.05$). The weighted mean change was **-1,92 (-1,94, -1,90 CI 95%)** after adjusting to the mean change, sample size, and duration of the intervention. An increase was detected in one of the included studies, which, however, did not demonstrate statistically significant results ($p > 0.05$).

In relation to the decrease of this parameter after KD administration, no correlation was found with age, gender, or intervention interval.

Nine studies examined HOMA-IR change after different dietary regimen (control groups) of which 5 found a decrease in the value (HOMA-IR), while 4 found an increase with the weighted mean being **-0,53 (-0,54, -0,51 CI 95%)** after adjusting for the mean change, sample size and duration of the intervention. Statistical results were obtained in 3 of the studies ($p > 0.05$).

HbA1c

The variation in HbA1c was reflected qualitatively, as the results of the included studies were not homogeneous in terms of their method of measurement (some studies reported the percentage change, while others reported the pmol/mol change). However, of the 14 studies that measured the change in this parameter, 13 showed a decrease in relative value (8 of which had statistically significant results, $p > 0.05$), while 1 showed no change (no statistically significant results, $p > 0.05$).

Compared with studies that examined interventions with a different dietary pattern from the KD, ketogenic diet interventions showed a greater and more frequent reduction compared with studies that examined different dietary patterns

Body composition parameters

Weight

Body weight was reduced in all the studies that measured it after the KD intervention. Specifically, 22 studies examined this body composition parameter, with 16 of them having statistically significant results ($p < 0.05$). The weighted average of the change in this parameter was **-8,02 kg (-8,10, -7,95 CI 95%)** after adjusting for the mean change, sample size, and duration of the intervention. One study reported weight reduction qualitatively and, therefore, was not included in the calculation of the weighted mean.

Weight reduction appears to have been smaller in studies with shorter durations compared to studies with longer intervention durations. Specifically, studies with an intervention duration of up to 8 weeks had less weight loss. The same was observed for the control groups, but with smaller overall changes compared to the KD interventions. In studies with longer durations (more than 12 weeks), no clear pattern of a greater weight loss-to-intervention duration ratio was observed.

In addition, weight reduction appears to have been greater in studies examining individuals with metabolic disease or obesity compared to studies examining normal-weight individuals without metabolic risk parameters.

Regarding the studies with control group interventions, all 16 studies that measured weight detected a relative reduction in the value, with 11 of them having statistically significant results ($p < 0.05$). The weighted mean adjusted for the variables of mean change, sample size, and duration of intervention was **-4,89 kg (-4,97, -4,82 CI 95%)**.

Waist circumference

The change in W.C after intervention of KD was measured in 15 of the included trials. All of the trials showed a decrease, with 10 of the trials showing statistically significant results ($p < 0.05$). The overall change in this parameter of body composition was **-8,33 cm (-8,41, -8,24 CI 95%)** after adjusting for the mean change, sample size, and duration of the intervention.

Studies that examined another dietary intervention (control groups) measuring this parameter were 10 in total, 8 of which showed a decrease in WC (6 had statistically significant results ($p < 0.05$) and 2 showed an increase in the relative value, with no statistically significant results ($p > 0.05$). The weighted mean change in WC of the control groups was **-4,68 cm (-4,75, -4,60 CI 95%)** after adjusting for the mean change, sample size, and duration of the intervention.

Other parameters

Systolic Blood Pressure

Systolic blood pressure was measured in 11 of the included studies, and 8 of them found a decrease in this parameter (with 3 showing statistically significant results, $p < 0.05$). Two studies recorded no difference after the intervention with the KD, and 1 study recorded an increase (without statistically significant results, $p > 0.05$). The weighted mean change in systolic blood pressure following the KD intervention was calculated as **-5,75 mmHg (-5,83, -5,67 CI 95%)**, accounting for the magnitudes of mean change, sample size, and duration of the intervention.

Change in systolic blood pressure was examined in 8 studies where the intervention was performed using a different dietary model (as control groups). Among these, one study showed statistically significant results ($p < 0.05$). Additionally, one study (with no statistically significant results, $p > 0.05$) recorded an increase in systolic blood pressure. The weighted mean change for the control groups was **-4,65 mmHg (-4,75, -4,56 CI 95%)**, determined after calculating the mean change, sample size, and duration of the intervention.

Diastolic Blood Pressure

Diastolic blood pressure (DBP) was measured in 9 KD intervention studies. Of these, 8 identified a decrease in DBP value (2 showed a statistically significant result $p > 0.05$). One study, with no statistically significant results ($p < 0.05$), showed a relative increase in this value. The weighted mean change in DBP was **-3,52 mmHg (-3,60, -3,44 CI 95%)** adjusted for the mean change, sample size, and duration of the intervention.

Regarding the studies that used a different dietary model (control groups), out of a total of 7 studies, 6 identified a decrease in the parameter under consideration, with no statistically significant results ($p < 0.05$) and one identified an increase in the parameter, also with no statistically significant results ($p < 0.05$). The overall change in the parameter (weighted mean) was **-2,12 mmHg (-2,25, -2 CI 95%)** adjusted for the mean change, sample size and duration of the intervention.

Adverse effects, dropouts, and compliance issues

The included trials reported some adverse effects during interventions with ketogenic or other dietary models and some cases of discontinuation of the study for various reasons. In the trials that examined KD interventions, symptoms of gastroenterological nature were reported in the Tay study (Tay et al., 2015), nausea, vomiting, fatigue, and cases of ketoacidosis (Turton et al., 2023). A total of 17 non-significant adverse events were reported in the trials that examined the KD intervention, and 2 serious adverse events were also reported in the KD group in the Retterstøl trial (Retterstøl et al., 2018). Although no study has attributed certain causality to the association between KD and adverse events.

Additionally, nausea and headache were also reported in the Retterstøl trial (Retterstøl et al., 2018), although it is not exactly determined if or how many people experienced these symptoms in control groups. However, no adverse events were reported in the other trials that included control groups.

It seems that adverse events were more common and more severe in the KD trials, which will be discussed in more detail in the Discussion section of this review.

With regard to the KD intervention groups, it seems that participants experienced a higher degree of difficulty in adherence than participants in trials with other dietary interventions. Specifically, the studies of Salvador, Harvey, Li, Michalzie, Cyprian and Hansen (Vargas-Molina et al., 2021; Harvey et al., 2019; Li et al., 2022; Michalczyk et al., 2020; Cipryan et al., 2022; Hansen et al., 2023) reported that participants failed to adhere to the diet or reported difficulties. In addition, the total number of dropouts seemed to be higher in the KD trials than in the trials of other dietary models. Specifically, the trials reported a total of 93 dropouts in the KD groups and 61 in the other dietary intervention groups. The reported dropouts specifically pertain to studies that included both ketogenic diet (KD) and control groups. In addition, some studies such as (Tragni et al., 2021; Vargas-Molina et al., 2021) report exclusions for negative ketone tests.

Table 4: Summary of Results

Study Type Ref. number	Keto Type and Macros	Sample Size Sex Baseline Characteristics	Primary Outcomes	Secondary Outcomes	Adverse Effects	Control Group and Comments
Randomized Clinical Trial ACTRN12616 001579482	Low Carb High Fat <45% Carbs	14 (Both) Obesity	<ul style="list-style-type: none"> ↑ LDL¹: +10 (mg/dL) ↑ HDL²: +8,5 (mg/dL) ↓ TG³: -32,8 (mg/dL) ↓ Glucose: -18,2 (mg/dL) ↓ Insulin: -34,4 (pmol/mol) ↓ HOMA-IR⁴: -1,57 ↓ HbA1c⁵: -0,1 (mmol/mol) 	<ul style="list-style-type: none"> ↓ Weight: -5kg ↓ WC⁶: -4,8 cm 	Not mentioned	In comparison to HCLF ⁷ diet: keto had better metabolic outcomes and weight related outcomes for every domain except from LDL cholesterol
Randomized Clinical Trial ACTRN1261 2000369820,	Low Carb (14% carbohydrate [<50 g/day],	46 (both) Overweight /obese &T2DM ⁸	<ul style="list-style-type: none"> ↓ Fasting glucose: -19.8 (mg/dL) ↓ Insulin: -46,2 (pmol/L) ↓ TC⁹: -11.6 (mg/dL) ↓ LDL-C: -11.6 (mg/dL) ↑ HDL-C: +7.7 (mg/dL) ↓ TG: -44.3 (mg/dL) ↓ HOMA-IR: -1,1 ↓ HbA1c: -28.4 (mmol/mol) 	<ul style="list-style-type: none"> ↓ Weight: -12kg ↓ WC: -10,6 cm ↓ SBP¹⁰: -11.0 (mmHg) ↓ DBP¹¹: -8.2 (mmHg) ↓ FM-to-FFM ratio¹² ↓ Antglycemic Medications 	Gastrointe- stinal disorders (n=2)	In comparison to Low carb diet: LC ¹³ diet induced greater improvements in glycemic control, blood glucose profiles, and reductions in diabetes medication requirements compared with the HC ¹⁴ diet. The LC diet also promoted a more favorable CVD risk profile. Although adverse effects only occurred in keto-type diet. Body composition changes were almost the same.
Randomized Clinical Trial -	Very Low calorie - Ketogenic	44 (Both) Overweight /obese &T2DM	<ul style="list-style-type: none"> ↓ LDL: -2.1 (mg/dL) ↓ HDL: - 1.4 (mg/dL) ↓ Triglycerides: -35,9 (mg/dL) 	<ul style="list-style-type: none"> ↓ Weight -14,7 (kg) ↓ WC: -12 (cm) ↓ Oral antidiabetic medication 	nausea associated with ketosis(n=1)	In comparison to low calorie diet: VLCK ¹⁵ had better results on weight loss along with marked amelioration of glycemic control and triglycerides. No

	<50 G Daily (From Vegetables)		<p>↓ Fasting Glucose: -28 (mg/dL)</p> <p>↓ HOMA-IR: -3,4</p> <p>↓ HbA1c: -0,9 %</p> <p>↓ TC- 12,6 (mg/dL)</p>			adverse effects associated with control group
Randomized Clinical Trial NCT03729479	Very Low Carb carb intake to 20 -35 g/day(nonfiber)	23 (Both) Overweight/obese	↓ HbA1c -0.35 (%)	<p>↓ Weight: -8,68 kg</p> <p>↓ SBP: -9.77 (mmHg)</p>	None	In comparison to DASH ¹⁶ diet: VLC diet showed greater improvements in SBP, glycemic control, and weight
Randomized Clinical Trial -	nutrition drink exclusively (KD 4:1) *	8 (Both) Healthy adults	<p>↓ TC: -18.3 (mg/dL)</p> <p>↓ Triglycerides:-27.7 (mg/dL)</p> <p>↓ LDL: -11.6 (mg/dL)</p> <p>↓ HDL: -0.6 (mg/dL)</p>	<p>↓ Body fat mass: -2,2 (kg)</p> <p>↓ WC: -4,8 (cm)</p> <p>↓ Weight: -5,9 (kg)</p>	None	In comparison to balanced nutrition drink: Blood lipid profile was more efficient on the KD diet. Keto interventions had more dropouts than non-keto.
Randomized Clinical Trial -	Low Carb High Fat <30g Carbs Per Day	18 (Both) Overweight/obese	<p>↑ HDL: +1.7 (mg/dl)</p> <p>↑ LDL: + 14.9 (mg/dl)</p> <p>↓ Triglycerides: -108.6 (mg/dl)</p> <p>↓ HOMA-IR: -1.4</p>	↓ Weight -9,6 (kg)	None	In comparison to “Ultra-low-fat diet”: Keto had better results in Triglycerides and HDL, although increased LDL cholesterol
Randomized Clinical Trial -	LCHF ¹⁷ 30-40g carbs /day	10 (Women) Young & healthy	no test for cvd biomarkers	<p>↓ SBP -6.3 (mmHg)</p> <p>↓ DBP: -2.0 (mmHg)</p>	None	In comparison to non-keto diet: both groups had similar beneficial results, KD had better results regarding systolic blood pressure. KD had One drop-out and mentioned as “hard to follow” (non-keto had none)
single-arm clinical trial	Low Carb 25-75 g carbs/day	20 (Both)	<p>↑TC+ 11.6 (mg/dL)</p> <p>↑HDL: + 3.9 (mg/dL)</p> <p>↑LDL:+ 3.9 (mg/dL)</p>	<p>↓ Weight:-2,14 (kg)</p> <p>↓ WC: -2,4 (cm)</p> <p>↓ DBP: -2,3 (mmHg)</p>	Hospitalized for Ketoacidosis(n=1), high	No other intervention: LC diet improved markers of blood glucose control and

ACTRN12621 000764831		≥ 1 Metabolic Syndrome Factors	↓ Triglycerides: - 26.5 (mg/dL) ↓ HbA1c -6.4 (mmol/mol/or 0,6%) ↓ Fasting Blood Glucose: - 48.6 (mg/dL) ↓ Mean Glucose: - 23.4 (mg/dL)	↑Increased diabetes quality of life	ketone levels (N=2)	quality of life (reduced exogenous insulin Requirements) Additionally increased LDL. Adverse effects mentioned (ketone levels)
multi-center, prospective, trial -	VLCKD ¹⁸ <50G CARBS	30 (Women) Overweight/Obese & ≥ 1 Metabolic Syndrome Factors	↓ HbA1c:-2.47 (mmol/mol) ↓ HOMA-IR:-1.39 ↓ Insulin:-32,78 (pmol/L) ↑ HDL-C: +3.3 (mg/dL) ↓ LDL-C:-11.2(mg/dL) ↓ Triglycerides -27.1 (mg/dL)	↓ WEIGHT:-11,5 kg ↓ BMI:-4,4 ↓ WC:-11,9 cm ↓ SBP: -3.5(mmHg) ↓ DBP: -3.5 (mmHg)	None	No other intervention: Improvement of cardiometabolic parameters, thus leading to benefits including body composition and blood lipid profile
Randomized Clinical Trial NCT03934476	VLCHF <50 g of carbs/day	25 (Both) Overweight/Obese	↓Glucose: -5.59 (mg/dL) ↓Triglycerides: -24.80 (mg/dL) ↑HDL: +1.16 (mg/dL) ↑ LDL: +2.32 (mg/dL) ↓HbA1c: -2.0 (mmol/mol)	↓SBP:- 3 (mmHg) ↓ DBP:-5 (mmHg)	not able to follow diet (n=1)	In comparison to pre-existing diet & HIIT ¹⁹ exercise: Ketogenic diet seemed to have beneficial results, similar to control group
Randomized Clinical Trial NCT02760641	VLCD ²⁰ ≤10% calories from Carbs	19 (Both) Obesity	↓Fasting glucose: -2.6 (mg/dL) ↓ Fasting insulin: -29,6 (pmol/L) ↓ HOMA-IR: -1.0 ↓ TC: -10.6 (mg/dL) ↓ LDL: -10.2 (mg/dL) ↑ HDL: +7.3 (mg/dL)	↓ Weight -5,9 kg ↓ Fat-4,1 kg	None	In comparison to low-fat diet: VLCD had better metabolic outcomes and body composition related outcomes for every domain

			↓ Triglycerides: -39.3 (mg/dL)			
Randomized Clinical Trial ACTRN12617 000421336p	VLCKD 5%energy from carbs	14 (Both) Healthy Adults	↑ LDL-c: +19,35 mg/dL ↑ HDL-c: +9,29 mg/dL ↓ Triglycerides: -15,95 mg/dL ↓Glucose: -3.60 mg/dL ↓ Insulin: -10,33 pmol/L	↓Weight-4,12 (kg) ↓WC-2,81 (cm)	amenorrhea (n=1) difficult sustain (n=3)	to In comparison to 25% carb Keto: (Three keto types were measured) 5% carb keto had more beneficial results, although an LDL increase occurred. (All keto types seemed to have beneficial results)
Randomized Clinical Trial -	Keto 30-50 g carbs	24 (Both) overweight/obese newly diagnosed T2DM	↓ Glucose: -25.04 (mg/dL) ↓ LDL: -15.85 (mg/dL) ↑ HDL: +5.03 (mg/dL) ↓ Triglycerides: -28.32 (mg/dL) ↓ TC: -20.49 mg/dL ↓ Hba1c: - 0,92%	↓ Weight: -8,06 kg ↓ WC: -9,29cm	Could not comply with diet (n=6)	In comparison to Diabetes control Diet: Keto diet was more beneficial regarding body composition parameters, blood glucose and blood lipid in overweight/obese patients with T2DM. Although had more dropout rate.
Randomized Clinical Trial -	LCKD 8% carbs	46 (Both) Overweight/obese	↑ HDL-c: +16,28 (mg/dL) ↓ Triglycerides: -84,32 (mg/dL) ↓ Glucose: -21,6 (mg/dL) ↓Insulin: -12,98 (pmol/L) ↓ HOMA IR -2,35 ↓ HbA1c: -0,49 (mg/L)	↓Weight: -13,72 kg ↓ WC:-14,06 cm	Could not comply with diet (n=4)	In comparison to Obesity prevention diet (WHO): Keto resulted in weight loss in all participants, amelioration of glycaemic control. Although had higher dropout rate
Randomized Clinical Trial	VLCK 20-50g carbs	16 (Both) overweight&	↓ HbA1c :- 0.6 (%)		None	In comparison to MCCR ²¹ diet: VLCD group induced more beneficial results in HbA1c and

NCT01713764	(excluding fiber)	T2DM/prediabetes	<p>↓ Triglycerides: - 16,4 mg/dL (mg/dL)</p> <p>↑ LDL: + 9.2 mg/dL (mg/dL)</p> <p>↑ Total Cholesterol: (mg/dL) + 15.7 mg/dL</p> <p>↑ HOMA-IR: + 0.2</p> <p>↑ HDL: + 3.5 mg/dL</p> <p>↑ Fasting Insulin: + 1,2 pmol/L</p>	<p>↓ Weight -6,1 (kg)</p>		weight than control group. Although LDL was increased in keto group and
Randomized Clinical Trial -	VLCKD 30–50 g carbs/day	135 (Both) Obesity /overweight	-	<p>↓ Weight -6,75 (kg)</p> <p>↓ WC: -6,86 (cm)</p>	Similar dropout rate/no adverse effects	In comparison to Mediterranean Diet: Both MD ²² and VLCKD were efficient in reducing body weight, WC, and fat mass while preserving FFM ²³ and BCM ²⁴ in Overweight /Obese subjects. Although KD had faster results, MD had better results in the long term
Randomized Clinical Trial NCT01476436	LCHF 20g carbs/day (5%)	15 (Both) Healthy Adults	<p>↑ Total Cholesterol: +46.4 mg/dL</p> <p>↑ HDL: +11.6 mg/dL</p> <p>↑ LDL: +34.8 mg/dL</p> <p>↓ Glucose: -1.8 mg/dL</p> <p>Triglycerides: No change</p> <p>↓ HbA1c: -0.1%</p>	<p>↓ Weight: -1,2 (kg)</p> <p>↓ WC: -0,5 (cm)</p> <p>↓ fat mass: -0,4 (kg)</p> <p>↑ SBP: +2 (mm Hg)</p> <p>↑ DBP: +2 (mm Hg)</p>	chest pain (n=1) auto-immune thyroiditis (n=1)	In comparison to pre-existing diet: KD had beneficial results in all parameters, although mean plasma LDL and SBP & DBP increased.
Randomized Clinical Trial NCT01890070	VLCKD 10% calories (=carbs) (<20 g)	20 (Both) Obesity	<p>↓ Total Cholesterol: -32 mg/dL</p> <p>↓ LDL: -27.2 mg/dL</p> <p>↓ HDL: - 6.6 mg/dL</p> <p>↓ Triglycerides: -16.6 mg/dL</p>	<p>↓ Body fat: -2,46 (kg)</p> <p>↓ WC: -4,45 (cm)</p> <p>↓ SBP: -1,50 (mm/Hg)</p> <p>↓ DBP: -6 (mm/Hg)</p>	None	All interventions were keto-type diets: All induced beneficial results

			↓ Blood Glucose: -8.28 mg/dL			
Randomized Clinical Trial NCT01865448	VLCD <50 g carbs (vegetables)	15 (Both) Obesity	↓HOMA-IR: -2.1. ↓Insulin: -52,09 (pmol/L) ↓Triglycerides: -56.5 (mg/dL) HDL: +0.1 (mg/dL) ↓LDL:-20.2 (mg/dL) ↓TC -29.0 (mg/dL) ↓Glucose -12.7 (mg/dL)	↓Weight:-20,4 (kg) ↓WC:-21,8 (cm) ↓fat mass:-13,5 (kg)	diet intolerance (vomiting) (N=1)	Compared to the same diet plan & DHA ²⁵ supplementation: both interventions effectively improve metabolic parameters, although DHA supp arm does better when it comes to anti-inflammatory results
Randomized Clinical Trial NCT03068078	LCHF <20% carbs	110 (Both) T2DM	↓HbA1c: -9.52 mmol/mol ↓Blood glucose: -25.41 mg/dl ↓Triglycerides: -32.74 mg/dL. ↑HDL:+3.86 mg/dL. ↑LDL:+ 8.88 mg/dL. ↓HOMA-IR -2.38.	↓Weight:-5,5kg ↓ WC:-5,1 cm ↓SBP:-5,5 mm Hg ↓DBP:-1,2 mm Hg	severe hypertriglyceridemia (n=1) nausea, fatigue, headachetizziness, constipation, diarrhea And no severe hypoglycemic episodes (n=11)	In comparison to HCLF: KD had better results in almost every parameter. Although increased LDL cholesterol in addition had more adverse results than control diet
Cross-over Trial NTC02417350	LCHF 4% calories from carbs	17 (Both) Healthy	↑LDLc: +70.38 (mg/dL) ↓Glucose: -8.82 (mg/dL) ↑HDL: +12.37 (mg/dL) ↓ Insulin: -20.41 (pmol/L). ↓Triglycerides: -11.6 (mg/dL) ↓TC: -87.2 (mg/dL)	↓ Weight	headache, fatigue and nausea (n = 4) feeling depressed (n = 1)) fatigue, nausea, and abdominal pain (n=1))	In comparison to Swedish National Food Agency recommended diet: Ketogenic diet induced beneficial results in blood glucose profile and HDL, although increased LDL, Triglycerides. In addition,

						adverse effects were reported only in keto-diet intervention
Cross-over Trial NCT03810378	WFKD ²⁶ 20–50 g Carbs/day	33 (Both) Prediabetes	<ul style="list-style-type: none"> ↑LDL-c: +13,4 (mg/dL) ↑HDL-c: +5,1 (mg/dL) ↓Triglycerides: -19,3 (mg/dL) ↓Glucose: -13,1 (mg/dL) ↓Insulin: -32,24 (pmol/L) ↓HbA1c: -0.64 (%) 	↓Weight -7,5 (kg)	high levels of ALT ²⁷ (n=1)	Both Diets Had Beneficial Results (Especially WFKD) Although Was Increased LDL in KD Type Diet
Cross-over Trial IRCT201105131485N3	MRC ²⁸ 43%-47% Total carbs	30 (Women) Overweight/obese With Mets ²⁹	<ul style="list-style-type: none"> ↓Insulin: -12,22 pmol/L ↓HOMA-IR: -0.34 ↓Triglycerides:-31.30 (mg/dL) ↑HDL: +1.50 (mg/dL) ↑LDL: +1.27 mg/dL ↓Total cholesterol: -2.70 (mg/dL) 	<ul style="list-style-type: none"> ↓SBP: -8.93 (mmHg) ↓DBP:-12,7 (mmHg) ↓Weight:-1,72 (kg) ↓Fat mass:-1,3 (kg) ↓WC: -3,93 (cm) 	None	In comparison to Iranian typical diet (65% carbs): Ketogenic diet had more beneficial results, although LDL cholesterol was increased
Cross-over Trial -	LCHF <50 g carbs/day	7 (Men) Healthy, runners	<ul style="list-style-type: none"> ↑TC: +54.4 (mg/dL) ↑HDL-C: +6.2 (mg/dL) ↑LDL-C :+44.2 (mg/dL): ↑Triglycerides: +2.6 (mg/dL) ↑Glucose: +2.3 (mg/dL) HbA1c: No change (0.0) (%) 	-	None	In comparison to HCLF: Keto diet both positive but also negative effects on blood lipid markers, suggesting it may improve HDL levels but could increase cardiovascular risk for some individuals.
Cross-over Trial -	KD 5% carbs	11 (Both) Overweight/obese	<ul style="list-style-type: none"> ↓HDL - 7.73 mg/dL ↑LDL + 11.60 mg/dL ↓Triglycerides - 61.99 mg/dL ↓TC- 19.34 mg/dL 	<ul style="list-style-type: none"> ↓ weight -2,7 (kg) ↓ fat mass -1,2 (kg) 	None	In comparison to pre-existed diet: Kd type diet had more beneficial results, although there was also increase of LDL

Cross-over Trial NCT01890070	VLCKD <20 g carbs	40 (Both) Overweight/obese	↓Blood Glucose: -9.54 (mg/dL) ↓ Insulin: -64.68 (pmol/L) ↓ HOMA-IR: - 2.36	↓ Weight -4,61 (kg)	None	Results for both groups (arm1: amino acids-arm2: placebo): VLCKD, with 50% of protein replaced by synthetic aminoacidic had more beneficial results than placebo group in which there occurred a negative change in blood lipid profile
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1= **LDL**: Low-Density Lipoprotein, 2= **HDL**: High-Density Lipoprotein, 3= **TG**: Triglycerides, 4= **HOMA-IR**: Homeostatic Model Assessment for Insulin Resistance, 5= **HbA1c**: Glycated Hemoglobin, 6= **HCLF**: High Carbohydrate Low Fat, 7= **T2DM**: Type 2 Diabetes Mellitus, 8= **LC**: Low Carbohydrate, 9= **SBP**: Systolic Blood Pressure, 10= **DBP**: Diastolic Blood Pressure, 11= **TC**: Total Cholesterol, 12= **FM-to-FFM ratio**: Fat Mass to Fat-Free Mass Ratio, 13= **HC**: High Carbohydrate, 14= **VLCK**: Very Low Calorie Ketogenic, 15= **DASH**: Dietary Approaches to Stop Hypertension, 16= **LCHF**: Low Carbohydrate High Fat, 17= **VLCKD**: Very Low Calorie Ketogenic Diet, 18= **HIIT**: High Intensity Interval Training, 19= **VLCD**: Very Low Carbohydrate Diet, 20= **MCCR**: Moderate-Carbohydrate Calorie-Restricted, 21= **MD**: Mediterranean Diet, 22= **FFM**: Free Fat Mass, 23= **BCM**: Body Cellular Mass, 24= **DHA**: Docosahexaenoic Acid, 25= **WKFM**: Well Formulated Ketogenic Diet, 26= **MRC**: Moderate Restricted Carbohydrate, 27= **ALT**: Alanine Transaminase, 28= **METS**: Metabolic Equivalent

*Bold Values indicate statistically significant results

** Keto drink (KD 4:1) every 4 grams of fat, there is a combined total of 1 gram of carbohydrates and protein

5. Discussion

In this systematic review, a total of 26 trials (comprising 24 RCTs and 2 non-randomized single-arm trials) investigated the possible association between changes in CVR factors and the KD, with comparisons to control groups where applicable. Based on the included trials, the KD (which was administered for up to 6 months in the longer trials and up to 2 weeks in the shorter trials) appeared to have a positive effect on changes in CVR factors for all the parameters examined (HDL, triglycerides, fasting glucose, fasting insulin, HOMA-IR, HbA1c, weight, WC, SBP, DBP), with the exception of LDL cholesterol.

With regard to the lipid profile of the blood, where the parameters LDL cholesterol, HDL cholesterol, and triglycerides were examined, it appears that the KD had deteriorating effects in terms of increasing LDL cholesterol. Still, beneficial effects contribute to an increase in HDL cholesterol and a reduction in triglycerides. In the studies reviewed, the KD increased LDL cholesterol by **12,73 mg/dL** compared with the control groups, which is a marker of CVR at high levels. Cases of KD inducing increases in LDL cholesterol have been reported in the literature, such as Patikorn's review of meta-analyses of clinical trials (Patikorn et al., 2023), which found a clinically meaningful increase in LDL-C associated with KD interventions.

In the trials included in the systematic review, there did not seem to be a clear pattern associated with a greater increase in LDL after KD intervention, such as a possible association with age, time of intervention, sex, or baseline weight of the participants. The exact mechanism associated with the increase in LDL cholesterol, as well as the potential change in particle size, could be a promising area for further investigation. In addition, the association with the type of fat intake, which was not examined in this study, could also be the subject of further research.

As such, it is worth noting that when a healthcare professional or a nutritionist is formulating the diet plan, efforts are made to target the addition of good fat in the diet; thus, in the setting of clinical trials, it makes sense to have a reduction of “bad” cholesterol. In numerous studies, both LDL and HDL cholesterol levels appear to increase. Given the nature of the ketogenic diet, this elevation may be attributed to the increased intake of dietary fats. However, replacing saturated fats with monounsaturated and polyunsaturated fats appears to improve lipid profiles and reduce cardiovascular risk. In particular, consumption of dairy products enriched with polyunsaturated fats have been shown to improve LDL and endothelial function in a clinical trial (Vasilopoulou et al., 2020), while replacing saturated fats with unsaturated fats from nuts or vegetable oils reduced LDL, non-HDL and total cholesterol in another study (Tindall et al., 2020). Omega-6 monounsaturates reduce LDL but may have a negative effect on LDL particle size and HDL2 (a larger form of HDL), whereas marine omega-3 monounsaturates (EPA, DHA) appear to have a protective effect by improving LDL density, reducing TGs, and increasing HDL (DiNicolantonio & O’Keefe, 2018). Therefore, a dietary strategy aimed at incorporating healthy fats is supported by clinical evidence and helps to reduce 'bad' LDL cholesterol.

Based on the above, when formulating dietary interventions, it is critical to consider potential adverse biochemical effects (such as an increase in total cholesterol or triglycerides due to high intakes of saturated fat or simple carbohydrates), particularly in the context of clinical trials, where researchers are emphasizing the inclusion of healthy fats that may help to reduce LDL cholesterol (Peters et al., 2016). Researchers should be careful to avoid adverse effects by tailoring interventions accordingly and possibly including a correction period after the trial has ended (Peters et al, 2016). At the same time, dietary advice is essential, especially for participants with increased body weight, to ensure their health. Overall, the rational design of nutritional interventions in clinical trials is crucial for the protection and well-being of participants (Lichtenstein et al., 2021; Tien et al., 2024).

The beneficial effect of the KD on the lipid profile is primarily associated with an increase in HDL cholesterol and a reduction in triglycerides. Specifically, HDL cholesterol showed favorable changes in nearly all trials following KD intervention, with an increase of **3,79** mg/dL compared to trials involving other dietary models (control groups). Additionally, a significant decrease in triglycerides was observed in the majority of trials, with a difference of **-23,02** mg/dL compared to the pooled results from trials investigating alternative dietary models. The findings of this systematic review regarding the increase in HDL cholesterol and the reduction in triglycerides are consistent with the results of a 2024 meta-analysis conducted by (Ghasemi et al., 2024). Commonly known as the “good cholesterol”, HDL helps transport the excess cholesterol from tissues and arteries back to the liver for removal. As such, HDL is praised for its atheroprotective functions, including its anti-inflammatory (protect artery walls), antioxidant, and cholesterol efflux-promoting properties (Welty, 2013). However, elevated triglyceride (TG) levels are associated with HDL dysfunction, impairing its antioxidant capacity and reducing its ability to exert anti-inflammatory effects. Lowering TG levels has been shown to improve HDL functionality by decreasing the pool of TG-rich lipoproteins and associated inflammatory mediators (Meneses et al., 2022). Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), (which promote HDL), exert cardioprotective effects partly by reducing hepatic very-low-density lipoprotein (VLDL) production and through direct anti-inflammatory actions, contributing to improved HDL particle quality and function (Peña-de-la-Sancha et al., 2023).

Although HDL is involved in atheroprotection, particularly through reverse cholesterol transport, the presence of elevated TG may compromise this role. This suggests that simply increasing HDL-C levels may not suffice to reduce cardiovascular risk, especially in the context of persistent hypertriglyceridemia (Tall et al., 2022). In particular, Welty (Welty, 2013) reported that elevated TG levels negatively affect HDL function by impairing its cholesterol efflux capacity. In individuals with high TG (mean 215 mg/dL) and low HDL-C (31 mg/dL), CEC was significantly reduced compared to normolipidemic controls. This dysfunctional HDL phenotype may contribute to residual cardiovascular risk, even in statin-treated patients who have achieved optimal LDL-C levels (<70 mg/dL), underscoring the importance of addressing both TG levels and HDL functionality in comprehensive cardiovascular risk management.

Reduction of the proportion of consumed carbohydrates has been associated in the literature with beneficial effects on the blood glucose profile. An overview of systematic reviews found a beneficial effect of low-carbohydrate dietary interventions for metabolic control in individuals with T2DM (Beretta et al., 2024). The data from this systematic review showed that the KD improved the glycemic profile in all parameters examined (fasting glucose, fasting insulin, HOMA-IR, and HbA1c).

The changes in fasting glucose levels seem to be correlated with the duration of the dietary intervention. In particular, in trials where the intervention lasted 3 to 8 weeks, a smaller reduction in fasting glucose was observed than in trials where the intervention lasted 12 weeks or more.

Additionally, the relative reduction in fasting glucose was more evident in studies with participants who had diabetes or prediabetes compared with studies that included people with obesity without a co-existing glucose metabolism disorder or healthy participants. A similar trend was observed in terms of fasting insulin reduction, with obese or overweight patients having a greater reduction in levels after the intervention was completed. In a study examining glucose changes in subjects with metabolic disorders and obesity, the effect of KD was greater than in a control group of normal weight patients without metabolic disease factors (Klonek et al., 2024), although as not many studies comparing ketogenic intervention to subjects with metabolic disorders and obesity to normal studies were detected, this could be a potential field for further research.

The effect of the KD was more favorable than that of the control groups on all parameters of the blood glycemic profile, in particular the differences with the control groups were **-7,07 mg/dL** for fasting glucose, **-14,21 pmol/mol** for fasting insulin and **-1,39** for HOMA-IR.

The results of this systematic review were also consistent with the literature in the body composition-related results. All of the included trials showed a reduction in body weight after the KD intervention. The direct and beneficial effect of the KD was also found in other systematic reviews and meta-analyses (Liao et al., 2024; Patikorn et al., 2023). In addition, the greater change in body weight mentioned in the results section of this study in obese or overweight individuals, is also a finding in the literature (Klonek et al., 2024).

In addition, the results of this systematic review suggest that weight loss was greater in trials that lasted more than 8 weeks. However, there was no linear relationship between duration and weight loss in trials that lasted more than 12 weeks. This pattern of greater weight loss within shorter intervals, followed by a reduction in the rate of weight loss over time, has been widely reported in the literature. Although the mechanism or cause of this phenomenon was not investigated in this systematic review. The potential cause, whether related to metabolic adaptations or challenges in adhering to the KD over extended periods, needs to be further investigated.

It should be noted that the control groups showed smaller overall weight changes compared to the KD interventions, confirming its effectiveness in weight regulation. The mean difference in weight loss between the control groups and the KD groups is **-3,13 kg**.

In terms of other body composition parameters, a reduction in WC is also a known effect of ketogenic diets in overweight and obese as well as healthy individuals (Lee & Lee, 2021; Patikorn et al., 2023). Similar results were found in this systematic review, with a reduction in WC in both obese or overweight participants and normal-weight participants. The KD also showed better results in this aspect, with the mean difference in WC reduction being **-3,65 cm**.

Furthermore, the reduction in Systolic and Diastolic blood pressure found in the present study for KD interventions links the results to the existing literature. Carbohydrate reduction was examined in subsequent analyses of ketogenic diets that found improvements in systolic and blood pressure (Ghasemi et al., 2024). The literature reports that carbohydrate reduction itself has a beneficial effect, in addition to the reduction caused by sodium chloride reduction (Appel et al., 2005).

The findings from the KD groups showed a clear improvement in both systolic and diastolic blood pressure. Additionally, the KD demonstrated superior outcomes compared to the control groups where such comparisons were conducted. The difference in reduction observed with the KD, compared to the control groups, was **-1,10 mmHg** for systolic blood pressure and **-1,40 mmHg** for diastolic blood pressure. However, the results of this review suggest that the KD appears to be less sustainable than other dietary models. The higher incidence of recorded adverse events, such as gastrointestinal symptoms and cases of ketoacidosis, along with the increased number of withdrawals and exclusions due to non-compliance, highlight challenges faced by participants in adopting and maintaining the diet. Taken together, these data demonstrate that, despite its potential benefits, the KD may be less acceptable and more difficult to maintain over the long term than other dietary interventions. This highlights the need for further, more structured and systematic research focusing on the relationship between ketogenic diets and adverse effects, as well as the factors influencing adherence during long-term interventions and the underlying reasons for participant dropouts.

Based on the above findings and considering the restrictive nature of this dietary model, the potential impact of the KD on lipid profile deterioration, associated risks, and possible adverse effects or deficiencies in essential nutrients (e.g., vitamins, trace elements) underscores the necessity for regular monitoring of individuals following this dietary regimen, as well as consultation with a healthcare professional. Although the KD appears to yield positive and rapid results, as demonstrated by this systematic review and supported by existing literature, including additional systematic reviews and meta-analyses, its safety remains a critical concern that requires further clarification. For instance, its effect on individuals without metabolic disorders, such as diabetes, with regard to potential further reductions in blood glucose levels highlights the need for additional research on its broader impacts. Moreover, the administration of the KD in individuals with elevated lipid profile biomarkers should be carefully examined, particularly concerning the observed increase in LDL cholesterol and the potential risk of reaching dangerous levels. Given the rapid and pronounced outcomes of this dietary approach in both healthy and obese individuals or those with metabolic abnormalities,

its implementation should be accompanied by continuous and thorough monitoring of key biomarkers.

This study has a number of limitations that need to be acknowledged. Firstly, the search was conducted in only two databases, which may have influenced the identification of suitable trials. Additionally, the time period reviewed included studies with relatively short intervention durations of up to 6 months, which may limit the long-term applicability of the findings. Furthermore, the included trials were relatively heterogeneous, with variations in the intervention interval, the age of the patients, and the different dietary patterns of the control groups. These factors may have contributed to the variability of the results.

In terms of the included studies, there were several notable limitations. Many of the trials did not report in detail on adverse effects or adherence to the ketogenic diet (KD). As a result, data on these aspects were recorded qualitatively, which may reduce the reliability of these findings. Furthermore, an important issue across all trials was that participants lost weight, which may complicate the interpretation of the effects of the KD itself. This highlights that investigating the benefits of the KD under conditions of weight maintenance is a potential area of future research.

6. Conclusions

The findings of this systematic review indicate that the ketogenic diet intervention appears to yield positive outcomes in improving glycemic profile, body composition parameters, and blood pressure. Furthermore, the KD demonstrates beneficial effects on the lipid profile, specifically by increasing HDL cholesterol and reducing triglycerides. However, it is crucial to emphasize that this dietary model was associated with an increase in LDL cholesterol levels, which are directly linked to atherosclerosis. Additionally, the KD has been reported to cause adverse effects and presents challenges in adherence for many study participants.

Additionally, the KD demonstrated superior outcomes across all parameters (except for LDL) compared to the control groups, where assessed. This finding highlights the need for further investigation into the safety of this dietary approach and underscores its potential for significant clinical applications.

Therefore, while the KD emerges as a potentially beneficial intervention with rapid positive metabolic outcomes, it should not be implemented under unclear conditions or without prior evaluation of the patient's specific pathological profile by qualified healthcare professionals. This dietary approach could serve as an effective initial strategy, potentially delaying the need for pharmacological treatment. However, it should always be administered under strict clinical supervision and based on medical guidance to ensure both the improvement of metabolic parameters and the simultaneous management of risks, such as excessive LDL cholesterol elevation, adverse events, and possible nutrient deficiencies stemming from the restrictive nature of this dietary pattern.

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Appendix

Appendix 1 Exact search strategy

PubMed: 377 results

((("Ketogenic diet" OR keto OR "very low carbohydrate diet" OR Ketosis OR "Ketone Bodies" OR "Low Carbohydrate High Fat Diet") OR ("Diet, Ketogenic/adverse effects" [Mesh] OR "Diet, Ketogenic" [Mesh])) AND (cvd OR "cardiovascular disease" OR "cardiovascular risk" OR "Heart Disease" OR Atherosclerosis OR Hypertension OR "Blood Pressure" OR Triglycerides OR "Lipid Profile" OR "Cardiovascular Risk Factors" OR "Myocardial Infarction" OR diabetes OR ("Heart Disease Risk Factors" [Mesh] OR "Cardiovascular Diseases/diet therapy" [Mesh])) AND ("Randomised control trial" OR "clinical trial" OR "controlled clinical trial" OR rct OR "Randomized Controlled Trial"[Publication Type])).

Scopus: 468 results

(TITLE-ABS-KEY ("Ketogenic diet" OR keto OR "very low carbohydrate diet" OR ketosis OR "Ketone Bodies" OR "Low Carbohydrate High Fat Diet") AND TITLE-ABS-KEY (cvd OR "cardiovascular disease" OR "cardiovascular risk" OR "Heart Disease" OR atherosclerosis OR hypertension OR "Blood Pressure" OR triglycerides OR "Lipid Profile" OR "Cardiovascular Risk Factors" OR "Myocardial Infarction" OR diabetes) AND TITLE-ABS-KEY ("Randomised control trial" OR "clinical trial" OR "controlled clinical trial" OR rct)) AND PUBYEAR > 2013 AND PUBYEAR < 2025

Appendix 2: Comparative outcomes to control groups

The table below lists the results of the KD interventions and the control groups, where available.

Appendix table 1 Comparison of the selected studies results with control group

Duration	Intervention (Ketogenic diet)				Control Groups			
	Sample Size & Sex	Primary Outcomes	Secondary Outcomes	Adverse Effects	Sample Size & Sex	Primary Outcomes	Secondary Outcomes	Adverse Effects
12 Weeks	14 (Both)	↑ LDL ¹ :+10 (mg/dL) ↑ HDL²:+8,5 (mg/dL) ↓ TG³:-32,8 (mg/dL) ↓ Glucose:-18,2 (mg/dL) ↓ Insulin: -34,4 (pmol/mol) ↓ HOMA-IR ⁴ : -1,57 ↓ HbA1c ⁵ : -0,1 (mmol/mol)	↓ Weight: -5kg ↓ WC: -4,8 cm	Not mentioned	12 (Both)	↓ LDL: -7.35 mg/dL ↓HDL: -1.16 mg/dL ↓TG -21.26 mg/dL ↓Glucose: -1.98 mg/dL ↑Insulin: +4,48 pmol/mol ↑HOMA-IR: + 0.12 ↑HbA1c: + 0,3 (mmol/mol)	↓ Weight:-2kg ↓ WC:-3,3 cm	Not mentioned
24 weeks	46 (both)	↓ Fasting glucose: 19.8 (mg/dL) ↓ Insulin:-46,2 (pmol/L) ↓ TC ⁶ :-11.6 (mg/dL) ↓ LDL-C:-11.6 (mg/dL) ↑ HDL-C:+7.7 (mg/dL) ↓ TG :-44.3 (mg/dL) ↓ HOMA-IR:-1,1 ↓ HbA1c:-28.4 (mmol/mol)	↓Weight:-12kg ↓WC:-10,6 ↓ SBP ⁷ :-11.0 (mmHg) ↓ DBP ⁸ : -8.2 (mmHg) ↓ FM-to-FFM ratio ⁹ : ↓Antiglycemic Medications	Gastrointestinal disorders (n=2)	47 (Both)	↓LDL: -11.6 mg/dL ↑ HDL: +1.9 mg/dL ↓ TG -8.9 mg/dL ↓Glucose:-28.8 mg/dL ↓Insulin: -39 pmol/mol ↓HOMA-IR: -1 ↓HbA1c: -20.8 mmol/mol	↓Weight:-11,5 kg ↓WC:-9,1 ↓FM-to-FFM ratio:0,1 kg/kg ↓Antiglycemic Medications ↓SBP:-8,7 (mmHg) ↓DBP: -6,4 (mmHg)	10 Dropouts (No Adverse Effects Mentioned)
17 Weeks	44 (Both)	↓ LDL:-2.1 (mg/dL) ↓ HDL:- 1.4 (mg/dL) ↓ TG:-35,9 (mg/dL) ↓ Glucose:-28 (mg/dL) ↓ HOMA-IR:-3,4 ↓ HbA1c:-0,9 % ↓TC:- 12,6 (mg/dL)	↓ Weight:-14,7 (kg) ↓ WC:-12 (cm) ↓Oral antidiabetic medication	nausea associated with ketosis(n=1)	44 (Both)	↓LDL: -2,7 mg/dL ↑HDL: +2,7 mg/dL ↓TG: -17,8 mg/dL ↓Glucose: -17,2 mg/dL ↓ HOMA-IR: -1,2 ↓HbA1c: -0,4 %	↓Weight:-5,05 kg ↓ WC:-5,4 cm	No Adverse Effects Mentioned

		↓Fasting glycemias:-28 (mg/dL)						
17 Weeks	23 (Both)	↓HbA1c:-0.35 (%)	↓Weight:-8,68 kg ↓ SBP:-9.77 (mmHg)	None	25 (Both)	↓HbA1c, % -0.14	↓Weight:-4,68 kg ↓ SBP: -5,18 (mm Hg)	3 Dropouts (No Adverse Effects Mentioned)
2 Weeks	8 (Both)	↓ TC:-18.3 (mg/dL) ↓ TG:-27.7 (mg/dL) ↓ LDL:-11.6 (mg/dL) ↓ HDL:-0.6 (mg/dL)	↓Body fat:-2,2 (kg) ↓WC:-4,8 (cm) ↓Weight:-5,9 (kg)	None	11 (Both)	↓TC :-11,9 (mg/dL) ↓TG: -1,2 (mg/dL) ↓LDL :-10.4 (mg/dL) HDL : -3,7 (mg/dL)	↓Weight:-3,4 kg ↓WC :-4,5 cm ↓Hip circumference :-2.1 cm ↓body fat :-1,3 kg	1 Dropout (No Adverse Effects Reported)
12 Weeks	18 (Both)	↑HDL:+1.7 (mg/dl) ↑LDL: + 14.9 (mg/dl) ↓TG:-108.6 :(mg/dl) ↓ HOMA-IR-1.4	↓Weight:-9,6 (kg)	None	21 (Both)	↑ HDL:+3 (mg/dl) ↓ LDL:-2,9 (mg/dl) ↓ TG: -25,1 (mg/dl) ↓HOMA-IR : -1.4	↓Weight:-8,7 kg	No Dropouts
8 Weeks	10 (Women)	-	↓SBP:-6.3 (mmHg) ↓DBP:-2.0 (mmHg)	None	11 (Women)	-	↓SBP: -0.4 (mmHg) ↓ DBP: -1.0 (mmHg)	No Dropouts
16 Weeks	20 (Both)	↑TC:+ 11.6 (mg/dL) ↑HDL:+ 3.9 (mg/dL) ↑LDL:+ (3.9 mg/dL) ↓ TG:- 26.5 (mg/dL) ↓ HbA1c:-6.4 (mmol/mol/or 0,6%) ↓ Fasting Blood Glucose:-48.6 (mg/dL) ↓ Mean Glucose:- 23.4 (mg/dL)	↓ Weight:-2,14 (kg) ↓WC:-2,4 (cm) SBP:no change ↓DBP:-2,3 (mmHg) ↑Increased diabetes quality of life	Hospitalized for Ketoacidosis(n=1), high ketone levels (N=2)	Single arm study			
24 Weeks	30 (Women)	↓HbA1c:-2.47(mmol/mol) ↓HOMA-IR:-1.39 ↓Insulin:-32,78 (pmol/L)	↓ Weight:-11,5 kg ↓BMI:-4,4 ↓ WC :-11,9 cm	None	Single arm study			

		<p>↑HDL-C:(mg/dL) +3.3 ↓LDL-C:-11.2(mg/dL) ↓TG:-27.1 (mg/dL)</p>	<p>↓SBP:-3.5 (mmHg) ↓DBP:-3.5 (mmHg)</p>					
12 Weeks	25 (Both)	<p>↓Glucose:-5.59 (mg/dL) ↓TG:-24.80 (mg/dL) ↑HDL-C:+1.16 (mg/dL) ↑LDL-C:+2.32 (mg/dL) ↓HbA1c:-2.0 (mmol/mol)</p>	<p>↓SBP:- 3 (mmHg) ↓DBP:-5 (mmHg)</p>	not able to follow diet (n=1)	19 (Both)	<p>↓Glucose: -3,78 mg/dL ↑ TG: +8,86 mg/dL ↓HDL-C: -1.16 mg/dL ↓LDL-C: -12,76 mg/dL ↓HbA1c: -1.0 mmol/mol</p>	<p>↓SBP: - 4 (mmHg) ↓ DBP: -3 (mmHg)</p>	2 (No Adverse Effects)
8 Weeks	19 (Both)	<p>↓Fasting glucose:-2.6 (mg/dL) ↓Fasting insulin:-29,6 (pmol/L) ↓HOMA-IR:-1.0 ↓ Cholesterol:-10.6 (mg/dL) ↓ LDL:-10.2 (mg/dL) ↑HDL:+7.3 (mg/dL) ↓ TG:-39.3 (mg/dL)</p>	<p>↓Weight -5,9 kg ↓Fat-4,1 kg</p>	None	15 (Both)	<p>↓ Fasting glucose: -1,8 mg/dl ↓Fasting insulin: -2,78 pmol/L ↑HOMA-IR: +0,1 ↑LDL: +1,9 mg/dl ↑HDL: +0,5 mg/dl ↓TG: -20,9 mg/dl</p>	<p>↓Weight -0,9 kg ↓Fat Loss-0,8</p>	No Adverse Effects Reported
12 Weeks	14 (Both)	<p>↑LDL-c: +19,35 mg/dL ↑HDL-c: +9,29 mg/dL ↓TG -15,95 mg/dL ↓Glucose -3.60 mg/dL ↓ Insulin:-10,33 pmol/L</p>	<p>↓Weight -4,12 (kg) ↓ WC: -2,81 (cm)</p>	amenorrhea (n=1) difficult to sustain (n=3)	Also Keto group (higher carbs %)			
12 Weeks	24 (Both)	<p>↓Glucose:-25.04 (mg/dL) ↓LDL:-15.85 (mg/dL) ↑HDL:+5.03 (mg/dL) ↓TG: -28.32 (mg/dL)</p>	<p>↓ Weight: -8,06 kg ↓ WC:-9,29cm</p>	Could not comply with diet (n=6)	29 (Both)	<p>↓Glucose: -9.73 mg/dL ↓LDL: -6,96 mg/dL ↑HDL: +1.16 mg/dL ↓TG: -13.28 mg/dL</p>	<p>↓Weight: -0,61 kg ↓ WC: -0,77 cm</p>	1(No Adverse Effects)

		↓TC: -20.49 mg/dL ↓Hba1c: - 0,92%						
12	46 (Both)	↑HDL-c:+16,28 (mg/dL) ↓TG:-84,32 (mg/dL) ↓Glucose:-21,6 (mg/dL) ↓Insulin:-12,98 (pmol/L) ↓HOMA IR: -2,35 ↓HbA1c: -0,49 (mg/L)	↓Weight: -13,72 kg ↓ Waist -14,06 cm	Could not comply with diet (n=4)	45 (Both)	↓HDL-c: -1,13 mg/dL ↓TG: -4,13 mg/dL ↓Glucose:-7,2 mg/dL ↓Insulin: -0,344 pmol/L ↑HOMA IR:+0,01 ↑HbA1c: +0,04 mg/L	↓weight: -0,77 kg ↑WC: +0,74 cm	Do Adverse Effects
26 Weeks	16 (Both)	↓ HbA1c :- 0.6 (%) ↓ TG: - 16,4 mg/dL (mg/dL) ↑ LDL: + 9.2 mg/dL (mg/dL) ↑TC (mg/dL) + 15.7 mg/dL ↑HOMA-IR: + 0.2 ↑HDL: + 3.5 mg/dL ↑Fasting Insulin: +1,2 pmol/L	↓ Weight -6,1 (kg) SBP: NO CHANGE	None	18 (Both)	↓ HbA1c : - 0.2 % ↓ TG (mg/dL) : - 15,7 mg/dL ↓ LDL: -10 mg/dL ↑HOMA-IR: + 0.3 points ↑HDL : + 2,3 mg/dL ↑Fasting Insulin: +18 pmol/L	↓Body Weight -1,7 (kg) ↓SBP: -0,3 (mmHg)	No Adverse Effects Mentioned
≥ 12 Weeks (Until Lost 5% Body Mass)	135 (Both)	-	↓Weight: - 6,64(kg) ↓ WC: -5,74(cm)	No Adverse Effects Mentioned	133 (Both)	-	↓Weight : -6,75 (kg) WC: -6,86 (cm)	No Adverse Effects Mentioned
3 Weeks	15 (Both)	↑TC +46.4 mg/dL ↑HDL: +11.6 mg/dL ↑LDL: +34.8 mg/dL ↓Glucose: -1.8 mg/dL • TG: No change ↓HbA1c: -0.1%	↓ weight:-1,2 (kg) ↓WC:-0,5 (cm) ↓fat mass: -0,4 (kg) ↑ SBP: +2 (mm Hg) ↑ DBP: +2 (mm Hg)	chest pain (n=1) auto-immune thyroid-it is (n=1)	15 (Both)	TC:No change HDL:No change LDL:No change Glucose:No change TG:No change ↓ HbA1c: -0.2%	↓ Weight:-2kg (kg) ↑WC:+2cm ↓ fat mass :-1kg ↑SBP:+8(mmHg) ↓DBP:6(mmHg)	7 (Headache And/Or Fatigue Or Withdrawn Consent Both Groups)
3 Weeks	20 (Both)	↓TC: -32 mg/dL ↓LDL:-27.2 mg/dL ↓HDL:- 6.6 mg/dL ↓TG: -16.6 mg/dL	↓Body fat: 2,46 (kg) ↓WC: -4,45 (cm) ↓SBP: -1,50	None	Also Keto group (higher carbs %)			

		↓ Blood Glucose: -8.28 mg/dL	(mm/Hg) ↓DBP: -6 (mm/Hg)					
26 Weeks	15 (Both)	↓HOMA-IR: -2.1. ↓Insulin: -52,09 (pmol/L) ↓TG: -56.5 (mg/dL) ↑HDL: +0.1 (mg/dL) ↓LDL: -20.2 (mg/dL) ↓TC: -29.0 (mg/dL) ↓Glucose: -12.7 (mg/dL)	↓Weight: -20,4 (kg) ↓WC: -21,8 (cm) ↓Fat Mass: -13,5 (kg)	diet intolerance (vomiting) (N=1)	Also Keto group (with DHA ¹⁰ sup)			
26 Weeks	110 (Both)	↓HbA1c: -9.52 mmol/mol ↓Blood glucose: -25.41 mg/dl ↓TG: -32.74 mg/dL. ↑HDL:+3.86 mg/dL. ↑LDL:+ 8.88 mg/dL. ↓HOMA-IR:-2.38.	↓Weight:-5,5kg ↓ WC:-5,1 cm ↓ SBP:-5,5 (mmHg) ↓ DBP:-1,2 (mmHg)	severe hypertriglyceridemia (n=1) nausea, fatigue, headachedizziness constipation ,diarrhea And no severe hypoglycemic episodes (n=11)	55 (Both)	↓HbA1c:- 3,47 mmol/mol (or - 0,27%) ↓Blood glucose: - 10,63 mg/dl ↓TG:-17,7 mg/dL. ↑HDL: +1,54 mg/dL. ↓LDL:-5,79 mg/dL. ↓HOMA-IR:-0,25	↓Weight:-1,7 kg ↓WC:-2,3 cm ↓SBP:-3,7 (mmHg) ↑DBP:+1,4 (mmHg)	Adverse Effects Mentioned But Less Than In Keto Arm. Total Drop Outs 4
23 Weeks (15 weeks Washout)	17 (Both)	↑LDL:+70.38 (mg/dL) ↓Glucose:-8.82 (mg/dL) ↑HDL:+12.37 (mg/dL) ↓ Insulin:-20.41 (pmol/L). ↓TG:-11.6 (mg/dL) ↓TC:-87.2 (mg/dL)	Weight ↓	headache, fatigue and nausea (n = 4) feeling depressed (n = 1)) fatigue, nausea, and abdominal pain (n=1))	17 (Both)	Not available data	Not available data	Not available data
24 Weeks	33 (Both)	↑LDL:+13,4 (mg/dL) ↑HDL:+5,1 (mg/dL)	↓Weight:-7,5 (kg)	high levels of ALT ¹¹ (n=1)	33 (Both)	↓LDL: -16,2 mg/dL ↓HDL: -0,1 mg/dL	↓Weight: -5,1	1(ransient ischemic attack

(No washout)		↓TG:-19,3mg/dL ↓Glucose:-13,1 (mg/dL) ↓Insulin:-32,24 (pmol/L) ↓HbA1c:-0.64 (%)				↓TG: -9,4 mg/dL ↓Glucose: -8,5 mg/dL ↓Insulin: -22,22 pmol/L ↓HbA1c: -0.32%		that occurred during the study followup, and was probably not related to the study)
6 Weeks (2 Weeks washout)	30 (Women)	↓Insulin:-12,22 pmol/L ↓HOMA-IR:-0.34 ↓TG:-31.30 (mg/dL) ↑HDL:+1.50 (mg/dL) ↑LDL:+1.27 mg/dL ↓TC:-2.70 (mg/dL)	↓SBP-8.93 (mmHg) ↓DBP- 12,7 (mmHg) ↓Weight:-1,72 (kg) ↓Fat mass-1,3 (kg) ↓WC -3,93 (cm)	None	30 (Women)	↓Insulin: -10,07 pmol/L ↓HOMA-IR -0.39 ↑TG:+0,13 (mg/dL) ↓HDL: -0,03 (mg/dL) ↓LDL: -3,30 (mg/dL) ↓TC: -4,83 (mg/dL)	↓Weight:-1,7 kg ↓Fat mass:-1,29 kg ↓WC:-2,6 cm ↓SBP:-2,97 (mmHg) ↓DBP:-1,77 (mmHg)	No Dropouts Due To Adverse Events
12 Weeks (2 Week-washout)	7 (Men)	↑TC: +54.4 (mg/dL) ↑HDL-C: +6.2 (mg/dL) ↑LDL-C : +44.2 (mg/dL) ↑TG:+2.6 (mg/dL) ↑Glucose:+2.3 (mg/dL) HbA1c:No change	-	None	7 (Men)	TC: No change ↓HDL: -4,5 (mg/dL) ↑LDL: +4 (mg/dL) ↓TG: -1,7 (mg/dL) ↓Glucose: -1,2 (mg/dL) ↑HbA1c:+ 0,1%	-	No Dropouts
3 Weeks (1 week Washout)	11 (Both)	↓HDL:- 7.73 mg/dL ↑LDL:+ 11.60 mg/dL ↓TG:- 61.99 mg/dL ↓TC:- 19.34 mg/dL	↓ weight:- 2,7 (kg) ↓ fat mass:- 1,2 (kg)	None	11 (Both)	↓HDL: -3,87 mg/dL ↓LDL -3,87 mg/dL ↓TG - 17,71 mg/dL ↓TC: - 19.34 mg/dL	↓ weight:- 0,5 kg ↓fat mass: -0,1 kg	No Dropouts Due To Adverse Events
3 Weeks (3 weeks washout)	40 (Both)	↓Blood glucose: -9.54 (mg/dL) ↓Insulin: -64.68 (pmol/L) ↓HOMA-IR:- 2.36	↓ weight:- 4,61 (kg)	None		Also keto group (with placebo)		

1= LDL: Low-Density Lipoprotein, 2= HDL: High-Density Lipoprotein, 3= TC: Total Cholesterol, 4= HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, 5= HbA1c: Glycated Hemoglobin, 6= SBP: Systolic Blood Pressure, 7= TG: Triglycerides, 8= DBP: Diastolic Blood Pressure, 9= FM to FFM ratio: Fat Mass to Fat-Free Mass Ratio, 10= DHA: Docosahexaenoic Acid, 11= ALT: Alanine Transaminase. *Bold Values indicate statistically significant results