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Review

Effect Of Ketogenic Diet In Obese Patients With Type 2 Diabetes : A Systematic Literature Review

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ABSTRACT

Background: Diabetes is non communicable diseases and fastest growing diseases worldwide, that cause many complications, lead to increased mortality and decreased quality of life in individuals. Diabetes complications can controlled by dietary intervention. Ketogenic Diet (KD) is one of trusted method that having beneficially effects for patients with Type 2 Diabetes Mellitus (T2DM). This paper aim to investigate the effect of KD in the patients T2DM.

Methods: This paper used the systematic review. Articles are selected using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analysis) based on google scholar and PubMed. The inclusion criteria in this writing are articles published within the last 5 years with keywords “Ketogenic Diet, Type 2 diabetes, clinical trial.

Results: The results show that KD had significantly beneficial effects on weight, Body Mass Index, Cholesterol, Blood Sugar, Fasting Insulin and HbA1c were decrease and quality of sleep were increased after intervention (p value < 0,001).

Conclusion: KD can controlled the body weight, blood glucose, lipids and also good for increased sleep quality in patients T2DM but have a low adherence for long term persistence.

INTRODUCTION

Diabetes is one of the diseases of the endocrine system characterized by increased blood sugar levels and causes various complications that can cause death and disability that reduce a person's quality of life. The prevalence of the disease continues to increase every year and is expected to affect 693 million adults by 2045[1]. According to the World Health Organization (WHO), diabetes is a non-communicable disease that is a major burden on health globally and is ranked 7th cause of death due to non-communicable diseases worldwide[2].

Diabetes is categorized into two types, namely type 1 diabetes (T1DM) caused by damage to pancreatic beta cells that produce insulin and type 2 diabetes (T2DM) caused by disruption of the body's response to insulin (insulin resistance)[3,4]. T2DM is a type of

chronic metabolic disease with a high incidence rate of disease that causes high morbidity and death rates worldwide due to multiple complications[5,6]. T2DM can cause complications in both the macrovascular system (cardiovascular disease) and the microvascular system (diabetic kidney disease, blindness, kidney failure and neuropathy[1,4,7,8], which pose a very high financial burden for treatment and care both in developed and developing countries[1].

Therefore, research on the management and efforts to prevent disease as well as prevent disability and complications due to this disease continues. One of them is through an approach to nutritional modification with various diet programs for people with T2DM disease. There is a lot of empirical evidence that supports that modification of the diet of T2DM sufferers is a very cost-effective strategy and has high efficacy in prevention and management efforts in T2DM sufferers[9,10]. One diet recommended for T2DM sufferers is a low-carbohydrate diet that contributes to a decrease in blood glucose in T2DM sufferers. However, the optimal amount and source of carbohydrates in this case is still unclear[9].

Based on relevant data, a low-carbohydrate diet, adequate and quality sleep and adequate physical activity can maintain blood sugar levels and help lose weight in T2DM sufferers with obesity[8,10]. There are several types of low-carb diets, including the ketogenic diet and the Mediterranean-plus diet[4,6,10-15]. The ketogenic diet is a diet pattern with a very low carbohydrate diet composition (20-50 grams per day), high in fat and enough protein[15]. Ketogenic diets force the body to break down fat into energy. Very little carbohydrate intake will encourage the occurrence of a condition of "ketosis" where the body will break down fat as a source of energy as a substitute for glucose[5,15-19].

At first, KD was used as a therapy for epilepsy in children and adults then continued to develop use in therapy in patients with cancer, heart, diabetes including obesity[15]. The application of KD as an intervention for T2DM sufferers began with various studies that found that obesity is one of the risk factors that greatly affect the incidence of T2DM and its complications[5]. In addition, KD is also believed to improve sleep quality which is also an important factor in the stability of blood sugar levels[20]. Seeing the many benefits of KD on T2DM sufferers, it is necessary to conduct further reviews on what are the effects of KD on T2DM sufferers as an effort to improve the quality of life of T2DM sufferers and efforts to prevent complications from this disease.

METHOD

The systematic preparation of this review is carried out by the process of searching, identifying, reviewing, selecting and selecting studies related to the effects of dietary ketogenesis on T2DM patients. The systematic preparation of the review begins with the search for articles relevant to the study on the search engines google scholar and PubMed by applying the PRISMA guidelines which contain guidelines for preparation steps consisting of Identification, Screening, Eligibility and Included.

To be eligibility, the article search format in this study uses the PICO (Population, Intervention, Comparator, Outcome) question format:

P – Population = T2DM sufferers, population at risk of DM

I – Intervention = Ketogenesis diet

C – Comparator = Other types of low carbo diets

O – Outcome = HbA1C, body weight, lipids, glycemic index and sleep quality.

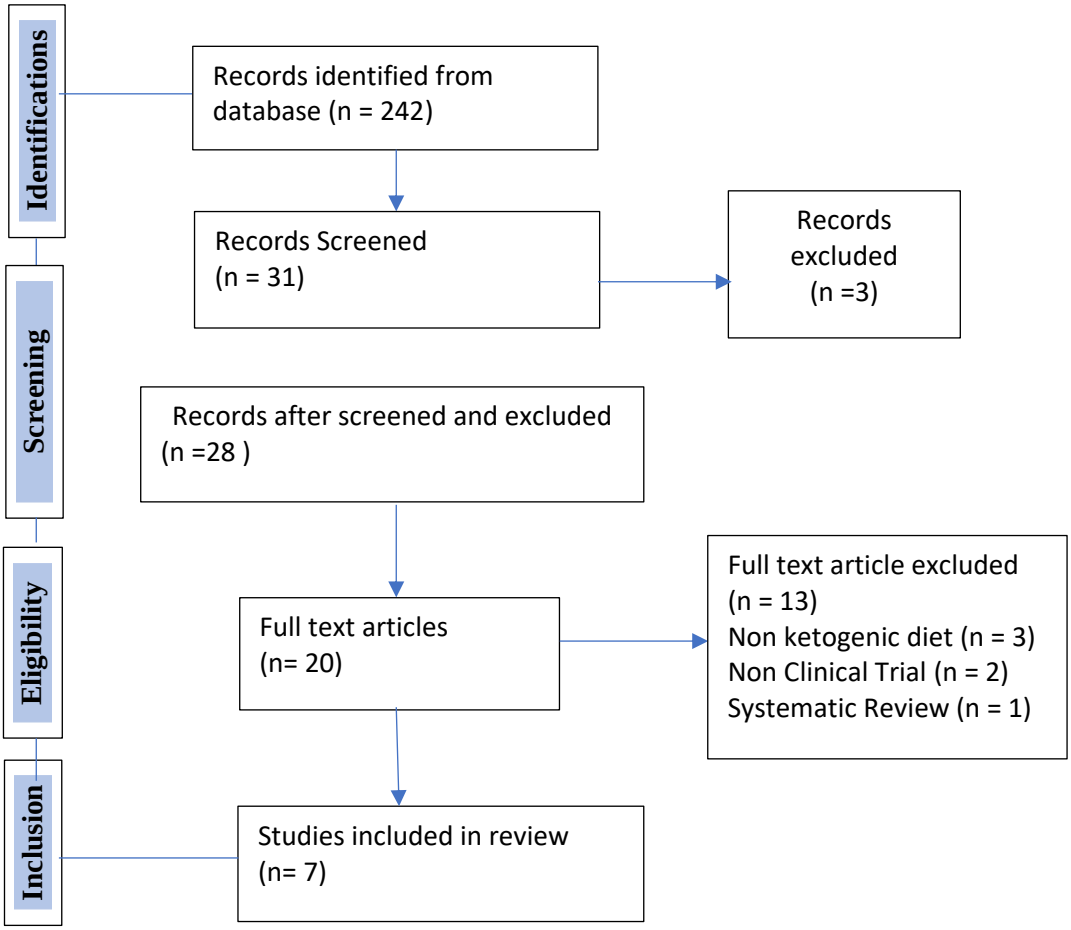

Figure 1. Study selection PRISMA flowchart diagram

The approach in data analysis used is quantitative descriptive study design. Data analysis was carried out by reviewing various previous studies. Furthermore, the data will be displayed in the form of a table containing descriptive text about the effect of dietary ketogenesis on T2DM sufferers. The inclusion criteria in this study are research conducted in the period 2018 – 2023, using a clinical trial study approach with variables of weight, cholesterol, fat, HbA1c, glucose in the blood and glycemic index.

Initial search results in the database using the keyword "diet ketogenesis and type 2 diabetes, clinical trial" resulted in 24 2 articles related to dietary ketogenesis and type 2 diabetes in the last 5 years. After screening, 31 articles with relevant titles and 3 duplicated articles were obtained so that 28 were obtained. Of the 28 articles, only 20 articles can be accessed in full, but 3 articles do not use clinical trial methods, 2 articles do not apply dietary ketogenesis as an intervention and 1 article is a systematic review so that the final results of the articles reviewed are 7 articles.

RESULT AND DISCUSSION

In all reviewed articles found that ketogenesis diet has a significant effect on weight loss, HbA1c levels in the blood, fasting blood glucose, fasting insulin, glycemic index, triglycerides, High Density Lipid (HDL), Low Density Lipid (LDL), Body Mass Index (BMI) with significant values (p value < 0.005). However, in one article it was also found that

although ketogenesis diet provides benefits for patients with type 2 diabetes mellitus (T2DM).

In addition, one article found that ketogenesis diet can continuously improve sleep patterns in patients with T2DM and prediabetes where sleep quality increases, sleep disturbances decrease and sleep duration becomes significantly longer (p value < 0.001). Improvements in sleep quality in patients with T2DM and prediabetes in this study affect diabetes status (glicemic control and drug use). However, this type of diet is difficult to implement in the long term because of the low level of adherence. The results of the reviewed articles are as shown in the following **Table 1.**

DISCUSSION

From the results of the systematic review, it was found in the results of the 7th study that ketogenic diet in T2DM patients has a significant influence and can be considered as one of the diet therapies in interventions to lose weight and glycemic levels and control the improvement of cholesterol levels in T2DM patients with obesity and increase high density lipid (HDL) levels which are good for health. Obesity that is often found in diabetic patients has a very close relationship with health status, especially in inflammatory conditions in mitochondrial dysfunction, oxidative stress in the endoplasmic reticulum and hyperinsulinemia. Weight control is one of the efforts in intervention strategies to reduce insulin resistance triggered by obesity[5].

Ketogenesis diet which is a low-carbohydrate, high-fat and normal protein diet which in these 7 studies provides ketogenesis diet intervention with an average carbohydrate intake of 30 gr, 60 g protein and 130 g fat is proven to be able to reduce HbA1c levels, body weight and triglyceride levels in the blood. This is in accordance with the results of research that ketogenesis diet will cause a ketosis condition in the body[21]. Low carbohydrates consumed will reduce glucose levels in the blood and also force the body to look for alternative ingredients as energy sources, one of which is fat so that it affects weight loss.

This restriction of carbohydrate intake also contributes to a decrease in monosaccharide absorption, more stable fluctuations in blood glucose and even a decrease in glucose in the blood which indicates an improvement in glucose metabolism for T2DM sufferers[5]. As in 2 studies which found that Kd caused a decrease in average glucose concentration by 1.29 mmol / L and a decrease in HbA1c by 1.07%. in addition, KD also increases HDL concentrations. So we can conclude that KD has a good role in controlling glycemia and lipid profiles in T2DM sufferers. The control group in the study that followed a routine diet of diabetes or other types of diets with higher carbohydrate intake levels in 4 studies showed higher HbA1c values and body weight and lipid profiles compared to the group identified with KD and slower decreases in HbA1c and body weight when compared to the KD group. Researchers also found that KD would be more effective when applied as an intervention to patients who were still in the prediabetes phase[4-6,8,16].

In addition to macrovascular and microvascular complications, T2DM sufferers also tend to experience sleep disorders related to hyprglicemia conditions. Lack of quality sleep in patients with T2DM will be a risk factor for obesity and various disorders of the body system including causing oxidative stress in the body[18,21]. In one study it was found that weight loss and blood sugar levels in T2DM sufferers were effective in improving the quality and quantity of sleep which triggered a decrease in the incidence of apnea and hyponea indices (AHI) which can help reduce HbA1c levels in the blood in T2DM sufferers[20].

Table 1. Summary of characteristics of Included Studies

Place	Study Design	Intervention Duration	Inclusion Criteria	Exclusion Criteria	Interventions	N	Outcomes
Sand Bay Area	RCT	12 weeks	Age ≥ 18 years with prediabetes diagnosis (HbA1c 5.7 - 6.4% or fasting glucose 100-125 mg/dL) or T2DM (HbA1c ≥ 6.5% or fasting glucose ≥ 126 ,g/dL)	Weight <110 lbs (50kg); BMI ≥40 kg/m2; LDL cholesterol 190mg/dL; systolic blood pressure > 160 mg/dl; or diastolic blood pressure > 90 mmHg; taking antihyperglycemic medications and weight loss medications	Comparing 2 metabolically distinct diets between well-formulated ketogenic diet (WFKD) and Mediterranean-plus diet (Med-Plus)	33	HbA1c, LDL Cholesterol, Weight Loss and HDL
Fujian Province, China	RCT	12 weeks	Age 18 - 50 years, BMI ≥25 kg/m2, newly diagnosed as T2DM (Type 2 Diabetes Mellitus), HbA1c <10% and without medication history of hypoglycemic agent.	Patients who had complication with serious heart, liver, lung, kidney or brain disease or history of serious acute or chronic complications for diabetes those who underwent infection, pregnancy, trauma or surgery and pregnant or lactating women and those who used drugs that may cause glucose metabolism disorders	Randomized intervention into two groups, ketogenic diet (KD) group which was given ketogenic diet and Control Group with routine diet for diabetes	60	HbA1c, Weight, Body Mass Index (BMI), Waist, Triglyceride, Cholesterol, Fasting Glucose and Fasting Insulin
Kelowna, BC Canada	Randomized Trial	4 days	Individuals with physician-diagnosed T2D with glycated hemoglobin (HbA1c) 6.5%, fasting plasma glucose (FPG) 7.0 mmol/l, or 2-h glucose oral glucose tolerance test 11.1 mmol/l and age 48 - 72 years.	Patient with exogenous insulin, and have been diagnosed cardiovascular, kidney, or any other diabetes complications, involved in a regular exercise routine (3 days of structured exercise per week) LCHF diet, or unwilling to consume the provided meat-containing diet	three short-term controlled-intervention periods in a randomized crossover design: 1) low-fat low-GI diet (GL), 2) low-carbohydrate high-fat diet (LC), and 3) LC with 15-min postmeal walks.	16	Glycemic Index

Place	Study Design	Intervention Duration	Inclusion Criteria	Exclusion Criteria	Interventions	N	Outcomes
Massachussets, Boston	Non Randomized Trial	1 years	Patients between age 21 and 65 years with either a diagnosis of T2D and a BMI > 25 kg/m2 or pre diabetes and a BMI > 3	Patient with diabetes complications	Patients received individual ized guidance in achieving nutritional ketosis, typically including restriction of daily dietary carbohydrates to less than 30 g	262	Sleep quality index, weight, fasting blood glucose, HbA1c, homeostatic model assessment of insulin resis tance (HOMA-IR), BHB and high sensitivity C-reactive protein (hsCRP)
United States	Randomized Trial	8 weeks	Age between 18 and 65 years of age with a BMI ≥ 30 kg/m2 , body weight less than 192.8 kg (425 lbs, the limit of the smart scale), had a tablet/smartphone with a camera and internet access, were not taking any medications for weight loss or diabetes, had no history of serious food allergies, no current eating or severe psychiatric disorders, were not currently taking psychiatric medications, had no special dietary requirements, and were not currently pregnant or breastfeeding.	Taking any medications for weight loss or diabetes, have history of serious food allergies, medication for severe psychiatric disorders or taking psychiatric medications,pregnant or breastfeeding.	200 kcal of mixed nuts (18 g fat, 5 g protein, 4 g carbohydrate) 12 h after the start of the fast for 5 days each week. The 12:12 (control) group consisted of a daily 12-h fast that began after dinner (between 5 and 8 pm) and ended with consumption of breakfast 12 h later. No fasting snack was administered in the 12:12 group. Dietary regimens for both the 14:10 and 12:12 groups were based on the Jenny Craig® Rapid Results™	78	Weight Loss and Fasting Blood Glucose
Standford	RCT	12 months	healthy women and men, aged 18–50years, with body mass index (BMI) 28–40kg/m2	Obesity and Severe Disease	During the first eight weeks of Limbo phase, participants were instructed to cut back on fat or carbohydrate intake progressively until they achieved a daily intake of no more than 20g of carbohydrate (HLC) or fat (HLF), which is consistent with a ketogenic or ultra low-fat dietary pattern, respectively. During the Titrate phase, participants were instructed to increase their fat or carbohydrate intake slowly, by 5–15g each week, until they achieved a comfortable maintenance level. In this phase participants were instructed to strive for the lowest intake of fat or carbohydrates they could realistically maintain for the 12-month intervention period, and even beyond the end of the trial should they experience positive benefits from their diet assignment.	609	Weight, Insulin Resistence, Blood Lipids
San Fransisco Bay Area	RCT	3 months	Age ≥ 18 with diagnosis of T2DM	Weighing < 110lbs (45 kg); BMI≥40; LDL cholesterol > 190 mg/dL; hypertension	Comparison of the effects of KD and Med-Plus diet on glycemic control, medication use and weight loss among overweight or obese individuals with type 2 diabetes mellitus or prediabetes	34	HbA1c, weight loss, dicontinued one or more diabetes medications

However, KD intervention in T2DM patients must also be kept under supervision because KD not only has a positive effect on the body but also negative effects such as hunger, constipation, nausea, vomiting and abdominal discomfort as well as muscle cramps. In addition, the application of KD in the long term can also increase ketone levels in the blood which results in ketones detected in urine, decreased appetite, acidosis and headaches to the formation of kidney stones, hypoproteinemia and macronutrients deficiency[8,11,13].

Another challenge in implementing KD as an intervention in T2DM sufferers is the low level of patient compliance in carrying out KD. In the studies reviewed, almost all studies had samples drop out because they did not want to continue the diet that was considered strenuous and tended not to continue when patients were asked to prepare their own food for KD therapy. In one study, ketogenesis diet was difficult to run persistently due to limitations in the ability to provide food, difficult access to food, increased hunger and discomfort that arose after running KD for more than 3 months (9), while KD therapy applied only in the short term tended to provide more positive results and higher patient compliance in running KD[4,8,9,16].

The limitation of this study is that the number of articles reviewed is only 7 articles and the group of cases taken is only limited to cases that do not have complications of diabetes and are not in other treatments such as hypertension and other diseases. In addition, there have been no studies in specific age groups in the study, so it is not yet known how effective the ketogenic diet is at various age levels.

CONCLUSION

The results of the current meta-analysis reveal that ketogenic diet intervention has remarkable benefits on body weight and glycemic control, as well as the improvement of lipid profiles in overweight T2DM patients. Specifically, a ketogenic diet can reduce body weight, waist circumference, HbA1c, and triglycerides, and increase HDL levels. Thus, the ketogenic diet intervention for overweight T2DM patients could be considered. Moreover, the ketogenic diet could reveal more benefits to the improved body compositions for mitigating the development and progression of T2DM due to overweight or obesity by lowering body weight, reducing glycemic levels, and improving lipid profiles. In the future, comprehensive mechanistic studies need to be conducted to underpin associations between ketogenic diets and overweight patients with T2DM, and even confirmed by experimental exploration.

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