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Effect of a Ketogenic Diet on Glycemic Control in Type 2 Diabetics

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by

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Abstract

With the increasing rate of patients diagnosed with type 2 diabetes mellitus (T2DM) and the serious complications associated with this disease, there continues to be controversy surrounding the most effective way to manage glycemic control in this population. The intention of this meta-analysis is to determine the effect of a ketogenic diet as a first-line treatment option on glycemic control in type 2 diabetic patients. Effectiveness was determined by comparing the ketogenic diet to other popular diets recommended to diabetics by practitioners following guidelines set forth by the American Diabetes Association. Several high-quality studies were selected utilizing PubMed, Dynamed plus, Cochrane Library, CINAHL, and Clinical Key databases with keyword and MeSH terms to narrow search results. The studies in the analysis provides data on the effects of the diets on HbA1c along with other parameters such as body weight, lipids, fasting and postprandial blood glucose levels of which can increase the risk of complications and associated diseases in T2DM patients. According to several studies, initiation of a ketogenic diet as a first-line treatment plan does not improve health parameters more than the current recommended diets for T2DM patients. With multiple diet plans providing health benefits in a type 2 diabetics, the main component of success was diet adherence. The research does show promise, but the treatment plan will need to be individualized based on the patient's readiness and willingness to implement lifestyle changes.

Keywords: ketogenic diet, type 2 diabetes mellitus, HbA1c, blood glucose, low carbohydrate diet

Introduction

In the United States alone there are more than 34 million Americans with a diagnosis of diabetes mellitus, with the majority (90-95%) being type 2 diabetics, and 1.5 million new cases annually (American Diabetes Association [ADA], 2020). With these drastic numbers and the obesity rate rising, it is time to investigate the most effective, long-term, and cost-efficient way for this population to successfully manage their disease. According to the ADA (2020), T2DM is the seventh leading cause of mortality in the United States, with about 10% to 15% listed as the underlying cause of death along with countless unaware and undiagnosed. There are several medications available to treat diabetes, but what is often ignored is the possibility of treating T2DM with diet and exercise. With the billions of dollars spent on medical costs and reduced productivity due to T2DM, this disease is a serious health and economic problem. One-way people living with T2DM manage their blood sugar is through diet. A ketogenic diet consists of drastically reducing carbohydrate intake with the replacement of high fat. The ketogenic diet is a strict nutritional regimen consisting of low-carbohydrates, high-fat, and sufficient protein that pushes one into a state of ketosis, where the body's fat storage provides most of the fuel for the body as the glucose reserve is depleted (Blanco et al., 2019). The purpose of this study is to determine if a ketogenic diet will improve the glycemic control of people living with T2DM.

Statement of Problem

With the persistent rising number of patients with T2DM, medical providers encounter these patients daily and face the challenge of the abundant possibilities available as treatment options. These options need to be backed by evidence-based medicine to prove their effectiveness as a first-line treatment option along with the ability of the treatment to be successfully implemented into the patient's lifestyle. A ketogenic diet should be a first-line treatment option in terms of effectiveness on glycemic control in patients living with T2DM. This research will help guide medical providers and patients with a nutritional option as their treatment plan for managing blood sugar in a T2DM patient.

Research Question

Does a ketogenic diet influence the improvement of glycemic control in patients who are living with T2DM?

Methodology

Studies included in the review of literature will focus on a ketogenic diet and its effect on glycemic control in people living with T2DM. This literature review utilizes electronic search databases that include PubMed, Dynamed plus, Cochrane Library, CINAHL, and Clinical Key to research the above-mentioned topic. Keyword and MeSH terms were used to narrow search results. The MeSH terms included: “ketogenic diet AND type 2 diabetes mellitus” with 33 studies, “ketogenic diet AND blood glucose” with 100 studies, and “low carbohydrate diet AND type 2 diabetes mellitus” with 227 studies. Several of the studies were excluded since the focus did not coincide with the topic of a ketogenic diet in glycemic control in a T2DM patient. Most of the research came from peer-reviewed articles from the last 10 years. The articles selected demonstrated an in-depth study of diet and type 2 diabetics. Excluded from this study were articles that did not include diet effects on health parameters.

The literature review generated high-quality research studies that explored the efficacy of treatment for T2DM. The studies focused on the ketogenic diet and the effectiveness of glycemic control in treatment for T2DM. In addition to a ketogenic diet, the studies include other low-carbohydrate diet variations because a ketogenic diet as a solo treatment for T2DM is not currently widespread. With the limited studies on diet alone in glycemic control, this area of research will grow with the increasing costs of healthcare and the loss of productivity due to T2DM. There are several diet treatments utilized by practitioners and nutritionists that claim to benefit type 2 diabetics, but the diet therapy that is going to be focused on in this project will be the ketogenic diet, which includes low-carbohydrate, high-fat diets. The main parameter that will be studied is the effect on glycemic control by using fasting and post-prandial blood glucose levels and hemoglobin A1c (HbA1c). Additionally, the research will include information regarding the treatment's effect on other health parameters including body weight, waist circumference, body mass index (BMI), total cholesterol, low-density lipoproteins (LDL) cholesterol, high-density lipoproteins (HDL) cholesterol and triglycerides to name a few. The ketogenic diet will be explored to determine what recommendations and education can be given to patients diagnosed with T2DM by evaluating the safety, advantages, disadvantages, and the effectiveness of the therapy.

Ketogenic Diet Management of T2DM

To understand the theory behind treating patients living with T2DM with a ketogenic diet, we must first understand the underlying pathophysiology of T2DM. According to Feinman et al. (2015), there is a fundamental disturbance with the metabolism of carbohydrates in diabetic patients. Hyperglycemia is the result of this disturbance due to an increase of carbohydrates that are not metabolized (Feinman et al.). It then is sensible that if a person takes in fewer carbohydrates, there will be fewer carbohydrates left unmetabolized, which would lead to decreased glycemic levels in the body.

The ketogenic and low-carbohydrate diets are used interchangeably in many of the research studies. The definition of these diets is not well defined and varies throughout the studies on the topic. Feinman et al. (2015) and Huntriss, Campbell and Bedwell (2018) agree on the guidelines for classifying carbohydrate ranges. A low-carbohydrate diet was defined as <130 g/d amounting to less than 26% of the 2000 kcal/d diet. This range is obtained from the levels of carbohydrates to induce ketosis for most of the population. The range of carbohydrates to be classified as a low-carbohydrate diet is defined as between 51-130 g/d which is less than 26% of a 2000 kcal/d diet, a moderate-carbohydrate diet is 26-45% of a 2000 kcal/d diet, and a high-carbohydrate diet is defined as greater than 45% of a 2000 kcal/d diet coming from carbohydrates which have been the recommended target placed by the ADA (2020).

Safety of Using Ketogenic Diet Management as First-Line Treatment of T2DM

The safety with the use of a ketogenic diet in diabetic participants has been of concern due to the risks of developing diabetic ketoacidosis. Blanco, Khatri, Kifayat, Cho, and Aronow, (2019) performed a case study of starvation ketoacidosis due to ketogenic diet and prolonged fasting in a 60-year old male. This study looked at the concerns of intermittent fasting throughout a ketogenic diet presenting the challenges of a broad differential. This case report consisted of a 6o-year-old male with well-controlled T2DM who was following a strict ketogenic diet who then underwent prolonged fasting which resulted in starvation ketoacidosis. The patient presented to the emergency department after having a witness report an episode of syncope at home. He was a follower of the ketogenic diet who engaged in intermittent fasting. Following this diet and increasing his exercise for the past year, he reported losing 20 pounds and decreasing his HbA1c from 11.5% to 7.0%. Wanting to continue to improve his diabetes management he decided to omit food and only drink water for 5 days intending to transition into ketosis at a quicker rate. He broke his fast by eating soup and taking his usual chlorophyll supplement which caused him to vomit and become dizzy which later resulted in a syncope episode. In the emergency department his laboratory evaluation showed a glucose of 133 mg/dL, serum bicarbonate 19 mEq/L, anion gap 15 mEq/L, venous lactic acid 1.8 mmol/L, positive serum acetone in a diluted serum 1:4, plasma osmolality 305 mOsm/kg, sodium 139 mEq/L, and HbA1c 7.0%. A urinalysis had 2+ ketones and was negative for glucose and pH from a venous blood gas on admission was 7.20. These results indicated ketoacidosis being the most probable cause due to starvation. With treatment in the emergency department, his lab values normalized the next day. In the research by Blanco et al., a review of the study by Mohorko et al. (2018) was performed about obese adults that underwent a 12-week ketogenic diet, there was considerable weight loss with –18±9 kg in men and –11±3 kg in women. Emotional eating decreased and body image satisfaction increased. Another study Blanco et al. reviewed written by Goday et al. (2016), found that participants who followed a very low-calorie ketogenic diet had a significant reduction in weight loss, waist circumference and improved glycemic control compared to those following a hypocaloric diet. There is data regarding the short-term success of a ketogenic diet, with only limited data regarding the long-term success. This may be due to the difficulty of maintaining a strict low-carbohydrate diet for longer periods. Even though the ketogenic diet might yield short-term weight loss, there are potentially dangerous side effects, including ketoacidosis, especially those with comorbidities such as T2DM. Clinicians must keep a broad differential when evaluating acute metabolic acidosis according to Blanco et al. The small, one-person population is a limitation to this study. This case study involved a subject that went to the extreme of fasting for 5 days due to the previous success of the shorter fasting periods, which is not recommended in the ketogenic diet.

In the research that Blanco et al. (2019) performed there was a review of the study by Goday et al. (2016) that conducted a prospective, open-label, multi-centric randomized clinical trial to evaluate the short term safety and tolerability of a very low-calorie-ketogenic diet. The study consisted of T2DM participants restricted to <50 g of carbohydrate a day as an interventional weight loss program that included support for lifestyle and behavioral modification. The sample size contained 31 males and 58 females with T2DM and BMI of 30-35 kg/m^2 that were between the ages of 30 and 65 years old. This was a 4-month study with 45 subjects that consisted of 15 males and 30 females, randomly assigned to the very low-calorie-ketogenic diet, and 40 subjects that consisted of 16 males and 28 females, to the standard low-calorie diet. The research subjects had their parameters checked at baseline, after 2 weeks, 2 months, and 4 months. The results of the study based on the 89 individuals showed no significant differences in the laboratory safety parameters between the two study groups. Goday et al. found that throughout the 4-month timeframe, sodium, potassium, chloride, calcium, and magnesium remained stable and within the normal limits in both the very low-calorie-ketogenic diet group and the standard low-calorie diet group. There were no significant changes in the urine albumin-to-creatinine ratio in the very low-calorie-ketogenic diet group and were comparable to the standard low-calorie diet group. Baseline urine albumin-to-creatinine ratio and creatinine and blood urea nitrogen did not change substantially with either group. There were no serious adverse events that were reported with mild adverse events of increased alanine aminotransferase (45.16 vs 26.85 IU ml^{-1}, $p<0.005$) and aspartate amoinotransferase (38.53 vs 22.15 IU ml^{-1}, $p<0.001$) in the ketogenic diet group which had declined at the last follow up. Another mild adverse event was the increase of mean uric acid level in the ketogenic diet group at 2 weeks ($p=0.021$), but not at the 2- or 4-month checks. The bilirubin plasma concentration remained invariable over the study and did not differ between the groups. Among the pre-defined adverse events, asthenia, headache, nausea, and vomiting were more common in the very low-calorie-ketogenic diet group at 2 weeks (all $p <0.05$). The number of subjects reporting these adverse events in the very low-calorie-ketogenic diet group declined at the last follow-up. At the end of the study, eight participants had an adverse event of constipation ($p < 0.005$) and six with orthostatic hypotension ($p < 0.05$), these adverse events come from subjects in the very low-calorie-ketogenic diet group. The pre-defined adverse events were more frequent in the very low-calorie-ketogenic diet group at 2 weeks but not at 4 months. The very low-calorie-ketogenic diet group had a significantly larger reduction in weight loss and waist circumference compared to the standard low-calorie diet group (both $p < 0.001$). At the completion of the study, 85% of the very low-calorie-ketogenic diet subjects achieved a weight loss of 10% relative to baseline. The very low-calorie-ketogenic diet group also had a greater decline in HbA1c and better glycemic control ($p < 0.05$). Fasting plasma glucose decreased significantly in the two study groups relative to baseline (both $p < 0.05$), although the decline in HbA1c was statistically significant only in the very low-calorie-ketogenic diet group ($p < 0.0001$). Insulin sensitivity at the end of follow up was statistically lower in the very low-calorie-ketogenic diet than in the standard low-calorie diet group (3.51 vs 4.61; $p < 0.05$). It was concluded that the ketogenic diet is safe over a 4-month period with good tolerance and accepted medical nutritional therapy option for T2DM participants. The limitations to this study were some of the exclusions which included duration of type 2 diabetics greater than 10 years, HbA1c ≥ 9%, and insulin therapy. With the aging population with T2DM, many patients have been living with T2DM for over 10 years so this information may not pertain to them. The benefits this study found by following a very low-calorie-ketogenic diet may have an even larger impact on those who do not have very good control on their blood glucose and on the very high end of HbA1c (≥ 9%) but this group was excluded. Many T2DM patients need to have better glycemic control and are likely taking insulin trying to maintain their blood sugars but this population was not allowed to take part of this study. The short duration of the study is another limitation, so a long-term safety and efficacy of a very low-calorie-ketogenic diet as a medical nutritional therapy strategy warrants further evaluation.

With the limited evidence for acid-base safety and the potential risks of ketoacidosis for diabetics following a very low-calorie-ketogenic diet, Gomez-Arbelaez et al. (2017) performed a clinical trial that evaluated the acid-base safety throughout the course of a very low-calorie-ketogenic diet. This research looked at the anthropometric (muscle, bone, and adipose tissue), biochemical parameters, and venous blood gasses of participants following the ketogenic diet over a 4-month period. The study population consisted of participants attending the obesity unit at a university hospital to receive treatment for obesity. The patients needed to meet the inclusion criteria that involved a BMI of $\geq$ 30 kg/m^2, stable body weight in the previous 3 months, a desire to lose weight, and a history of failed dietary efforts, with an age range of 18 to 65. The weight loss program included a lifestyle and behavior modification support and was broken down into five steps. The first three steps consisted of a very low-calorie-ketogenic diet where subjects consumed 600-800 calories a day, less than 50 grams of carbohydrates daily from vegetables and lipids consisting of only 10 grams of olive oil per day. The ketogenic phases ended in step four and the patients started a low-calorie diet of 800-1500 calories a day. In step five the calories increased slightly, between 1500 and 2000 calories a day depending on the individual, and the target was to maintain the weight loss. Throughout the study, the patients completed visits every 15 $\pm$ 2 days for a complete physical, anthropometric, and biochemical assessment, to control adherence and to evaluate side effects. The first visit was baseline with a normal level of ketone bodies, the next few visits were at maximum ketosis at approximately 1 to 2 months of treatment, during steps four and five there was a reduction of ketosis due to partial reintroduction of normal nutrition at 2 to 3 months and the last visit at 4 months there was no ketosis. The total ketosis state lasted for only 60-90 days. The results showed that there were some differences in electrolytes and blood urea nitrogen but none of them were considered clinically relevant. The baseline blood pH was 7.37 ± 0.03, almost 40 days on the ketogenic diet and the point of maximum ketosis the pH was 7.37 ± 0.02 and remained unchanged for the remainder of the study. With the literature defining diabetic ketoacidosis at ≤7.30, all measurements retained baseline levels and well away from the cut-off associated with diabetic ketoacidosis. It is also notable that the values for plasma bicarbonate remained unchanged and within the normal ranges with levels ranging from baseline of 24.7 ± 2.5 mmol/l to the final visit of 25.8 ± 2.0 mmol/l. Lactic acid did not show significant variations during the study, and the calculated anion gap or osmolarity was not statistically altered and always in the reference range. This observation shows a considerable improvement in insulin sensitivity with regards to body weight reduction and agrees that a ketogenic diet induces a well-tolerated ketosis rather than ketoacidosis in patients with an acceptable insulin function. This research by Gomez-Arbelaez et al. compared a cohort of diabetic patients with ketoacidosis. It was stated that the blood pH was significantly lower in diabetic patients with ketoacidosis than the group studied in their research. The diabetic patients with ketoacidosis with a pH of 7.16 ± 0.12 ($p < 0.001$) vs. the very low-calorie-ketogenic diet group with a pH of 7.37 ± 0.02 ($p < 0.001$). The serum bicarbonate was also significantly lower in the cohort of diabetics at 12.3 ± 5.7 ($p < 0.001$) compared to the very low-calorie-ketogenic diet group at 23.6 ± 2.4 ($p < 0.001$). There were also significant differences in electrolytes values, including the anion gap which was much higher in the cohort of diabetic patients with 30.3 ± 7.9 ($p < 0.001$) vs. 13.5 ± 2.2 ($p < 0.001$) in the very low-calorie-ketogenic diet group. The plasma glucose levels were substantially higher in the diabetic patients, strengthening the idea that underlying alterations in glucose metabolism play a critical role in the pathogenesis of ketoacidosis (Gomez-Arbelaez et al.). There were limitations to this research, one of which was the exclusion of diabetes mellitus patients. Even with the exclusion of diabetics, the research provided important information by comparing their results to a cohort of diabetic patients. When comparing diet-induced ketosis and diabetic ketoacidosis it was not stated whether the cohort of diabetics were type 1 or type 2 diabetics. This is important since the research by Blanco et al. (2019) stated that there is a much larger risk for ketoacidosis in a type 1 diabetic compared to a very small risk in patients living with T2DM.

Advantages of Using Ketogenic Diet Management as First-Line Treatment of T2DM

The most common parameters when examining the many research articles looking at the effects of a ketogenic diet on T2DM, seem to have a focus and highlight the effects on weight loss, lipids, glycemic control with plasma glucose and HbA1c. These topics will all be discussed, but the focus will continue to be the effect of the ketogenic diet on glycemic control. Through a systematic review and meta-analysis, Ajala, English, and Pinkney (2013) researched different dietary approaches to the management of T2DM. The glycemic control, lipids, and weight loss of various diets were assessed for their effectiveness on these parameters. Outcome measurements of interest were HbA1c, used as the measure of glycemic control, difference in weight loss, and changes in HDL cholesterol, LDL cholesterol, and triglycerides. This research utilized a search of PubMed, Embase, and Google Scholar. A total of 20 randomized controlled trials were included with interventions that lasted 6 months or longer. The diets compared low-carbohydrate, vegetarian, vegan, low-glycemic index, high-fiber, Mediterranean, and high-protein diets with control diets including low-fat, high-glycemic index, American Diabetes Association recommended diet, European Association for the Study of Diabetes recommended diet, and low-protein diets. A total of 1,801 records were identified from the initial electronic search, with an additional 64 records from other sources. Ajala et al. studied 55 articles, excluding 35 of those studies because they were not randomized trials, or the intervention lasted less than 6 months. There were 3,460 patients included in the 20 studies with the final analysis of 3,073 patients. Four of the studies included patients with and without diabetes, with one of those studies that provided data on the change in glycemic control in the diabetic group. All participants were ≥18 years old, and all but one study included both males and females. There were six studies omitted for two reasons, insufficient evidence, and participants without T2DM. There were four studies with insufficient evidence to compare to other studies in the subgroup and two studies had participants without T2DM within their research. The results of this study revealed that the low-carbohydrate, Mediterranean, high-protein, and low-glycemic index diets all were able to reduce HbA1c by a range of 0.12% to 0.5% when compared to the control groups. The impact of these numbers was noted that a 0.5% decrease in HbA1c is comparable to the amount accomplished by medication management. Ajala et al. found that the low-carbohydrate diet successfully raised the participant's HDL cholesterol an average of 10% ($p < 0.00001$) from the included studies. The LDL cholesterol did not change for the low-carbohydrate diet group in the same studies. According to Ajala et al., an argument can be made that a low-carbohydrate diet would be beneficial for patients with T2DM due to the added benefit of possibly increasing HDL cholesterol and decreased triglycerides. There are limitations with this meta-analysis, one being that none of the trials included in the research reported any significant differences in characteristics of participants in the intervention or treatment groups. There are substantial confounders with this meta-analysis of such varied interventions. The control diets were different in terms of the specific macronutrient composition, study participants sometimes had different baseline characteristics with parameters such as weight and HbA1c, the duration of the studies ranged between 6 months and 4 years and some studies failed to report on allocation concealment and assessor blinding even though all studies included in this meta-analysis were random control trials. Therefore, with all these various features, it introduces confounding effects in the analysis. Ajala et al. stated that additional research should involve large trials that compare these diets in subjects with similar characteristics for the same duration. With the few studies analyzed on the Mediterranean and high-protein diets, the results should be interpreted with caution. The independent effect of weight change on the other measured variables such as glycemic control and lipid profile was another major confounder. It is difficult to isolate the effect of weight change on these cardiovascular risk markers. The results could be due to weight loss rather than the low-carbohydrate diet. Future research aims to keep weight constant or ensure an equal caloric intake in subjects would be useful to help clarify this issue (Ajala et al.).

A review was performed by Jung and Choi (2017) exploring the impact of a high-carbohydrate diet versus a low-carbohydrate diet on many metabolic parameters in patients with T2DM. This review examined different aspects, definitions and populations from various organizations and research on high-carbohydrate and low-carbohydrate diets. In this meta-analysis the parameters of concern that were compared included HbA1c, LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides that they compiled in their literature review. The authors referenced many studies though out their research with 98 resources sited but did not state how they produced these resources. The authors found no meaningful differences between the two diets in terms of the capability to decrease LDL cholesterol and total cholesterol. It was found that the low-carbohydrate diet was more effective at raising HDL cholesterol and lowering triglycerides. There were equivalent results that produced no difference in HbA1c when comparing the low-carbohydrate and high-carbohydrate diet groups. Even though these studies resulted in no difference in the HbA1c at their conclusion, there were still health parameters other than HbA1c that the participants benefitted from utilizing the low carbohydrate diet that would greatly improve the health of patients living with T2DM. Jung and Choi concluded that there are conflicting results with the numerous studies that have compared the effectiveness of high-carbohydrate diets with low-carbohydrate diets on weight reduction, glucose control and lipid profiles in patients with T2DM. Many of the studies highlighted the difficulties in achieving good patient compliance with the dietary treatment in the long-term, independent of what the diet was composed of. Choosing an easy diet that the patient can follow is an important aspect of the medical nutrition therapy for T2DM. There are several limitations to this meta-analysis regarding the lack of a standardized definition for what a high-carbohydrate and low-carbohydrate diet consists of, which makes it difficult to interpret the effects of dietary carbohydrates. Many of these studies have been mainly obtained from Western populations neglecting many groups that struggle with the same issues. Data derived from large, randomized control trials involving populations of diverse ethnicity are required to fully understand the impact these diets have on the population as a whole. With the debate around what constitutes high and low-carbohydrate intake, it becomes difficult to define the ideal amount of daily carbohydrate intake.

In a meta-analysis for the American Diabetes Association, Kodama et al. (2009) researched the influence of fat and carbohydrate proportions on the metabolic profile in patients with T2DM. In this study a low-fat, high-carbohydrate diet was compared to a high-fat, low-carbohydrate diet, with the effect on glycemic control being one of the parameters. The methods of the study involved a search for randomized trials with search criteria that included MEDLINE with a date range between 1966 through 2007, the Cochrane Library Central Registry of

Controlled Trials between 1984 and 2007, medical subject heading terms: diabetes and (food or diet) and utilized those reference lists of those publications to identify additional studies. The search was restricted to randomized controlled trials published in English. The search involved two types of prescribed diets and their effects on patients excluding type 1 diabetics. The energy and protein intake did not differ significantly between the two dietary groups among these studies. There were 19 studies analyzed that included 306 patients that met their inclusion criteria. Median diet composition of carbohydrate/fat in the low-fat, high-carbohydrate diet group was 58%/24% and the high-fat, low-carbohydrate diet group was 40%/40%. The results found that there was a 13.4% ($p < 0.001$, CI = 95%) decrease in triglycerides with the high-fat, low-carbohydrate diet when compared to the low-fat, high-carbohydrate diet group. The research results by Kodama et al. showed that the low-fat, high-carbohydrate diet had an increase of fasting glucose by 8.4% ($p = 0.02$, 95% CI = 7.2% to 9.6%) along with higher two-hour glucose and insulin values in the low-fat, high-carbohydrate group than in the high-fat, low-carbohydrate group by 10.3% ($p < 0.001$) and 12.8% ($p < 0.001$) respectively. Changes in fasting plasma glucose and HbA1c did not vary between the two diets, despite considerable elevations in two hour and fasting insulin with the low-fat, high-carbohydrate diet. Kodama et al. stated that a possible explanation for this is that the elevation in postprandial glucose level were overcorrected by increased insulin secretion. The data collected came from three studies that simultaneously assessed HbA1c, fasting insulin, and fasting plasma glucose values, with the longest trial being 6 weeks in length. The authors could not conclude whether the elevation in postprandial glucose and insulin level achieved by raising the dietary carbohydrate to fat ratio led to the worsening of glycemic control represented by elevations in fasting plasma glucose and HbA1c. These results by Kodama et al. do support the current dietary guidelines stating that replacing fat with carbohydrate significantly elevates postprandial glucose and insulin levels when total energy intake is consistent. It was also found that there were significant positive relationships among the change in fasting plasma glucose with the amount of elevation in fasting insulin and triglycerides. Postprandial hyperglycemia with postprandial hyperinsulinemia and failure to have glycemic control are often grouped in insulin resistant individuals, classified as T2DM. This suggests that low-fat, high-carbohydrate diet is unfavorable compared with a high-fat, low-carbohydrate diet for insulin resistant patients. The finding does not support the benefit of an extremely high-fat diet since the carbohydrate proportion in the high-fat, low-carbohydrate diets included in the analyses was ≤50% (Kodama et al.). This meta-analysis by Kodama et al. had limitations, including if the effects of fiber influenced the metabolic effects regardless of the change in carbohydrates to fat ratio. The authors also assumed that the energy intake from the two diets would be similar stating that more research needs to be done on the relationship between energy intake and body weight with dietary carbohydrates and fats. There were very few studies that Kodama et al. included with long-term data and many of the studies provided insufficient data on baseline glucose and lipid levels with little information on black or Asian populations. Kodama et al. also pointed out evidence of publication bias and its likely effect on estimates of outcomes. One of the studies included in the meta-analysis had a relatively strong suspicion of publication bias for HDL cholesterol stating that the effect of this publication bias would slightly underestimate the adverse effect of the low-fat, high-carbohydrate diet.

A non-calorie restricted low-carbohydrate diet was analyzed to find out if it is an effective alternative therapy for patients with T2DM in a randomized trial by Yamada et al. (2014). The goal of this study was to examine the effects of a non-calorie restricted, low-carbohydrate diet in patients previously unable to follow a calorie-restricted diet. The study methods included comparative, two-arm, randomized, and open-label trials. The duration of the study was 6 months. The participants were T2DM patients from an outpatient clinic who had received previous calorie restriction guidance with an HbA1c level between 6.9%-8.4%. A total of 24 patients with a mean age of 63.3±11.7 years. These patients were randomly assigned to a calorie-restricted diet or low-carbohydrate diet with meetings every 2 months from a registered dietician for the duration of the study. The primary purpose was to compare the reductions in the HbA1c level and body weight, with secondary variables including lipid levels, cardiovascular markers, renal function, and liver enzymes. A few meta-analyses were included in this article to compare the results of similar studies. The results showed a significant decrease in HbA1c in the low-carbohydrate diet group with baseline at 7.6±0.4% and at the conclusion of the study 7.0±0.7%, ($p=0.03$) but not in the calorie-restricted group with a baseline at 7.7±0.6% and at the conclusion of the study 7.5±1.0%. The fasting plasma glucose levels were similar between baseline and at 6 months in both groups. Bodyweight, BMI and blood pressure did not change significantly in either group. In terms of the lipid levels, the triglyceride levels significantly decreased in the low-carbohydrate group from a baseline of 141.7±76.2 mg/dL and finished with 83.5±40.6 mg/dL ($p=0.02$), whereas no significant changes occurred in the calorie-restricted group but the difference between the groups was not statistically significant ($p=0.08$). The other lipid and cardiovascular markers were not altered in either group. In the conclusion of Yamada et al. their findings suggest that a low-carbohydrate diet is effective in lowering the HbA1c and triglyceride levels and is a safe alternative therapy for patients with T2DM who are unable to adhere to a calorie-restricted diet. This study was not without limitations, starting with a limited number of subjects enrolled to detect significant differences. This study did not observe any significant improvements in body weight, BMI, blood pressure or HDL cholesterol which was contradicted by other meta-analysis reviewed within their research. These parameters may have been improved by increasing the number of subjects. Several other clinical trials cited in the research by Yamada et al. had shown small or moderate rebounds in the clinical parameters between 6 and 12 months after starting the low-carbohydrate intervention. With this study only being 6 months, these findings did not occur.

Disadvantages of Using Ketogenic Diet Management as First-Line Treatment of T2DM

Two diets were compared in the study by Feinman et al. (2015): a low-carbohydrate diet and a generalized healthy diet. Feinman et al. felt that failure of the low-fat diets to improve obesity, cardiovascular risk, or general health of patients with T2DM, along with the success of low-carbohydrate diets in the treatment of diabetes and metabolic syndrome, point to the need for a reevaluation of dietary guidelines. This article is a critical review and evidence-based research composed from 99 references on the topic of dietary carbohydrate restriction as the first-line approach in diabetes management. This review was a description that included 12 points of evidence-based on published clinical and experimental studies and the experience of the authors. The points made in this evidence-based research are supported by established principles in biochemistry and physiology and emphasize that the benefits are immediate and documented while the concerns about risk are hypothetical and long-term. The results of the review by Feinman et al. provide some disadvantages with the most noticeable being patient adherence of using a low-carbohydrate diet as first-line treatment for T2DM. However, it was found that adherence to the low-carbohydrate diet was at least equal to if not better than other types of diets and it was also comparable to the adherence of medication treatment plans. Feinman et al. went on to say that it is thought that the adherence to the low-carbohydrate diet is due to the satiety and appetite suppression that came along with eating a diet with restricted carbohydrates. The satiety within the low-carbohydrate group is due to the increased protein and fat. Also, the low-carbohydrate diet group had unlimited access to food, but they had to restrict their carbohydrate intake. The participants thought this was easier to adhere to than other types of diets that had a strict reduction in calories leading to a lower adherence rate. Due to the effectiveness of carbohydrate restriction on glycemic control, there is a danger of hypoglycemia for those patients on glucose-lowering medication. It is recommended that medication be reduced prior to the initiation of a low-carbohydrate diet. Upon Feinman et al. review of the study by Dyson, Beatty, and Matthews, (2007) comparing a low-carbohydrate diet to a "healthy-eating diet", the low-carbohydrate group had an average of 6.9 kg ($p \geq 0.09$) weight loss and 2.1 kg ($p \geq 0.09$) weight loss in the healthy eating group over a period of 3 months. These results showed a greater influence on weight loss with the more defined and detailed approach of the low-carbohydrate diet than a generalized healthy diet. In this critical review by Feinman et al. the findings showed an average decrease in triglycerides of approximately 22% and no notable difference in LDL cholesterol, HDL cholesterol, or total cholesterol in the low-carbohydrate group. It was also stated that a low-carbohydrate diet decreased HbA1c by an average of 0.68% as a first-line treatment for managing diabetes. This is the only study that has mentioned that the low-carbohydrate diet was used as a first-line treatment. The limitations of this study pertain to the meta-analysis referenced in this research in that it did not go into detail about how they concluded the study or how results were formulated. Without this information, it makes it hard to determine the relevance of the data provided.

The effect of a low carbohydrate diet in the management of T2DM was interpreted by Huntriss et al. (2018). This was a systematic review and meta-analysis of randomized controlled trials. The methods used by Huntriss et al. involved a search for randomized controlled trials that included adults with T2DM with an age range of ≥18 years with a diagnosis of T2DM with the intervention group being a low-carbohydrate diet. The following search terms were used: 'type 2 diabetes' or 't2dm' or 'non-insulin-dependent diabetes' or 'NIDDM' and 'low-carbohydrate diet' or 'low-CHO diet' or 'carbohydrate-restricted diet' or 'CHO restricted diet'. These criteria were searched on MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, ISRCTN, ProQuest and opengrey.eu. Two independent experts were contacted, and reference lists of selected papers were checked. Results were analyzed, and meta-analyses were completed to include trials that presented data at 1-year. There were 18 studies selected for this review with data analyzed from 1,937 participants. Huntriss et al. had results that differed from a previous review and found that adherence of the low-carbohydrate diet group to be high. The amount of carbohydrates played a key role in the adherence of the participants since the very low-carbohydrate diet was determined to be an unrealistic diet for type 2 diabetics to adhere to but found that the low-carbohydrate diet was an achievable goal for these patients. Out of the six trials that tried the very low-carbohydrate diet that consisted of <50 g per day, only one of the trials was completed with the average carbohydrate intake within the prescribed range. On the contrary, all 12 studies that used the low-carbohydrate diet with a carbohydrate intake of <130g per day were able to complete the trial with average carbohydrates falling within the prescribed range. It was determined by the end of the trial periods there were five of the 15 total studies included in their systemic review that had a statistically significant decrease in weight when compared to the control group. There were no studies showing that the control group had a higher weight loss when compared. Several studies did not provide enough information relating to the meta-analysis being performed so these were omitted. This meta-analysis involved 17 studies with glycemic control, measured by HbA1c, with data available at trial end. These trials ranged anywhere from 3 months to 1-year with 12 of the 17 studies completed had a decrease in HbA1c of more than 0.2% and four of those 12 studies with a greater than 0.5% decrease. Four of the studies in the meta-analysis showed no difference in the patient's HbA1c levels and one study had an increase of 0.2% in HbA1c. This review concludes that reducing carbohydrate intake may promote favorable health outcomes in the management of T2DM. Guidance continues to remain to individualize dietary advice to patients with diabetes. More research is needed to determine whether there is an optimal intake of dietary carbohydrate for patients with T2DM (Huntriss et al.). This systematic review and meta-analysis stated that 15 out of the 18 studies were considered high risk of bias in one or more of the six criteria. The risk of performance bias was a common issue for these trials with 83% (15 out of 18 trials) at high risk. The authors had difficulty blinding the participants and study personnel due to the nature of the intervention. In some studies, the outcome assessor was not sufficiently blinded which was found to be at risk of detection bias. A lack of blinding of those assessing nutritional composition of diets was observed in some studies, this assessment of objective measures was not deemed as threatening. Insufficient detail of study processes often resulted in the categorization of unclear risk of bias. Due to the difficulties faced in blinding participants or study personnel to the assigned dietary intervention these biases are commonplace in many trials comparing dietary interventions.

Kirk, Graves, Craven, Lipkin, Austin, and Margolis (2008) conducted a meta-analysis on restricted carbohydrate diets in patients with T2DM. With the risks and benefits of these low-carbohydrate diets being unclear for patients with diabetes, this research was meant to help with the understanding of these kinds of diets and the role they play with T2DM. The method for collecting data was conducted by a MEDLINE search in PubMed, Cumulative Index to Nursing and Allied Health, Combined Health Information Database, Cochrane Library, and Web of Science using Medical Subject Heading from 1980 to 2006. The medical subject heading term diabetes mellitus, type 2 and combined it with the medical subject heading term, dietary carbohydrates was utilized for this search. Subjects >19 years old, comparing restricted carbohydrate diets in patients with type 2 diabetes, were reviewed. The studies that contained an amount of carbohydrate up to 45% of total calories from carbohydrate, in people with T2DM was obtained. Available data on study design, participant characteristics, carbohydrate composition, duration of diet, outcomes of weight, plasma levels of fasting glucose, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides was evaluated if reported. A total of 56 studies or reviews were evaluated with 13 studies that met the inclusion criteria. This article by Kirk et al. discussed the concern about the sustainability of the results achieved by the low-carbohydrate diet once the patient goes back to a higher carbohydrate intake. Another disadvantage of the low-carbohydrate diet is that it did not improve diabetic parameters significantly more than any other type of diet. It would be logical to think that since carbohydrates are the major component of the diet that influences postprandial blood glucose, decreasing the amount of carbohydrates would have a greater effect on lowering both blood glucose and HbA1c than other types of diets. That is not what the data shows in this meta-analysis. Weight reduction seems to be the most important parameter for T2DM patients, which can be obtained by any type of diet that causes a person to decrease their weight. It was concluded that there was no statistical difference in weight loss between the low-carbohydrate diets and the control groups. Weight stability during the duration of the trial was the goal of some of the studies, while other studies resulted in weight loss due to a low-carbohydrate or low-calorie diet. With the low-carbohydrate ketogenic diet, it is recommended to consume a high amount of fat, which causes a concern for high cholesterol levels. Lipid levels were another parameter that was commonly found in the literature when searching for the effect of a ketogenic diet on glycemic control. There was not a significant difference in LDL cholesterol, HDL cholesterol, or total cholesterol, seen in this meta-analysis, but they did find a significant decrease in triglycerides. With a decrease in carbohydrate intake from 65% to 35%, the data provided by Kirk et al. showed an average of 23% decrease in the participant's triglyceride level. It was found that the low-carbohydrate diet decreased HbA1c significantly with an average of 0.79%. The studies included in their meta-analysis had rates of HbA1c decrease that ranged from 0.3% to 2.2% with one of the 11 completed studies by Garg, Bonanome, Grundy, Zhang and Unger (1988) had an increase in HbA1c, this research was by far the oldest study used as a resource in this meta-analysis. Kirk et al. also went on to say that until further research is done showing the safety and long-term adherence, the low-carbohydrate diet as a first-line treatment for T2DM will remain a debatable topic. There are several limitations to this meta-analysis mainly with the duration of included studies, with most a relatively short-term of 120 days. With only 13 studies available for inclusion, the analysis really limited the number of covariates that could be introduced simultaneously. The study designs were mixed and diverse in participant settings, from inpatient feeding studies to outpatient self-selected diets. There was also a mix of diabetes medication criteria for patient inclusion, ranging from drug nonadherence to stable doses of insulin or oral hypoglycemic agents throughout the study period. Several of the studies allowed for modification of doses of diabetes medication based on blood glucose results. Few of the studies included elderly participants in this meta-analysis. The dropout rate in many of the studies was high, and lack of long-term adherence to the diets being studied was also noted. Most of the studies did not examine the impact of these diets on other important parameters of cardiovascular risk, such as inflammation and endothelial dysfunction. Studies have also taken different approaches to restriction of carbohydrate intake, including raising the protein component of the diet or increasing fat content.

Effectiveness of Using Ketogenic Diet Management as First-Line Treatment of T2DM

Ahmed, Bellamkonda, Zilbermint, Wang, and Kalyani (2020) completed a community-based cohort looking at the effects of a low-carbohydrate, high-fat diet on glycemic control and body weight in patients with T2DM. With this study, they investigated real-world settings to help clarify the optimal diet to improve glycemia in patients with T2DM. The research design investigates the effects of the low-carbohydrate, high-fat diet compared with usual care in a community-based cohort of overweight patients with T2DM. This was done by performing a retrospective analysis of 49 patients following a low-carbohydrate, high-fat diet for a minimum of 3 months and compared glycemic outcomes with 75 age matched and BMI matched controls who received usual diabetic care. The change in HbA1c from baseline to the end of follow-up was the primary parameter measured. Participants had four visits with the first visit being baseline measurements, visit two was between 6 and 11 weeks, visit three between weeks 12–16 and visit four between 17–21 weeks. Secondary outcomes included change in total body weight, BMI, fasting plasma glucose, lipid profile consisting of LDL cholesterol, HDL cholesterol, and triglycerides. Also measured was alanine aminotransferase and blood pressure. Patients were recommended to restrict net carbohydrate (total carbohydrates minus fiber) intake to ≤20g a day or 5%-10% of their total calories, whichever was lower, a daily recommendation for protein of 20%-25% of total calories and total fat intake of 65%-70% of total calories. To avoid hypoglycemia, patients were also recommended to discontinue the use of sulfonylurea drugs and reduce insulin doses by 30%–50% if they were taking these medications. The results from

Ahmed et al. indicated that the low-carbohydrate, high-fat group had improvement of HbA1c at every visit compared with the usual diabetic care group, and visit four had a mean HbA1c of 6.67% (95% CI 6.13 to 7.22) compared with a mean HbA1c of 7.8% in the diabetic care group (95% CI 7.36 to 8.29). This difference was statistically significant with a reduction of 1.29% (95% CI −1.75 to −0.82; $p < 0.001$). Patients on the low-carbohydrate, high-fat diet also lost significantly more weight at each visit compared with those in the usual diabetic care group, with a mean change of −12.3 kg ($p < 0.001$), representing a mean reduction of 11.9% of total body weight compared with baseline measurements, at visit four. By comparison, the usual diabetic care group had a non-significant increase of 0.5 kg ($p=0.4$) in mean weight at follow up. Fasting plasma glucose improved significantly in the low-carbohydrate, high-fat group, with a mean reduction of 43.5±76.3 mg/mL ($p < 0.05$) compared with a non-significant reduction of 8.5±8.0 mg/mL ($p=0.29$) in the usual diabetic care group. The reduction in serum triglycerides in the low-carbohydrate, high-fat group had a non-significant reduction of 25.61±7.96 mg/mL, ($p=0.09$), along with the usual diabetic care group of +18.41±159.84 mg/mL ($p=0.40$) with other lipid measurements remaining stable in both groups. There was also a non-significant reduction in alanine aminotransferase in the low-carbohydrate, high-fat group of 3.70±11.02 mg/mL ($p=0.09$), while it remained stable in the usual diabetic care group. There were no significant changes in blood pressure in either group. It was concluded by Ahmed et al. that in a community-based cohort of overweight T2DM patients, the low-carbohydrate, high-fat diet was associated with superior HbA1c reduction and greater weight loss suggesting that the low-carbohydrate, high-fat diet may be a metabolically favorable option in the dietary management of T2DM. This study did have important limitations. Other factors that may have contributed to the differences in the reduction of HbA1c between the low-carbohydrate, high-fat group, and the usual diabetic care group. With this research not being a randomized study, the low-carbohydrate, high-fat group patients were self-selected and may have had more motivation to comply. This emphasizes the potential benefits for a provider to discuss a low-carbohydrate, high-fat diet as an option. Due to the recommended bi-monthly or monthly visits, the low-carbohydrate, high-fat diet patients had more face-to-face time with a healthcare provider than the usual diabetic care group which may have impacted their outcomes. About half of the low carbohydrate, high-fat group elected to start phentermine which may have impacted weight but the HbA1c change was similar in participants who used phentermine compared with those that did not among low-carbohydrate, high-fat patients. There is also a need for additional long-term studies to gain further insight into the metabolic impact of a low-carbohydrate, high-fat diet, including verification of ketosis.

A longer-term study was conducted by Davis et al. (2009) who compared the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight loss and glycemic control in T2DM patients. The research design and methods of this study was a randomized clinical trial of 105 overweight adults with T2DM. The eligible participants were >18 years old with a diagnosis of T2DM for a minimum of 6 months. The subjects must have a HbA1c between 6%-11% and a BMI ≥ 25 kg/m^2. The primary outcomes analyzed are weight and HbA1c with the secondary parameters being blood pressure and lipids. The subject's outcome measures were gathered at 3, 6 and 12 months. The results indicated that there was no difference in the rate of change in HbA1c in either the early or late phase of dietary intervention. During the first 3 months participants underwent a decrease in HbA1c of 0.12 on average per month with an increase of 0.06 per month during months 3 through 12. Subjects with higher baseline HbA1c levels had more rapid declines during the first 3 months ($r = -0.35$, 95% CI –0.11 to –0.55), but baseline levels did not affect the rate of change in months 3 through 12. The low-carbohydrate group lost an average of 1.7 kg/month (95% CI 1.4–2.0) the first 3 months and in months 3 through 12 gained an average of 0.23 kg/month (95% CI 0.09–0.35). In contrast, the low-fat group lost weight at a slower rate of 1.2 kg/month (95% CI 0.86–1.5) with a plateau during months 3 through 12 with an average weight gain of $<$0.01 kg/month (95% CI -0.13 to 0.14). Both groups had a weight loss of 3.4% at the completion of the study. The difference in the early- and late-phase rates of weight change between the dietary groups was significant ($p=0.005$). Over the 12 months, there were no significant differences in blood pressure, total cholesterol, triglycerides, or LDL cholesterol between dietary groups. The low-carbohydrate group did however have a significant increase in HDL cholesterol occurring at 6 months that was sustained through the completion of the study. It was concluded that after 1-year a low-carbohydrate diet had effects on weight and HbA1c like those seen with a low-fat diet among patients with T2DM along with no significant effect on blood pressure. The difference between the groups came as an increase in HDL cholesterol in the low-carbohydrate group (Davis et al.). There were several limitations to consider with these findings. There was a heavier baseline weight in the low-fat group when compared with those in the low-carbohydrate group. The authors controlled for this imbalance statistically, but other unmeasured differences between the groups may have been missed. The use of a single day dietary recall or a single day food record to assess dietary intake may contain bias when reporting. The recall of participant's dietary intake may have been altered due to not fully remembering, which would have altered their data recorded. Additionally, there was not an objective measure of physical activity, which could be a confounder.

With obesity in T2DM being closely linked, effective management of body weight with changes to nutritional habits becomes important for this population. There is more emphasis placed on the amount of carbohydrates consumed and the glycemic index of the diet in subjects with glucose intolerance like type 2 diabetics. The research done by Hussein et al. (2007) looked at a ketogenic diet and its beneficial effect in subjects that are obese diabetics. In this study, the effect of a ketogenic diet in obese subjects with high blood glucose levels was compared to those with normal blood glucose levels for 56 weeks. The methods utilized in this study included a group of 31 obese subjects with body mass index ≥ 30 kg/m^2 and having blood glucose level of >6.1 mmol/l. Compared to a group of 33 subjects with normal blood glucose levels that were selected in this study, with 64 total subjects who were otherwise healthy. Subjects with other complex medical histories were not included in this study. The parameters measured were body weight, BMI, blood glucose level, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, urea, and creatinine. These parameters were determined at baseline and 8, 16, 24, 48, and 56 weeks after the administration of the ketogenic diet. All subjects were instructed to follow a ketogenic diet that consisted of less than 20g of carbohydrates and 80–100g of proteins, with an additional 20g of carbohydrates given after 12 weeks. The meta-analysis conducted in the research by Hussein et al. examined cardiovascular disease risk factors of a low-carbohydrate diet compared to a low-fat diet. As a result, both groups significantly decreased body weight and BMI in the 56-week study duration. The high glucose group had a starting weight at 108.081 kg ± 21.245 kg and finished at 83.536 kg ± 18.030 kg ($p < 0.0001$) and the normal glucose group starting weight was 105.273 kg ± 15.377 kg and an end weight of 74.923 kg ± 11.384 kg ($p < 0.0001$). The most significant blood glucose results came from the group whose baseline glucose levels where 10.481 mmol/l ($p < 0.0001$) ± 3.026 and completing the study at 4.874 mmol/l ± 0.556 ($p < 0.0001$). By far the most drastic change in blood glucose levels came at the first measurement within the 8 weeks of administering the ketogenic diet. Upon the review by Hussein et al. of the research by Nordmann et al. (2006) and the study by Malik and Hu (2007) on cardiovascular disease risk factors of a low-carbohydrate diet compared to a low-fat diet there were beneficial changes that were observed in the low-carbohydrate group with the level of triglyceride and HDL cholesterol after a 6 months. However, it was found that total cholesterol and LDL cholesterol level changes were more favorable in the low-fat group. This contradicted the study performed by Hussein et al. in which the total cholesterol, LDL cholesterol and triglycerides showed a significant decrease in the low-carbohydrate group from week 1 to week 56 ($p < 0.0001$), with a significant increase in the level of HDL cholesterol ($p < 0.0001$). There were limitations in this study involving the subjects that could have other dietary habits. It stated that all subjects had similar dietary habits, but it did not go into detail about those dietary habits. The meta-analysis compared research of different populations studied with a variety of carbohydrate intake habits. Also, the small sample size limited the validity of the outcomes reported in this study.

The group noted above realized the need for a larger sample size so 5 years later a study was organized by many of the same authors. Talib et al. (2012) performed a similar study to provide more concrete information on the effect of low-calorie versus low-carbohydrate-ketogenic diet in T2DM subjects. To be effective with the management of diabetic patients' reasonable weight control is essential which involves healthy nutritional habits. This research is done to compare two popular dietary habits and the effects they have on the management of T2DM. The methods used in this study consisted of 363 overweight and obese participants that were recruited for a 24-week diet intervention trial, with 102 of them that have been previously diagnosed with T2DM. Of the 363 participants, 23.7% were men, with 28 of them being diabetic and 58 were non-diabetic and 76.3% were women, with 74 diabetics and 203 non-diabetic. On a low-calorie diet, there were 27 men and 116 women, with 16.8% of them having diabetes. On the ketogenic diet, there were 59 men and 161 women, with 35.5% of them being diabetic. The participants were included in this study if they were at least 18 years old, had a BMI greater than 25 kg/m^2 and a fasting serum glucose level higher than 125 mg/dL. The participants chose between a low-calorie diet or a low-carbohydrate-ketogenic diet, depending on their preference. Subjects in the low-carbohydrate-ketogenic diet had an initial goal of 20g of daily carbohydrates. When a participant approached half the weight loss goal or developed cravings, they increased the carbohydrate intake by approximately 5g a day each week only if the weight loss continued. The parameters measured in this study consisted of body weight, BMI, changes in waist circumference, blood glucose level, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, uric acid, urea, and creatinine. Participants recorded measurements at baseline, 4, 8, 12, 16, 20, and 24 weeks after the administration of either the low-calorie or low-carbohydrate-ketogenic diet. In the low-carbohydrate-ketogenic group, the initial dose of some antidiabetic medications decreased to half while others were discontinued. Bi-weekly the participants took part in dietary counseling and further medication adjustments. In this meta-analysis, Talib et al. performed a comparison of their results with similar research on the topic of a ketogenic diet and T2DM. The results noticed a significant difference ($p < 0.0001$) in body weight and blood sugar level in the low-calorie and low-carbohydrate-ketogenic diet groups compared with their initial baseline and final measurements, with the low-carbohydrate-ketogenic diet being more effective than the low-calorie diet. In the diabetic group, the HbA1c level significantly decreased with the low-carbohydrate-ketogenic diet when compared with the other participants. The low-carbohydrate-ketogenic diet appears to improve glycemic control and should be under strict medical supervision due to the significantly lower blood glucose levels and the potential for episodes of hypoglycemia according to Talib et al. The effect on the lipid profile showed a significant decrease ($p < 0.0001$) in triglycerides, total cholesterol, and LDL cholesterol levels, whereas the HDL cholesterol level was significantly ($p < 0.0001$) increased over the 24-week duration of the study. Urea levels were significantly increased for the two diet groups in diabetic and non-diabetic participants. The uric acid level increased in the low-calorie diet group, whereas it decreased in the low-carbohydrate-ketogenic diet group with similar changes in the creatinine level. Talib et al. concluded that after the 24-week study, the low-carbohydrate-ketogenic diet resulted in a major improvement of glycemic control by way of fasting glucose and HbA1c measurements in patients with T2DM even after some antidiabetic medications had been decreased to half or discontinued in this group. In the meta-analysis, several recent studies have indicated similar effects of the low-carbohydrate-ketogenic diet and its effectiveness on glycemic control. A few studies showed that a low-carbohydrate-ketogenic diet is more effective than higher carbohydrate diets in both diabetics and non-diabetics at improving fasting serum glucose, insulin and at improving insulin sensitivity. Some of the limitations with this study involved meta-analysis referenced did not detail how the study was performed or how the results were formulated, questioning if there was bias with the conclusions provided in this paper. There was no bias or conflict of interest noted in this study. It was noted that biweekly the participants took part in further medication adjustments but did not mention what those adjustments were. The food records to determine each participant's adherence to the dietary program were mentioned but that information was not provided.

Tay et al. (2015) conducted a randomized trial comparing a low-carbohydrate and high-carbohydrate diet for T2DM management. The diets that were compared consisted of a very low-carbohydrate, high-unsaturated fat, low-saturated fat diet with a high-carbohydrate, low-fat diet. The comparison involved the effects on glycemic control and cardiovascular disease risk factors in T2DM patients. This study was conducted in an outpatient research clinic as a randomized control trial that consisted of 115 obese adults with T2DM. The mean age was 58 ± 7 years with a BMI of 34.6 ± 4.3 kg/m^2, HbA1c 7.3 ± 1.1% and a duration of diabetes of 8 ± 6 years. The participants were randomly assigned to consume either a low-carbohydrate diet or a high-carbohydrate diet. The low-carbohydrate diet consisted of daily carbohydrate consumption of <50g (14%), 28% of energy as protein, and 58% of energy as fat (<10% saturated fat). The high-carbohydrate diet consisted of 53% of energy as carbohydrate, 17% of energy as protein, and 30% of energy as fat (<10% saturated fat). These diets had supervised aerobic and resistance exercise for 60 minutes, 3 days a week. The parameters measured are glycemic control, fasting blood glucose, glycemic variability, diabetes medication, weight, blood pressure, and lipids that were assessed at baseline, 24, and 52 weeks. The results of this study by Tay et al. found that the low-carbohydrate group had a decrease of 3.2 kg/m^2 (p=0.31) in their BMI and the high-carbohydrate diet group had a drop of 3.5 kg/m^2 (p=0.31) in their BMI. Both groups achieved similar reductions in weight with the low-carbohydrate diet losing an average of 9.8 kg and the high-carbohydrate diet losing an average of 10.1kg. HbA1c also dropped in both groups with the same average of 1.0% reduction (p=0.65). Fasting glucose was reduced in the low-carbohydrate group on average of 0.7 mmol/L and the high-carbohydrate group lowered on average of 1.5 mmol/L (0.10). Both groups also reduced their triglycerides with the low-carbohydrate group dropping on average 0.4 mmol/L and the high-carbohydrate group reducing on average 0.01 mmol/L (p=0.001). The LDL cholesterol dropped as well with the low-carbohydrate group down by 0.1 mmol/L, ranging from -0.3 to -0.1 mmol/L and the high-carbohydrate group down by 0.2 mmol/L, ranging from -0.4 to -0.03 mmol/L (p=0.76) along with increases in HDL cholesterol with the low-carbohydrate diet increasing on average 0.1 mmol/L and the high-carbohydrate on average 0.06 mmol/L ($p=0.002$). Both diets achieved substantial weight loss and reduction in their HbA1c and fasting glucose. Patients that followed a low-carbohydrate diet spent a lesser amount of time in a hyperglycemic range with more time spent in the euglycemic range. Also, the time spent in a hypoglycemic range did not differ between the low-carbohydrate group and the control group. The HbA1c was decreased the same amount in a low-carbohydrate diet group compared to a high-carbohydrate diet group which contrasts with many of the studies that have been looked at. The low-carbohydrate group, which was high in unsaturated fat and low in saturated fat, achieved greater improvements in the lipid profile, blood glucose stability, and reductions in diabetes medications, suggesting an effective strategy for the optimization of T2DM management (Tay et al.). There are some limitations to this study, some of the changes in laboratory values were not very significant. Since this study included exercise 3 days a week for 60 minutes, the changes in laboratory values may be due to the increased exercise and not in the diets alone.

In a controlled trial designed by Tessari and Lante (2017) looked at exchanging multifunctional bread rich in beta-glucans and low in starch to improve metabolic control in T2DM patients. Hypothesizing that functional foods may be useful for people with diabetes. This study was not looking specifically at a low-carbohydrate diet but replacing carbohydrate heavy bread with bread rich with soluble fibers beta-glucans that can modify starch digestion and improve postprandial glucose response. The methods utilized in this controlled trial was clinical and metabolic data from two groups of diabetic participants with similar age, male to female ratio and glycated hemoglobin taking either the functional bread or regular white bread, over a roughly six month observation period. The inclusion criteria comprised of a diabetes duration longer than 2 years, HbA1c values $> 7\%$, age between 50 and 80 years, treatment with diet only, or diet plus either oral hypoglycemic, basal insulin or using both, and a reported daily intake of at least 50g of carbohydrates as either white bread, breadsticks or other bread substitutes. Bread intake did not change during the trial. The patients were visited at 3- to 6-month intervals. The functional bread decreased patients HbA1c levels by 0.52% vs. pre-treatment values ($p = 0.028$), and by 0.6% vs. the control group ($p = 0.027$). Post-prandial and mean plasma glucose was decreased in the treatment group as well. Bodyweight, blood pressure and plasma lipids did not change. Except for taste, the acceptance of the functional bread was good in most subjects. Tessari and Lante concluded that the regular intake of a low-starch functional bread, enriched with beta-glucan fibers, could improve the medium to long-term glycemic control in T2DM subjects in addition to the drugs used for glycemic control. The limitations, as it pertains to this research, was the fact that this study was not looking specifically at a low-carbohydrate diet but replacing carbohydrate heavy bread with bread rich with soluble fibers beta-glucans. Other factors may have played a role in the glycemic control including the pharmacotherapy used. This study did not go into depth on the topic of medications used for glycemic control.

Discussion

With the prevalence of newly diagnosed T2DM on the rise, effective treatment options have become increasingly important for successful patient outcomes. One of those treatment options is through the utilization of a ketogenic diet that helps lower HbA1c, raise HDL cholesterol, lower triglycerides, lower body weight, and lower fasting and postprandial blood glucose levels. Almost all the research studies reviewed found that using a low-carbohydrate diet decreased the participant's HbA1c except in one meta-analysis done by Huntriss et al. (2017) where there was an increase of 0.2%. This study had its limitations including the lack of blinding the participants and personnel conducting the study. The other studies included in the meta-analysis by Huntriss et al. and the meta-analysis performed by Kirk et al. (2008) had a decrease in HbA1c between 0.2% and 2.2%.

Safety of Using a Ketogenic Diet for Glycemic Control

The ketogenic diet has been around for many years but has recently become popularized due to the health benefit claims of increased energy and weight loss. Participants of the ketogenic diet strive to push themselves into a state of ketosis with claims for the risk of ketoacidosis or illness. Blanco et al. (2019) stated that most do not experience these metabolic complications or illness unless put under certain circumstances such as stress and prolonged fasting. In these certain conditions, this ketosis can develop into ketoacidosis which causes a decrease in pH and serum bicarbonate level that can lead to a serious medical condition. Ketoacidosis is most frequently associated with diabetes mellitus type 1 and alcoholism with starvation ketoacidosis being uncommon. Besides the uncommon risk of ketoacidosis, the ketogenic diet may lead to electrolyte abnormalities, hypoglycemia, acute pancreatitis, and dyslipidemia. Following this high-fat diet, it is unlikely to be cardioprotective, since it might cause an increase in LDL cholesterol and serum triglycerides (Blanco et al.). In contrast, the study by Goday et al., (2016) found that throughout the 4-month timeframe, sodium, potassium, chloride, calcium, and magnesium remained stable and within the normal limits in both the ketogenic diet and the standard low-calorie diet groups. Similar results were found in the study by Gomez-Arbelaez et al., (2017) noting some differences in electrolytes and blood urea nitrogen but none of them were considered clinically relevant. In patients with an acceptable insulin function, a ketogenic diet induces a well-tolerated ketosis rather than ketoacidosis. As a result, the ketogenic diet can be considered a safe nutritional intervention in terms of acid-base equilibrium (Gomez-Arbelaez et al.). In the study by Hussein et al. (2007) it was concluded that the beneficial changes of a ketogenic diet over a 56-week duration were more significant in subjects with high blood glucose levels as compared to those with normal blood glucose levels. In addition to its therapeutic value, these findings demonstrate that a ketogenic diet is safe to use for a longer period in obese diabetic subjects. However, there is a need for further research to understand the exact mechanisms of the results observed in this study.

Effectiveness of Using a Ketogenic Diet for Glycemic Control

All T2DM patients can benefit from a ketogenic diet since it can improve health parameters such as lowering LDL cholesterol and triglycerides, bodyweight reduction, and the largest health parameter being glycemic control utilizing HbA1c as a way for long term monitoring. According to Hussein et al. (2007), there is a close link between obesity and the incidence of T2DM. Therefore, a decrease in weight would be a plausible treatment for T2DM and an additional benefit of utilizing a ketogenic diet to treat diabetes. Gomez-Arbelaez et al, (2017) noted that in their analysis they observed considerable improvement in insulin sensitivity with regards to bodyweight reduction. The conclusion of the 52-week study by Tay et al. (2015) showed a significant weight loss in both the low- and high-carbohydrate diet groups. The results from the study by Feinman et al. (2015) showed that there was a greater influence on weight loss with the more defined and detailed approach of the low-carbohydrate diet than a generalized healthy diet. It was determined by Huntiss et al. (2017) that by the end of the trial periods there were five of the 15 total studies included in their systemic review that had a statistically significant decrease in weight when compared to the control group, with no studies showing that the controlled group had a higher weight loss when compared. Several of the studies did not provide enough information relating to the meta-analysis being performed so these were omitted by Huntriss et al. It was concluded by Kirk et al. (2008) that there were no statistical difference in weight loss between the low-carbohydrate diets and the control groups. This was determined due to the variation in the goals of the studies that they were looking at. Weight stability during the duration of the trial was the goal of some of the studies while other studies resulted in weight loss due to low-carbohydrate and low-calorie diets that were being examined. In the study by Hussein et al. that looked at subjects starting with high glucose readings and subjects with a normal level of glucose, both groups were placed on a ketogenic diet. As a result, both groups significantly decreased body weight and BMI in the 56-week study duration. According to Goday et al. (2016), the ketogenic diet group had a significant increase in weight loss and reduction in waist circumference than in the controlled group along with a larger decrease in HbA1c and better glycemic control. Goday et al. concluded that the ketogenic diet in subjects with T2DM is associated with a significantly larger weight loss and more effective with enhancing glycemic control over the standard care nutritional intervention based on the ADA (2020) guidelines. It is important to note that the optimal mix of macronutrients of medical nutritional therapy for people with T2DM remains unresolved (Goday et al.). Diet adherence was the main component affecting body weight with the subjects who participated in these studies which means there may be more flexibility to individualize the diet to better align with the lifestyle of each patient.

With the low-carbohydrate-ketogenic diet, it is recommended to consume a high amount of fat, which causes a concern for high cholesterol levels. Type 2 diabetic patients have a twofold increased risk of cardiovascular disease which is the principal cause of death in this patient group (American Heart Association [AHA], 2020). Lipid levels were another parameter that was commonly found in the literature when searching for the effect of a ketogenic diet on glycemic control. There was not a significant difference in LDL cholesterol, HDL cholesterol, or total cholesterol, seen in a meta-analysis conducted by Kirk et al. (2008), but they did find a significant decrease in triglycerides. Comparable results were found in a critical review by Feinman et al. (2015), with a decrease in triglycerides and no notable difference in LDL cholesterol, HDL cholesterol, or total cholesterol. In a similar meta-analysis performed for the American Diabetes Association, Kodama et al. (2009) found that there was a decrease in triglycerides with the high-fat, low-carbohydrate diet when compared to the low-fat, high-carbohydrate diet group. Jung and Choi (2017) found no meaningful differences between a high-carbohydrate diet versus a low-carbohydrate diet in terms of the capability to decrease LDL cholesterol or total cholesterol and also found that the low-carbohydrate diet was more effective at raising HDL cholesterol and lowering triglycerides. Upon Hussein et al. (2007) review of the research by Nordmann et al. (2006) and the study by Malik and Hu (2007) there were beneficial changes in the low-carbohydrate group with the level of triglyceride and HDL cholesterol. However, it was found that total cholesterol and LDL cholesterol level changes were more favorable in the low-fat group. This contradicted the study performed by Hussein et al. in which the total cholesterol, LDL cholesterol and triglycerides showed a significant decrease in the low-carbohydrate group, with a significant increase in the level of HDL cholesterol. This difference may be due to the populations studied with a different carbohydrate intake and the general food habits along with genetic factors may affect the lipid profile. However, further studies are required to understand the exact mechanisms of the results observed in this study (Hussein et al.). In a similar study, Talib et al. (2012) found that the effect on the lipid profile revealed a significant decrease in triglycerides, total cholesterol, and LDL levels, whereas the HDL level was significantly increased. The study by Ajala et al. (2013) indicated a 10% increase in HDL cholesterol in patients that successfully followed a low-carbohydrate diet for T2DM treatment.

Along with increasing HDL cholesterol, a low-carbohydrate diet had a significant decrease in triglycerides levels in those T2DM subjects according to the studies by Kodama et al., Kirk et al., Jung and Choi, and Feinman et al. with a decrease ranging from 13.4% to 22%. This reduction of triglycerides and raising of HDL cholesterol are important for this T2DM patients because it improves overall cardiovascular health, which reduces the risk for cardiovascular related issues including stroke, myocardial infarction, and peripheral vascular disease which are at an increased risk in this patient population.

Now, a closer look at the studies involving glycemic control and how the ketogenic diet may affect these measurements. After exploring other advantages of having a patient with T2DM use a ketogenic diet, the effects of this diet on a patient's glycemic control can now be examined. Huntress et al. (2017) found that utilizing a low-carbohydrate diet in the management of T2DM the participants had a decrease in HbA1c in 12 of the 17 studies analyzed. Kirk et al. (2008) conducted research on restricted carbohydrate diets in patients with T2DM and found that the low-carbohydrate diet decreased HbA1c significantly. Similar results were found in the research study done by Yamada et al. (2014) showing a significant decrease in HbA1c with the patients in the low-carbohydrate diet group along with no change in HbA1c in the calorie-restricted group. The most significant results on glycemic control in the study by Hussein et al. (2007), came from the group whose baseline glucose levels were the highest in the study with by far the most drastic reduction in blood glucose levels coming at the first measurement after administering the ketogenic diet. According to Talib et al. (2012), the ketogenic diet resulted in a significant improvement of glycemia in patients with T2DM even after some antidiabetic medications had been decreased to half emphasizing their statement that diabetic patients utilizing this diet will need to have blood sugars monitored closely due to the risk of hypoglycemia. In the critical review of carbohydrate restriction on diabetes management, Feinman et al. (2015) observed that a low-carbohydrate diet decreased HbA1c as a first-line treatment for managing diabetes. Patients that followed a low-carbohydrate diet spent a lesser amount of time in a hyperglycemic range with more time spent in the euglycemic range according to Tay et al. (2015). Also, the time spent in a hypoglycemic range did not differ between the low-carbohydrate group and the control group. Tay et al. (2015) discovered that the HbA1c was decreased the same amount in a low-carbohydrate diet group compared to a high-carbohydrate diet group which contrasts with other studies that have been looked at. Kodama et al. (2009) has a similar meta-analysis indicating that both groups were comparable and at the end of the studies with no meaningful difference in the HbA1c. Another study by Jung and Choi (2017) also had equivalent results that produced no difference in HbA1c when comparing the low-carbohydrate and high-carbohydrate diet groups. It was observed in the study by Tessari and Lante (2016) that exchanging carbohydrate-heavy bread with a unique 'functional' bread into participant's diets provided a decrease in their HbA1c levels over the 6-month trial period. Participant's HbA1c was reduced nearly the same with the low-carbohydrate, Mediterranean, high-protein, and low-glycemic index diets according to Ajala et al. (2013). Similar results were found in the studies by Jung and Choi, Kodama et al., and Tay et al. in that the low-carbohydrate and high-carbohydrate diets showed no significant differences in the amount that the HbA1c was decreased with their subjects. All the studies included in this meta-analysis had a decrease in HbA1c but many of them saw no significant difference between the low-carbohydrate diet when compared to the other types of diets included in the studies. Since carbohydrates have a significant impact on postprandial blood glucose according to Kirk et al., one would think that decreasing carbohydrate intake would have a larger effect on lowering blood glucose and ultimately HbA1c than other diets. It does not look like this is true, the patient's weight reduction seems to have a greater impact on glycemic control, which can be an outcome of many diets that patients can adhere too. The evidence provided by this research suggests that the type of diet is not as important as the participant's adherence to the specifics of the diet other than just calorie restriction.

According to several studies, one could argue that a low-carbohydrate-ketogenic diet as a first-line treatment plan for T2DM does not improve diabetic parameters any more than many of the other diets that have been popularized in the public. Also, of the many studies analyzed in the meta-analysis, the only study stating that a dietary carbohydrate restriction was used as the first approach in diabetes management was by Feinman et al. (2015). The remaining studies either stated that a low-carbohydrate diet was used in combination with other therapies or it was not specified as the solo treatment utilized in the participants studied. As a result, the decreases in HbA1c from the data collected may not be exclusively contributed to the low carbohydrate diet these participants were following.

Low-carbohydrate diet was a focus of this meta-analysis but many of the studies differed on specific guidelines for the amount of carbohydrates the participants were consuming, with a large range of cutoffs when it came to low-carbohydrate consumption between the studies. Two of the studies by Huntriss et al. (2018) and Feinman et al. (2015) did agree on the amount of carbohydrates the participants could consume and still be considered a low-carbohydrate diet. In both of those studies, a low-carbohydrate diet was defined as <130 g/d amounting to less than 26% of the 2000 kcal/d diet. It is not clear the number of carbohydrates the participants were allowed to consume to be considered a low-carbohydrate diet with many of the other studies which could alter the findings depending on a higher or lower threshold of daily carbohydrates allowed. All the studies used the term low-carbohydrate diet and ketogenic diet interchangeably except the study by Feinman et al. who further classified a ketogenic diet as a “very low-carbohydrate-ketogenic diet” defined as 20-50 g/d which is less than 10% of the 2000 kcal/d diet, whether ketosis occurs or not. Huntriss et al. also had a classification for a lower amount of carbohydrates labeled “very low-carbohydrate diet” with similar restrictions of <50 g/d consisting of <10% of a 2000 kcal/d diet. Participants with more restrictions on daily carbohydrate consumptions such as stated above may lead to a failed treatment due to difficulties with patient adherence.

Patient adherence may be another disadvantage with a low-carbohydrate or ketogenic diet especially living in a society where high carbohydrate foods are abundantly available. Even if a treatment plan is flawless but is not followed by the patient, the success rate is diminished. However, it was found in the study by Feinman et al. (2015) that the adherence rate of a low-carbohydrate diet was equivalent, if not better than other diets along with even being comparable to pharmacologic treatment plans. Feinman et al. stated that this may be due to a greater feeling of satiety and appetite suppression that eating more protein and fats and restricting carbohydrate produce or the fact that the low-carbohydrate group had unlimited access to food as long as they were able to maintain carbohydrates under the daily threshold. The participants in this study thought this diet plan was easier to maintain than other more calorie-restricted diets which lead to lower adherence. The research by Huntriss et al. (2017) had different results that contraindicated the findings by Feinman et al., discovering that T2DM patients found a very low-carbohydrate diet unlikely to maintain whereas a low-carbohydrate diet was a much more attainable goal to sustain. The very low-carbohydrate group had a strict, less than 50g daily carbohydrate limitation in which only one out of the six trials were able to be completed within range when compared to all 12 trials of the low-carbohydrate diet completing within the prescribed daily range of less than 130g of carbohydrates. It was stated in the study performed by Kirk et al. (2008) their concerns about the sustainability of the beneficial results on several health parameters that were achieved by the low-carbohydrate diet after the trial was over and the participants went back to their previous higher carbohydrate diets. Many patients may not be willing to make such a change and abide by a diet that is restricting carbohydrate consumption to lower their HbA1c especially with other less lifestyle-altering treatment options available. The patient needs to be driven and have the motivation for this treatment option to be successful. The provider will need to have a conversation with the patient and share in the decision making as to what treatment option will produce the greatest results. This might mean a combination of therapies to provide the highest possibility of patient success. Even with the data of the short-term success that the low-carbohydrate, ketogenic diet produces, there is very little long-term data on its success. This might be due to patient adherence with the difficulties of maintaining such a carbohydrate-restricted diet in the long-term (Blanco et al., 2019). Utilizing a low carbohydrate diet as a first-line intervention for T2DM patients will remain a controversial topic, according to Kirk et al., until further research is provided on the safety and longevity of this treatment option.

Applicability to Clinical Practice

The ketogenic diet seems to be a safe option to include in the treatment plan for T2DM patients with an acceptable insulin function. The most significant health parameters affected by a ketogenic diet included raising HDL cholesterol, lowering triglycerides and bodyweight, with the most crucial parameter being the reduction in HbA1c. With this substantial impact on HbA1c, diabetic patients will need to monitor blood glucose closely and adjust antidiabetic medications accordingly. The beneficial changes were the most significant early in the intervention in obese patients with a high blood glucose level. Diet adherence was the most important factor regardless of the diet chosen. The adherence rate of a low-carbohydrate diet was equivalent, or better to other diets and comparable to pharmacologic treatment plans. There will need to be a conversation with a shared decision on treatment options that might include combination therapies to produce the greatest results. With the limited long-term data, and the unresolved optimal mix of macronutrients for therapy, utilizing a low-carbohydrate diet as a first-line intervention for T2DM patients will remain a controversial topic.

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