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Comparison of Low Carbohydrate Diets on Renal and Glucose Function in Subjects with Type 2 Diabetes: A Systematic Review and Meta-analysis

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COMPARISON OF LOW CARBOHYDRATE DIETS ON RENAL AND GLUCOSE FUNCTION IN SUBJECTS WITH TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

by

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Abstract

Background - Type 2 Diabetes Mellitus (T2DM) is a growing crisis that can lead to more problems if left untreated. One of these problems includes diabetic nephropathy or Chronic Kidney Disease (CKD). While there have been many advances in the field of treating CKD with medication, there are currently no medications with the capability of stopping the progression of or reversing diabetic nephropathy; however, recent studies have shown that diabetic nephropathy can be stopped and even reversed through dietary interventions. One of these studies went through the effects of a low protein diet on diabetic nephropathy and found very promising results. This meta-analysis was designed to explore the effects of a Low Carbohydrate Diet (LCD) on diabetic nephropathy.

Methods - An electronic search of PubMed and Google Scholar was conducted. To be considered eligible the studies had to contain (‘carbohydrate’ OR ‘carbohydrates’) AND (‘diet’ OR ‘diets’) AND (‘type 2’) AND (‘diabetes’ OR ‘diabetic’) AND (‘ketogenic’). The studies also had to measure Estimated Glomerular Filtration Rate (eGFR) and Glycated Hemoglobin (HbA1c). Statistics and calculations were performed by Review Manager version 5.3 while risk of bias was assessed using the Robvis ‘risk of bias’ tool.

Findings - 262 potential articles were identified by the search and 10 studies matched the search criteria with a total of 921 participants (450 were given the LCD and 471 were given control diets). Analysis of the total Standardized Mean Difference (SMD) for the eGFR studies showed that there was no difference between the LCD and the control (total SMD: -0.00; 95% CI, -0.20 to 0.19; P = 0.97). Analysis of the serum creatinine showed similar results (SMD: 0.13; 95% CI, -0.12 to 0.38; P = 0.31). The total SMD for the HbA1c (SMD: -0.29; 95% CI, -0.55 to -0.03; P = 0.03) showed that there was a lowering of the HbA1c in the LCD and not in the control diet.

Conclusion - In this meta-analysis there was no connection found between eGFR/serum creatinine and percent carbohydrates in the diets indicating the LCD did not negatively affect the kidneys. HbA1c was found to be lower in the LCD than in the control which points to a LCD possibly leading to the reversal of T2DM which would remove the main cause of diabetic nephropathy.

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Introduction

The occurrences of Type 2 Diabetes Mellitus (T2DM) have been on the rise worldwide. The Center for Disease Control (CDC) states that the rate of diabetes has risen from 2.39 million diabetics in 1965 to an estimated 34.2 million diabetics in just the U.S. in 2020 (1,2). Viewed another way, diabetics used to be 1.27 percent of the U.S. population fifty-five years ago but are now 10.5 percent (1,2). The current trend predictions indicate that by the year 2060 one out of every six adults in the U.S. will be diagnosed with diabetes. In addition, The National Diabetes Statistics Report for 2020 states that over 88 million adults in the U.S. alone are prediabetic and at a high risk of becoming diabetic soon (1).

Type 2 diabetes is caused when the body's blood glucose levels are kept high continuously for a long time (3). This causes the cells in the body to become resistant to insulin, a protein used to tell cells to absorb glucose from the bloodstream, to the point where the β-cells of the pancreas cannot produce enough insulin to maintain glucose homeostasis (3). According to the CDC, this imbalance in glucose levels can result in cardiovascular disease, retinopathy, neuropathy, nephropathy, and many more problems (4).

Of these long-term complications of diabetes, diabetic nephropathy, also known as Chronic Kidney Disease (CKD), has become of notable concern due to its growing number of incidences. While there are treatments and recommendations to relieve symptoms and slow down the progression of CKD, there are currently no known options available to reverse or even stop its progression. At the end stages of CKD, diabetic

patients are only left with options of dialysis or kidney transplants (5). With such a grim prognosis, more options for better treatment are greatly needed.

Diabetic nephropathy has three primary causes, an increased pressure state, mesangial expansion, and nephron ischemia (6). An increased pressure state can be caused by either vasoconstriction of the efferent blood vessels in the kidney or overall hypertension in the body (6, 7). This is most commonly measured as an increased Glomerular Filtration Rate (GFR) and is usually only able to be measured in the early stages of CKD (6, 7). Mesangial expansion is the mesangial cells of the kidney increasing in size to the point where the fenestrations (pores in the podocytes) are large enough to allow proteins and other large molecules to pass through (8, 9). This is detected by an increase in proteinuria (protein in the urine) (6, 7). Nephropathy is defined as the atrophy of nephrons and is usually found at the last stage of kidney disease and can be caused by nephron ischemia (6, 7). Nephron ischemia is the lack of blood flow to the kidney cells due to a reduction in the diameter of the blood vessels (6, 7, 10). This is commonly detected as a decrease in GFR (6, 7). It has been estimated that nearly 40% of all diabetics will eventually develop CKD leading it to become a major public health concern (5).

Over the past fifty years, there have been great achievements in drug development to provide options to lower blood glucose levels, decrease proteinuria, and even help lower hypertension in diabetics; However, even with these drugs, diabetic nephropathy still slowly progresses in the patients (5, 11). This slow progression still

seems to end in End Stage Renal Disease (ESRD) which can currently be treated with only dialysis or replacement of the kidneys (5).

Newer studies have shown options for treating diabetic nephropathy and even ESRD through diet. A meta-analysis on the effects of low protein diets showed that the low protein diet had a significant improvement of renal function in patients with differing stages of renal disease (12). The study showed that the GFR of patients on the low protein diet significantly improved while adverse effects such as decreasing glycemic control and malnutrition were not seen during the study's duration (12). While there is still much to be studied in the field of diet and nutrition on type 2 diabetics and diabetic nephropathy, new research shows that diet is capable of reducing the effects of and even reversing kidney damage especially in type 2 diabetics (8, 13). Unfortunately, in many of these studies, the food intake parameters were not well-defined which results in conflicting reports and outcomes. The goal of this research is to conduct a systematic review and meta-analysis of studies on moderately-low, low, and very low carbohydrate diets with type 2 diabetics in order to find the most effective dietary parameters to reduce and possibly halt the progression of nephropathy while also stopping or reversing the effects of diabetes in the patients. This will be done by examining the results of many studies that show the function of the kidney through estimated GFR (eGFR) or serum creatinine and the state of diabetes in the patient through their glycated hemoglobin (HbA1c).

Methods

The following methods are designed to closely follow the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist for systematic reviews and meta-analyses (14).

Data Sources and Searches

Literature search was conducted using the electronic databases Google Scholar and PubMed. The search included articles published from inception through February 2020. Articles selected were written in English and included the search terms: (‘carbohydrate’ OR ‘carbohydrates’) AND (‘diet’ OR ‘diets’) AND (‘type 2’) AND (‘diabetes’ OR ‘diabetic’) AND (‘ketogenic’). The date last searched was March 13, 2020.

Study Selection

Among the studies identified, only studies that included type 2 diabetics and that measured GFR, eGFR, or serum creatinine were included. In addition, at least one arm of the study had to include the use of a Moderately Low Carbohydrate Diet (MLCD), a Low Carbohydrate Diet (LCD), or a Very Low Carbohydrate Diet (VLCD) as part of the trial.

Data Synthesis and Analysis

Data extracted from the studies included: study title, authors, publication date, sample size, dropout rate, length of study, interventions, average age of the study group, the study design, duration of the study, and outcomes. Outcomes from the study were combined using Review Manager (RevMan) version 5.3 (15). The random effects model was used for the combined outcomes of these studies. Inverse variance was used for the statistical analysis. Standardized Mean Difference (SMD) and 95% Confidence Intervals (CI) were used in presenting the data. Heterogeneity was assessed using the I^2 statistic. All previously listed calculations were performed by RevMan version 5.3.

In this meta-analysis, Creatinine Clearance Rate (CCR) and GFR were considered as eGFR. Standard Deviation (SD) was calculated by hand using the formula outlined in the Cochrane Handbook (16) (Equation 1). Conversion of serum creatinine from µmol/L to mg/dL was performed by hand (Equation 2).

Equation 1 - Equation for standard deviation using a 95% confidence interval

$$SD = \sqrt{(N)} * (\text{upper limit} - \text{lower limit})/3.92$$

Equation 2 - Conversion of serum creatinine from µmol/L to mg/dL

$$\text{Serum Creatinine (µmol/L)} * 0.011312 = \text{Serum Creatinine (mg/dL)}$$

Publication Bias

Risk of bias was assessed by using the Robvis ‘risk of bias’ assessment tool (17). Potential risk of bias included: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, and selective outcome reporting. An evidence based high, low, or unclear bias assessment was made for the domains after a thorough study of each article.

Results

Search Results

A review of Google Scholar and PubMed listed 262 potential articles for the meta-analysis (Figure 1). Of them, 150 records were excluded due to their abstract not meeting the search criterial. An additional 42 articles were duplicate articles. Of the remaining 70 articles, 56 of these studies did not measure eGFR, GFR, or serum creatinine and were removed. Another 4 studies were set aside because they lacked controls. A final total of 10 studies were included for this review.

Characteristics of Studies and Participants

The 10 selected studies included a total of 921 type 2 diabetic patients (Table 1). The average age of the participants ranged between 50 and 69 years old. The length of the studies varied from 5 weeks to 24 months. The studies stated the percentage of carbohydrates, proteins, and fats were typically consumed in a day for both the low carbohydrate and control diets. Of the ten studies, five contained data on eGFR, six contained data on serum creatinine levels, and eight contained data on HbA1c. Also noted in the studies was whether the renal function of the patient was impaired at the start of the study (Table 1).

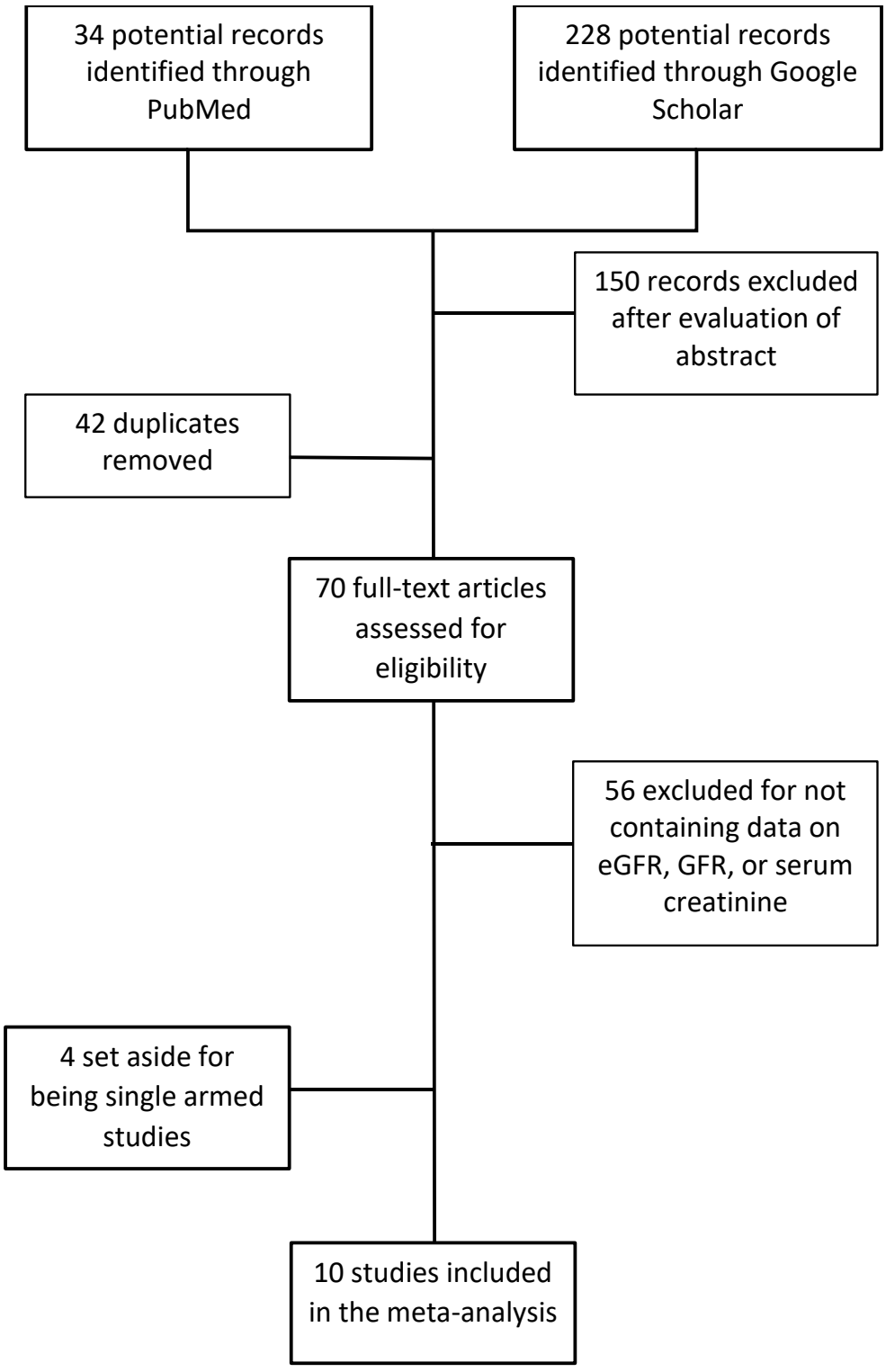

Figure 1 - PRISMA flow diagram of selection of studies

Study Diet Characteristics

For this meta-analysis the diets containing 45% of caloric intake as carbohydrates (carbs) and lower were considered as low carb. The controls of the studies varied between 48% carbs and 57% with the exception of the study by Westman et. al. which had a control of 44% carbs and a Low Carb Diet (LCD) with 13% carbs. Most of the studies gave the participants a restriction list of what the patients could eat from and the patients were to return with journaled entries of what they ate or were to keep in contact with the study designers every one to three weeks. This was done to make the diets easy for the patients to stay on and to reduce the dropout rate that is normally high with restricted dietary studies.

Table 1 - Main characteristics of the studies included in the meta-analysis. No Data (ND), Standard Deviation (SD), n = number of participants, Carbohydrates% / Proteins% / Fats% = C/P/F

References	Study Length	Intervention Low Carb n C/P/F Control n C/P/F	Baseline - Final Low Carb eGFR(SD) Control eGFR(SD)	Baseline - Final Low Carb Creatinine(SD) Control Creatinine(SD)	Baseline - Final Low Carb HbA1c(SD) Control HbA1c(SD)	Average Age	Impaired Renal Function?
Ruggenenti et al 2017	6m	n=34 44/22/36 n=36 48/18/34	107.8(21.0) - 100.2(16.5) 109.2(19.0) - 106.5(20.2)	ND	6.8(1.0) - 6.3(0.7) 6.6(0.7) - 6.8(1.0)	59.8 59.8	No
Larsen et al 2011	12m	n=53 40/30/30 n=46 55/15/30	70.2(11.9) - 73.4(11.9) 72.6(14.2) - 74.6(14.2)	ND	7.9(0.5) - 7.7(0.5) 7.8(1.0) - 7.5(1.0)	59.6 58.8	No
Krebs et al 2011	24m	n=144 40/30/30 n=150 55/15/30	ND	0.89(0.29) - 0.94(0.27) 0.84(0.21) - 0.89(0.25)	8.1(1.2) - 8.2(1.5) 8.0(1.2) - 8.1(1.4)	57.7 58.0	No
Haimoto et al 2007	24m	n=45 45/18/33 n=57 57/16/26	ND	0.86(0.20) - 0.73(0.22) 0.86(0.17) - 0.70(0.16)	7.4(1.1) - 6.7(0.6) 7.1(1.0) - 7.5(1.3)	64.0 69.0	No
Yamada et al 2013	6m	n=12 30/25/45 n=12 51/17/32	69.0(14.5) - 69.4(15.0) 69.1(13.2) - 65.0(12.6)	ND	7.6(0.4) - 7.0(0.7) 7.7(0.6) - 7.5(1.0)	63.3 63.2	No
Sato et al 2016	6m	n=30 45/20/35 n=32 52/17/31	ND	0.78(0.45) - 0.75(0.45) 0.68(0.35) - 0.70(0.26)	8.0(1.8) - 7.3(2.2) 8.3(1.9) - 8.3(1.7)	60.5 58.4	No
Nuttall et al 2005	5wk	n=8 20/30/50 n=8 55/15/30	ND	0.90(0.05) - 1.0(0.05) 0.90(0.10) - 0.90(0.05)	UNCLEAR	63.0 63.0	No
Westman et al 2008	6m	n=21 13/28/59 n=29 44/20/36	ND	ND	8.8(1.8) - 7.3(1.5) 8.3(1.9) - 7.8(2.1)	51.2 50.0	No
Tay et al 2015	12m	n=58 14/28/58 n=57 53/17/30	96.0(11.7) - 92.0(11.7) 92.0(11.6) - 90.0(11.6)	0.78(0.16) - 0.81(0.17) 0.80(0.17) - 0.83(0.17)	ND	58.0 58.0	No
Goday et al 2016	4m	n=45 25/64/11 n=44 50/20/30	75.6(17.4) - 75.6(17.4) 74.9(14.5) - 74.9(14.5)	0.90(0.17) - 0.90(0.17) 0.92(0.28) - 0.92(0.28)	6.9(1.1) - 6.0(0.7) 6.8(1.1) - 6.4(0.8)	54.5 54.9	No

Outcome

This meta-analysis will show some clinical heterogeneity due to the study designs being different for each diet. This is especially true in studies that allowed the patients to select their own food while keeping a food journal of what they consumed. Heterogeneity is classified as $P < 0.05$ and the amount of heterogeneity is defined as $I^2 = X\%$ ($X < 25\%$ = low, $25\% < X < 75\%$ = moderate, and $75\% < X$ = high).

The Effects of Low Carbohydrate Diet on eGFR

The five studies used in the analysis of the effects of LCD on eGFR contained a total of 397 patients and showed no difference between the control and the LCD (19, 20. 23, 26, 27). The analysis of the effect of a low carbohydrate diet on eGFR in type 2 diabetic patients showed no heterogeneity ($P = 0.46$, $I^2 = 0\%$) (Figure 2). This is because the eGFR between the control and the low carbohydrate diets were not significantly different (total SMD: -0.00; 95% CI, -0.20 to 0.19; $P = 0.97$) (Figure 2). Analysis of the change in eGFR vs percent carbohydrates also reflects that there is no difference between the change in eGFR in both low carb vs control (Figure 5).

The Effects of Low Carbohydrate Diet on Serum Creatinine

The six studies used in the analysis of the effects of LCD on serum creatinine contained a total of 678 patients and showed no difference in the serum creatinine in the low carb vs the control diets (21, 22, 24, 25, 26, 27). Analysis of the effect of a low carbohydrate diet on serum creatinine in type 2 diabetic patients showed a moderate

amount of heterogeneity (P = 0.05, I^2 = 54%) (Figure 3); however, this heterogeneity comes primarily from an outlier study, possibly due to the very short (5 week) duration of the study (25). The test for the overall effect showed no difference between the two diets (SMD: 0.13; 95% CI, -0.12 to 0.38; P = 0.31) (Figure 3). Analysis of the graph showing the change in serum creatinine vs percent carbohydrates also provided no evidence of a difference between the low carb and the control diets (Figure 6).

The Effects of Low Carbohydrate Diet on HbA1c

The eight studies used in the analysis of the effects of LCD on HbA1c contained a total of 758 patients and showed that HbA1c was lowered when on the low carb diet (18, 19, 20, 21, 22, 23, 24, 27). The analysis of the effect of a low carbohydrate diet in type 2 diabetic patients on HbA1c is similar to the serum creatinine in that it also contains moderate heterogeneity (P = 0.007, I^2 = 64%) (Figure 4); however, the meta-analysis of these studies showed a significant difference between the low carbohydrate and the control which was the HbA1c favoring the low carbohydrate diet (SMD: -0.29; 95% CI, -0.55 to -0.03; P = 0.03) (Figure 4). The graph showing the change in HbA1c also reflects this with both trendlines becoming more negative as the percent carbohydrates became lower (Figure 7).

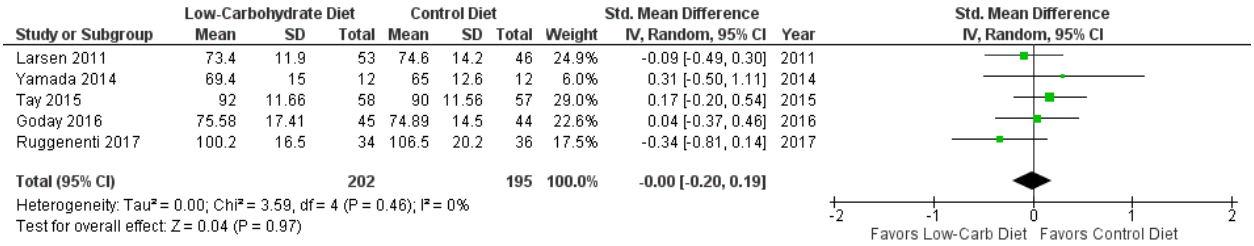

Figure 2 – Effects of a low carbohydrate diet on eGFR in T2D subjects

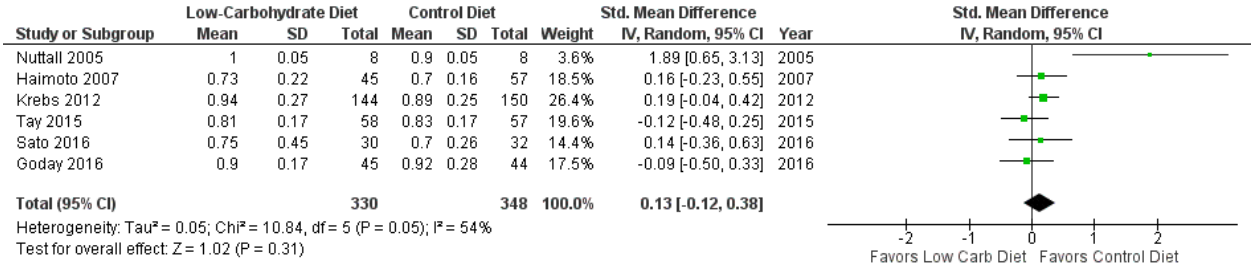

Figure 3 – Effects of low carbohydrate diet on serum creatinine in T2D subjects

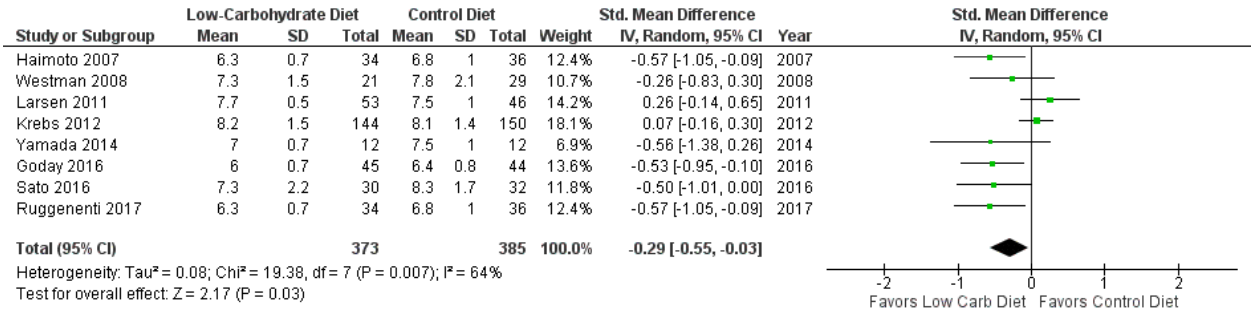

Figure 4 – Effects of low carbohydrate diet on HbA1c T2D subjects

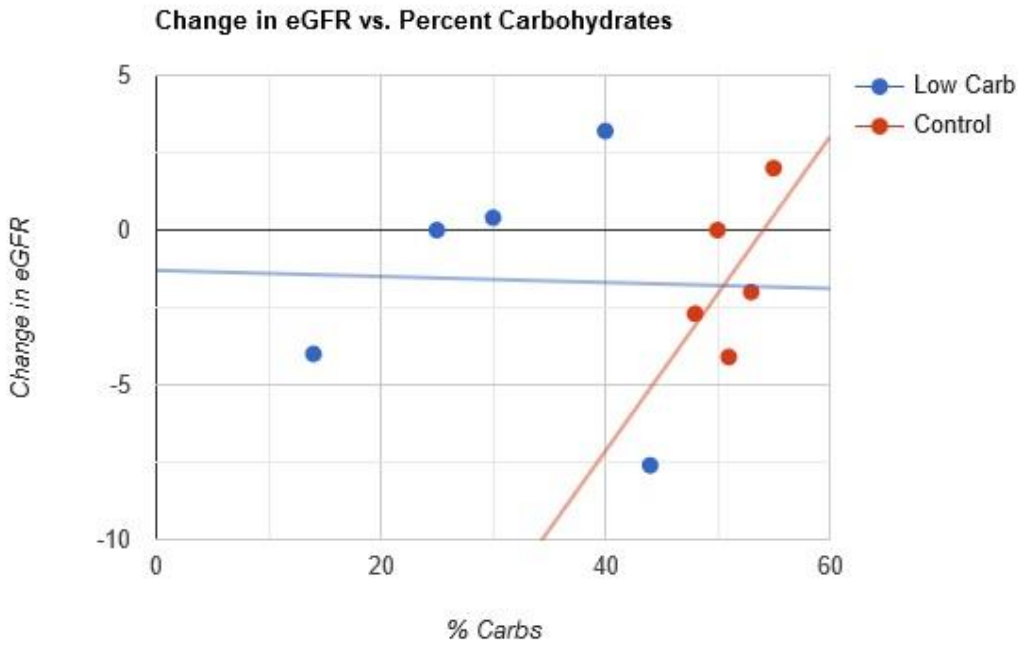

Figure 5 – Graph showing the change in eGFR vs percent carbohydrates in both low carb and control diets

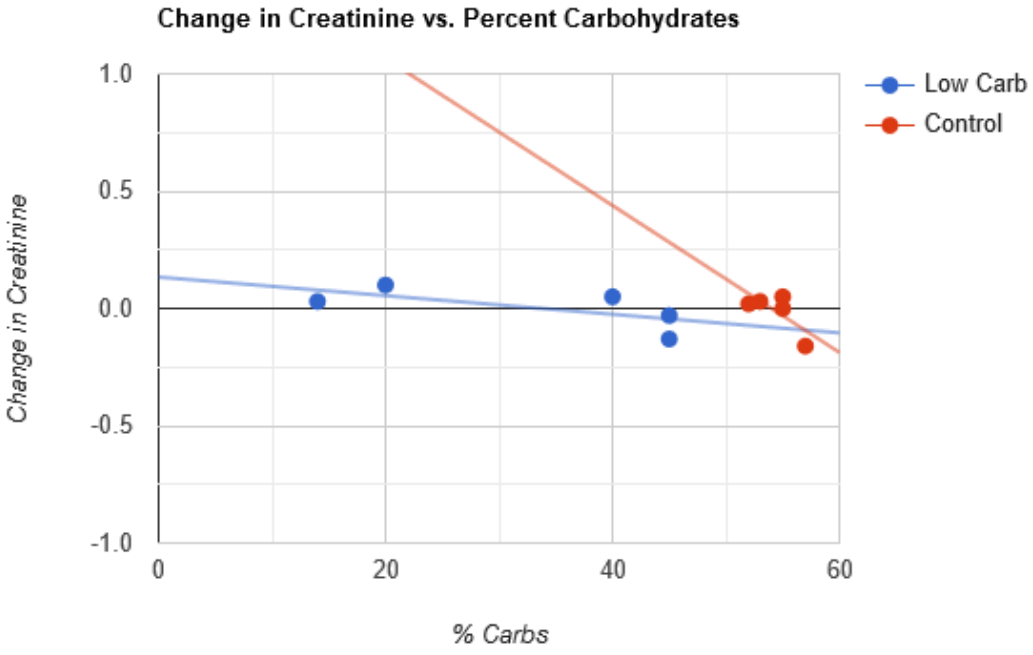

Figure 6 – Graph showing change in serum creatinine vs percent carbohydrates for both low carb and control diets

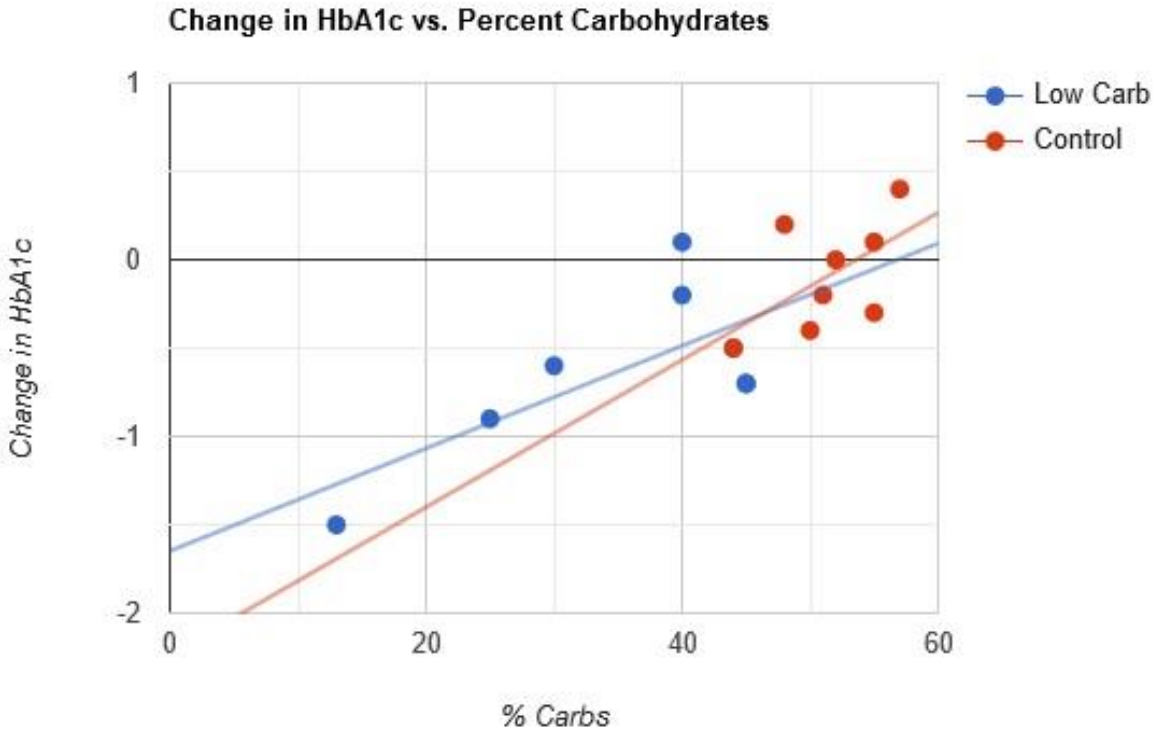

Figure 7 – Graph showing the change in HbA1c vs the percent carbohydrates with both control and low carb diets.

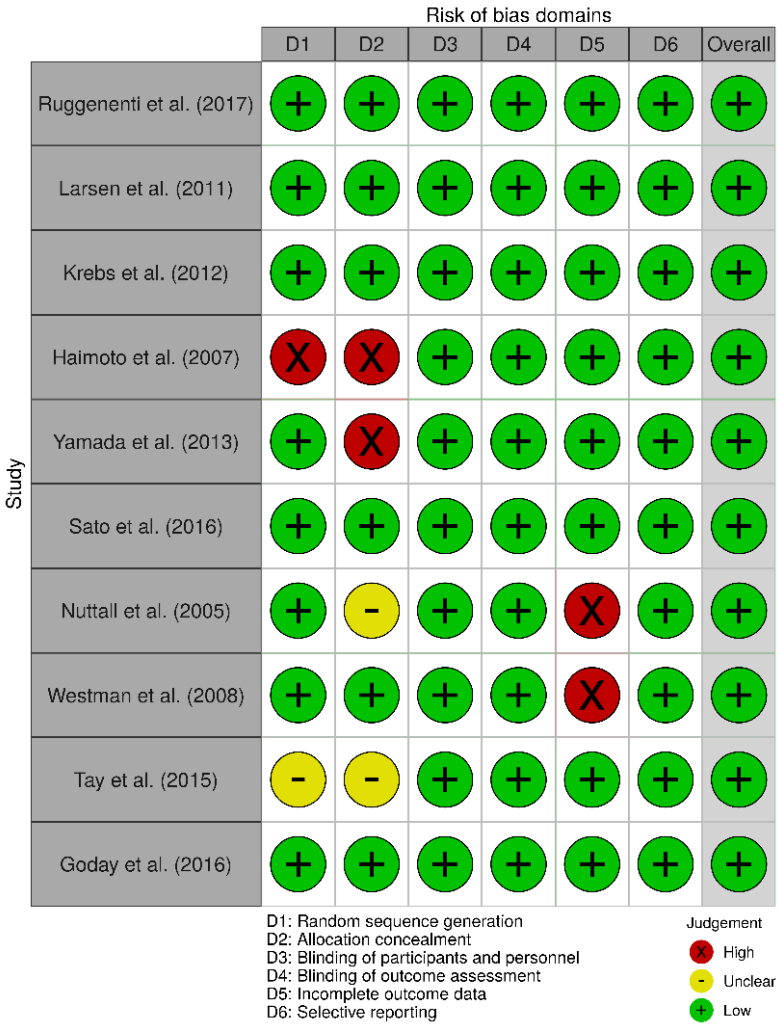

Figure 8 - Risk of bias summary

Publication Bias Assessment

Analysis of the studies showed little risk of bias (Figure 8). The allocation concealment was determined to not influence publication bias due to the patients knowing what diet they were on as soon as they received the food.

Discussion

Summary of Results

The objective of this meta-analysis was to investigate the impact of a low-carb diet on kidney function in type 2 diabetics. This was done because type 2 diabetics have a high blood sugar which has been shown to cause damage to renal function. Renal function is best measured with GFR; however, most studies provide only eGFR or serum creatinine which can both give an estimate on renal function. The National Kidney Foundation lists the values of GFR and their corresponding relationship with renal functions (Table 2). The state of a diabetic can be estimated through their HbA1c levels which is the amount of glycated hemoglobin in comparison to the total amount of hemoglobin. Figures provided by the CDC shows at what stages HbA1c is related to diabetes (Table 3).

The results of the search showed a very small amount of studies on the topic area. The majority of these studies were on weight loss by dietary intervention rather than how the LCD affected the renal system. One of the included studies did not provided values for eGFR or creatinine but did state that the values did not change during the course of the study (18). The meta-analysis of the rest of the data showed that eGFR does not change when measured from LCDs or control diets. This could be due to the relatively short time frame as most of the studies were done in under a year. A change in eGFR was also checked to see if a LCD would produce a greater change in kidney function than the control diet. This produced Figure 5 which shows that regardless of the amount of carbohydrates in the diet, eGFR did not change. Serum

creatinine showed similar results, with the exception of a moderately high heterogeneity (I^2 = 54%) (Figure 3). This was from the shortest duration study (5 weeks) which might not have been enough time for the diet to have a notable effect on renal function (25). A graph showing the change in serum creatinine (Figure 6) was also created to check the results of the eGFR and confirmed the results found in the eGFR graph (Figure 5). HbA1c was also examined in this meta-analysis to confirm the patients' diabetic state. All the studies containing data on HbA1c showed that the patients were on average pre-diabetic or diabetic. The meta-analysis of this data showed that HbA1c was on average lowered in patients who were on the LCD. The amount of carbohydrates consumed seemed to be the main factors in determining the change in HbA1c. The HbA1c graph (Figure 7) shows this correlation nicely.

An interesting study showed that mice with either Akita or *db/db* diabetic nephropathy when put on a ketogenic diet (5% carbohydrates, 8% proteins, and 87% fats) and compared to the mice on the control diet (64% carb, 23% protein, and 11% fat). The researchers found that the diabetic nephropathy was completely reversed within two months (8). Since this research was done in mice, it was not incorporated into this meta-analysis; however, ketogenic diets have been shown in humans to produce positive results such as lower amount of seizures in people with epilepsy and weight loss in obese patients (27, 33). This data was very promising and lead to the initiation of this meta-analysis. After an extensive search, very little data like this could be found in humans as most of the trials did not contain patients with diabetic nephropathy. The studies that were found to contain data similar to the mice study, did not have a control arm in the study and were not able to be incorporated in the meta-

analysis. These studies are listed in the references should the reader wish to look at the results of these studies (28, 29, 30).

Limitations of Study

The meta-analysis, as used in this study, is designed to take data from multiple small studies and compile that data into a single study so that the new study has a much larger data pool to draw from. This allows for a more conclusive result to be determined. This drawing from multiple sources, however, has a few drawbacks. These drawbacks include a lack of consistency as to what is considered the control group, how long the study duration should be, what the results should be measured in, and how the treatment should be administered. This meta-analysis had similar limitations in that most of the low carb diets were between 25% and 45% carbohydrates, however, some studies were between 20% and 13% carbohydrates making those studies very low carbohydrate studies by current standards. Another limitation was that six of the ten studies used in this meta-analysis were conducted in under a year which would not allow for notable renal dysfunction to occur.(18, 19, 23, 24, 25, 27) A third limitation with this study was the subjectivity of the food journals as they were kept by the participants themselves.

Conclusion

This meta-analysis investigated the effect of a low-carb diet on renal function. The results of this study have shown that the eGFR and serum creatinine were not different between patients in the control arm and in the low carb arm of the study. This provides evidence that renal function was not negatively impacted by the low

carbohydrate diet. The HbA1c, however, was lowered when the percent of carbohydrates was lowered which could lead to the reversal of T2DM. Since these studies were done in the short term, a longer trial duration with a greater number of participants should be done before conclusive evidence can be stated about a low carb diet. Future research should also focus on very low carb diets and renal function as a study by Poplawski showed that diabetic nephropathy was able to be reversed through a ketogenic diet (13). Another focus of research should include the effects of a ketogenic diet on liver function of type 2 diabetics due to the low carbohydrates possibly stimulating gluconeogenesis in the liver.

Table 2 – Stages of CKD (National Kidney Foundation guidelines) (31)

Stage	Description	GFR mL/min/1.73 m^2 body surface area
1	Kidney damage* with normal or increased GFR	≥ 90
2	Kidney damage* with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	< 15 or dialysis

* Kidney damage defined as abnormalities on pathologic, urine, blood, or imaging test

Table 3 – Stages of T2DM (CDC Managing Diabetes guideline) (32)

Diagnosis	HbA1c level
Normal	Below 5.7%
Prediabetes	5.7% to 6.4%
Diabetes	6.5% or greater

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