Review
Comparison of the Effectiveness of Low Carbohydrate Versus Low Fat Diets, in Type 2 Diabetes: Systematic Review and Meta-Analysis of Randomized Controlled Trials

Tanefa A. Apekey 1,*, Maria J. Maynard 1, Mitchell. J. Kittana 1 and Setor K. Kunutsor 2,3

1 School of Health, Leeds Beckett University, Leeds LS1 3HE, UK
2 Diabetes Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester LE5 4WP, UK
3 Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol BS8 1QU, UK
* Correspondence: t.a.apekey@leedsbeckett.ac.uk; Tel.: +4-(0)113-812-4991

Abstract: The clinical benefit of low carbohydrate (LC) diets compared with low fat (LF) diets for people with type 2 diabetes (T2D) remains uncertain. We conducted a meta-analysis of randomized controlled trials (RCTs) to compare their efficacy and safety in people with T2D. RCTs comparing both diets in participants with T2D were identified from MEDLINE, Embase, Cochrane Library, and manual search of bibliographies. Mean differences and relative risks with 95% CIs were pooled for measures of glycaemia, cardiometabolic parameters, and adverse events using the following time points: short-term (3 months), intermediate term (6 and 12 months) and long-term (24 months). Twenty-two RCTs comprising 1391 mostly obese participants with T2D were included. At 3 months, a LC vs. LF diet significantly reduced HbA1c levels, mean difference (95% CI) of −0.41% (−0.62, −0.20). LC diet significantly reduced body weight, BMI, fasting insulin and triglycerides and increased total cholesterol and HDL-C levels at the short-to-intermediate term, with a decrease in the requirement for antiglycaemic medications at intermediate-to-long term. There were no significant differences in other parameters and adverse events. Except for reducing HbA1c levels and adiposity parameters at short-to-intermediate terms, a LC diet appears to be equally effective as a LF diet in terms of control of cardiometabolic markers and the risk of adverse events in obese patients with T2D.

Keywords: low carbohydrate diet; low fat diet; type 2 diabetes; glucose; body weight; lipids; blood pressure; inflammation; adverse events; meta-analysis

1. Introduction

Type 2 diabetes (T2D) is a chronic and life-changing metabolic disorder that occurs when the pancreas does not produce enough insulin, or the body cannot effectively use the insulin it produces to regulate blood sugar. It is characterised by hyperglycaemia and associated with an unhealthy lifestyle [1–3]. Glycated hemoglobin also known as HbA1c is a preferred diagnostic test for T2D because it reflects an individual’s average blood glucose levels over the previous 3 months [4]. Reduction in levels of HbA1c is associated with reduction in T2D complications such as damage to the heart, nerves, blood vessels, eyes and kidneys, and death [4,5]. T2D is a major global public health concern due to the rising prevalence and its impact on the health of affected individuals, their families and the substantial costs associated with its management. According to the World Health Organisation, [3] the number of people with diabetes has quadrupled since 1980, with T2D as the vast majority (over 95%) of cases. In addition, the prevalence of T2D is now rising rapidly in both adults and children, and in low- and middle-income countries than in high-income countries. It is now the ninth leading cause of death, with over 6 million people dying from the disease in 2021 [6].
With appropriate interventions, early detection and support, T2D can be prevented, delayed, managed and even result in remission [7,8]. Modifiable risk factors such as active lifestyles, maintaining a healthy body mass index (BMI), smoking cessation, reduced alcohol intake and a healthy diet have been shown to be effective at preventing and delaying the onset of T2D as well as its remission [9–11]. For example, high resistant starch rice has commonly been used as an effective food product to prevent diabetes via its ability to control gluconeogenesis, promote glycogenesis, maintain glucose and lipid homeostasis, and improve pancreatic function [12]. Another nutritional food product known to combat chronic diseases including diabetes is barley [13]. However, there are variations in nutritional advice by guideline recommendations and healthcare systems [8,14,15] and in the effectiveness of dietary interventions [1,16,17] for people living with T2D. In addition, fat and carbohydrate recommendations for adults with T2D vary across diabetes organisations [18]. The most common variations in dietary approaches to the treatment of T2D are in the amount and type of carbohydrate and fat consumed. However, it is not clear as to whether low carbohydrate (LC) or low fat (LF) diet is superior for weight loss and the treatment of T2D. Similarly, there is no agreed definition for LC diets, hence there is variation across studies [18], ranging from 20 g/day (<10% total energy) to 130 g/day (<26% total energy) carbohydrates [19]. For the purposes of this review, LC diet was defined as diets with less than 130 g/day or less than 26% of total energy from carbohydrates (based on an energy intake of 2000 kcal/day). This definition of LC (26% total energy) was based on the proposed classifications of dietary carbohydrate intake by Feinman et al. [18], and to avoid overlap of carbohydrate intake between the intervention and comparator groups. A recent systematic review evaluated the effectiveness of low and very LC diets on T2D remission but only 78% of the comparator diets were LF [20]. The UK Scientific Advisory Committee on Nutrition (SACN) [18] also reviewed the evidence on LC diets compared to current UK government advice on carbohydrate intake for adults with type 2 diabetes. However, LC diet in this review was defined as carbohydrate intake ranging from 14% to 50% total energy per day. Both reviews did not consider other important outcomes such as liver markers, renal function, and systolic and diastolic blood pressure (SBP and DBP). We conducted a meta-analysis of randomized controlled trials (RCTs) to compare the efficacy and safety of LC diets compared with LF diets for people with T2D using a comprehensive list of cardiometabolic outcomes including blood pressure and markers of renal and liver function.

2. Materials and Methods

2.1. Data Sources and Search Strategy

This review was conducted using a predefined protocol, registered in the PROSPERO prospective register of systematic reviews (CRD42021254388), and in accordance with PRISMA and MOOSE guidelines [21,22] (Tables S1 and S2). A systematic search for RCTs was carried out on PubMed, MEDLINE, Embase, Web of Science, Clinical Trials.gov, and the Cochrane electronic databases from January 1981 till July 2021. The search was updated on 12 October 2022 following initial review. The computer-based searches combined terms related to the exposures (e.g., low carbohydrate diet, low fat diet, calorie-restricted diet) and population (e.g., prediabetes, type 2 diabetes) in humans, without any language restriction. Full details of the MEDLINE search strategy are provided in Table S3. Two authors (TA and SKK) independently screened titles and abstracts of the retrieved citations to assess their suitability for potential inclusion, which was followed by the acquisition of full texts for detailed evaluation. Full-text evaluation was also independently conducted by two authors (TA and SKK). Disagreements regarding eligibility of an article were discussed and resolved by consensus. The reference lists of relevant studies and review articles were manually scanned for additional studies.
2.2. Eligibility Criteria

Studies were eligible if they were randomized controlled, open or blinded trials that: (i) enrolled adults classified as prediabetes and those living with T2D regardless of medication use, glucose and glycated haemoglobin (HbA1c) levels, and comorbidities; (ii) compared a LC diet (<26% of total energy or <130 g of carbohydrate a day) with a LF diet (>26% of total energy or >130 g of carbohydrates a day); (iii) reported at least 12 weeks duration of the trial; (iv) and reported on any of the outcomes below.

2.3. Outcomes Evaluated

Our primary outcomes of interest were measures of glycaemia including fasting plasma glucose, mean glucose, and HbA1c levels. Secondary outcomes were measures of body composition (e.g., body weight, BMI, waist circumference, total fat free mass); cardiovascular risk markers (e.g., SBP, DBP, lipids, fasting insulin, measures of insulin resistance, measures of inflammation such as C-reactive protein (CRP)); liver function tests (e.g., alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT)); renal function tests (e.g., creatinine, estimated glomerular filtration rate (GFR), urinary albumin); measures of medication changes (e.g., medication effect score (MES)); and adverse events. Non-randomized studies that compared the desired interventions were excluded.

2.4. Data Extraction and Risk of Bias Assessment

Two authors (TA and SKK) independently extracted data, with inconsistencies resolved by discussion. A predesigned data extraction form was used to extract all the relevant information on publication date, geographical location, study design characteristics (e.g., randomization, allocation concealment, blinding, duration), population (e.g., baseline age, percentage of males, baseline BMI and HbA1c), intervention and comparator, and outcomes. Outcome data were extracted for the specific time points reported by the trials. For multiple publications of studies using data from the same trial, non-overlapping data based on the most comprehensive results were extracted. We used the Cochrane Collaboration’s risk of bias tool to assess the risk of bias of included RCTs [23]. This tool evaluates seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. For each individual domain, studies were classified into low, unclear and high risk of bias. We also used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool to assess the quality of the body of evidence, based on study limitations, inconsistency of effect, imprecision, indirectness and publication bias [24].

2.5. Statistical Analysis

Summary measures of effect were presented as relative risks (RRs) (95% CIs) for binary outcomes and mean differences (95% CIs) for continuous outcomes and. Relative risks and 95% CIs were estimated from the extracted raw counts for the interventions and comparators. For studies that reported data such as medians (ranges and 95% CIs) and means (SDs and standard errors), these were converted to means and standard deviations using methods described by Hozo and colleagues [25]. For each outcome, effect estimates (RRs and mean differences) were estimated for the time points of 3 months (±1 month), 6 months (+2 months), 12 months (±3 months), and 24 months (±6 months), based on the distribution of the time points reported by the eligible studies and to maintain some consistency with that of a previous review [20]. The time points were categorised as short-term (3 months), intermediate term (6 and 12 months) and long-term (24 months). Measures of effect were pooled using random effects models to minimize the effect of heterogeneity [26]. Where appropriate, fixed effects models were used in parallel analyses. We planned to investigate sources of heterogeneity using subgroup analysis and random effects meta-regression [27] as well as assess for small study effects using formal tests such
as Begg’s funnel plots [28] and Egger’s regression symmetry test [29]. However, these could not be performed because of the limited number of studies (<10) for each outcome assessed. All analyses were conducted using Stata version MP 16 (Stata Corp, College Station, TX, USA). For outcomes that could not be pooled, a narrative synthesis was used to summarise the results.

3. Results

3.1. Study Identification and Selection

Our initial search of relevant databases and manual scanning of reference lists identified 19,029 potentially relevant citations. After screening based on titles and abstracts, 38 articles remained for full text evaluation. Following detailed assessments, 13 articles were excluded because (i) intervention/comparator was not relevant (n = 8); (ii) they were not randomized studies (n = 2); (iii) population was not relevant (n = 2); and (iv) was based on a conference presentation (n = 1). The remaining 25 articles [30–54] which were based on 22 unique RCTs, met our inclusion criteria and were included in the meta-analysis (Figure 1).

![PRISMA flow diagram.](image)

3.2. Study Characteristics and Risk of Bias

Tables 1 and 2 summarises the key characteristics of the RCTs included in the review. In aggregate, the included trials published between 2003 and 2022, comprised 1391 participants (711 assigned to LC diet and 680 assigned to LF diet). All RCTs were open-labelled and recruited patients with T2D, with the majority being obese and/or overweight. No study was identified to have recruited people with prediabetes. The mean baseline age, BMI, HbA1c, and duration of T2D of participants ranged from 36.8–67.0 years, 25.8–38.1 kg/m², 6.0–9.1 %, 0.3–13.5 years, respectively; with weighted means of 57.2 years, 34.4 kg/m², 7.8%, and 7.6 years, respectively. Overall, 8 studies were conducted in Asia (China, Iran, Israel, Japan, and Taiwan), 6 in North America (USA) and 5 in Europe (Denmark, Italy, Sweden, and UK) and 3 in Australasia (Australia). The mean duration of trials or interventions in the trials ranged from 2–24 months with a weighted mean of 12.4 months. Not all studies provided information on dietary adherence. Exercise was usually encouraged as part of the
dietary interventions in some studies but was not evaluated in separate analyses. Using the Cochrane Risk of Bias tool, all 22 trials demonstrated a high risk of bias in blinding of participants & personnel; all but 2 demonstrated a high risk of bias in blinding of outcome assessments; and 7 trials demonstrated a high risk of bias in 3 or more domains (Figure S1).
Table 1. Characteristics of included trials.

| Author, Year of Publication | Country | Population | Baseline Year | Mean Age, years | Male % | Mean BMI, kg/m² | Mean HbA1c, % | Diabetes Duration, years | Trial Duration, years | No. Randomized | No. In Intervention | No. In Comparator | Overall Risk of Bias * |
|-----------------------------|---------|------------|----------------|-----------------|--------|-----------------|----------------|--------------------------|----------------------|----------------|---------------------|---------------------|------------------------|
| Samaha, 2003 [42]           | USA     | Obese with diabetes | 2001            | NR               | NR     | NR              | NR             | NR                       | 6.0                  | 79            | 41                  | 38                  | High                   |
| Daly, 2006 [32]              | UK      | Obese with poorly controlled T2DM | NR             | 58.7             | 48.0   | 36.1            | 9.1            | NR                       | 3.0                  | 102           | 51                  | 51                  | High                   |
| Westman, 2008 [50]          | USA     | Obesity and T2DM     | NR             | 51.8             | 21.4   | 38.1            | NR             | NR                       | 6.0                  | 84            | 38                  | 46                  | High                   |
| Shai, 2008 [47]              | Israel  | Obese with T2DM      | NR             | NR              | NR     | NR              | NR             | NR                       | 24.0                 | 31            | 19                  | 12                  | High                   |
| Davis, 2009 [33]             | USA     | T2DM with BMI ≥ 25 kg/m², and A1C between 6 and 11% | 2004-2006     | 53.5             | 21.9   | 36.0            | 7.5            | NR                       | 12.0                 | 105           | 55                  | 50                  | High                   |
| Iqbal, 2010 [36]             | USA     | Obese with T2DM      | 2004-2008      | 60.0             | 89.6   | 37.5            | NR             | NR                       | 24.0                 | 144           | 70                  | 74                  | High                   |
| Goldstein, 2011 [34]         | Israel  | Obese T2DM           | 2001-2004      | 56.0             | 48.1   | 33.2            | 8.9            | 8.0                      | 12.0                 | 52            | 26                  | 26                  | High                   |
| Khoo, 2011 [38]              | Australia | Obese with T2DM     | 2007-2008      | 59.7             | 35.3   | 4.5             | 2.0            | 4.5                      | 3.0                  | 31            | 12                  | 19                  | High                   |
| Guldbrand, 2012 [35]; Jonasson, 2014 [37] | Sweden | Diagnosis of T2DM treated with diet with or without additional oral glucose-lowering medication, incretin-based therapy or insulin | 2008-2009     | 62.0             | 44.3   | 32.7            | 7.3            | 9.3                      | 24.0                 | 61            | 30                  | 31                  | High                   |
| Tay, 2014 [48]; Tay 2015 [54] | Australia | Obese adults with T2DM, taking antglycaemic medication | 2012-2013     | 58.0             | 57.4   | 34.6            | 7.3            | 8.0                      | 12.0                 | 115           | 58                  | 57                  | High                   |
| Yamada, 2014 [51]            | Japan   | Poorly controlled T2DM | 2011-2012     | 63.3             | 50.0   | 25.8            | 7.7            | 9.2                      | 6.0                  | 24            | 12                  | 12                  | High                   |
| Saslow, 2014 [43]            | USA     | Overweight or obese adults with T2DM or prediabetes | 2012          | 59.7             | 26.5   | 36.8            | 6.8            | 7.1                      | 3.0                  | 34            | 16                  | 18                  | High                   |
| Sato, 2017 [45]; Sato 2017a [46] | Japan | T2DM with poor glycaemic control | 2013-2014     | 59.4             | 75.8   | 26.6            | 8.2            | 13.5                     | 18.0                 | 66            | 33                  | 33                  | High                   |
| Saslow, 2017 [44]            | USA     | Overweight with T2DM  | 2013           | 55.7             | 40.0   | 7.2             | 5.5            | 7.4                      | 25                  | 12            | 13                  | 13                  | High                   |
| Nishimori, 2018 [40]         | Japan   | T2DM and NFLD        | NR             | 49.5             | 64.0   | NR              | NR             | NR                       | 3.0                  | 28            | 14                  | 14                  | High                   |
| Zadeh, 2018 [30]             | Iran    | Obese and T2DM       | NR             | 48.2             | 34.1   | 7.0             | 6.5            | 6.0                      | 22                  | 11            | 11                  | 11                  | High                   |
### Table 1. Cont.

| Author, Year of Publication | Country | Population | Baseline Year | Mean Age, years | Male % | Mean BMI, kg/m² | Mean HbA1c, % | Diabetes Duration, years | Trial Duration, years | No. Randomized | No. In Intervention | No. In Comparator | Overall Risk of Bias * |
|----------------------------|---------|------------|---------------|----------------|--------|----------------|--------------|-------------------------|----------------------|----------------|----------------|----------------|---------------------|
| Tay, 2018 [49]             | Australia | T2DM under the care of a GP/endocrinologist | 2012–2014 | 58.0 | 57.4 | 34.5 | 7.3 | 7.0 | 24.0 | 115 | 58 | 57 | High |
| Perna, 2019 [41]           | Italy | Obese and overweight with T2DM, only treated with metformin | NR | 67.0 | 35.3 | 31.4 | 6.0 | NR | 3.0 | 17 | 8 | 9 | High |
| Chen, 2020 [31]            | Taiwan | Poorly controlled T2DM | 2016 | 63.6 | 38.8 | NR | NR | 9.9 | 18.0 | 92 | 47 | 45 | High |
| Morris, 2020 [39]          | UK | T2D and BMI of at least 30 kg/m² | 2018 | 67.0 | 45.0 | 35.4 | NR | 9.2 | 3.0 | 33 | 21 | 12 | High |
| Gram-Kampmann, 2022 [53]   | Denmark | T2DM with HbA1c > 48 mmol/mol | 2016–2018 | 56.6 | 43.7 | NR | NR | 5.1 | 0.5 | 71 | 49 | 22 | High |
| Li, 2022 [52]              | China | Overweight or obese with T2DM | 2018–2020 | 36.8 | NR | 29.4 | 8.7 | 0.3 | 0.25 | 60 | 30 | 30 | High |

NR—Not Report; T2DM—Type 2 Diabetes Mellitus; NFLD—Non-alcoholic Fatty Liver Disease; GP—General Practitioner; BMI—Body Mass Index; HbA1c—Glycated Haemoglobin; * demonstrated a high risk of bias in one or more domains of the Cochrane risk of bias tool.

### Table 2. Characteristics of interventions and comparators in included trials.

| Author, Year of Publication | Intervention | Description of Intervention | Comparator | Description of Comparator | Exercise Recommendations |
|----------------------------|--------------|----------------------------|------------|---------------------------|-------------------------|
| Samaha, 2003 [42]          | Low carb diet | 30 g/day or less | Low fat diet | Caloric restriction sufficient to create a deficit of 500 calories per day, with 30 percent or less of total calories derived from fat. | None recommended |
| Daly, 2006 [32]            | Low carb diet | 70 g/day | Low fat diet | | Both groups |
| Westman, 2008 [50]         | Low carb ketogenic diet | <20 g of carbohydrate daily | Low-glycemic, reduced-calorie diet | 500 kcal/day deficit from weight maintenance diet | Both groups |
| Shai, 2008 [47]            | Low-carb, non-restricted-calorie diet | 20 g/day for the 2 month induction phase | Low-fat, restricted-calorie diet | Energy intake of 1500 kcal per day for women and 1800 kcal per day for men, with 30% of calories from fat, 10% of calories from saturated fat, and an intake of 300 mg of cholesterol per day | Not specifically recommended |
Table 2. Cont.

| Author, Year of Publication | Intervention | Description of Intervention | Comparator | Description of Comparator | Exercise Recommendations |
|-----------------------------|--------------|------------------------------|------------|---------------------------|-------------------------|
| Davis, 2009 [33]            | Low carb diet | Initial 2-week phase of carbohydrate restriction of 20–25 g daily depending on baseline weight; increased intake at 5-g increments each week as participants lost weight | Low fat diet | Fat gram goal was 25% of energy needs, based on baseline weight; 53 energy percent | General recommendations made |
| Iqbal, 2010 [36]            | Low carb diet | <30 g/day | Low fat diet | ≤30% of calories from fat with a deficit of 500 kcal/day | Not specifically recommended |
| Goldstein, 2011 [34]        | Modified Atkins diet (very low carb diet) | Containing up to 25 g of carbs daily for the first 6 weeks after randomization, thereafter increasing to a ceiling of 40 g daily | Standard recommended ADA calorie-restricted diet | Containing 10–20% of the daily energy intake from protein and the other 80% divided between fats [which provided 18–20% of calories as MUFA, 8–10% as polyunsaturated fatty acids (PUFA) and 9–10% as SFA], carbohydrates and 35 g of fibre | Both groups |
| Khoo, 2011 [38]             | Low-fat, high-protein, reduced-carb diet | Reduction in daily energy intake by ~600 kcal | Low-calorie diet | 1000 kcal/day | Not specifically recommended |
| Guldbrand, 2012 [35]; Jonasson, 2014 [37] | Low carb diet | 20 energy percent from carb | Low fat diet | 55–60 energy percent | Not specifically recommended |
| Tay, 2014 [48]; Tay 2015 [54] | Low-carbohydrate, high unsaturated/low saturated fat diet | 14% carbohydrate [<50 g/day], 28% protein, and 58% fat [<10% saturated fat] plus structured exercise | High unrefined carbohydrate, low fat diet | 53% carbohydrate, 17% protein, and 30% fat [<10% saturated fat] plus structured exercise | Both groups |
| Yamada, 2014 [51]           | Low carb diet | <130 g/day | Calorie restricted diet | Carbohydrates = 50–60%, protein = 1.0–1.2 g/kg (<20%) and fat = <25% | Not reported |
| Saslow, 2014 [43]           | Low carb ketogenic diet | Reduce carbohydrate intake over 7–10 days to between 20–50 g of carbohydrates a day with the goal of achieving nutritional ketosis | Moderate carb, calorie-restricted diet | 45% to 50% of calories derived from carbohydrates | Both groups |
| Sato, 2017 [45]; Sato 2017a [46] | Low carb diet | 130 g/day | Calorie restricted diet | The percentage of carbohydrate per total calorie was 50–60%, and that of proteinwas 1.0–1.2 g/kg | Both groups |
| Author, Year of Publication | Intervention | Description of Intervention | Comparator | Description of Comparator | Exercise Recommendations |
|----------------------------|--------------|-----------------------------|------------|---------------------------|--------------------------|
| Saslow, 2017 [44]          | Very low-carb ketogenic diet with lifestyle factors; “intervention” | Reduce carb intake to between 20–50 g of nonfiber carbohydrates a day | Online diet program based around a plate method diet | A low-fat diet that emphasizes green vegetables, lean protein sources, and somewhat limited starchy and sweet foods | Intervention group received exercise recommendations |
| Nishimori, 2018 [40]       | Low carb diet | 70–130 g./day | Calorie restricted diet | 25 kcal/kg of ideal body weight per day | Not reported |
| Zadeh, 2018 [30]           | Low carb diet plus high intensity interval training | 45% energy (E %) from fat, 20 E% from carbohydrate and 35 E% from protein | Low fat diet plus high intensity interval training | 30 E% from fat (less than 10 E% from saturated fat), 50 E% from carbohydrate and 20 E% from protein | Both groups |
| Tay, 2018 [49]             | Low-carb, high-unsaturated/low-saturated fat diet | 14% energy as carb, 28% as protein, 58% as fat (<10% saturated fat) | High-carbohydrate, low-fat diet | 53% as CHO, 17% as protein, 30% as fat (<10% saturated fat) | Both groups |
| Perna, 2019 [41]           | Low carb diet and metformin | CHO <125 g/day, 1600 kcal/day for females and 1800 kcal/day for males | Balanced standard diet | Carbohydrates 55-60%, lipids 25-30%, proteins 15-20% | Not reported |
| Chen, 2020 [31]            | Low carb diet | 90 g/day | Traditional diabetic diet | Macronutrient percentage was 50–60% for CHO, 1.0–1.2 g/kg for protein and ≤30% for fat | Both groups |
| Morris, 2020 [39]          | Low-energy, low-carb diet | 800–1000 kcal/day, with <26% of daily energy intake from carb and a minimum of 60 g protein/day | Usual care dietary advice | Healthy balanced eating | Not reported |
| Gram-Kampmann, 2022 [53]   | Low carb diet | Maximum of 20 E% of carbohydrates (mainly complex and water-soluble); 50–60 E% fat, and 25–30 E% protein. | Control diet | 50–60 E% carbohydrates mainly from fruit, vegetables, and whole-grain sources, 20–30 E% fat | Both groups |
| Li, 2022 [52]              | Ketogenic diet | Carbohydrate 30–50 g, protein 60 g, fat 130 g, and total calories (1500 ± 50) Kcal | Routine diet for diabetes | Carbohydrate 250–280 g, protein 60 g, fat 20 g, total calories (1500 ± 50) Kcal | Not reported |
3.3. Measures of Glycaemia

Comparing LC with LF diets, there were no significant differences in fasting glucose levels at 3, 6, 12, and 24 months: mean differences (95% CIs) of $-2.05 (-18.99, 14.89)$, $-11.48 (-27.37, 4.41)$, $-1.42 (-3.98, 1.14)$ and $-6.06 (-25.07, 12.94)$ mg/dL, respectively (Figure 2).

At 3 months, a LC vs. LF diet significantly reduced HbA1c levels, mean difference (95% CI) of $-0.41% (-0.62, -0.20)$, with no differences at 6, 12, and 24 months: mean differences (95% CIs) of $-0.18% (-0.57, 0.21)$, $0.11% (-0.06, 0.29)$, and $-0.31% (-0.96, 0.35)$ mg/dL, respectively (Figure 3).

![Figure 2. Low carbohydrate versus low fat diet and fasting glucose levels [31,34,36,41–43,50,51].](image-url)
Figure 3. Low carbohydrate versus low fat diet and HbA1c levels [31–36,41,42,44,46,47,50–52,54].

3.4. Body Composition

At 3 and 6 months, a LC vs. LF diet significantly reduced body weight, mean differences (95% CIs) of $-3.07$ kg ($-4.49$, $-1.66$) and $-3.02$ kg ($-5.18$, $-0.87$), respectively; with no differences at 12 and 24 months: mean differences (95% CIs) of $0.36$ kg ($-1.63$, $2.35$) and $-1.29$ kg ($-3.71$, $1.12$), respectively (Figure 4). At 3 and 6 months, a LC vs. LF diet significantly reduced BMI, mean differences (95% CIs) of $-1.79$ kg/m$^2$ ($-2.99$, $-0.60$) and $-1.43$ kg/m$^2$ ($-2.32$, $-0.55$), respectively, with no differences at 12 and 24 months: mean differences (95% CIs) of $-0.43$ kg/m$^2$ ($-2.46$, $1.60$) and $0.04$ kg/m$^2$ ($-0.81$, $0.89$), respectively (Figure 5). At 6 and 24 months, a LC vs. LF diet significantly reduced waist circumference: mean differences (95% CIs) of $-4.20$ cm ($-7.77$, $-0.64$) and $-3.44$ cm ($-6.77$, $-0.12$), respectively, with no differences at 3 and 12 months: mean differences (95% CIs) of $-2.27$ cm ($-8.06$, $3.51$) and $-0.89$ cm ($-3.64$, $1.87$), respectively (Figure 6). Results from single reports showed no significant differences in fat free mass at 3, 6, and 12 months comparing a LC with a LF diet (Figure S2).
Figure 4. Low carbohydrate versus low fat diet and body weight [31–35,38–41,43–46,48,50–53].

Figure 5. Low carbohydrate versus low fat diet and body mass index [31,35,37,38,41,43,45,46,48,50–53].
3.5. Blood Pressure

When LC and LF diets were compared, except for a reduction in SBP at 3 months: mean difference (95% CI) of $-4.53$ mmHg ($-8.57$, $-0.48$) (Figure 7), there were no significant differences in SBP and DBP at all other time periods (Figure 7; Figure S3).

3.6. Lipids

A comparison of LC and LF diets showed there were significant increases in total cholesterol levels at 6 and 12 months: mean differences (95% CIs) of $2.24$ mg/dL ($0.50$, $3.99$) and $6.41$ mg/dL ($3.10$, $9.73$), respectively, with no significant differences at 3 and 24 months (Figure S4). There were no significant differences in low-density lipoprotein cholesterol (LDL-C) levels at 3, 6, 12, and 24 months (Figure S5). The LC diet significantly increased high-density lipoprotein cholesterol (HDL-C) levels compared with the LF diet at 3 and 12 months: mean differences (95% CIs) of $2.85$ mg/dL ($0.33$, $5.36$) and $1.62$ mg/dL ($1.20$, $2.04$), respectively, with no significant differences at 6 and 24 months (Figure S6). At 3 and 6 months, a LC vs. LF diet significantly reduced levels of triglycerides, mean differences (95% CIs) of $-25.33$ mg/dL ($-44.78$, $-5.87$) and $-20.62$ mg/dL ($-37.91$, $-3.32$), respectively, with no differences at 12 and 24 months (Figure S7). A LC diet reduced the total cholesterol/HDL-C at 3 months: mean difference (95% CI) of $-0.33$ ($-0.56$, $-0.11$) (Figure S8).

3.7. Measures of Inflammation

There were no significant differences in CRP levels between the LC and LF diets at 3, 6, 12, and 24 months (Figure S9). Results from single reports showed that a LC diet reduced interleukin-6 (IL-6) levels at 6 months, with no significant difference at 3 months (Figure S10).
3.6. **Lipids**

A comparison of LC and LF diets showed there were significant increases in total cholesterol levels at 6 and 12 months: mean differences (95% CIs) of 2.24 mg/dL (0.50, 3.99) and 6.41 mg/dL (3.10, 9.73), respectively, with no significant differences at 3 and 24 months (Figure S4). There were no significant differences in low-density lipoprotein cholesterol (LDL-C) levels at 3, 6, 12, and 24 months (Figure S5). The LC diet significantly increased high-density lipoprotein cholesterol (HDL-C) levels compared with the LF diet at 3 and 12 months: mean differences (95% CIs) of 2.85 mg/dL (0.33, 5.36) and 1.62 mg/dL (1.20, 2.04), respectively, with no significant differences at 6 and 24 months (Figure S6). At 3 and 6 months, a LC vs. LF diet significantly reduced levels of triglycerides, mean differences (95% CIs) of $-25.33 \text{mg/dL} (-44.78, -5.87)$ and $-20.62 \text{mg/dL} (-37.91, -3.32)$, respectively, with no differences at 12 and 24 months (Figure S7). A LC diet reduced the total cholesterol/HDL-C at 3 months: mean difference (95% CI) of $-0.33 (-0.56, -0.11)$ (Figure S8).

3.7. **Measures of Inflammation**

There were no significant differences in CRP levels between the LC and LF diets at 3, 6, 12, and 24 months (Figure S9). Results from single reports showed that a LC diet reduced interleukin-6 (IL-6) levels at 6 months, with no significant difference at 3 months (Figure S10).

3.8. **Other Cardiovascular Risk Markers**

The LC diet significantly reduced fasting insulin levels compared with the LF diet at 3 months: mean difference (95% CI) of $-2.83 \mu \text{IU/mL} (-4.73, -0.93)$, but with no significant differences at 6, 12, and 24 months (Figure S11). Results from single reports showed no significant differences in HOMA2-IR at all time points comparing a LC with a LF diet (Figure S12). The LC diet significantly reduced HOMA-IR compared with the LF diet at 3 months: mean difference (95% CI) of $-0.71 (-1.05, -0.37)$ (Figure S13). A single report showed no significant difference in HOMA2-%B at all time points comparing a LC with a LF diet (Figure S14).

3.9. **Liver Function**

At 3 months, a LC vs. LF diet significantly reduced ALT levels, mean difference (95% CI) of $-8.86 \text{U/L} (-17.09, -0.62)$. Results from a single report showed that at 6 months, a LC vs. LF diet reduced ALT levels (Figure S15). Comparing a LC with a LF diet, there were no significant differences in AST and GGT levels at 3 and 6 months (Figures S16 and S17).

3.10. **Renal Function**

Based on a single report, a LC vs. LF diet significantly increased creatinine levels at 6 months; with no differences at 3 and 24 months (Figure S18). Results from single reports showed no significant differences in estimated GFR at 3, 6, and 24 months comparing a LC with a LF diet (Figure S19). Results from single reports showed no significant differences in microalbumin at 3, 6, and 12 months comparing a LC with a LF diet (Figure S20). Results from single reports showed a significant increase in urea at 3 months, with no significant differences at 6 and 12 months comparing a LC with a LF diet (Figure S21). Results from single reports showed no significant differences in urinary albumin at 6 and 24 months comparing a LC with a LF diet (Figure S22). Results from single reports showed a significant increase in uric acid at 3 months with no difference at 24 months comparing a LC with a LF diet (Figure S23).

3.11. **Medication Changes**

The LC diet achieved a significant reduction in antiglycemic MES compared with the LF diet at 12 and 24 months, with no significant difference at 6 months (Figure S24).
3.12. Adverse Events

With respect to the two diets, there was no significant difference in risk of adverse events (e.g., musculoskeletal ailments with exercise training, hypoglycaemia and gastrointestinal complaints): RR (95% CI) of 1.27 (0.74–2.18; \( p = 0.38 \)) (Figure S25).

3.13. GRADE Summary of Findings

The GRADE working group recommends up to 7 patient-important outcomes to be listed in the “summary of findings” tables in systematic reviews [24]. In addition to the primary outcomes of fasting glucose and HbA1c levels, we selected body weight, BMI, SBP, and total cholesterol based on their frequency of reporting. We also included the outcome of adverse events since it is recommended that the 7 selected outcomes should include a safety outcome. GRADE ratings for the outcomes are reported in Table S4. GRADE quality of the evidence ranged from moderate to very low.

4. Discussion

4.1. Key Findings

Given the persisting uncertainty regarding the net clinical benefits of LC diets compared with LF diets for people with T2D remains uncertain, we conducted an aggregate meta-analysis to compare the efficacy and safety of LC with LF diets in people with T2D. For the primary endpoints, LC compared with LF diet reduced HbA1c levels only at the 3-month time point, with no differences in fasting glucose levels at all time points. For body composition measures, LC diet reduced body weight, BMI, and waist circumference mostly at short and intermediate terms. LC diet reduced SBP at 3 months, with no significant differences in SBP and DBP at other time points. Findings for lipid parameters were inconsistent: at short and intermediate terms, there were reductions in levels of triglycerides and total cholesterol/HDL-C ratio; increases in total cholesterol and HDL-C; and no significant differences in levels of LDL-C. There were no significant differences for CRP, AST, GGT, and the risk of adverse events comparing LC with LF diet. LC diet significantly reduced fasting insulin and ALT at short-to-intermediate terms and antiglycemic MES at intermediate-to-long terms. Results from single reports showed LC diet reduced IL-6 levels; increased levels of creatinine and urea; with no differences for fat free mass, HOMA2-IR, HOMA2-%B, estimated GFR, microalbumin, and urinary albumin between the two interventions. The GRADE quality of evidence for the 7 relevant outcomes ranged from moderate to very low.

4.2. Comparison with Previous Studies

Similar to the findings of the review by Goldenberg et al. [20] we found moderate evidence for a beneficial effect of a LC diet on weight and BMI at short to intermediate term (3–6 months). However, according to SACN [18], this beneficial effect only occurred at 3 months. Although the quality of evidence for HbA1c in our study was ‘very low’ compared to ‘adequate’ in the SACN review [18] and ‘high’ as reported by Goldenberg et al. [20] all three reviews showed a beneficial effect of a LC diet over the control diet in the short and intermediate term for this glycaemic marker. The short to intermediate term reduction in fasting insulin observed from a LC diet is consistent with the findings of Goldenberg et al. [20] and SACN [18]. In contrast to these two reviews, we observed beneficial effects of a LC diet over LF diet on triglyceride and HDL-C levels, and total cholesterol/HDL-C ratio. The increase in levels of total cholesterol when a LC diet was compared with a LF diet was inconsistent with the findings of Goldenberg et al. [20] who found no effect. Similar to the findings of SACN [18] and Goldenberg et al. [20] we found no significant difference in adverse events between the two diets, but a LC diet resulted in greater reduction in MES compared to a LF diet in our review, whereas our review specifically compared a LC diet with a low LF diet (>26% of total energy or >130 g of carbohydrates a day), the review by Goldenberg et al. [20] compared low and very low carbohydrate diets with a wide range of diets including dietary programs higher in carbohydrates (>26%), palaeolithic diet as well as no treatment; however, most of the trials included in their review used low fat diets.
as their control parameters. Furthermore, our review considered only patients with T2D and was based on RCTs, which are the gold standard for evaluating the effectiveness of interventions; whereas, other reviews have included observational studies, people with type 1 diabetes, and a variety of comparator diets [55–58]. In addition, we evaluated a comprehensive list of cardiometabolic outcomes including blood pressure and markers of renal and liver function which were not evaluated by previous reviews. We also showed that a LC diet was associated with significant reduction in waist circumference at 12 months; an outcome not considered by the reviews of SACN [18] and Goldenberg et al. [20].

4.3. Explanations for Findings

Dietary protein is associated with greater satiety and therefore reduction in calorie intake [59]. The satiety effect would explain the significantly higher reduction in weight and BMI from the LC compared to LF diet in the short-to-intermediate term. In addition, our findings suggest that weight loss irrespective of carbohydrate and fat restriction resulted in reduction in BMI, serum lipids, and measures of inflammation and glycaemia. Therefore, it was not possible to distinguish between the impact of carbohydrate compared to fat restriction on these outcomes. The improvement in the clinical outcomes may be attributed to calorie-restriction and associated weight loss rather and macronutrient restriction. Thus, a calorie-restricted balanced diet could produce similar favourable clinical outcomes. This is supported by the results from the ongoing DiRECT study (Diabetes Remission Clinical Trial), where a daily calorie intake of 825–853 kcal/day resulted in remission to a non-diabetic state and off antidiabetic drugs for over half the study participants [60]. The short-to-intermediate term beneficial effect of the LC compared to the LF could be due to the difficulty with adherence to the LC, and therefore unsustainable weight loss in the long term. This is also supported by evidence from the DiRECT programme, where sustained remissions at 24 months, was associated with sustained weight loss [7,61]. The DiRECT study involves total meal replacement, stepped food introduction and structured support for long term weight maintenance. Thus, a calorie-restricted balanced diet accompanied by regular behavioural support could be superior to a LC at improving clinical outcomes including remission for people living with T2D.

4.4. Implications of Findings

Based on our analysis, a short-to-intermediate term LC diet rather than a LF diet could be recommended for overweight and obese adults with uncontrolled T2M to achieve glycaemic control and weight loss. The LC diet also decreased the requirement for antihyperglycaemic medications at intermediate-to long-term. Though no adverse findings were observed at long-term, the LC diet may not be beneficial in the long term given no significant evidence of differences between the two diets at 24 months with respect to all outcomes. These findings are in contrast to previous studies, which have reported that LC diets have adverse effects on lipids, blood pressure and renal function [33,34,36,38,45,46,62]. LC diets which are also higher in dietary protein loads cause accumulation of ketones, resulting in abnormal metabolic functioning. However, it should be acknowledged that the literature on the metabolic effects of LC diet comprises heterogeneous studies with small sample sizes. By pooling relevant literature on the topic, our findings suggest that LC diets may only be suitable for short term control of glycaemia and weight loss. Given that a LC diet is characterised by the consumption of large amounts of saturated fat and small amounts of fruits, vegetables and fiber, there is a potential for LC diets to adversely impact on lipid profiles, which are major risk factors for coronary heart disease [63]. Indeed, our results showed that LC significantly increased levels of total cholesterol at short-to-intermediate term. Given that patient-centred care is a key aspect of T2D management, [64] patients who choose a LC diet could be supported to manage their diabetes effectively. Patients on this diet should be advised to base their carbohydrates on foods rich in fibre, variety of fruits and vegetables, given their beneficial effect on glycaemic control and cardiometabolic
risk factors [65]. In line with general healthy eating advice, limited intake of salt, trans and saturated fats and regular hydration should also be recommended [66].

4.5. Strengths and Limitations

Based on evidence from 20 unique RCTs, our review represents an up-to-date comprehensive systematic review and meta-analysis evaluating the efficacy and safety of LC compared with LF diets. Other strengths of the current review included (i) the evaluation of a comprehensive panel of outcomes, which were reported according to time points; (ii) the utilisation of several meta-analytic approaches including ensuring consistency to enhance pooling of most of the data; and (iii) detailed assessment of the risk of bias of included trials and quality of the evidence using the Cochrane risk of bias and GRADE tools, respectively (iv) the evaluation of the effects on blood pressure, renal and liver function, and other markers which were not included in the most recent comprehensive reviews. The limitations were mostly inherent to the studies and included: (i) the inconsistencies in outcome definitions, time points and assessments; (ii) the results of some outcomes were based on single reports; (iii) all trials had a high risk of bias in the domains of blinding of participants and personnel (iv) limited information provided on types of carbohydrates consumed (v) inability to generalise our findings to other populations such as black ethnicities, and (vi) inability to conduct subgroup analysis by relevant characteristics such as age, sex, geographical location, ethnicity, and BMI as prescribed in the protocol, due to the limited studies available for pooling for each outcome and lack of specific data such as ethnic-specific data analyses.

5. Conclusions

Except for reducing HbA1c levels and body composition measures at short-to-intermediate term and decreasing the requirement for antihyperglycaemic medications at intermediate-to-long term, a LC diet appears to be equally effective as a LF diet in terms of control of cardiometabolic markers and the risk of adverse events in obese patients with T2D. The current evidence suggest that LC diets may not be beneficial over the long-term.

6. Key Points

Question: Is a low carbohydrate diet more effective for control of cardiometabolic markers and the risk of adverse events in obese patients with T2D compared to a low fat diet?

Findings: Except for reducing HbA1c levels and adiposity parameters at short to intermediate terms, a LC diet appears to be equally effective as a LF diet in terms of control of cardiometabolic markers and the risk of adverse events in obese patients with T2D.

Meaning: A short to intermediate term LC diet could be recommended for overweight and obese adults with uncontrolled T2M to achieve glycaemic control and weight loss.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu14204391/s1, Table S1. PRISMA checklist. Table S2. MOOSE checklist. Table S3. Literature search strategy. Table S4. GRADE summary of findings. Figure S1. Risk of bias assessment. Figure S2. Low carbohydrate versus low fat diet and fat free mass. Figure S3. Low carbohydrate versus low fat diet and total fat. Figure S4. Low carbohydrate versus low fat diet and total cholesterol. Figure S5. Low carbohydrate versus low fat diet and LDL-cholesterol. Figure S6. Low carbohydrate versus low fat diet and HDL-cholesterol. Figure S7. Low carbohydrate versus low fat diet and triglycerides. Figure S8. Low carbohydrate versus low fat diet and total cholesterol/HDL-C ratio. Figure S9. Low carbohydrate versus low fat diet and C-reactive protein. Figure S10. Low carbohydrate versus low fat diet and IL-6. Figure S11. Low carbohydrate versus low fat diet and fasting insulin. Figure S12. Low carbohydrate versus low fat diet and HOMA2-IR. Figure S13. Low carbohydrate versus low fat diet and HOMA-IR. Figure S14. Low carbohydrate versus low fat diet and HOMA2-%B. Figure S15. Low carbohydrate versus low fat diet and ALT. Figure S16. Low carbohydrate versus low fat diet and AST. Figure S17. Low carbohydrate versus low fat diet and GGT. Figure S18. Low carbohydrate versus low fat diet and creatinine. Figure S19. Low carbohydrate versus low fat diet and estimated GFR. Figure S20.
carbohydrate versus low fat diet and microalbumin. Figure S21. Low carbohydrate versus low fat diet and urea. Figure S22. Low carbohydrate versus low fat diet and urinary albumin. Figure S23. Low carbohydrate versus low fat diet and uric acid. Figure S24. Low carbohydrate versus low fat diet and medication effect score. Figure S25. Low carbohydrate versus low fat diet and risk of adverse events.

**Author Contributions:** Conceptualization, T.A.A., S.K.K., M.J.M. and M.K.; methodology, T.A.A. and S.K.K.; software, T.A.A. and S.K.K.; validation, T.A.A. and S.K.K.; formal analysis, S.K.K.; data curation, T.A.A. and S.K.K.; writing—original draft preparation, T.A.A. and S.K.K.; writing—review and editing, T.A.A., S.K.K., M.J.M. and M.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Ajala, O.; English, P.; Pinkney, J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am. J. Clin. Nutr.* 2013, 97, 505–516. [CrossRef] [PubMed]
2. Zhao, Y.; Xu, G.; Wu, W.; Yi, X. Type 2 Diabetes Mellitus- Disease, Diagnosis and Treatment. *J. Diabetes Metab.* 2015, 6, 1–6.
3. World Health Organisation. Diabetes. 2021. Available online: https://www.who.int/news-room/fact-sheets/detail/diabetes. (accessed on 12 December 2021)
4. Joy, S.M.; Little, E.; Maruthur, N.M.; Purnell, T.S.; Bridges, J.F. Patient preferences for the treatment of type 2 diabetes: A scoping review. *Pharmacoeconomics* 2013, 31, 877–892. [CrossRef] [PubMed]
5. Chin, S.O.; Hwang, J.K.; Rhee, S.Y.; Chon, S.; Hwang, Y.C.; Oh, S.; Ahn, K.J.; Chung, H.Y.; Woo, J.T.; Kim, S.W.; et al. Risk factors for the progression of intima-media thickness of carotid arteries: A 2-year follow-up study in patients with newly diagnosed type 2 diabetes. *Diabetes Metab.* J. 2013, 37, 365–374. [CrossRef] [PubMed]
6. IDF Diabetes Atlas 10th Edition. Available online: https://diabetesatlas.org/ (accessed on 2 December 2021).
7. Lean, M.E.J.; Leslie, W.S.; Barnes, A.C.; Brosnahan, N.; Thom, G.; McCombie, L.; Peters, C.; Zhyzhneuskaya, S.; Al-Mrabeh, A.; Hollingsworth, K.G.; et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol.* 2019, 7, 344–355. [CrossRef]
8. Diabetes UK. Diabetes Remission. What is Diabetes Remission and How Does It Work? 2021. Available online: https://www.diabetes.org.uk/guide-to-diabetes/managing-your-diabetes (accessed on 12 December 2021).
9. Bi, Y.; Wang, T.; Xu, M.; Xu, Y.; Li, M.; Lu, J.; Zhu, X.; Ning, G. Advanced research on risk factors of type 2 diabetes. *Nutrients* 2022, 14, 4391.
10. Tuomilehto, J.; Lindstrom, J.; Eriksson, J.G.; Valle, T.T.; Hamalainen, H.; Ilanne-Parikka, P.; Keinanen-Kiukaanniemi, S.; Laakso, M.; Louheranta, A.; Rastas, M.; et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* 2001, 344, 1343–1350. [CrossRef] [PubMed]
11. Chen, L.; Pei, J.H.; Kuang, J.; Chen, H.M.; Chen, Z.; Li, Z.W.; Yang, H.Z. Effect of lifestyle intervention in patients with type 2 diabetes: A meta-analysis. *Metabolism* 2015, 64, 338–347. [CrossRef]
12. Zeng, Y.; Ali, M.K.; Du, J.; Li, X.; Yang, X.; Yang, J.; Pu, X.; Yang, L.E.; Hong, J.; Mou, B.; et al. Resistant Starch in Rice: Its Biosynthesis and Mechanism of Action Against Diabetes-Related Diseases. *Food Res. Int.* 2022, 12, 1–24. [CrossRef]
13. Zeng, Y.; Pu, X.; Du, J.; Yang, X.; Li, X.; Mandal, M.S.N.; Yang, T.; Yang, J. Molecular Mechanism of Functional Ingredients in Barley to Combat Human Chronic Diseases. *Oxidative Med. Cell. Longev.* 2020, 2020, 3836172. [CrossRef]
14. Diabetes Canada Position Statement on Low-Carbohydrate Diets for Adults With Diabetes: A Rapid Review. *Can. J. Diabetes* 2020, 44, 295–299. [CrossRef]
15. NICE. Type 2 Diabetes in Adults: Management [NG28]. 2021. Available online: www.nice.org.uk/Guidance/NG28 (accessed on 21 December 2021).
16. Schwingshackl, L.; Chaimani, A.; Hoffmann, G.; Schwedhelm, C.; Boeing, H. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. *Eur. J. Epidemiol.* 2018, 33, 157–170. [CrossRef]
17. Mozaffarian, D. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review. *Circulation* 2016, 133, 187–225. [CrossRef]
18. SACN Report: Lower Carbohydrate Diets for Type 2 Diabetes. 2021. Available online: https://www.gov.uk/government/publications/sacn-report-lower-carbohydrate-diets-for-type-2-diabetes (accessed on 2 December 2021).
19. Feinman, R.D.; Pogozelski, W.K.; Astrup, A.; Bernstein, R.K.; Fine, E.J.; Westman, E.C.; Accurso, A.; Frassetto, L.; Gower, B.A.; McFarlane, S.L.; et al. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. Nutrition 2015, 31, 1–13. [CrossRef]

20. Goldenberg, J.Z.; Day, A; Brinkworth, G.D.; Sato, J; Yamada, S; Jonsson, T; Beardsley, J; Johnson, J.A; Thabane, L; Johnston, B.C. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: Systematic review and meta-analysis of published and unpublished randomized trial data. BMJ 2021, 372, m4743. [CrossRef]

21. Moher, D.; Liberati, A.; Tetzlaff, J; Altman, D.G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009, 6, e1000097. [CrossRef]

22. Stroup, D.F.; Berlin, J.A.; Morton, S.C.; Olkin, I; Williamson, G.D.; Rennie, D; Moher, D; Becker, B.J.; Sipe, T.A.; Thacker, S.B.; et al. Meta-analysis of Observational Studies in Epidemiology. JAMA 2000, 283, 2008–2012. [CrossRef]

23. Higgins, J.P.; Altman, D.G.; Gotzsche, P.C.; Juni, P; Moher, D; Oxman, A.D.; Savovic, J; Schulz, K.F.; Weeks, L; Sterne, J.A. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011, 343, d5928. [CrossRef]

24. Guyatt, G.; Oxman, A.D.; Akly, E.A.; Kunz, R.; Vist, G; Brozek, J; Norris, S; Falck-Ytter, Y; Glasziou, P; DeBeer, H; et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J. Clin. Epidemiol 2011, 64, 383–394. [CrossRef]

25. Hozo, S.P.; Djulbegovic, B.; Hozo, I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. 2005, 5, 13. [CrossRef]

26. DerSimonian, R; Laird, N. Meta-analysis in clinical trials. Control. Clin. Trials 1986, 7, 177–188. [CrossRef]

27. Thompson, S.G.; Sharp, S.J. Explaining heterogeneity in meta-analysis: A comparison of methods. Stat. Med. 1999, 18, 2693–2708. [CrossRef]

28. Begg, C.B.; Mazumdar, M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994, 50, 1088–1101. [CrossRef] [PubMed]

29. Egger, M.; Davey Smith, G.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997, 315, 629–634. [CrossRef]

30. Asle Mohammadi Zadeh, M.; Kargarfard, M.; Marandi, S.M.; Habibi, A. Diets along with interval training regimes improves inflammatory & anti-inflammatory condition in obesity with type 2 diabetes subjects. J. Diabetes Metab. Disorder. 2018, 17, 253–267. [CrossRef]

31. Chen, C.Y.; Huang, W.S.; Chen, H.C.; Chang, C.H.; Lee, L.T.; Chen, H.S.; Kang, Y.D.; Chie, W.C.; Jan, C.F.; Wang, W.D.; et al. Effect of a 90 g/day low-carbohydrate diet on glycaemic control, small, dense low-density lipoprotein and carotid intima-media thickness in type 2 diabetic patients: An 18-month randomised controlled trial. PLoS ONE 2020, 15, e0240158. [CrossRef]

32. Daly, M.E.; Paisley, R.; Paisley, R.; Millward, B.A.; Eccles, C.; Williams, K.; Hammersley, S.; MacLeod, K.M.; Gale, T.J. Short-term effects of severe dietary carbohydrate-restriction advice in type 2 diabetes—a randomized controlled trial. Diabet Med. 2006, 23, 15–20. [CrossRef]

33. Davis, N.J.; Tomuta, N.; Schechter, C.; Isasi, C.R.; Segal-Isaacson, C.J.; Stein, D.; Zonszein, J.; Wylie-Rosett, J. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. Diabetes Care 2009, 32, 1147–1152. [CrossRef]

34. Goldstein, T.; Kark, J.D.; Berry, E.M.; Adler, B.; Ziv, E.; Raz, I. The effect of a low carbohydrate energy-unrestricted diet on weight loss in obese type 2 diabetes patients—a randomized controlled trial. e-SPEN Eur. J. Clin. Nutr. Metab. 2011, 6, e178–e186. [CrossRef]

35. Guldbrand, H.; Dizdar, B.; Bunjaku, B.; Lindstrom, T.; Bachrach-Lindstrom, M.; Fredrikson, M.; Ostgren, C.J.; Nyström, F.H. In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. Diabetologia 2012, 55, 2118–2127. [CrossRef]

36. Iqbal, N.; Vetter, M.L.; Moore, R.H.; Chittams, J.L.; Dalton-Bakes, C.V.; Dowd, M.; Williams-Smith, C.; Cardillo, S.; Wadden, T.A. Effects of a low-intensity intervention that prescribed a low-carbohydrate vs. a low-fat diet in obese, diabetic participants. Obesity 2010, 18, 1733–1738. [CrossRef]

37. Jonasson, L.; Guldbrand, H.; Lundberg, A.K.; Nyström, F.H. Advice to follow a low-carbohydrate diet has a favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. Ann. Med. 2014, 46, 182–187. [CrossRef]

38. Khoo, J.; Plantadosi, C.; Duncan, R.; Worthley, S.G.; Jenkins, A.; Noakes, M.; Worthley, M.I.; Lange, K.; Wittert, G.A. Comparing effects of a low-energy diet and a high-protein low-fat diet on sexual and endothelial function, urinary tract symptoms, and inflammation in obese diabetic men. J. Sex. Med. 2011, 8, 2868–2875. [CrossRef]

39. Morris, E.; Aveyard, P.; Dyson, P.; Noreik, M.; Bailey, C.; Fox, R.; Jerome, D.; Tan, G.D.; Jebb, S.A. A food-based, low-energy, low-carbohydrate diet for people with type 2 diabetes in primary care: A randomized controlled feasibility trial. Diabetes Obes. Control. Clin. Trials 2011, 8, 2868–2875. [CrossRef]

40. Nishimori, E.; Tetsu, O.; Takasugi, K.; Yoda, T.; Oi, S.; Sekiguchi, K.; Kudo, K.; Yoda, A.; Minami, S.; Naka, M. Carbohydrate-restricted diet is a non-alcoholic fatty liver disease associated with type 2 diabetes Improve calorie-restricted diet. Diabetes 2018, 61, 297–306. [CrossRef]

41. Perna, S.; Alalwan, T.A.; Gozzer, C.; Infantino, V.; Peroni, G.; Gasparri, C.; Spadaccini, D.; Riva, A.; Rondanelli, M. Effectiveness of a hypocaloric and low-carbohydrate diet on visceral adipose tissue and glycemic control in overweight and obese patients with type 2 diabetes. Bahrain Med. Bull. 2019, 41, 159–164.
42. Samaha, F.F.; Iqbal, N.; Seshadri, P.; Chicano, K.L.; Daily, D.A.; McGorry, J.; Williams, T.; Williams, M.; Gracey, E.J.; Stern, L. A low-carbohydrate as compared with a low-fat diet in severe obesity. *N. Engl. J. Med.* 2003, 348, 2074–2081. [CrossRef]

43. Saslow, L.R.; Kim, S.; Daubenmier, J.J.; Moskowitz, J.T.; Phinney, S.D.; Goldman, V.; Murphy, E.J.; Cox, R.M.; Moran, P.; Hecht, F.M. A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes. *PLOS ONE* 2014, 9, e91027. [CrossRef]

44. Saslow, L.R.; Mason, A.E.; Kim, S.; Goldman, V.; Ploutz-Snyder, R.; Bayandorian, H.; Daubenmier, J.; Hecht, F.M.; Moskowitz, J.T. An Online Intervention Comparing a Very Low-Carbohydrate Ketogenic Diet and Lifestyle Recommendations Versus a Plate Method Diet in Overweight Individuals With Type 2 Diabetes: A Randomized Controlled Trial. *J. Med. Internet Res.* 2017, 19, e36. [CrossRef]

45. Sato, J.; Kanazawa, A.; Hatae, C.; Makita, S.; Komiya, K.; Shimizu, T.; Ikeda, F.; Tamura, Y.; Ogihara, T.; Mita, T.; et al. One year follow-up after a randomized controlled trial of a 130 g/day low-carbohydrate diet in patients with type 2 diabetes mellitus and poor glycemic control. *PLoS ONE* 2017, 12, e0188892. [CrossRef]

46. Sato, J.; Kanazawa, A.; Makita, S.; Hatae, C.; Komiya, K.; Shimizu, T.; Ikeda, F.; Tamura, Y.; Ogihara, T.; Mita, T.; et al. A randomized controlled trial of 130 g/day low-carbohydrate diet in type 2 diabetes with poor glycemic control. *Clin. Nutr.* 2017, 36, 992–1000. [CrossRef]

47. Shai, I.; Schwarzfuchs, D.; Henkin, Y.; Shahar, D.R.; Witkow, S.; Greenberg, I.; Golan, R.; Fraser, D.; Bolotin, A.; Vardi, H.; et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N. Engl. J. Med.* 2008, 359, 229–241. [CrossRef]

48. Tay, J.; Luscombe-Marsh, N.D.; Thompson, C.H.; Noakes, M.; Buckley, J.D.; Wittert, G.A.; Yancy, W.S., Jr.; Brinkworth, G.D. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: A randomized trial. *Diabetes Care* 2014, 37, 2909–2918. [CrossRef]

49. Tay, J.; Thompson, C.H.; Luscombe-Marsh, N.D.; Wycherley, T.P.; Noakes, M.; Buckley, J.D.; Wittert, G.A.; Yancy, W.S., Jr.; Brinkworth, G.D. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-saturated fat diet in type 2 diabetes: A 2-year randomized clinical trial. *Diabetes Obs. Metab.* 2018, 20, 858–871. [CrossRef]

50. Westman, E.C.; Yancy, W.S., Jr.; Mavropoulos, J.C.; Marquart, M.; McDuffie, J.R. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutr. Metab.* 2008, 5, 36. [CrossRef]

51. Yamada, Y.; Uchida, J.; Izumi, H.; Tsukamoto, Y.; Inoue, G.; Watanabe, Y.; Irie, J.; Yamada, S. A non-calorie-restricted low-carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes. *PLOS ONE* 2014, 9, e91027. [CrossRef]

52. Li, S.; Lin, G.; Chen, J.; Chen, Z.; Xu, F.; Zhu, F.; Zhang, J.; Yuan, S. The effect of periodic ketogenic diet on newly diagnosed overweight or obese patients with type 2 diabetes. *BMC Endocr. Disord.* 2022, 22, 34. [CrossRef]

53. Gram-Kampmann, E.M.; Hansen, C.D.; Hugger, M.B.; Jensen, J.M.; Brond, J.C.; Hermann, A.P.; Krag, A.; Olsen, M.H.; Beck-Nielsen, H.; Hojlund, K. Effects of a 6-month, low-carbohydrate diet on glycaemic control, body composition, and cardiovascular risk factors in patients with type 2 diabetes: An open-label randomized controlled trial. *Diabetes Obs. Metab.* 2022, 24, 693–703. [CrossRef]

54. Tay, J.; Luscombe-Marsh, N.D.; Thompson, C.H.; Noakes, M.; Buckley, J.D.; Wittert, G.A.; Yancy, W.S., Jr.; Brinkworth, G.D. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: A randomized trial. *Am. J. Clin. Nutr.* 2015, 102, 780–790. [CrossRef]

55. Sainsbury, E.; Kizirian, N.V.; Partridge, S.R.; Gill, T.; Colagiuri, S.; Gibson, A.A. Effect of dietary carbohydrate restriction on glycemic control in adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Res. Clin. Pract.* 2018, 139, 239–252. [CrossRef]

56. Van Zuuren, E.J.; Fedorowicz, Z.; Kuipers, T.; Pijl, H. Effects of low-carbohydrate- compared with low-fat-diet interventions on metabolic control in people with type 2 diabetes: A systematic review including GRADE assessments. *Am. J. Clin. Nutr.* 2018, 108, 300–331. [CrossRef] [PubMed]

57. Korstmo-Haugen, H.K.; Brurberg, K.G.; Mann, J.; Aas, A.M. Carbohydrate quantity in the dietary management of type 2 diabetes: A systematic review and meta-analysis. *Diabetes Obs. Metab.* 2019, 21, 15–27. [CrossRef] [PubMed]

58. Huntriss, R.; Campbell, M.; Bedwell, C. The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: A systematic review and meta-analysis of randomised controlled trials. *Eur. J. Clin. Nutr.* 2018, 72, 311–325. [CrossRef] [PubMed]

59. Pesta, D.H.; Samuel, V.T. A high-protein diet for reducing body fat: Mechanisms and possible caveats. *Nutr. Metab.* 2014, 11, 53. [CrossRef] [PubMed]

60. Lean, M.E.; Leslie, W.S.; Barnes, A.C.; Brosnahan, N.; Thom, G.; McCombie, L.; Peters, C.; Zhyzhneuskaya, S.; Al-Mrabeh, A.; Hollingsworth, K.G.; et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial. *Lancet* 2018, 391, 541–551. [CrossRef]

61. Astbury, N.M.; Aveyard, P.; Nickless, A.; Hood, K.; Corfield, K.; Lowe, R.; Jebb, S.A. Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): Pragmatic randomised controlled trial. *BMJ* 2018, 362, k3760. [CrossRef] [PubMed]

62. Tay, J.; Luscombe-Marsh, N.D.; Thompson, C.H.; Noakes, M.; Buckley, J.D.; Wittert, G.A.; Yancy, W.S., Jr.; Brinkworth, G.D. Response to comment on Tay et al. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: A randomized trial. *Diabetes Care* 2014, 37, 2909–2918. *Diabetes Care* 2015, 38, e65–e66. [CrossRef] [PubMed]
63. Emerging Risk Factors Collaboration; Di Angelantonio, E.; Sarwar, N.; Perry, P.; Kaptoge, S.; Ray, K.K.; Thompson, A.; Wood, A.M.; Lewington, S.; Sattar, N.; et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009, 302, 1993–2000. [CrossRef]

64. Hackel, J.M. ‘Patient-centered care’ for complex patients with type 2 diabetes mellitus-analysis of two cases. *Clin. Med. Insights Endocrinol. Diabetes* 2013, 6, 47–61. [CrossRef]

65. Reynolds, A.N.; Akerman, A.P.; Mann, J. Dietary fibre and whole grains in diabetes management: Systematic review and meta-analyses. *PLoS Med.* 2020, 17, e1003053. [CrossRef]

66. World Health Organization. Healthy Diet. Available online: https://www.who.int/news-room/fact-sheets/detail/healthy-diet (accessed on 21 September 2022).