Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Review

Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: A systematic review and meta-analysis

Emma Sainsbury, Nathalie V. Kizirian, Stephanie R. Partridge, Timothy Gill, Stephen Colagiuri, Alice A. Gibson *

The University of Sydney, The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, Charles Perkins Centre, NSW 2006, Australia

ARTICLE INFO

Article history:
Received 19 July 2017
Received in revised form
20 December 2017
Accepted 19 February 2018
Available online 6 March 2018

Keywords:
Carbohydrates
Diabetes
Diet
HbA1c
Weight

ABSTRACT

Nutrition therapy is considered a key component of diabetes management, yet evidence around the ideal macronutrient composition of the diet remains inconclusive. A systematic review and meta-analysis was performed to assess the effects of carbohydrate-restricted diets (≤45% of total energy) compared to high carbohydrate diets (>45% of total energy) on glycemic control in adults with diabetes mellitus. Six databases were searched for articles published between January 1980 and August 2016. Primary outcome was between-group difference in HbA1c change. Individual effect sizes were standardized, and a meta-analysis performed to calculate pooled effect size using random effects. 25 RCTs involving 2412 participants were included. Carbohydrate-restricted diets, in particular those that restrict carbohydrate to <26% of total energy, produced greater reductions in HbA1c at 3 months (WMD −0.47%, 95% CI: −0.71, −0.23) and 6 months (WMD −0.36%, 95% CI: −0.62, −0.09), with no significant difference at 12 or 24 months. There was no difference between moderately restricted (26–45% of total energy) and high carbohydrate diets at any time point. Although there are issues with the quality of the evidence, this review suggests that carbohydrate-restricted diets could be offered to people living with diabetes as part of an individualised management plan.

Contents

* Corresponding author at: Level 2, Charles Perkins Centre D17, The University of Sydney, NSW 2006, Australia.
E-mail addresses: emma.sainsbury@sydney.edu.au (E. Sainsbury), nathalie.kizirian@sydney.edu.au (N.V. Kizirian), Stephanie.partridge@sydney.edu.au (S.R. Partridge), tim.gill@sydney.edu.au (T. Gill), Stephen.colagiuri@sydney.edu.au (S. Colagiuri), alice.gibson@sydney.edu.au (A.A. Gibson).
https://doi.org/10.1016/j.diabres.2018.02.026
0168-8227/

1. Introduction

Diabetes mellitus is a chronic and progressive disease, characterized by elevated blood glucose levels that cause disability and premature death if sustained [1]. In 2014, 422 million adults (8.5% of the global population) were estimated to be living with diabetes, with a projected rise to 10.1% by 2035 [1,2]. Maintaining glycemic control (target HbA1c < 7.0%) is the cornerstone of diabetes management [3]. Chronic hyperglycemia associated with poorly managed diabetes is a causative factor for long-term microvascular complications including nephropathy, neuropathy, and retinopathy, as well as macrovascular complications such as cardiovascular disease [4]. An observational analysis of data from the United Kingdom Prospective Diabetes Study showed that every 1% decrease in HbA1c, achieved through diet therapy and pharmacological intervention, significantly reduced diabetes-related deaths by 21%, myocardial infarction by 14%, and microvascular complications by 37% [4].

Although it is acknowledged by the World Health Organisation (WHO) and International Diabetes Federation that there is no one-size-fits-all diet for diabetes management, traditional dietary guidelines recommend individuals consume 45–65% of total energy intake from fibre-rich carbohydrate, 20–35% from fat, and 15–25% from protein [5–7]. Weight loss is also routinely recommended, with more than three out of every four adults with diabetes classified as overweight or obese [6,8]. There is strong evidence for the benefits of diet-induced weight loss on HbA1c, with ≥5% weight loss associated with a significant reduction in HbA1c of 0.6–1.0% [9,10]. Despite the diet therapies available, rates of obesity, diabetes and associated complications have continued to rise and attention has turned to alternative dietary approaches for achieving glycemic control. There is growing research into carbohydrate-restricted diets for diabetes management, due to the direct impact of carbohydrate ingestion on postprandial glucose and insulin levels [11]. There is also a substantial body of evidence demonstrating the efficacy of carbohydrate-restricted diets for weight loss in people with and without diabetes, particularly in the short-term [12,13].

A number of systematic reviews and meta-analyses have been conducted comparing the effects of carbohydrate-restricted diets to high carbohydrate diets on HbA1c in people

with diabetes, but the results remain variable and inconclusive [14–17]. Key limitations of these reviews include the small sample size and short duration of included studies (<6 weeks) [16,17], inclusion of non-randomized controlled trials (RCTs) [14,15], and exclusion of type 1 diabetes studies [14–18]. Variations in the definition of a carbohydrate-restricted diet further confuse the evidence, with some reviews capturing a more moderate intake of 40% of total energy as representative [16], while others investigate a more severe restriction of 50–70 g per day [15,19]. A key consideration when evaluating the efficacy of carbohydrate-restricted diets is the effect of weight loss. While the above reviews did not account for this in their interpretation of results, two other reviews have attempted to control for the confounding effects of weight loss. A recent systematic review by Emadian et al. which included only studies with no significant between-group difference in weight loss reported no benefits of low carbohydrate diets over other dietary interventions for reducing HbA1c [20]. Similarly, a systematic review and meta-analysis comparing low carbohydrate diets to isoenergetic balanced diets in people with and without diabetes found no significant difference in weight loss, glycemic control and cardiovascular (CVD) risk-factors between groups [21]. In light of these limitations, and the recent publication of RCTs comparing carbohydrate-restricted diets to high carbohydrate diets [22,23], an update of the evidence is warranted in order to determine the optimal dietary approach for glycemic control in individuals with diabetes.

Determining the ideal diet for glycemic control is of clinical significance, given the increasing prevalence of diabetes and the significant health benefits of improved control. This systematic review and meta-analysis aims to: (1) compare the effectiveness of carbohydrate-restricted diets (≤45% of total daily energy) with high carbohydrate diets (>45% of total energy) in reducing HbA1c in adults with diabetes mellitus; and (2) investigate if greater restriction of carbohydrate is associated with greater reductions in HbA1c in adults with diabetes mellitus.

2. Methods

2.1. Protocol and registration

This systematic review was registered with PROSPERO (Registration number: CRD42016047752), and was informed by the PRISMA reporting guidelines [24].

2.2. Data sources and searches

Two authors (ES and SRP) worked with a research librarian to develop and finalise the search strategies. Electronic databases including Medline, Embase, Cumulative Index to Nursing and Allied Health (CINAHL), Global Health and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1st January 1980 to 31st August 2016 for identification of trials. Key search terms included combinations, truncations and synonyms of diabetes mellitus, low carbohydrate, carbohydrate restricted, dietary protein, dietary fat, ketogenic, and HbA1c. Search strategies are available in Supplementary File 1. Back referencing and citation searching of included studies was undertaken to identify additional published studies.

2.3. Study selection

2.3.1. Selection of studies

Citations and abstracts of all retrieved studies were downloaded to Endnote X7 citation management software (Thomson Reuters, Philadelphia, PA, USA). Duplicates were removed. Titles and abstracts of retrieved articles were independently reviewed by two authors (ES and NVK). Full text articles of potentially eligible studies were checked against inclusion criteria by the same two authors (ES and NVK). Discrepancies were resolved by consensus with a third author (AAG or SRP).

2.3.2. Eligibility criteria

Randomized controlled trials (RCTs) comparing a carbohydrate-restricted diet (≤45% of total energy) to a high carbohydrate diet (>45% of total energy) for glycemic control in adults (≥18 years) with type 1 or type 2 diabetes were included. Studies had to report on change in HbA1c, and be minimum 3 months duration in order to detect glycemic changes. Only original human research studies published in English where the full study text was available were included. Where people with and without diabetes were recruited, studies were only included if ≥80% of participants had diabetes or if sub-group analysis was conducted for this group. Where studies did not report on the prescribed carbohydrate content for the intervention or control diets, inclusion was based on self-reported intake at follow-up for that group. Trials were excluded if one intervention arm included a non-dietary weight loss component (physical activity advice, pharmaceutical intervention) while the other arm did not, as well as trials of meal replacement drinks or enteral feeds. Crossover trials were included if first period data, of at least 3 months, could be extracted. Studies of prediabetes, gestational diabetes, pregnant or lactating women were excluded.

Studies were initially grouped into three diet categories based on the degree of carbohydrate restriction of the intervention diet, as previously reported [25]. Very low carbohydrate ketogenic diets (VLCKD) were defined as ≤10% of total energy from carbohydrate or ≤50 g per day. A low carbohydrate diet was defined as <26% of total energy from carbohydrate or <130 g per day. Moderate carbohydrate-restricted diets were defined as between 26% and 45% of total energy from carbohydrate or 130 g to 225 g per day. All grams values are based on a 2000 kcal diet. Due to insufficient numbers of studies, the VLCKD and low carbohydrate diet groups were combined into one group (low carbohydrate diets <26% of total energy) for the meta-analyses.

2.4. Data extraction and quality assessment

A data extraction form was developed and data was collected in the following areas by two authors (ES and NVK): (1) study information (first author, country of origin, year); (2) participant information (number of participants, baseline characteristics); (3) intervention duration; (4) intervention and control diet prescription; (5) concomitant interventions (nutrition counseling, physical activity advice, oral medication or insulin therapy); (6) retention rate; (7) HbA1c outcomes; (8) secondary outcomes. Where carbohydrate intake was

presented as a percentage of total energy, the grams of carbohydrate were calculated on the basis that 1 g carbohydrate = 4 kcal or 17 kJ. For studies that included more than one high-carbohydrate comparator diet, the results from both comparator arms were combined to create a single pair-wise comparison [26]. Where multiple publications from the one study were retrieved, relevant data from each publication was extracted. One author extracted data from each study and a second author checked all data entry for accuracy.

For HbA1c and weight outcomes, the mean change and standard deviation (SD) of change from baseline for the intervention and control groups were extracted. Data were extracted for 3, 6, 12 and 24 month time-points. For studies in which time-points did not match these exactly, the data were included in the closest time-point. For example, in the study by Brehm et al. data were collected at 4 and 8 months and these were included in the 3 and 6 month time-points, respectively. Where data were missing, authors were first contacted by email for additional data. Where no response was received, the SD of change from baseline was estimated from the baseline and final SDs, assuming a correlation of 0.5 for HbA1c, and 0.96 for weight [27]. The following formula was used, as applied in a recent meta-analysis of dietary interventions for type 2 diabetes [16]: $\sqrt{(\text{SD baseline})^2 + (\text{SD final})^2 - (2 * r * (\text{SD baseline}) * (\text{SD final}))}$. We calculated between-group difference by subtracting the mean change of the control group from the mean change in the intervention group. Intention-to-treat estimates were extracted, where reported.

The quality of each included study was independently evaluated by two study authors (ES and NVK) using the Cochrane Collaboration risk of bias tool [26]. Domains for assessment included minimization of selection bias, performance bias, detection bias, reporting bias and attrition bias. Criteria for low risk, high risk and unclear risk per the Cochrane Handbook for Systematic Reviews of Interventions was used [26]. Risk of bias summary figures were generated using Review Manager (Revman) 5.3 software [28].

2.5. Data synthesis and analysis

2.5.1. Primary outcomes

The primary outcome was the weighted mean difference (WMD) in HbA1c change (%) between the carbohydrate-restricted and high carbohydrate diet groups. A random effects model was used to estimate the WMD for HbA1c change at 3, 6, 12 and 24 months. Sub-group analysis was conducted at each time point to test the effect of different levels of carbohydrate restriction on HbA1c. Studies were grouped as low (<26%), or moderate (26–45%) restricted diets based on the prescribed carbohydrate intake for the intervention group. Where prescribed intake was not available, studies were grouped by self-reported intake. Heterogeneity between studies was assessed using the I^2 statistic. In analyses which included ≥10 studies, publication bias was investigated visually with a funnel plot and confirmed with an Egger's test with statistical significance set at $P < 0.10$ [26]. All statistical analyses were conducted using Revman 5.3 software [28]. Quality of evidence was assessed using the GRADE system [26]. Studies excluded from meta-analysis were qualitatively evaluated.

2.5.2. Secondary outcomes

Due to the known effect of weight loss on HbA1c, a meta-analysis of the mean difference in weight change between the carbohydrate-restricted and high carbohydrate diet arms was conducted. Sensitivity analyses were also run on the primary meta-analysis of HbA1c change, excluding studies with significantly greater weight loss on the carbohydrate-restricted diet. Post-hoc meta-analyses of within-group change in HbA1c for the carbohydrate-restricted and high carbohydrate diet groups were conducted in order to determine the overall effect of each intervention type on HbA1c. All other secondary outcomes were qualitatively evaluated, including lipid profile (triglycerides, total-cholesterol, LDL and HDL-cholesterol), blood pressure (systolic and diastolic), medication use, and renal function.

3. Results

3.1. Study selection

A total of 7184 records were retrieved from the database search, with an additional 16 articles identified through citation searching (Supplementary File 1). Of these records, 2265 were duplicates and 4779 were excluded based on titles and abstracts. Full-text articles were retrieved and screened for 156 studies. From these, 25 studies (28 papers), totaling 2412 participants, met the inclusion criteria and were included in the review. Additional data were requested for outcomes in 20 studies (18 corresponding authors). Requested data were provided for six papers (five studies) [29–34].

3.2. Characteristics of included studies

3.2.1. Subject characteristics

The characteristics of the included studies (n = 25) are shown in Table 1. All studies were parallel-group RCTs of participants with type 1 [35] or type 2 diabetes. Sample size of studies ranged from 24 to 419 participants. Excluding the type 1 diabetes study that recruited healthy weight, younger adults (mean age 37.9 years) [35], all studies recruited overweight or obese older adults (age range 52–63 years old). Mean baseline HbA1c varied across studies that reported on this outcome (24/25); 75% recruited participants with adequately controlled diabetes (HbA1c < 8.0%) [3], while the remaining six studies recruited participants with suboptimal diabetes control (HbA1c range 8.0–9.1%). Of the studies reporting on duration of diabetes (n = 12), mean diabetes duration was 10 years. Majority of studies recruited participants on oral diabetes medication and/or insulin, with one diet treatment only study [32]. Eleven studies allowed medication adjustments to be made during the intervention [23,31,34,36–43], with five studies stating they accounted for this in analysis [34,38,39,42,44]. Retention rates were high for studies of short duration (3–6 months) (n = 10), at >70% for all but one study [45]. Studies of 12–24 month duration (n = 14) had more moderate retention rates, with six studies reporting 50–69% retention, and eight studies reporting ≥70%.

Table 1 – Characteristics of included studies.

Nb	Author, Year, Country	Total (n)	Follow up time points (months)	Retention at final follow up (%)	Population	Age (yrs)	BMI (kg^2/m)	Female (%)	Diabetes inclusion criteria	HbA1c (%)	Diabetes duration (yrs)	Diabetes treatment
	VERY LOW CARBOHYDRATE KETOGENIC DIETS (≤10% of total energy, or ≤ 50 g/day)											
1	Dyson et al. 2007, UK	26 (13 diabetics)	3	92	ow/ob type 2	54	34.8	70.0	NS	7.3	NS	oral agents
2	Samaha et al. 2003[a], US	132 (54 diabetics)	6, 12	66 I/C: 69/63	ob type 2	NS	NS	NS	FBG > 6.94 mmol/L or use of antidiabetic medication	7.4	NS	oral agents, insulin
3	Saslow et al. 2014, US	34 (30 diabetics)	3	94 I/C: 94/94	ow/ob type 2	60	36.8	73.5	HbA1c ≥ 6.5%	6.8	7.1	oral agents
4	Tay et al. 2015, Aus	115	12	68 I/C: 71/65	ow/ob type 2	58	34.6	42.6	HbA1c ≥ 7.0%	7.3	8.0	oral agents, insulin
5	Westman et al. 2008, US	84	3, 6	58 I/C: 55/63	ow/ob type 2	51.8	38.1	78.4	HbA1c > 6.0%	8.5*	NS	oral agents, insulin
	LOW CARBOHYDRATE DIETS (<26% of total energy, or <130 g/day based on a 2000 kcal diet)											
6	Daly et al. 2005, UK	102	3	78 I/C: 78/76	ob type 2	58.7	36.1	52.0	HbA1c 8–12%	9.1	NS	oral agents, insulin
7	Davis et al. 2009, US	105	3, 6, 12	81	ow/ob type 2	53.5	36.0	78.1	HbA1c 6–11%	7.5	NS	oral agents, insulin
8	Guldbrand et al. 2012, Sweden	61	6, 12, 24	89 I/C: 87/90	type 2	62	32.7	55.7	NS	7.3	9.3	oral agents, insulin
9	Shai et al. 2008, Israel	322 (46 diabetics)	24	78 I/C: 63/89	ob type 2	NS	NS	NS	ADA criteria**	NS	NS	oral agents, insulin
10	Yamada et al. 2014, Japan	24	6	100	type 2	63.3	25.8	50.0	HbA1c 6.9–8.4%	7.7	9.2	oral agents, insulin
	MODERATE CARBOHYDRATE DIETS (26–45% of total energy, or 130–225 g based on a 2000 kcal diet)											
11	Brehm et al. 2009, US	124	4, 8, 12	77 I/C: 69/84	ow/ob type 2	56.5	35.9	62.9	HbA1c 6.5–9.0%	7.3	NS	oral agents
12	Brunerova et al. 2007, Czech Republic	58 (27 diabetics)	3	NS	ow/ob type 2	54.5	34.0	NS	FBG ≥ 7 mmol/l or random blood glucose ≥ 11.1 mmol/l	7.1	NS	oral agents
13	Elhayany et al. 2010, Israel	259	12	69 I/C: 72/68	ow/ob type 2	55	31.4	48.0*	HbA1c 7–10%	8.3*	5.6	oral agents
14	Fabricatore et al. 2011, US	79	5, 9	63 I/C: 60/67	ow/ob type 2	52.7	36.3	79.7	NS	6.8	NS	oral agents
15	Krebs et al. 2012, NZ	419	6, 12, 24	70 I/C: 70/71	ow/ob type 2	58	36.6	59.9	WHO criteria # and HbA1c ≤ 9.5%	8.1	8.2	oral agents, insulin
16	Larsen et al. 2011, Aus	108	3, 12	81 I/C: 81/80	ow/ob type 2	59.2*	NS	51.5*	HbA1c 6.5–10%	7.8*	8.7	oral agents, insulin
17	Luger et al. 2013, Austria	44	3	95 I/C: 91/100	ob type 2	62.4	33.3	54.5	NS	7.7	16.9	oral agents, insulin
18	Parker et al. 2002[b], Aus	66	3, 15	58 I/C: 58/61	ob type 2	61.2*	34.0*	64.8*	NS	6.4*	NS	oral agents, insulin
19	Pedersen et al. 2014[c], Aus	76	12	69 I/C: 62/77	ob type 2	59.5	35.5	31.3	FBG > 7 mmol/l, 2hr-OGTT > 11.1 mmol/l or taking a drug treatment	7.3	9.9	oral agents, insulin
20	Rock et al. 2014, US	227	6, 12	90 I/C: 87/91	ow/ob type 2	56.5	36.2	51.1	history of type 2 diabetes confirmed by a physician	7.4	NS	oral agents, insulin
21	Sato et al. 2016, Japan	66	6	94 I/C: 91/97	ow/ob type 2	59.5*	26.6*	24*	HbA1c > 7.5%	8.2*	13.5	oral agents, insulin
22	Strychar et al. 2009, Canada	30	6	100	type 1	37.9	24.3	NS	HbA1C < 8.4%	7.2	16.5	insulin
23	Watson et al. 2016, Aus	61	3, 6	72 I/C: 72/72	ow/ob type 2	54.5	34.3	45.9	HbA1c 6.5–10.5%	8.0	7.2	oral agents, insulin
24	Wolever et al. 2008, Canada	162	3, 6, 12	80 I/C: 81/80	type 2	59.9	31.0	54.3	FPG ≥ 7.0 mmol/L or 2hr-OGTT ≥ 11.1 mmol/L	6.2	NS	diet only
25	Wycherley et al. 2010, Aus	40 (diet arms only)	4	80 I/C: 71/89	ow/ob type 2	NS for diet arms	35.1*	NS	NS	7.8*	NS	oral agents

I/C = intervention/control, ow = overweight, ob = obese, NS = not specified, FBG = fasting blood glucose, FPG = fasting plasma glucose, OGTT = oral glucose tolerance test, ADA = American Diabetes Association.

* Baseline data for completers only.

** ADA criteria: HbA1c ≥ 6.5% or FPG ≥ 7.0 mmol/L or 2-h PG ≥ 11.1 mmol/L during an OGTT or random PG ≥ 11.1 mmol/L [American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care 2015; 38(1): S8-S16].

WHO criteria: FPG ≥ 7.0 mmol/L or 2 h post glucose load ≥ 11.1 mmol/L or both [Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diab Med 1998; 15:539–553].

[a] Study data from two papers: Samaha et al. [56] and Stern et al. [58].

[b] Study data from two papers: Parker et al. [32] and Brinkworth et al. [31].

[c] Study data from two papers: Pedersen et al. [42] and Jesudason et al. [30].

Table 2 – Prescribed diet interventions for the carbohydrate-restricted and high carbohydrate groups.

Nb	Author, Year	Diet arms	Prescribed daily diet				
			Energy	Protein	Carbohydrate	Fat	Fibre
	VERY LOW CARBOHYDRATE KETOGENIC DIETS (≤10% of total energy, or ≤ 50 g/day)						
1	Dyson et al. 2007	low-CHO	ad libitum		≤40 g/day		
		healthy eating	500 kcal deficit		low GI advice		
2	Samaha et al. 2003	low-CHO	ad libitum		≤30 g		
		low-fat	500 kcal deficit			≤30%	
3	Saslow et al. 2014	low-CHO, ketogenic	ad libitum		20–50 g		
		medium-CHO	500 kcal deficit		45–50%		
4	Tay et al. 2015	low-CHO	500–1000 kcal deficit	28%	14% (<50 g)	58%	
		high-CHO		17%	53% (low GI)	30%	
5	Westman et al. 2008	low-CHO, ketogenic	ad libitum		<20 g		
		Low-GI	500 kcal deficit		55% (low GI)		
	LOW CARBOHYDRATE DIETS (<26% of total energy, or <130 g/day based on a 2000 kcal diet)						
6	Daly et al. 2005	low-CHO	ad libitum		≤70 g		
		low-fat					
7	Davis et al. 2009	low-CHO (Atkins)	ad libitum		Wk 0–2: 20–25 g Wk 2–52: +5g/wk (if weight lost)		
		low-fat (Diabetes Prevention Program)				25%	
8	Guldbrand et al. 2012	low-CHO	1600–1800 kcal	30%	20%	50%	
		low-fat		10–15%	55–60%	30%	
9	Shai et al. 2008	low-CHO	ad libitum		20–120 g		
		Mediterranean	1500–1800 kcal			≤35%	
		low-fat	1500–1800 kcal			30%	
10	Yamada et al. 2014	low-CHO	ad libitum		70–120 g		
		calorie-restricted	IBW x 25 kcal	<20%	50–60%	<25%	
	MODERATE CARBOHYDRATE DIETS (26–45% of total energy, or 130–225 g based on a 2000 kcal diet)						
11	Brehm et al. 2009	high-MUFA	200–300 kcal deficit	15%	45%	40%	
		high-CHO		15%	60%	25%	
12	Brunerova et al. 2007	high-fat	(REE x 1.5) - 600 kcal	10%	45%	45%	20 g
		conventional		10%	60%	30%	20 g
13	Elhayany et al. 2010	low-CHO Mediterranean	20 kcal/kg	20%	35% (low GI)	45%	30 g
		ADA		20%	50% (mixed GI)	30%	15 g
		Mediterranean		20%	50% (low GI)	30%	30 g
14	Fabricatore et al. 2011	low-GL	1200–1500 kcal for <113.4 kg; 1500–180 kcal for ≥113.4 kg		low GL		
		low-fat				≤30%	
15	Krebs et al. 2012	low-fat, high-protein	478 kcal deficit	30%	40%	30%	
		low-fat, high-CHO		15%	55%	30%	
16	Larsen et al. 2011	low-fat, high-protein	0–3mo: 1530 kcal (30% energy restriction) 3–12mo: energy balance	30%	40%	30%	
		low-fat, high-CHO		15%	55%	30%	
17	Luger et al. 2013	high-protein	BMR x PA level to calculate energy intake for energy balance	30%	40%	30%	
		standard diet		15%	55%	30%	
18	Parker et al. 2002	high-protein	Wk 0–8: 1600 kcal Wk 8–12: Energy balance (~30% energy increase)	30%	40%	30%	30 g
		low-protein		15%	60%	30%	30 g
19	Pedersen et al. 2014	high-protein, low-CHO	1434 kcal	30% (90–120 g)	40%	30%	31 g
		standard diet		20% (55–70 g)	50%	30%	36 g
20	Rock et al. 2014	low-CHO	1200–2000 kcal	25%	45%	30%	
		low-fat	1200–2000 kcal	20%	60%	20%	
		usual care	500–1000 kcal deficit	15%	55%	30%	
21	Sato et al. 2016	low-CHO	ad libitum		130 g		
		calorie-restricted	IBW x 28 kcal/kg	1.0–1.2 g/kg	50–60%		
22	Strychar et al. 2009	low-CHO/high-MUFA	eucaloric diet		43–46%	37–40%	25 g
		high-CHO/low-fat			54–57%	27–30%	25 g
23	Watson et al. 2016	high-protein	0–3mo: 1434–1673 kcal (30% energy restriction) 3–6mo: energy balance	32%	33%	30%	
		high-CHO		22%	51%	22%	
24	Wolever et al. 2008	low-CHO	ad libitum			increase by ~ 10%	
		low-GI			low GI		
		high-GI			high GI		
25	Wycherley et al. 2010	high-protein	1434–1673 kcal	33%	43%	22%	
		conventional		19%	53%	26%	

CHO = carbohydrate, kcal = kilocalorie, GI = glycemic index, IBW = ideal body weight, GL = glycemic load.
To convert kilojoules (kJ) into kcal, the following equation was used: 1 kcal = 4.18 kJ.

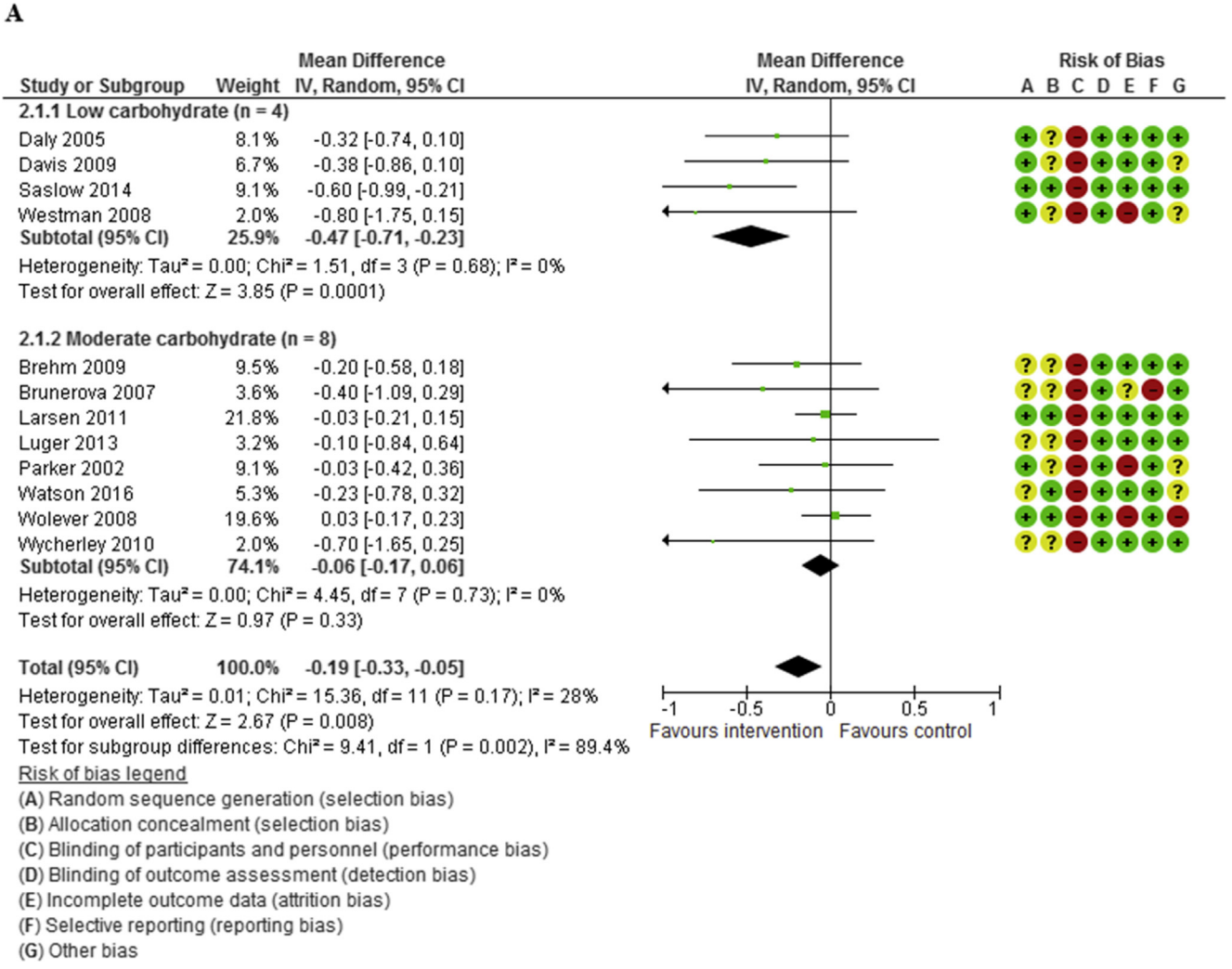

Fig. 1 – A–C. Meta-analyses of the weighted mean difference in HbA1c between carbohydrate-restricted and high carbohydrate diets at (A) 3months; (B) 6months; and (C) 12months. Sub-group analysis was conducted by prescribed carbohydrate quantity of the intervention diet, with studies grouped as low carbohydrate (<26% of total energy), or moderate carbohydrate (26–45% of total energy). I^2 statistic indicates measure of heterogeneity across studies.

3.2.2. *Dietary interventions*

Table 2 shows the prescribed macronutrient composition of the intervention and control diets across studies. The duration of the dietary interventions varied from 3 to 24 months. Five studies prescribed a VLCKD, five studies a low carbohydrate diet, and 15 studies a moderate carbohydrate diet. To compensate for a reduced carbohydrate intake, four studies increased the proportion of protein in the intervention arm [31,34,41,42], six studies increased the proportion of fat [32,35,36,46–48] and four studies increased both protein and fat as a proportion of total energy [22,40,49,50]. All studies reported a significant difference in carbohydrate intake between groups at follow-up. A small subset of studies provided the carbohydrate-restricted intervention group with specific advice to increase intake of monounsaturated fatty acids (MUFA) [32,35,36,46,47]. Five studies prescribed similar fibre intakes for the intervention and control groups [30,35,41,46,47]. Fourteen studies were isocaloric by design [22,30,34–36,39–42,46–48,50,51]. All but three studies [32,35,51] were designed to achieve overall weight loss, with four studies combining a period of energy restriction with a period of energy maintenance [22,30,42,49]. Fifteen studies combined physical activity advice (either to maintain level of activity or to increase) with the dietary intervention [22,36–39,41–43,45,47,49–53].

3.3. *Risk of bias*

Risk of bias summaries are presented on the forest plots in Fig. 1. Fifteen studies reported using random sequence generation, while the remaining studies did not provide sufficient information. Use of allocation concealment was poorly reported across the majority of studies (n = 22). Due to inherent difficulties in blinding participants and personnel in dietary intervention studies, it was assumed, unless otherwise stated, that no blinding was conducted. Consequently, there was a high risk of bias across all studies for self-reported outcomes due to possible bias in patient's self-reported dietary

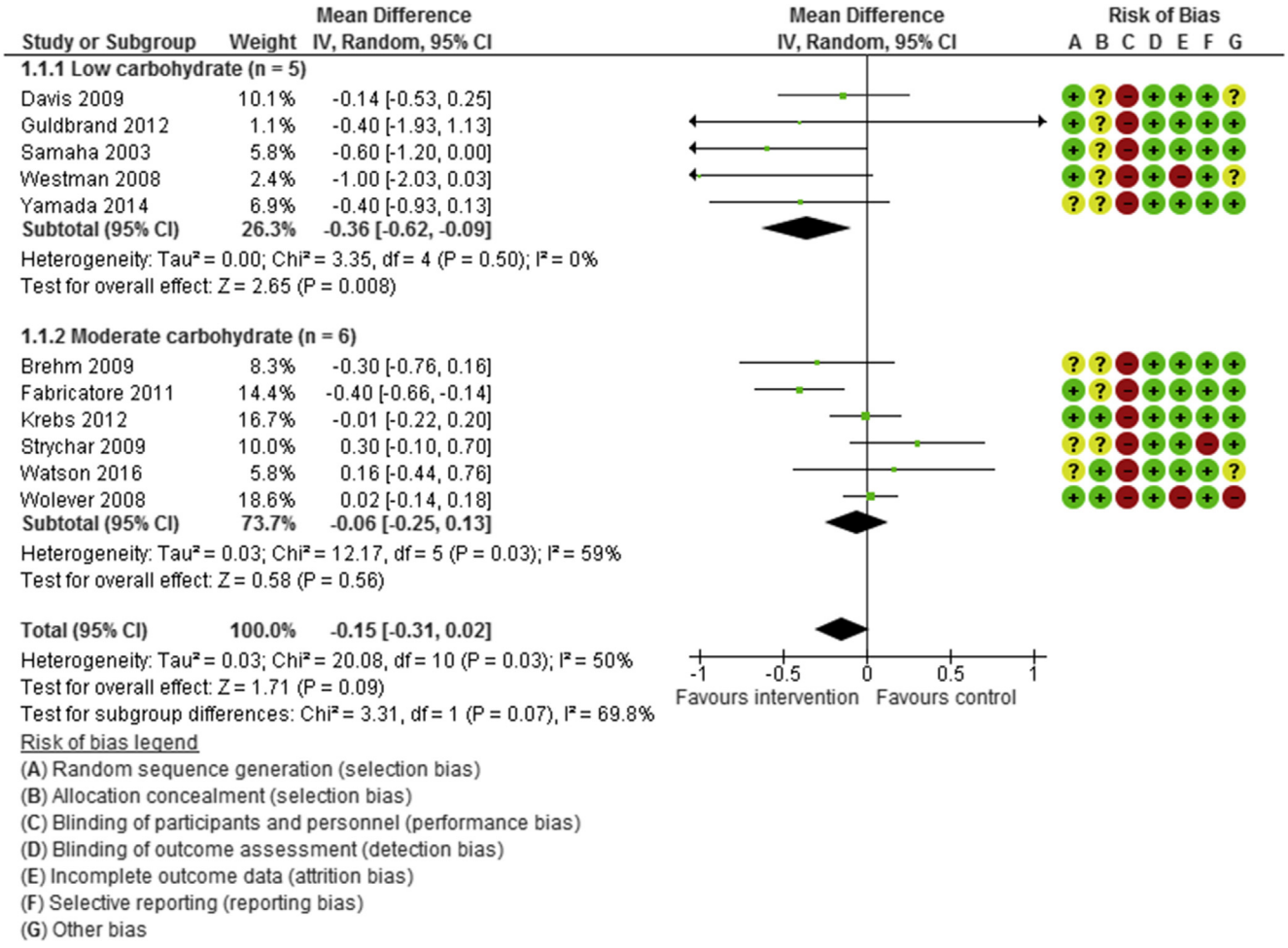

Fig 1. *(continued)*

intake and the analysis of food records. Eight studies were classified as being at high or unclear risk for the other biases domain due to stated conflicts of interest from funding sources. Overall, nine studies were classified as being low at risk, seven at high risk, and nine at unclear risk of bias (Supplementary File 2, Table A).

3.4. *Meta-analysis of HbA1c change*

3.4.1. *Between-group change*

Outcomes from 24 papers (22 studies) were included in the meta-analysis of the mean difference in HbA1c change between carbohydrate-restricted and high carbohydrate diets. Analysis was conducted by time point, with outcomes from 12 papers included in the 3 month analysis, 11 papers in the 6 month analysis, 12 papers in the 12 month analysis and three papers in the 24 month analysis. At 3 months, overall there was a greater reduction in HbA1c on the carbohydrate-restricted diets with WMD −0.19% (95% CI: −0.33, −0.05) (Fig. 1a). This appeared to be entirely due to the low carbohydrate diets, with sub-group analysis conducted by prescribed carbohydrate quantity of the intervention diet revealing a significantly greater reduction in HbA1c on the low carbohydrate (<26% of total energy) diets (WMD −0.47%, 95% CI: −0.71, −0.23), with no significant difference between the moderate and high carbohydrate diets (Fig. 1a). Overall there was no significant difference between the carbohydrate-restricted and high carbohydrate diets at 6-months (WMD −0.15%, 95% CI: −0.31, 0.02); however, sub-group analysis revealed a significantly greater reduction in HbA1c on the low carbohydrate diets only (WMD −0.36%, 95% CI: −0.62, −0.09) (Fig. 1b). Due to moderate heterogeneity at 6 months (I^2 = 50.0%, p = 0.03), a sensitivity analysis was performed. After exclusion of the type 1 diabetes study [35], there was a significant difference in HbA1c change between the carbohydrate-restricted and high carbohydrate diets (WMD −0.19%, 95% CI: −0.35, −0.02), and heterogeneity was slightly reduced (I^2 = 44.0%, p = 0.07).

At 12 months, there was no significant difference in HbA1c change between diet groups (WMD −0.09%, 95% CI: −0.21, 0.03) (Fig. 1c). In contrast to the 3 and 6 month analyses, sub-group analysis also showed no significant difference between the low and high carbohydrate diets, and the moderate and high carbohydrate diets. There was no significant difference in HbA1c change between diet groups at 24 months (WMD −0.11%, 95% CI: −0.38, 0.15). Due to the small number

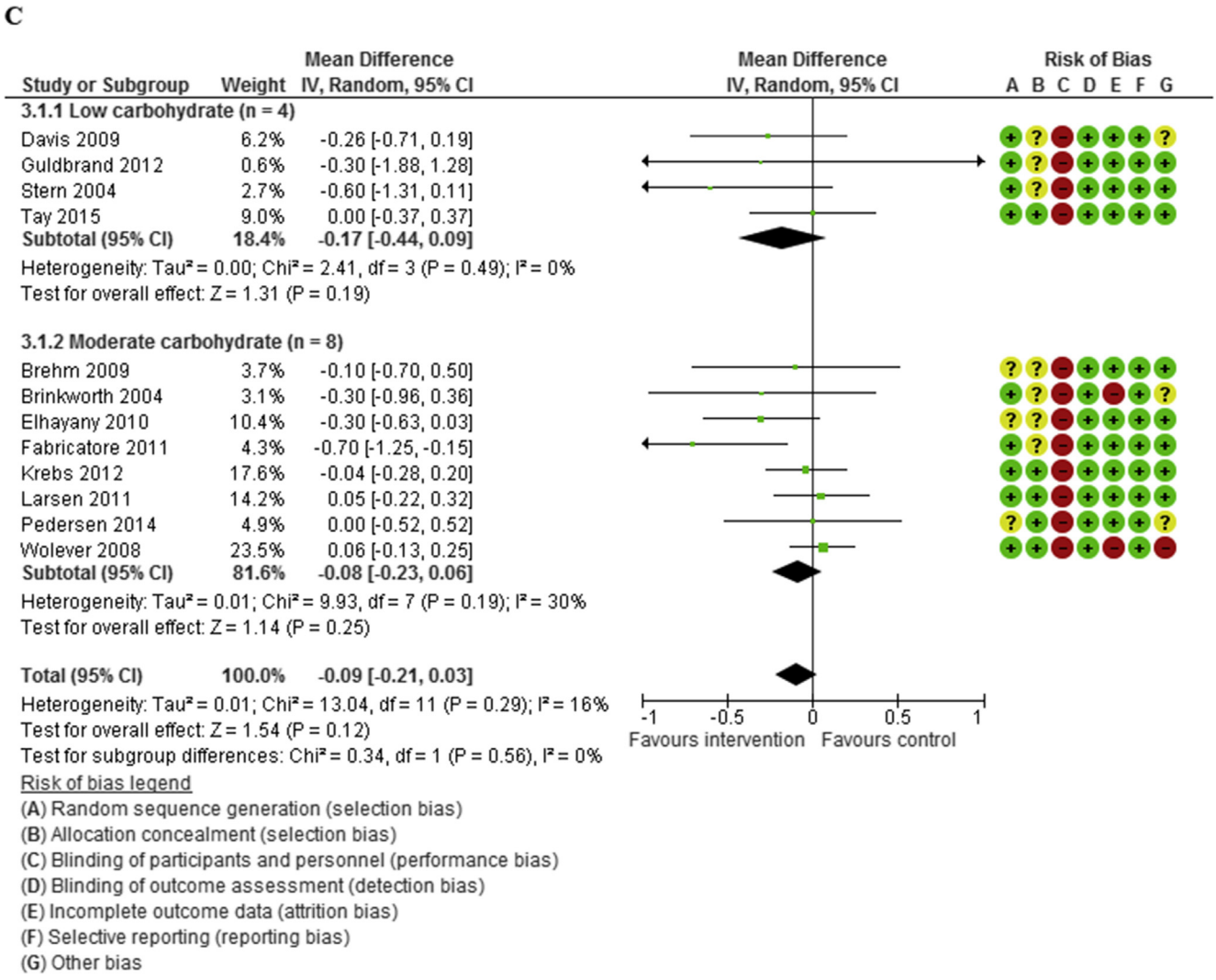

Fig 1. *(continued)*

of studies (n = 3), sub-group analysis was not considered for this time-point. Sensitivity analyses were performed, excluding studies at high risk of bias. Similar results were observed to the primary meta-analysis of HbA1c change, with significantly greater reductions in HbA1c on the low carbohydrate diets at 3 and 6 months only (Supplementary File 2, Table C).

3.4.2. *Within-group change*

Meta-analysis of within-group change at 3 months showed a significant reduction of −0.77% (95% CI: −1.15, −0.40) in the carbohydrate-restricted interventions, and −0.50% (95% CI: −0.77, −0.22) in the high carbohydrate interventions (Supplementary File 3). Similar results were seen at 6 months, with reductions of −0.52% (95% CI: −0.82, −0.21) for the carbohydrate-restricted group and −0.28% (95% CI: −0.51, −0.05) for the high carbohydrate group. At 12–24 months, there was a non-significant reduction in HbA1c in both diet groups.

3.5. *Test of publication bias*

Eggers test revealed publication bias was present at 3 months (p = 0.005) but not at 6 (p = 0.125) or 12 months (p = 0.052). Publication bias was not tested at 24 months since only three studies were included.

3.6. *Qualitative evaluation of studies excluded from HbA1c meta-analysis*

The results of three studies excluded from the meta-analyses of HbA1c change due to insufficient HbA1c outcome data [23,49,52] support the findings of the meta-analyses. Based on analysis of completers only, Rock et al. reported significantly lower HbA1c in the carbohydrate-restricted and low fat diet arms compared with usual care at both 6 months (6.4% vs. 7.2%, p < 0.001) and 12 months (6.9% vs. 7.5%, p = 0.001). The carbohydrate-restricted diet group also had significantly lower HbA1c than the low fat diet group at both 6 months (p = 0.024) and 12 months (p = 0.021) [49]. Dyson et al. reported a greater reduction in HbA1c at 3-months for adults with diabetes in the carbohydrate-restricted diet group compared to adults with diabetes in the healthy eating group (−0.4% vs. −0.2%), although difference between groups was not significant [52]. Sato et al. reported a significantly greater reduction in HbA1c for the carbohydrate-restricted diet group

at 6 months compared with the calorie restricted diet (−0.65% vs. 0.0%, p < 0.01) [23].

3.7. Secondary outcomes

3.7.1. Weight change

At 3 months there was greater weight loss on the carbohydrate-restricted diets, (WMD −1.08 kg, 95% CI: −1.93, −0.23, n = 12 studies) (Supplementary File 4). Sub-group analysis showed that the difference in weight loss observed was due to the low carbohydrate (<26% of total energy) diets only, which had 2.47 kg (95% CI: −3.33, −1.60) greater weight loss than the high carbohydrate diets. Meta-analysis of outcomes at 6 months showed no significant difference in weight change between diet groups (WMD −0.14 kg, 95% CI: −0.94, 0.65, n = 9 studies) (Supplementary File 4). Studies with 12 month outcomes showed no overall difference in weight loss between diet groups (WMD −0.43 kg, 95%CI: −0.93, 0.07, n = 10 studies), but sub-group analysis showed a small but significantly greater weight loss for the moderate carbohydrate diets compared with high carbohydrate diets (WMD −0.58 kg, 95%CI: −1.11, −0.04).

To test the effect of weight loss on the primary meta-analysis of HbA1c change, sensitivity analyses were conducted omitting studies with significantly greater weight loss on the carbohydrate-restricted diet. At 3 months there was no longer a significant difference in HbA1c change between the carbohydrate-restricted and high carbohydrate diets (WMD −0.05%, 95% CI: −0.17, 0.06). Sub-group analysis was unable to be performed at this time point due to the exclusion of all low carbohydrate diet studies. Similar results were observed at 6 months, with no significant difference between the carbohydrate-restricted and high carbohydrate diets overall (WMD −0.09% 95% CI: −0.25, 0.07), or for the low and moderate carbohydrate sub-groups (Supplementary File 5).

Five studies were excluded from the meta-analysis of weight change due to insufficient data [23,39,49,54,55]; three of which were included in the HbA1c meta-analysis [39,54,55]. Samaha et al. reported significantly greater weight loss for subjects on the carbohydrate-restricted diet at 6 months (mean difference −3.9 kg, 95% CI: −1.6, −6.3); the difference remaining significant after adjustment for the presence of diabetes [54]. Across both participants with diabetes and without diabetes, Shai et al. reported greatest weight loss for subjects on the carbohydrate-restricted diet up to 24 months [55]. In contrast, Fabricatore et al. showed no significant difference in weight loss between the carbohydrate-restricted (low glycemic load) group and the low-fat group at 5 months (p = 0.26) and 9 months (p = 0.28) [39].

3.7.2. CVD risk factors

Overall, changes from baseline were variable across studies. Short-term results (3–6 months) indicate either no change, or small reductions in total and LDL-cholesterol on both carbohydrate-restricted diets and high carbohydrate diets (Supplementary File 6). There was a greater increase in HDL-cholesterol reported for the carbohydrate-restricted diet group in 9 out of 20 studies, with three studies reporting a significant difference between diet-groups [37,38,45]. One study reported significantly greater reductions in triglycerides on a low carbohydrate diet compared with high carbohydrate diets [54]. Carbohydrate-restricted diets produced greater reductions in systolic blood pressure (−0.2 to −16.6 mmHg) and diastolic blood pressure (−0.93 to −10.0 mmHg) across majority of studies, with one study reporting a significant difference [42]. At 12–24 month follow-up, six studies reported a significantly greater increase in HDL-cholesterol [38,47,49,50,55,56] and five reported significantly greater reductions in triglycerides [47,49,50,55,56] for the carbohydrate-restricted diets compared with the high carbohydrate diets (Supplementary File 7). Renal function was inconsistently reported, with only six studies including a measure of renal function such as creatinine clearance or estimated glomerular filtration rate. There was no significant difference in renal function between diet groups in the short or long-term.

3.7.3. Diabetes medications

Methods of measuring medication use were variable across studies. Twelve studies reported on medication changes at 3–6 months, and six at 12–24 months. There was a greater reduction in medication use for participants on carbohydrate-restricted diets compared with high carbohydrate diets at every time point. Carbohydrate restriction either reduced the dosage of oral medications and/or insulin, or saw an elimination of medication for participants across all studies that reported on medication outcomes.

4. Discussion

This review provides evidence for the effectiveness of carbohydrate-restricted diets for short-term (3–6 months) improvements in glycemic control in adults with type 2 diabetes. Although both the carbohydrate-restricted and high carbohydrate diets were able to produce a clinically meaningful HbA1c reduction of ≥0.5% [57], our meta-analyses showed that carbohydrate-restricted diets produce greater reductions in HbA1c of up to 0.19% over six months. This effect was driven by the low carbohydrate diets (<26% of total energy) which produced a 0.47% greater reduction in HbA1c at 3 months (and 0.36% at 6 months), with no significant difference observed between moderate (26–45% of total energy) and high carbohydrate diets at 3 or 6 months. The beneficial effects of carbohydrate restriction were no longer observed beyond 12 months, with both diets demonstrating declining effectiveness over time.

4.1. Short-term impact on glycemic control

Carbohydrate-restricted diets produced a significantly greater short-term (3–6 months) reduction in HbA1c, supporting the findings of a recent meta-analysis which reported a 0.34% greater reduction in HbA1c on carbohydrate-restricted (<45% of total energy) diets compared with high carbohydrate (45–60% of total energy) diets over 3–6 months [18]. When considering what level of carbohydrate restriction is necessary for glycemic improvement, sub-group analysis suggests a low carbohydrate prescription (<26% of total energy) produces the greatest reductions in HbA1c, while moderately restricting carbohydrate to between 26 and 45% of total energy provides no additional benefits over high carbohydrate diets.

The greater reduction in HbA1c on low carbohydrate diets is likely driven by increased weight loss. A previous systematic review and meta-analysis reported significantly greater short-term weight loss on carbohydrate-restricted diets within people with and without diabetes [19] and our results support these findings, with low carbohydrate diets producing approximately 2.5 kg more weight loss than high carbohydrate diets at 3 months. Although no significant difference in weight loss was observed at 6 months, this was likely due to the exclusion of Samaha et al. which reported significantly greater weight loss for the low carbohydrate diet group. Results of the sensitivity analysis further confirm this association between weight loss and glycemic control, with no significant difference in HbA1c change between carbohydrate-restricted and high carbohydrate diets when restricted to studies with equal weight loss. One proposed metabolic effect of more severe carbohydrate restriction is the oxidation of fat for energy, resulting in both a loss of body fat stores and the production of ketone bodies that induce satiety [58–60]. Restrictions in the variety of foods available for consumption on VLCKDs may also act to inadvertently reduce energy intake. Due to insufficient numbers of studies, we were unable to isolate the effect of the VLCKDs, but they may be a suitable option in the short-term for overweight or obese people with diabetes, facilitating weight loss and subsequent improvements in HbA1c.

Alternative mechanisms of action, independent of energy restriction and weight loss, have also been proposed to explain the observed effect of low carbohydrate diets on glycemic control. Carbohydrates are the primary macronutrient to influence post-prandial glucose levels and insulin secretion; therefore it is intuitive that reductions in carbohydrate intake would limit glycemic fluctuations. While this review did not consider other markers of diabetes management, a systematic review by Kodama et al. showed a greater increase in fasting insulin and 2-h glucose and insulin levels on high carbohydrate diets compared with carbohydrate-restricted diets [16].

Only one type 1 diabetes study met our inclusion criteria and was included in this review [35], and therefore conclusions cannot be drawn around the effectiveness of carbohydrate-restricted diets for this population group. Strychar et al. showed HbA1c and weight reductions in favour of the high carbohydrate group at 6 months, in contrast to the findings of a recent study that found carbohydrate-restricted diets to be more effective than moderate carbohydrate diets (44%) for adults with type 1 diabetes [61]. The absence of effect seen in Strychar et al. is likely due to the moderate carbohydrate prescription, and recruitment of participants of healthy BMI and with relatively good glycemic control at baseline.

4.2. *Long-term impact on glycemic control*

This systematic review and meta-analysis indicates that carbohydrate-restricted diets may be at least as effective as high carbohydrate diets for long-term glycaemic control, with no significant difference in HbA1c change and weight loss between diets at 12 and 24 months. Both diets had declining effectiveness over time, showing small but non-significant reductions in HbA1c beyond 12 months. One potential reason for this loss of effect is declining dietary adherence, a recognised issue with real-world dietary interventions [62]. Three studies that reported on dietary intake at multiple time points reported a decline in adherence from 3 to 24 months [34,38,40], while a similar study by Iqbal et al. also reported declining adherence to a carbohydrate-restricted diet beyond 6 months [53]. When measuring the effectiveness of dietary interventions, it is also important to consider participant retention. Overall, the mean rate of retention was higher for short-term (3–6 months) compared with long-term (12–24 months) studies, with Tay et al. reporting a drop in retention from 80% at 6 months to 68% at 12 months [50,63]. One promising finding from this review was the similar retention rates between the carbohydrate-restricted and high carbohydrate diet groups, indicating that both diets may be equally appealing to people living with diabetes.

4.3. *Impact on secondary risk factors*

A criticism of carbohydrate-restricted diets has been their potential to detrimentally impact other CVD risk markers. While magnitude of change was variable across studies, evaluation showed similar effects of both diets on total cholesterol, LDL-cholesterol and blood pressure, with significantly greater improvements in HDL-cholesterol and triglycerides reported for the carbohydrate-restricted diet group in a small subset of studies. Similar effects on triglycerides and HDL-cholesterol have been reported in other meta-analyses of carbohydrate-restricted diets [12,16,17]. Weight loss is known to improve markers of cardiovascular risk, and may have mediated some of these effects. Five studies also replaced carbohydrate with monounsaturated fat, which has been suggested to reduce triglyceride levels in people with type 2 diabetes [64].

There were inconsistencies in the measurement and reporting of diabetes medications across studies, however the results suggest that carbohydrate-restricted diets are associated with a reduction in medication dosage. Many studies allowed medication changes to occur throughout the intervention due to the potential for hypoglycemic episodes on carbohydrate-restricted diets. While some studies recognised the potential confounding effect of medication change and corrected for this in analysis, majority either did not specify or stated they did not make adjustments for medication change. This may have attenuated the positive effect of carbohydrate restriction on glycemic control.

4.4. *Limitations*

Due to high risk of performance and detection bias, and inconsistency in the estimates of effect across studies, the evidence of HbA1c change was graded low quality. There was variability in methods of analysis across studies, with 13 studies presenting results for completers-only and 12 using intention-to-treat analysis. The inclusion of completers-only data in the meta-analyses of HbA1c change may have augmented the effect of carbohydrate-restricted diets. Due to

heterogeneity in dietary assessment methods, and problems inherent in using self-reported dietary intake data [65], carbohydrate quantity was based on prescribed rather than actual intake. While all studies reported a significant difference in carbohydrate intake between-groups at follow-up, we cannot be confident of the level of carbohydrate restriction that was achieved. This review did not provide a full assessment of the safety of carbohydrate-restricted diets, including the potential for micronutrient deficiencies and increased frequency of hypoglycemic episodes. Yamada et al. and Sato et al. reported three and four hypoglycemic episodes among the carbohydrate-restricted diet participants respectively, highlighting the need to carefully control medication if using this dietary approach. A recent study by Yabe et al. also reported an increased production of ketone bodies and risk of diabetic ketoacidosis in people living with type 2 diabetes taking luseogliflozin medication [66], highlighting the importance of considering what combination of treatments are recommended to patients. Finally, some dietary interventions were modeled on the Atkins diet which reduces carbohydrate and increases fat, while others were high protein diets modeled after the Zone diet [67]. This review did not consider the effect that altering fat and protein proportions may have had on outcomes, and which approach may be most effective.

5. Conclusions

This review suggests that over the short-term (3–6 months), carbohydrate-restricted diets produce greater reductions in HbA1c than high carbohydrate diets in people with type 2 diabetes. These effects were primarily driven by the low carbohydrate diets (<26% of total energy), with no significant difference between the moderate (26–45% of total energy) and high carbohydrate diets. The short-term glycemic improvements on low carbohydrate diets appear to be due to weight loss, with no significant difference in HbA1c change between diets when restricted to studies with equal weight loss. Both diets showed declining effectiveness over the longer-term (12–24 months), possibly due to declining adherence and participant retention which is inherent in dietary studies. Given this study found no evidence of any negative impacts on CVD risk factors, diets that restrict carbohydrate below the recommended 45% of total energy could be offered to people with diabetes as part of an individualised management plan. More research is required into the long-term effectiveness and safety of carbohydrate-restricted diets, and their potential use for people with type 1 diabetes.

Acknowledgements

We wish to thank Roderick Dyson, University of Sydney Assistant Librarian Academic Services for his help developing the systematic literature search strategy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

ES conducted the literature search, selected studies, extracted and interpreted the data, and wrote the manuscript. NVK selected studies, extracted and interpreted the data, and reviewed/edited the manuscript. SRP contributed to the search strategy design and study selection, and reviewed/edited the manuscript. SC and TG conceptualized the project, contributed to study selection, and reviewed/edited the manuscript. AAG provided final decisions on study selection, analysed and interpreted the data, and reviewed/edited the manuscript.

Conflicts of interest

Nil.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2018.02.026.

REFERENCES

[1] World Health Organization. Global Report on Diabetes. Geneva; 2016.
[2] Guariguata L et al. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014;103(2):137–49.
[3] Cheung NW et al. Australian diabetes society position statement: individualization of HbA1c targets for adults with diabetes mellitus; 2009.
[4] Stratton IM et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321(7258):405–12.
[5] Sheard NF et al. Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement by the american diabetes association. Diabetes Care 2004;27(9):2266–71.
[6] Dyson P. Diet and diabetes- the new recommendations. J Diabetes Nurs 2004;8(4).
[7] Mann JI et al. Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. Nutr Metab Cardiovasc Dis 2004;14(6):373–94.
[8] Inzucchi SE et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55(6):1577–96.
[9] Franz MJ et al. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet 2015;115(9):1447–63.
[10] Jensen MD et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the obesity society. Circulation 2014;129:S102–38.

[11] Arora SK, McFarlane SI. The case for low carbohydrate diets in diabetes management. Nutr Metab 2005;2. 16–16.
[12] Nordmann AJ et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:8.
[13] Hession M et al. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and it's comorbidities. Obes Rev 2009;10:36–50.
[14] 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(3):505–16.
[15] Castaneda-Gonzalez LM, Bacardi M, Bacardi Gascon M, Jimenez Cruz A. Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systemic review of RCT greater than 12 weeks. Nutr Hosp 2011;26(6):1270–6.
[16] Kodama S et al. Influence of fat and carbohydrate proportions on the metabolic profile in patients with type 2 diabetes: a meta-analysis. Diabetes Care 2009;32(5):959–65.
[17] Kirk JK et al. Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc 2008;108 (1):91–100.
[18] Snorgaard O et al. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. BMJ Open Diabetes Res Care 2017;5(1):e000354.
[19] Bueno NB et al. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr 2013;110(7): 1178–87.
[20] Emadian A et al. The effect of macronutrients on glycaemic control: a systematic review of dietary randomised controlled trials in overweight and obese adults with type 2 diabetes in which there was no difference in weight loss between treatment groups. Br J Nutr 2015;114(10):1656–66.
[21] Naude CE et al. Low carbohydrate versus isoenergetic balanced diets for reducing weight and cardiovascular risk: a systematic review and meta-analysis. PLoS ONE 2014;9(7): e100652.
[22] Watson N et al. Effects of low-fat diets differing in protein and carbohydrate content on cardiometabolic risk factors during weight loss and weight maintenance in obese adults with type 2 diabetes. Nutrients 2016;8(5):289.
[23] Sato J et al. A randomized controlled trial of 130g/day low-carbohydrate diet in type 2 diabetes with poor glycemic control. Clin Nutr 2016;36(4):992–1000.
[24] Moher D et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1.
[25] Feinman RD et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition 2015;31(1):1–13.
[26] Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration; 2011.
[27] Fu R et al. Handling continuous outcomes in quantitative synthesis. Methods guide for comparative effectiveness reviews. Publication No. 13-EHC103-EF: Rockville, MD: . Agency for Healthcare Research and Quality; 2013.
[28] The Nordic Cochrane Centre and The Cochrane Collaboration, Review Manager (RevMan) [computer program]. Version 5. Copenhagen; 2014.
[29] Jesudason DR, Pedersen E, Clifton PM. Weight-loss diets in people with type 2 diabetes and renal disease: a randomized controlled trial of the effect of different dietary protein amounts. Am J Clin Nutr 2013;98(2):494–501.
[30] Brinkworth GD et al. Long-term effects of advice to consume a high-protein, low-fat diet, rather than a conventional weight-loss diet, in obese adults with Type 2 diabetes: one-year follow-up of a randomised trial. Diabetologia 2004;47 (10):1677–86.
[31] Parker B et al. Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels in type 2 diabetes. Diabetes Care 2002;25 (3):425–30.
[32] Wolever TM et al. The Canadian trial of carbohydrates in diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. Am J Clin Nutr 2008;87(1):114–25.
[33] Yamada Y et al. A non-calorie-restricted low-carbohydrate diet is effective as an alternative therapy for patients with type 2 diabetes. Intern Med 2014;53(1):13–9.
[34] Krebs JD et al. The Diabetes Excess Weight Loss (DEWL) trial: a randomised controlled trial of high-protein versus high-carbohydrate diets over 2 years in type 2 diabetes. Diabetologia 2012;55(4):905–14.
[35] Strychar I et al. Effects of a diet higher in carbohydrate/lower in fat versus lower in carbohydrate/higher in monounsaturated fat on postmeal triglyceride concentrations and other cardiovascular risk factors in type 1 diabetes. Diabetes Care 2009;32(9):1597–9.
[36] Brehm BJ et al. One-year comparison of a high-monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes. Diabetes Care 2009;32(2):215–20.
[37] Daly ME et al. Short-term effects of severe dietary carbohydrate-restriction advice in Type 2 diabetes- a randomized controlled trial. Diabet Med 2005;23(1):15–20.
[38] Davis NJ et al. 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(7):1147–52.
[39] Fabricatore AN et al. Targeting dietary fat or glycemic load in the treatment of obesity and type 2 diabetes: a randomized controlled trial. Diabetes Res Clin Pract 2011;92(1):37–45.
[40] Guldbrand H et al. 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 (8):2118–27.
[41] Pedersen E, Jesudason DR, Clifton PM. High protein weight loss diets in obese subjects with type 2 diabetes mellitus. Nutr Metab Cardiovasc Dis 2014;24(5):554–62.
[42] Larsen RN et al. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. Diabetologia 2011;54(4):731–40.
[43] Saslow LR et al. 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 [Electronic Resource] 2014;9(4):e91027.
[44] Saslow LR et al. 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(4):e91027.
[45] Westman EC et al. 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).
[46] Brunerova L et al. A comparison of the influence of a high-fat diet enriched in monounsaturated fatty acids and conventional diet on weight loss and metabolic parameters in obese non-diabetic and Type 2 diabetic patients. Diabet Med 2007;24(5):533–40.

[47] Elhayany A et al. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. Diabetes Obes Metab 2010;12(3):204–9.
[48] Wycherley TP et al. A high-protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes. Diabetes Care 2010;33(5):969–76.
[49] Rock CL et al. Weight loss, glycemic control, and cardiovascular disease risk factors in response to differential diet composition in a weight loss program in type 2 diabetes: a randomized controlled trial. Diabetes Care 2014;37 (6):1573–80.
[50] Tay J et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr 2015;102(4):780–90.
[51] Luger M et al. Feasibility and efficacy of an isocaloric high-protein vs standard diet on insulin requirement, body weight and metabolic parameters in patients with type 2 diabetes on insulin therapy. Exp Clin Endocrinol Diabetes 2013;121 (5):286–94.
[52] Dyson PA, Beatty S, Matthews DR. A low-carbohydrate diet is more effective in reducing body weight than healthy eating in both diabetic and non-diabetic subjects. Diabet Med 2007;24(12):1430–5.
[53] Iqbal N et al. Effects of a low-intensity intervention that prescribed a low-carbohydrate vs. a low-fat diet in obese, diabetic participants. Obesity 2010;18(9):1733–8.
[54] Samaha FF et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003;348 (21):2074–81.
[55] Shai I et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359 (3):229–41.
[56] Stern L et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med 2004;140(10):778–85.
[57] National Institute for Health and Clinical Excellence (NICE). Type 2 diabetes. NICE clinical guideline 87. London; 2009.
[58] Pogozelski W, Arpaia N, Priore S. The metabolic effects of low-carbohydrate diets and incorporation into a biochemistry course. Biochem Mol Biol Educ 2005;33 (2):91–100.
[59] Khazrai YM, Defeudis G, Pozzilli P. Effect of diet on type 2 diabetes mellitus: a review. Diabetes/Metab Res Rev 2014;30 (Suppl 1):24–33.
[60] Gibson AA et al. Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. Obes Rev 2015;16 (1):64–76.
[61] Krebs JD et al. A randomised trial of the feasibility of a low carbohydrate diet vs standard carbohydrate counting in adults with type 1 diabetes taking body weight into account. Asia Pacific J Clin Nutr 2016;25(1):78–84.
[62] Gibson AA, Sainsbury A. Strategies to improve adherence to dietary weight loss interventions in research and real-world settings. Behav Sci (Basel) 2017;7(3).
[63] Tay J et al. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: a randomized trial. Diabetes Care 2014;37(11):2909–18.
[64] Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. Am J Clin Nutr 1998;67(3 Suppl):577s–82s.
[65] Trabulsi J, Schoeller DA. Evaluation of dietary assessment instruments against doubly labeled water, a biomarker of habitual energy intake. Am J Physiol Endocrinol Metab 2001;281(5):E891–9.
[66] Yabe D et al. Sodium-glucose co-transporter-2 inhibitor use and dietary carbohydrate intake in Japanese individuals with type 2 diabetes: a randomized, open-label, 3-arm parallel comparative, exploratory study. Diabetes Obes Metab 2017;19 (5):739–43.
[67] McAuley KA et al. Long-term effects of popular dietary approaches on weight loss and features of insulin resistance. Int J Obes Relat Metab Disord 2005;30(2):342–9.