REVIEW

High-Protein Diets for Treatment of Type 2 Diabetes Mellitus: A Systematic Review

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ABSTRACT

Diet has the potential to be a powerful and cost-effective tool for treatment of type 2 diabetes mellitus (T2D). High-protein diets have shown promise for this purpose. The objective of this systematic review was to evaluate whether high-protein diets improve glycemic outcomes in people with T2D. We conducted a systematic search of literature published prior to 1 February 2018 to find clinical studies of high-protein diet patterns for treatment of T2D in human participants. A high-protein diet was defined as a diet with protein content greater than that of a typical diet in the United States (>16% of total energy as protein). Studies were excluded if weight loss >5% occurred or if no glycemic outcomes were measured. A total of 21 independent articles met our criteria and were included. Most tested diets had a protein content of around 30% of total energy. Many studies supported the use of high-protein diets for patients with T2D, but were limited by small size ($n = 8–32$) and short duration (1–24 wk). Randomized controlled trials tended to be larger ($n = 12–419$) and longer (6 wk–2 y), and had mixed results, with many trials showing no difference between a high-protein diet and control. Many randomized controlled trials were limited by low compliance and high dropout rates >15%. There were no consistent beneficial or detrimental effects of high-protein diets on renal or cardiovascular outcomes. Evidence was insufficient to recommend 1 type of protein (plant or animal) over the other. Our review suggests that interventions to improve compliance with diet change over the long term may be equally important as specific macronutrient recommendations for treatment of T2D. *Adv Nutr* 2019;10:621–633.

Keywords: diet, diet therapy, type 2 diabetes mellitus, protein, medical nutrition therapy

Introduction

Type 2 diabetes mellitus (T2D) and its associated complications represent a significant public health challenge. In the United States it has been estimated that 30.3 million people (9.4% of the population) had diabetes in 2015, of whom 95% had T2D, and that diabetes was the seventh leading cause of death (1). The economic burden associated with diabetes is substantial, accounting for an estimated total cost of $245 billion in 2012 (1).

Medical nutrition therapy is a central component of T2D care, and has been shown to improve outcomes and reduce costs (2). A key goal of medical nutrition therapy is "modest" weight loss, as defined by the American Diabetes Association position statement as "a weight loss of >6 kg (approximately 7–8.5% loss of initial body weight)", achieved through reduction in energy intake and intensive lifestyle intervention (3). Unfortunately, dietary compliance and successful maintenance of weight loss are challenging for many patients. For example, even in the controlled setting of an intensive lifestyle intervention trial for T2D, half of all patients who lost >5% of their weight by year 1 regained some or all of this weight by year 8 (4). There are many reasons for inability to maintain weight loss, including socioeconomic status, unsupportive environment, and physiological and hormonal factors leading to metabolic compensatory changes that encourage weight regain (3). For diet composition, guidelines state that "there is not one ideal percentage of calories from carbohydrates, protein, or fat that is optimal for all people with diabetes," and that macronutrient recommendations should be individualized (3). Therefore, there has been an increased interest in

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Abbreviations used: BP, blood pressure; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; LoBAG, Low Biologically Available Glucose; PPG, postprandial plasma glucose; TC, total cholesterol; T2D, type 2 diabetes mellitus.

designing diets that are weight-neutral, easier to follow, and that may aid in satiety (5). Higher-protein diets have been shown to promote satiety through increases in anorexigenic, and decreases in orexigenic, hormones (6, 7). Thus, weight-neutral, high-protein diets may be an attractive option for individuals with T2D.

The typical diet in the United States contains 14–16% of total energy intake as protein (8). This percentage is slightly higher (17% of total energy) in those with T2D, and has remained stable over time (9). There is no consensus on a definition for a high-protein diet, with a wide range of protein intakes cited in previous literature (6). Given this lack of consensus, and to maximize identified articles for this review, we defined a high-protein diet as any diet containing more protein than the typical intake in the United States.

High-protein diets for patients with T2D have been of interest to researchers for decades. Animal and human studies have provided a mechanistic basis for efficacy, showing increased insulin and decreased postprandial glucose after protein administration (10–16). Subsequently, many clinical trials have investigated the effects of varying dietary macronutrient composition on outcomes for T2D in humans. A meta-analysis published in 2008 showed that restricted-carbohydrate diets resulted in improved glycemic control, despite equivocal effect on weight. However, it is not clear how much of that effect was attributable to varying protein content (17). Several studies were included in a systematic review conducted in 2010, looking at the effect of varying macronutrient content and eating patterns on outcomes in T2D, and no consistent effect of higher or lower protein content on glycaemia was shown (18). Many additional relevant studies have been published in subsequent years. A recent review published in 2018 examined in depth the metabolic effects of dietary protein and its role in multiple disorders. However, the review was not a systematic review, was not solely focused on outcomes in T2D, and did not comprehensively report all the intervention trials that were conducted in T2D patients (7).

The objective of this systematic review is to evaluate the effectiveness of weight-neutral, high-protein diet patterns in the treatment of patients with T2D, with glycemic control as the primary outcome. Potential risks and safety of such diets, including effects on renal function and cardiovascular risk factors, were also evaluated.

Methods

A search strategy was developed in accordance with the Cochrane Handbook (19). This strategy employed a mixture of controlled vocabulary and natural language to reflect the key concepts of T2D, high-protein diets, and hemoglobin A1c (HbA1c) changes. The searches were last conducted in February 2018. Complete search strategies are available in **Supplementary Data** (**Supplemental Methods: Details of Search Methods**). No limitations were based on language, date of publication, or study design. The search was conducted across 6 databases (Medline via Ovid, Embase via Ovid, CAB Abstracts via Ovid, Cochrane Library via Wiley, Web of Science, and CINAHL via EBSCO) and results were compiled in EndNote X8 (20). Reference lists of related systematic reviews and meta-analyses were hand-searched to identify additional relevant articles.

Two authors (CB, AB) used Rayyan to independently screen titles and abstracts to identify potentially relevant articles based on predefined inclusion and exclusion criteria (21, 22). Included articles described clinical studies designed to test a high-protein diet pattern for treatment of T2D in human participants. A high-protein diet was defined as any diet with protein intake greater than a typical diet in the United States (>16% of total energy) (8). Articles were excluded if they described studies that *1*) were limited to single-meal interventions or interventions of <1 wk; *2*) were cross-sectional or observational; *3*) tested protein supplement use rather than a diet pattern; *4*) were primarily weight-loss interventions (defined as weight loss >5%); *5*) were not designed to test a change in dietary protein; or *6*) did not report blood glucose or HbA1c as a result. Animal studies were excluded. Abstracts for posters were excluded, with 1 exception (23), which was included based on consensus (AB, CB) because it strongly matched the inclusion criteria.

Next, 2 authors (CB, AB) reviewed the full text of all potentially relevant articles to further refine the set. Any discrepancies between the 2 authors' assessments were resolved through discussion between the 2 screeners or through the intervention of a third screener (SM) when necessary. Detailed reasons for exclusion are documented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram outlining study selection (**Figure 1**) (24).

Data collection tables were developed and piloted by 1 author (SM) and variables were finalized in discussion with co-authors. Data extraction was completed by 2 authors (SM, AB) and compared for accuracy. The Oxford Centre for Evidence-Based Medicine Levels of Evidence were applied to each study. This scale provides a hierarchy of evidence, from strongest to weakest, based on the study design and its susceptibility to bias (25). Risk of bias was assessed with use of the Academy of Nutrition and Dietetics Quality Criteria Checklist for Primary Research, which evaluates the validity of research through a 10-item checklist that assesses issues of bias, generalizability, data collection and analysis, and reporting (26).

Results

Characteristics of included studies

A total of 1390 articles were identified, of which 451 were duplicate, leaving 939 independent articles for screening (Figure 1). Of these, an additional 835 were excluded with use of the criteria above after title and abstract review, leaving 104 articles for full text review. An additional 83 were excluded because they did not meet criteria, as detailed in Figure 1. This yielded 21 studies for inclusion in this review.

Included studies varied in design and duration. Seven studies were randomized interventional trials with a parallel

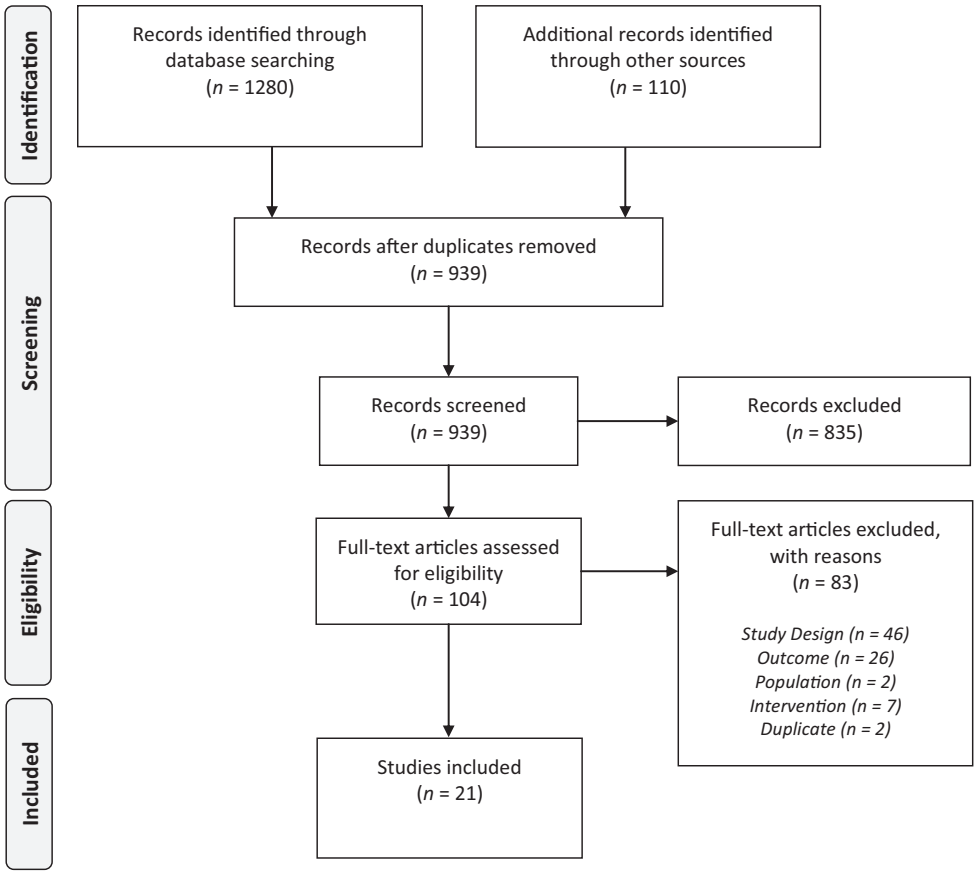

FIGURE 1 PRISMA flow diagram of included and excluded studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

design, of which the longest trial had a duration of 2 y (27) and the shortest had a duration of 6 wk (28). There were 10 studies that followed a crossover design in which participants were exposed to ≥2 dietary interventions, with each intervention lasting between 2 and 6 wk. Four studies had other designs: 2 were uncontrolled interventions (29, 30), 1 used a combined parallel group phase followed by partial crossover (31), and 1 was a combined followed by parallel group design (randomization not specified) (32). The number of participants in the included studies varied from 8 to 419, with the randomized controlled trials tending to include more participants. Protein content of the high-protein diet varied between studies from 17% to 62% of total energy, with the majority of studies (14 of 21) defining a high-protein diet as that with a protein content around 30% of total energy intake.

Characteristics of the included studies, including Oxford Centre for Evidence-Based Medicine Levels of Evidence and the Academy of Nutrition and Dietetics Quality Criteria Checklist for Primary Research risk of bias assessment, are summarized in **Table 1**. With regards to level of evidence, 2 studies were classified as 1b and 19 studies were classified as 2b. This reflects a lack of high-quality individual randomized controlled trials with narrow confidence intervals. In the risk of bias assessment, 13 of the 21 studies were rated positive, indicating that they had adequately addressed issues of bias, generalizability, and data collection and analysis. The remaining 8 studies were found to be neutral, meaning that they were neither exceptionally weak nor exceptionally strong. This was generally because of a lack of information provided regarding the selection and generalizability of the sample and the comparability between study groups.

The studies included in the review tended to group into 1 of 2 types: small proof-of-concept studies with crossover or other designs (**Table 2**) or randomized controlled clinical trials (**Table 3**).

Results of included studies

Proof-of-concept studies.

Fourteen studies were included in this group (Table 2). Of these, 8 provided evidence that a high-protein diet has glycemic benefit for participants with T2D (23, 29, 30, 32–36). Seven of the 8 included a protein content of ≥30% of total energy for the high-protein diet intervention, with control diets ranging from 15% to 20% of total energy as protein. An exception was an uncontrolled study in which 23 participants were given dietary advice, and baseline data was compared to

TABLE 1 Characteristics of included studies[1]

Study descriptors				Outcomes reported				Evidence grade[3]	QCC rating[4]
					Other outcomes				
Design	Study	Duration	*N*[2]	Glycemic outcomes	Renal	BP	Circulating lipids		
RCT	Scott et al. (37)	42 wk	35	FPG	NR	NR	LDL, TG	2b	Ø
	Brinkworth et al. (38)	15 mo[5]	38	HbA1c, FPG, HOMA	Urine Alb/Cr	Yes	TC, LDL, HDL, TG	2b	+
	Sargrad et al. (39)	8 wk	12	HbA1c, FPG	BUN, Cr	Yes	FFA, TC, LDL, HDL, TG	2b	+
	Larsen et al. (40)	12 mo	99	HbA1c	GFR, AER, calcium excretion ratio	Yes	TC, LDL, HDL, TG	1b	+
	Krebs et al. (27)	24 mo	419	HbA1c, FPG	Cr, Urine Alb/Cr	Yes	TC, LDL, HDL, TG	2b	+
	Luger et al. (41)	12 wk	44	HbA1c, insulin dose	GFR, serum Cr, UAE, urine calcium excretion	Yes	TC, LDL, HDL, TG	1b	Ø
	Sucher et al. (28)	6 wk	37	HbA1c	Urea, Cr, Cyctatin C, GFR, Urine Alb, Cr and Alb/Cr ratio	Yes	TC, LDL, HDL, TG	2b	+
Crossover	O'Dea et al. (36)	2 wk	10	FPG, PPG	NR	NR	LDL, LDL:HDL ratio, TG	2b	Ø
	Pomerleau et al. (42)	3 wk	12	FPG, PPG, Fructosamine	UAE, GFR, CrCl, proteinuria	Yes	NR	2b	Ø
	Gross et al. (43)	4 wk	28	FPG, Fructosamine	Urine AER, GFR	Yes	TC, HDL, LDL, Apo B, TG	2b	+
	Wheeler et al. (44)	6 wk	17	HbA1c, PPG	GFR, AER, RPF	Yes	TC, TG, HDL	2b	+
	Gannon et al. (34)	5 wk	12	%tGHb, PPG	CrCl, microalbuminuria	Yes	NEFA, TG, TC, HDL, LDL	2b	+
	Gannon and Nuttall (33)	5 wk	8	%tGHb, FPG, PPG	Cr Cl, microalbuminuria	Yes	NEFA, TG, TC, HDL, LDL	2b	+
	Nuttall et al. (35)	5 wk	8	%tGHb, FPG, PPG	Cr Cl, microalbuminuria	Yes	TG, TC, HDL, LDL	2b	+
	Papakonstantinou et al. (45)	4 wk	17	FPG, PPG, HOMA-R	NR	Yes	TC, TG, HDL, LDL	2b	Ø
	Navas-Carretero et al. (46)	4 wk	15	FPG, HbA1c, HOMA-IR	NR	NR	TC, TG, HDL, LDL	2b	+
	Skytte et al. (23)	6 wk	17	HbA1c, PPG	NR	NR	NR	2b	Ø
Other	Seino et al. (32)	8 d	15	FPG, PPG	NR	NR	NR	2b	Ø
	Gannon et al. (uncontrolled intervention) (29)	10 wk	8	%tGHb, FPG, PPG	Cr Cl, microalbuminuria, urine Na, K, Ca, glucose excretion	Yes	NEFA, TG, TC, HDL, LDL	2b	+
	Moosheer et al. (uncontrolled intervention) (30)	24 wk	23	HbA1c	Cr, UACR	NR	TC, HDL, LDL, TG	2b	Ø
	Von Bibra et al. (31)	Total: 5 wk Parallel: 3 wk + Crossover: 2 wk	32	HbA1c, FPG, PPG	NR	Yes	TC, TG, HDL, LDL	2b	+ NR NR

[1] AER, albumin excretion rate; Alb, albumin; Alb/Cr, albumin to creatinine ratio; BUN, blood urea nitrogen; Ca, calcium; Cr, serum creatinine; CrCL, creatinine clearance; FFA, free fatty acids; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high density lipoprotein cholesterol; HOMA, homeostatic model assessment; K, potassium; LDL, low density lipoprotein cholesterol; Na, sodium; NR, not reported; QCC, Dietetics Quality Criteria Checklist for Primary Research; RCT, randomized controlled trial; RPF, renal plasma flow; TC, total cholesterol; TG, serum triglycerides; UAE, urine albumin excretion; %tGHb, percent total glycated hemoglobin.

[2] Where there was discrepancy between number enrolled and number included in analysis, the number included in analysis is reported.

[3] Details of evidence grading have been described previously (25).

[4] QCC Rating: +, Report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis; Ø, Report is neither exceptionally strong nor exceptionally weak; –, Issues have not been adequately addressed (no studies were given this rating in our review) (26).

[5] Duration includes initial 12-wk weight-loss trial plus 12-mo follow-up trial, as described in Results.

TABLE 2 Glycemic outcomes of high-protein diets for T2D: crossover and other trials[1]

Study	Duration	*N*	Main protein source for HP diet	Actual diet consumed (% of total energy)				Diabetes treatment: medication	Effect on plasma glucose	Effect on HbA1c	Study favors?
					%P	%C	%F				
O'Dea et al. (36)	2 wk	10	Animal	Diet 1	24	65 (45 g fiber)	10	None or PO	FPG: Diet 1 and Diet 4: significant decrease, Diet 3: significant increase		HP (not well tolerated)
				Diet 2	25	63 (20 g fiber)	12		PPG: Diet 1: most improvement, Diet 2, Diet 4: improved, Diet 3: worsened		
				Diet 3	18	27 (14 g fiber)	55				
				Diet 4	62	23 (13 g fiber)	15			Diet 4: significant reduction in HbA1c vs. baseline (10.6 vs. 9.4%, $P < 0.05$)	
Pomerleau et al. (42)	3 wk	12	Mixed (diet + Bariatrix)	HP	22	54	22	None or PO	FPG and PPG: significant decrease after both HP and CD, no comparison between diets	NR	No difference
				CD	10	56	33				
Gross et al. (43)	4 wk	28	Animal (chicken vs. red meat)	(Reported in g/kg body weight)	P	C	F	PO	FPG: no change	NR	No difference
				Usual diet	1.43	2.99	0.92				
				Low-protein	0.66	3.53	0.86				
				Chicken diet	1.35	3.25	0.81				
Wheeler et al. (44)	6 wk	17	Animal vs. plant	AP	17	53	30	None or PO	PPG: no change	Significant decrease from baseline in both groups, no difference between groups	No difference
				PP	17	53	30				
Gannon et al. (34)	5 wk	12	Mixed	HP	30	40	30	None	FPG: no change vs. baseline	%tGHb: significant decrease in HP vs. CD	HP
				CD	15	55	30		PPG: HP: significant decrease vs. baseline		
Gannon and Nuttall (33)	5 wk	8	Mixed	HP	30	20	50	None	FPG and PPG: HP: significant decrease vs. baseline	%tGHb: significant decrease in HP vs. CD	HP
				CD	15	55	30				
Nuttall et al. (35)	5 wk	8	Mixed	HP	30	30	40	None	FPG: HP: significant decrease (by 40%)	%tGHb: significant decrease in HP vs. CD	HP
				CD	15	55	30		PPG: HP: significant decrease (by 45%)		

(*Continued*)

TABLE 2 (*Continued*)

Study	Duration	*N*	Main protein source for HP diet	Actual diet consumed (% of total energy)				Diabetes treatment: medication	Effect on plasma glucose	Effect on HbA1c	Study favors?
					%P	%C	%F				
Papakonstantinou et al. (45)	4 wk	17	Mixed (animal + Optifast)	HP	30	50	20	None	FPG and PPG: HP: significant decrease from baseline	Small decrease in both groups, with no significant difference between groups	No difference
				CD	15	50	35		No difference in change with HP vs. CD		
Navas-Carretero et al. (46)	4 wk	15	Diet + meal replacement	HP	22	31	39	NR	FPG and PPG: no change from baseline	No change from baseline	No difference
				CD	18	36	39		No difference between HP and CD	No difference between groups	
Skytte et al. (23)	6 wk	17	NR	HP	30	30	40	PO	PPG: significant decrease in HP vs. CD	HbA1c: HP: significant decrease from baseline	HP
				CD	17	50	33			No difference between groups	
Seino et al. (32)	8 d	15	Mixed	HP	50	35	15	None	FPG: 133 (HP) vs. 170 (baseline); $P < 0.01$	NR	HP
				CD	15	75	10		PPG improved with HP $P < 0.05$		
Gannon et al. (29) (uncontrolled)	10 wk	8	Mixed	HP	30	30	40	None	FPG and PPG: HP: significant decrease	%tGHb: significant decrease	HP (no comparison group)
Moosheer et al. (30) (uncontrolled)	24 wk	23	Mixed	Pre	17	44	39	PO or insulin	FPG: no significant change	Significant decrease	HP (no comparison group)
				Post	23	41	36				
Von Bibra et al. (31)	5 wk	32	NR	HP	30	25	45	None, PO or insulin	FPG: HP significant decrease vs. baseline	Significant decrease	No difference
				CD	20	55	25		FPG and PPG: no difference between HP and CD		

[1] AP, animal protein; C, carbohydrate; CD, control diet; F, fat; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HP, high-protein diet; NR, not reported; NS, not significant ($P > 0.05$); P, protein; PO, oral medication; PP, plant protein; PPG, postprandial plasma glucose; T2D, type 2 diabetes mellitus; %tGHb, percent total glycated hemoglobin.

TABLE 3 Glycemic outcomes of high-protein diets for T2D: randomized controlled trials[1]

Study	Duration	*N*	Main protein source for HP diet	Diet prescribed (% of total energy)				Actual diet consumed[2] (% of total energy)				Diabetes treatment: medication	Dropout (%)[3]	Mean HbA1c (%)			Other glycemic outcomes	Study favors?
					%P	%C	%F		%P	%C	%F			Baseline	Change (end of trial)	*P* value: HP vs. CD		
Scott et al. (37)	42 wk	35	NR	HP	25	35	40		NR	NR	NR	NR	34%	NR	NR		FPG improved in both groups; no difference between groups ($P = 0.15$)	No difference
Brinkworth et al. (38)	15 mo	38	Animal	CD	15	55	30											
				HP	30	40	30		NR	NR	NR	PO or insulin	42%	HP: 6.5	HP: +0.1	NS	No differences between groups	No difference
Sargrad et al. (39)	8 wk	12	Mixed	CD	15	55	30							CD: 6.2	CD: +0.4			
				HP	30	40	30	HP	27	43	30	NR	NR	HP: 7.6	HP: −1.0		CD only: FPG decreased compared to baseline	CD
Larsen et al. (40)	12 mo	99	Animal	CD	15	55	30	CD	19	51	30			CD: 8.2	CD: −1.3			
				HP	30	40	30	HP	27	42	31	None, PO or insulin	14%	HP: 7.9	HP: −0.2	NS	Trend toward less glucose-lowering medication in HP group	No difference
Krebs et al. (27)	24 mo	419	Participant preference	CD	15	55	30	CD	19	48	32			CD: 7.8	CD: −0.3			
				HP	30	40	30	HP	21	46	33	None, PO, or insulin	30%	HP: 8.1	HP: +0.1	NS	No differences between groups	No difference
Luger et al. (41)	12 wk	44	Mixed; emphasis on plant (soy)	CD	15	55	30	CD	20	48	30			CD: 8.0	CD: +0.1			
				HP	30	40	30	HP	26	38	35	Insulin ± PO	5%	HP: 7.8	HP: −0.3	NS	Insulin dose (primary outcome) and FPG significantly decreased in HP vs. CD group	HP
Sucher et al. (28)	6 wk	37	Animal: meat/dairy	CD	15	55	30	CD	17	50	30			CD: 7.7	CD: −0.2			
				AP	30	40	30	AP	30	40	30	None, PO or insulin	16%	AP: 7.0	AP: −0.4	AP vs. PP: NS	AP only: FPG decreased compared to baseline ($P = 0.043$)	No difference
			Plant: legumes	PP	30	40	30	PP	30	39	31			PP: 7.0	PP: −0.6			

[1] AP, animal protein; C, carbohydrate; CD, control diet; F, fat; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HP, high-protein diet; NR, not reported; NS, not significant ($P > 0.05$); P, protein; PO, oral medication; PP, plant protein; T2D, type 2 diabetes mellitus.

[2] At end of intervention, if reported.

[3] Percentage of participants who were enrolled in a trial but did not complete the intervention (usually these participants were not included in the trial results, and thus are not included in the *n* reported in Table 1). In the case of Larson et al.: 108 participants were randomized, 99 received diet instruction, 93 attended follow-up until end of study, and 74 consumed the assigned diet until end of study. All 99 who received any diet instruction were included in analysis.

data 24 wk later. A higher protein intake was achieved at the end of the intervention (23% of total energy) versus baseline (17% of total energy), with an improvement in HbA1c from 7.9% at baseline to 7.3% after 24 wk ($P = 0.001$) (30). On the other extreme of protein intake, 1 crossover study compared a high-protein diet containing 62% of energy as protein to 3 other diets in 10 participants over 2-wk interventions. The high-protein diet resulted in significant improvement in HbA1c and fasting plasma glucose (FPG) over baseline (from 10.6% to 9.4%, $P < 0.05$ and 156 to 110 mg/dL, $P < 0.01$, respectively), but the prescribed diet was not well tolerated by study participants (36). Of note, improvement in FPG over baseline was also seen with another diet in the same study, which contained 24% of total energy as protein (178 mg/dL at baseline to 148 mg/dL at 2 wk, $P < 0.01$) (36).

A group of small, randomized crossover studies by Nuttall and Gannon demonstrated the efficacy and tolerability of a specific high-protein diet they termed the Low Biologically Available Glucose (LoBAG) diet for treatment of T2D (33–35, 47). This diet was composed of 30% of energy as protein, 30–50% of energy as fat, and 20–40% of energy as carbohydrate, with emphasis on nonstarch choices. Three out of the 4 LoBAG diet trials were controlled, and 1 was uncontrolled. They otherwise had a similar intervention protocol and design: participants were taking no glucose-lowering medications, weight was held constant, activity level did not change during the course of the study, carbohydrate content was sufficient such that no ketosis occurred, all food was provided, participants saw the study dietitian every few days, and excellent compliance was demonstrated. The studies included 8–12 participants, lasted 5–10 wk, and measured FPG, postprandial plasma glucose (PPG), and percent total glycated hemoglobin. All 4 studies showed significant improvement in glycemic control with the high-protein diet, a result that was not seen after the control diet (when a control was present). The greatest improvement was seen in a randomized 5-wk crossover trial of the $LoBAG_{20}$ diet (20% of total energy as carbohydrate, 30% as protein) in 8 participants with untreated T2D, in which percent glycated hemoglobin decreased from 9.8% at baseline to 7.6% at 5 wk ($P < 0.0007$), and there was no significant change with control (33).

Four of the 14 proof-of-concept studies showed benefit with a high-protein diet and with a control diet, with no difference between groups (31, 42, 44, 45). Diet intervention periods in these studies lasted between 2 and 6 wk, and small but statistically significant improvements were reported in FPG (31, 45, 42) or HbA1c (31, 44) that did not differ between the high-protein diet and a control diet. Protein content of the high-protein diet arm ranged from 17% to 30% of total energy intake, compared to control diets with 10% to 20% of total energy as protein. Glycemic outcomes were not the primary outcome in any of the 4 studies.

Finally, of the 14 studies included in the proof-of-concept group, 2 studies did not demonstrate any glycemic benefit with a high-protein diet. In these studies, protein content of the high-protein intervention was only marginally higher than that of a typical diet in the United States. Navas-Carretero et al., achieved a 4% increase in protein intake (22% versus 18% of total energy as protein) with the addition of high-protein, low-glycemic index meal replacements, and demonstrated no change in glycemic outcomes with the higher protein diet in 15 participants over 4 wk (HbA1c 7.2% after higher protein diet versus 7.0% after baseline diet, $P > 0.05$; FPG 157 mg/dL after higher protein diet versus 159 mg/dL after baseline diet, $P > 0.05$) (46). Gross et al. showed no change in FPG or fructosamine with 4 wk of a chicken-based diet providing 1.35 g/kg protein compared with a low-protein diet (0.66 g/kg protein) or a usual diet (1.43 g/kg protein) in 28 participants ($P > 0.05$) (43). Both the chicken-based and usual diets contained protein contents similar to 0.92–1.47 g/kg body weight, the range of intakes for adults in the United States (8).

In summary, this group of studies overall provides efficacy data for the use of high-protein diets for glycemic management in T2D, particularly when the protein content of the intervention diet was at least 30% of total energy intake. Strengths of many of the studies in this group were rigorous control, crossover design, and high participant compliance with diet and with study procedures. Small size and short duration were limitations. Thus, these studies do not address the question of generalizability for a broader population of people with T2D in less ideally controlled, real-world conditions.

Randomized controlled trials.

Seven randomized controlled parallel design trials evaluated the utility of high-protein diet prescription in real-world settings (Table 3). In general, in these trials the intervention was diet instruction provided in the outpatient setting by registered dietitians, without food provided for participants. The number of participants was typically larger than in the proof-of-concept studies ($n = 12$–419), and the duration longer, ranging from 6 wk to 2 y. Compliance tended to be lower, with dropout rates ranging from 5% to 42%.

Only 1 study in this group clearly showed glycemic improvement with a high-protein diet compared to a control diet. In that study 44 participants taking insulin consumed either a high-protein diet containing 30% of total energy as protein, with emphasis on plant protein, or a control diet containing 15% of energy as protein for 12 wk. The primary outcome was demonstrated in the intervention group in the form of greater reduction in insulin dose compared to control at the end of the intervention (−9.4 units compared with +0.8 units, $P = 0.007$) (41). There were also improvements in FPG (−41.7 compared with −2.1 mg/dL, $P = 0.02$) and weight (−3.1 compared with −1.0 kg, $P = 0.004$) with the high-protein diet, and no difference between groups in HbA1c (−0.3 compared with −0.2%, $P > 0.05$) (41).

Two randomized controlled trials showed possible benefit in glycemic outcomes with a high-protein diet, but with no statistically significant differences from control. One included 99 participants who were randomly assigned to consume a high-protein diet containing 30% of energy as

protein or a control diet containing 15% energy as protein over 12 mo. Despite no difference in change in HbA1c between groups (−0.2 compared with −0.3%, $P > 0.05$), there was a trend for a reduction in glucose-lowering medications in the high-protein diet group ($P = 0.05$) (40, 37). The second study reported improved glycemic control in 35 participants with impaired fasting glucose or T2D after 42 wk of either a diet containing 25% of total energy as protein or a diet with 15% of energy as protein, but the difference between the diets was not statistically significant (FPG −57.6 compared with −39.6 mg/dL; $P = 0.15$) (37).

Three randomized controlled trials did not show any difference between diet interventions. Sucher et al. randomly assigned 44 participants (37 completed the intervention) to 6 wk of a high-animal-protein or high-plant-protein diet, both containing 30% of energy as protein. There was a statistically significant improvement in HbA1c in the plant protein group but not in the animal protein group (6.98% to 6.42%, $P < 0.0001$ compared with 6.98% to 6.54%, $P = 0.39$), and improvement in FPG in the animal protein group but not in the plant protein group (173 to 155 mg/dL, $P = 0.04$ compared with 170 to 168 mg/dL, $P = 0.24$), with no significant difference between groups ($P > 0.05$ for both comparisons). Of note, both diets in this study were high in protein content (28). Brinkworth et al. performed a study in which 66 participants were randomly assigned to a high-protein diet, containing 30% of energy as protein, or a typical protein diet, containing 15% of energy as protein. The initial trial was 12 wk and included 8 wk of energy restriction, and is not included in this review because it was a weight-loss trial. Participants were asked to continue the assigned diet for 12 additional mo (38 completed the intervention), and at the end of this follow-up weight regain had occurred such that weight loss was <5% from baseline, with no difference between groups. By the end of the follow-up there was no significant difference in FPG or HBA1c between groups (38). The study by Krebs et al. was the largest and the longest trial included in the current review. A total of 419 participants were randomly assigned to consume an energy-restricted high-protein, low-fat diet or a high-carbohydrate, low-fat diet for 24 mo in a real-world setting, in which participants attended group education sessions and received diet instruction and motivational messages from research dietitians. Despite assignment to different diet plans (30% compared with 15% of total energy as protein), by 6 mo both groups were eating almost the same diet composition (21% compared with 20% of total energy as protein) and this similarity continued until the end of the intervention. There were no differences between groups in weight loss or HbA1c at 24 mo (27). The trial was limited by the lack of participant compliance with assigned diets in addition to a high dropout rate of 30%.

The final study in the randomized controlled trial group found better glycemic outcomes with a control diet than with a high-protein diet. In this study 12 participants were randomly assigned to instruction in a hypocaloric high-protein diet, containing 30% of energy as protein, or a hypocaloric high-carbohydrate diet, containing 15% of energy as protein, to be consumed over 8 wk. HbA1c decreased significantly compared to baseline with the high-carbohydrate diet (8.2% to 6.9%, $P < 0.03$) but not with the high-protein diet (7.6% to 6.6%, not significant, P value not provided). A comparison between groups for HbA1c at the end of the intervention was not reported. FPG and insulin sensitivity, measured by euglycemic hyperinsulinemic clamp, also improved in the high-carbohydrate group, but not the high-protein group, as compared to baseline. The authors concluded that the high-carbohydrate diet advice was superior to the high-protein diet advice for glycemic control over 8 wk, and that this may have been attributable to a decrease in plasma free fatty acids with the high-carbohydrate diet (39).

Taken together, the evidence from randomized controlled trials suggests that multiple dietary patterns can result in improvement in glycemic control for participants with T2D, and does not support the superiority of a high-protein approach. Major limitations of these studies included high dropout rates and participant noncompliance with the diet advice that was provided. It is possible that higher compliance with the study diets would have led to different outcomes, and would better align with the results of the majority of the more tightly controlled, short duration proof-of-concept studies presented above. In addition, many studies in this group did not comment on medication changes during the intervention period, which could have profound effect on study results. Nonetheless, the current evidence from randomized controlled trials does not support the use of high-protein diets for glycemic benefit in participants with T2D.

Renal and cardiovascular outcomes

Some human studies have raised concern that higher-protein intake may increase the progression of kidney disease in individuals with or without pre-existing kidney disease. Possible mechanisms may include increase in glomerular filtration rate in response to a protein or amino acid load (48). As for cardiovascular effects of higher-protein diets, the data are mixed, with some epidemiologic studies suggesting an inverse relation between dietary protein and blood pressure (BP) and cardiovascular events. The source of protein may be important, as consumption of red meat has been shown to be associated with adverse cardiovascular outcomes (49). Current American Diabetes Association recommendations on medical nutrition therapy have found that the evidence was "inconclusive to recommend an ideal amount of protein intake for optimizing glycemic control or cardiovascular disease risk" in people with diabetes (2, 3). Because of the above concerns and uncertainties, several of the studies included in this review examined renal and/or cardiovascular effects of higher-protein diets as primary or secondary outcomes.

Renal outcomes.

Two studies examined renal effects of diets as their primary outcomes: Pomerleau et al. studied the effect of 2 diets

(22% compared with 10% of energy from protein) in nonhypertensive participants with T2D and early diabetic nephropathy, as evidenced by microalbuminuria. Compared to baseline, consumption of the higher protein diet for 3 wk resulted in no change in glomerular filtration rate (GFR), albuminuria, fractional clearance of albumin, and β-2-microglobulinuria. Proteinuria and creatinine clearance were reduced significantly. The lower protein diet (compared to baseline) resulted in additional significant reduction in GFR and albuminuria. It is thought that the latter resulted from the former, because of changes in hemodynamics of the filtration membrane. The authors concluded that the low-protein diet was protective and the high-protein diet was not harmful (42). Gross et al. examined the renal effects of varying protein content and source, in participants with and without microalbuminuria. Participants consumed a usual protein diet with meat source as either red meat only (usual diet) or chicken only (chicken diet), compared to a low-protein diet, for 4 wk per diet type in a crossover design. Significant reduction of 36% in urinary albumin excretion rate was seen in participants with microalbuminuria after the chicken diet (no change in normoalbuminuric participants). A reduction in GFR was seen in normoalbuminuric participants after the chicken diet or low-protein diet (43).

Additional studies showed no significant changes in renal parameters as secondary outcomes. Those parameters varied among the studies from urine microalbumin and creatinine clearance (34), to urine albumin excretion only (38), to serum creatinine and blood urea nitrogen (39), to GFR (40), and to GFR, serum creatinine, urinary calcium excretion, and urinary microalbumin excretion (43). Despite no change in urinary albumin/creatinine ratio after 12 wk on a high-protein diet, Moosheer et al. found that serum creatinine decreased significantly at the end of the study period (30).

Two studies looked at the differential effects of plant-protein-rich compared with animal-protein-rich diets on renal outcomes. Wheeler et al. showed no significant effect of animal or plant diets (both 17% of total energy from protein) on any renal parameter (renal plasma flow, GFR, albumin excretion rate) when compared to baseline between the 2 diets (44). Sucher et al. showed that GFR remained stable in both plant-protein and animal-protein diet groups; however, serum creatinine decreased in the plant-protein group. Synthesis of creatinine in the muscle requires methionine, so the authors hypothesized that the change in creatinine was an indicator of a change in methionine metabolism, resulting from the decreased availability of methionine in vegan diets. Finally, urinary albumin excretion decreased in both diet groups in participants with microalbuminuria, and was unchanged in participants with normoalbuminuria (28).

Cardiovascular outcomes.

BP. BP was assessed in most of the included studies (15 out of 21). In the randomized controlled trials, no difference was seen in BP between the intervention and the control diet groups in 3 out of 7 studies (27, 41, 40). The study by Brinkworth et al. showed that systolic and diastolic BP were significantly lowered in both diet groups during the initial 12-wk weight-loss phase, with no significant difference between the groups. However, in the follow-up phase, both systolic and diastolic BP rose significantly more in the low-protein diet group compared to the high-protein diet group. Results were also similar after adjustments for changes in weight (38). Similarly, a robust and differential effect on BP was seen by Sargrad et al., such that in a high-protein group both the diastolic (-18 mm Hg, $P < 0.05$) and systolic (-10.5 mm Hg, $P < 0.03$) BP decreased between the baseline and the 8-wk visits, whereas BP in a high-carbohydrate group remained unchanged (39). Along the same theme, Von Bibra et al. showed that a higher-protein diet resulted in reduction in BP (compared with baseline), whereas a control diet did not (31). One study showed that diastolic BP improved significantly after consumption of a plant-protein diet but not after consumption of an animal-protein diet (28).

In shorter duration crossover design studies, the effects on BP were mixed, with most showing no change in BP from baseline, and no differential effect of diet type on BP (29, 33–35, 43). Two studies showed an improvement in BP after both diets, with no differential diet effect (42, 44). One exception to these results was seen in the study by Papakonstantinou et al., which found that a high-protein, low-fat diet significantly improved both systolic and diastolic BP when compared with a low-protein, high-fat diet (45).

One study included cardiac function as an outcome. Von Bibra et al. studied the effect of different diets on cardiac function, and demonstrated that a higher protein diet resulted in improved myocardial diastolic function (31). This was the primary outcome measure of that study.

Serum lipid concentrations. The most common lipid parameters checked were fasting serum total cholesterol (TC), TG, LDL cholesterol, and HDL cholesterol concentrations. There was wide heterogeneity in changes seen in lipid parameters in different studies. Most of the randomized controlled trials showed improvement in some or all of the serum lipids in both the intervention and control groups compared to baseline, with no significant difference between diet groups, specifically: HDL cholesterol increase (38), TC and TG decrease, HDL cholesterol increase (40), TC decrease (27), TG decrease and TC/HDL cholesterol decrease (41), and TC, LDL cholesterol, and HDL cholesterol decrease (28). One study showed no significant change in any lipid value over time or in between groups (37), whereas another showed a decrease in HDL cholesterol in the high-carbohydrate group and a decrease in LDL cholesterol in the high-protein group (39). A similar heterogeneity was seen in the shorter-term crossover studies, with most showing no significant change in lipids in either diet groups over the course of the study or in between diet groups (29, 30, 33–35, 46). One study comparing diets high in plant or animal protein showed a significant decrease in TC after both diets, with no significant difference in change from baseline to end between the 2 diets (44). On the other hand, O'Dea et al. showed a reduced LDL

cholesterol and LDL cholesterol to HDL cholesterol ratio on a high-protein diet (36), and Papakonstantinou et al. showed that both diets reduced TC, TG, HDL cholesterol, and LDL cholesterol, but the reduction in TG was greater in the high-protein diet group (45).

Protein source: plant compared with animal

Suggested benefits of plant-based diets include improvement in cardiometabolic risk, lipid profiles, and possibly renal outcomes. Two of the studies included in this review evaluated the differential benefit of plant-protein compared with animal-protein diets, with mixed results on glycemic outcomes: Wheeler et al. showed that 2 diets consisting of 17% of energy from protein (plant compared with animal) resulted in reduction in HbA1c compared to baseline, with no significant difference between the diets (44), whereas Sucher et al. showed that higher-protein diets (30% of energy from protein) resulted in an improved inflammatory profile, reduced intrahepatic lipids, and improved insulin sensitivity when compared to baseline, with significant improvement in glycemic control after consumption of the plant-protein diet and no improvement after consumption of the animal-protein diet (28). One study specifically looked at animal-protein sources, comparing chicken to red meat as the primary source. Replacing red meat (usual diet) with chicken (chicken diet) as the protein source, compared with a low-protein diet, all did not alter glycemic control (43).

Compliance with diet interventions

Compliance was assessed in most of the studies with use of food records (self-report), 24-h dietary recalls, and weighed food. In some studies an increase in dietary protein intake was confirmed with use of urinary nitrogen or urea testing. Most short term (1–6 wk) trials demonstrated good compliance. However, O'Dea et al. reported poor tolerability of a high-protein diet (62% of energy from protein), and noted that some participants had difficulty eating enough to maintain isocaloric conditions while assigned to this diet. In the authors' words, "that diet is difficult to justify on either economic or ecological grounds" (36). Long-duration studies also demonstrated poor compliance: for example, in the 2-y randomized intervention by Krebs et al., the macronutrient composition at study end was similar among both groups, indicating poor long-term adherence to prescribed macronutrient composition (27). One 12-wk randomized controlled trial did show that participants were able to significantly increase protein and reduce carbohydrate intake for the study duration (41). In general, however, long-duration studies had lower compliance with diet interventions and higher dropout rates than shorter studies.

Conclusions

In this systematic review we evaluate current evidence regarding effectiveness of high-protein diets for improving glycemic control in people with T2D. We found that many studies provide support for use of high-protein diets. These tend to be small, short-duration randomized crossover or uncontrolled studies, which achieved rigorous control of study conditions and high participant compliance with assigned diets. Larger and longer-duration randomized controlled trials, on the other hand, did not collectively support use of high-protein diets for T2D in real-world settings. These studies tended to have high dropout rates and lower diet compliance, and reveal the major challenge of conducting diet intervention trials on a large scale. There was no consistent evidence of benefit or of harm for other outcomes, including serum lipids, BP, or kidney function. There was insufficient evidence to favor a plant or animal source of protein over the other.

There is a mechanistic basis to support the use of high-protein diets for treatment of T2D. In the early 1900s, experiments were performed to examine the role of macronutrient composition of ingested food on blood glucose response. In 1915, investigators showed that about half of the ingested protein in meat is converted to glucose via gluconeogenesis (5). However, a study in the 1920s showed that ingestion of 50 g of animal protein in a participant with diabetes resulted in stable blood glucose for the next 5 h, whereas ingestion of 25 g of glucose (which is the expected glucose equivalent of 50 g of protein) resulted in a significant spike in blood glucose from 280 mg/dL to a peak of 600 mg/dL (5). Potential explanations for this discrepancy were *1*) insulin production from ingested protein may ameliorate the rise in glucose, and *2*) the process of gluconeogenesis from protein is slow, and the glucose formed is rapidly stored as glycogen with the aid of secreted insulin (5). In the 1970s and 1980s, animal studies demonstrated higher insulin content in the plasma and pancreas of rats fed a high-protein diet (10). Moreover, streptozocin-diabetic rats fed a low-carbohydrate, high-protein diet had amelioration of hyperglycemia, in addition to increased pancreatic insulin content (11). It was found that in patients with diabetes, an intravenous infusion of mixed amino acids resulted in a sustained increase in insulin, and improved glucose response to carbohydrate intake (12). Several short-term single-meal feeding studies by the Gannon and Nuttall group showed that dietary protein was a strong insulin secretagogue, especially in participants with T2D. They also showed that dietary protein had a synergistic effect on insulin secretion when ingested with dietary glucose (13–16). Thus, the use of high-protein diets for T2D has a mechanistic basis that would suggest efficacy, even in the absence of caloric restriction and weight loss.

Our systematic literature review found many small studies, which we have termed proof-of-concept studies, that tested high-protein diets over short durations and in rigorously controlled research settings. Many, but not all, studies in this group provided further evidence in support of the diets and of this proposed mechanism. However, larger and longer randomized controlled trials showed that the diets may not be effective in real-world settings, which may be because of high dropout and poor diet compliance. This could be a limitation of real-world effectiveness of high-protein diets for treatment of T2D.

This review is unique in that it considers high-protein diet patterns for T2D with the exclusion of trials in which participants had >5% weight loss. The threshold of 5% was chosen because it has been shown that weight loss greater than this amount is needed for glycemic benefit in T2D (50). The exclusion of weight-loss trials was important so that the question of diet effectiveness, without the confounding contribution of weight change, could be evaluated. This is of clinical relevance. Although weight loss is a desirable goal for many patients with T2D, it is not always achieved and is difficult to maintain. Weight-neutral diets may be an empowering, effective, and relatively inexpensive tool, which would appeal to a broad range of patients with T2D.

Additional strengths of this review are the systematic nature and the large volume of literature included in the initial search. The inclusion and exclusion criteria were designed to maximize the number of studies that would be included. There are some limitations of this strategy. Some studies were included that were not designed to look at the effect of dietary protein content on glycemia as a primary outcome. Included studies used heterogeneous definitions for a high-protein diet, with some studies evaluating diets with protein intake marginally greater than typical American intake, and with overlap between intervention diets in some studies and control diets in others. Lastly, some studies of lower evidence quality, such as uncontrolled interventions, were included. We felt that acceptance of these limitations was necessary to conduct a comprehensive review of available evidence. To address this, we assigned a level of evidence grade and risk of bias assessment for each study included in the review.

Other limitations of this systemic review were the low compliance and high dropout rates in many studies, particularly randomized controlled trials, the heterogeneity of outcomes in the included studies, which made direct comparisons challenging, and the lack of reporting of changes to glucose-lowering medications during many studies. Medication changes were carefully accounted for in the minority of included studies, and may have confounded study results. Finally, an increase in protein content of a diet necessitates alteration of either or both carbohydrate and fat content. Although these macronutrients may also be expected to affect glycemic outcomes in people with T2D, a full review of these changes was beyond the scope of this paper.

In summary, proof-of-concept studies suggest that high-protein diets have beneficial effects for glycemic control in T2D, without a detrimental effect on renal function or cardiovascular outcomes. There is not sufficient evidence to recommend 1 type of protein over another. The potential benefits of high-protein diets over control have not been consistently demonstrated in randomized controlled trials, which tend to be larger and longer in duration than proof-of-concept studies. This may be an effect of low compliance and high dropout, a problem found throughout nutrition literature. Our review suggests that interventions that help patients comply with diet changes over the long term may be equally important to specific macronutrient recommendations for patients with T2D.

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References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta (GA): Centers for Disease Control and Prevention, US Department of Health and Human Services; 2017.
2. American Diabetes Association. 4. Lifestyle management: standards of medical care in diabetes—2018. Diabetes Care 2018;41(Suppl 1): S38–50.
3. Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, Neumiller JJ, Nwankwo R, Verdi CL, Urbanski P, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care 2014;37 (Suppl 1):S120–43.
4. Van Gaal L, Scheen A. Weight management in type 2 diabetes: current and emerging approaches to treatment. Diabetes Care 2015;38:1161–72.
5. Gannon MC, Nuttall FQ. Control of blood glucose in type 2 diabetes without weight loss by modification of diet composition. Nutr Metab (Lond) 2006;3:16.
6. Morales FEM, Tinsley GM, Gordon PM. Acute and long-term impact of high-protein diets on endocrine and metabolic function, body composition, and exercise-induced adaptations. J Am Coll Nutr 2017;36:295–305.
7. Drummen M, Tischmann L, Gatta-Cherifi B, Adam T, Westerterp-Plantenga M. Dietary protein and energy balance in relation to obesity and co-morbidities. Front Endocrinol (Lausanne) 2018;9:443.
8. Berryman CE, Lieberman HR, Fulgoni VL, 3rd, Pasiakos SM. Protein intake trends and conformity with the Dietary Reference Intakes in the United States: analysis of the National Health and Nutrition Examination Survey, 2001–2014. Am J Clin Nutr 2018;108: 405–13.
9. Casagrande SS, Cowie CC. Trends in dietary intake among adults with type 2 diabetes: NHANES 1988–2012. J Hum Nutr Diet 2017;30:479–89.
10. Blazquez R, Lopez Quijada C. The effect of a high-protein diet on plasma glucose concentration, insulin sensitivity and plasma insulin in rats. J Endocrinol 1970;46:445–51.
11. Siegel EG, Trapp VE, Wollheim CB, Renold AE, Schmidt FH. Beneficial effects of low-carbohydrate–high-protein diets in long-term diabetic rats. Metabolism 1980;29:421–8.
12. Seino Y, Ikeda M, Nakane K, Nakahara H, Seino S. Amino acid modulation of glucose-induced insulin and glucagon release in diabetic patients. Metabolism 1977;26:911–9.
13. Nuttall FQ, Mooradian AD, Gannon MC, Billington C, Krezowski P. Effect of protein ingestion on the glucose and insulin response to a standardized oral glucose load. Diabetes Care 1984;7:465–70.
14. Khan MA, Gannon MC, Nuttall FQ. Glucose appearance rate following protein ingestion in normal subjects. J Am Coll Nutr 1992;11:701–6.
15. Gannon MC, Nuttall JA, Damberg G, Gupta V, Nuttall FQ. Effect of protein ingestion on the glucose appearance rate in people with type 2 diabetes. J Clin Endocrinol Metab 2001;86:1040–7.
16. Gannon MC, Nuttall FQ, Neil BJ, Westphal SA. The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects. Metabolism 1988;37:1081–8.
17. Kirk JK, Graves DE, Craven TE, Lipkin EW, Austin M, Margolis KL. Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc 2008;108:91–100.
18. Wheeler ML, Dunbar SA, Jaacks LM, Karmally W, Mayer-Davis EJ, Wylie-Rosett J, Yancy WS, Jr. Macronutrients, food groups, and eating

patterns in the management of diabetes: a systematic review of the literature, 2010. Diabetes Care 2012;35:434–45.
19. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions (Version 5.1.0). 2011.
20. EndNote. Clarivate Analytics: Philadelphia (PA), 2016.
21. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
22. Rayyan QCRI, Qatar Computing Research Institute: Doha, Qatar, 2016.
23. Skytte MGJ, Samkani AA, Petersen AD, Thomsen MN, Astrup A, Chabanova E, Frystyk J, Holst JJ, Madsbad S, Thomsen H, et al. A carbohydrate-reduced high-protein diet significantly reduces postprandial plasma and diurnal blood glucose in subjects with type 2 diabetes. Diabetes 2017;66:A204.
24. Moher D, Liberati A, Tetzlaff J, Altman DG; Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
25. Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, et al. Oxford Center for Evidence-Based Medicine—Levels of Evidence (March 2009). [Internet]. Available from: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Last accessed 11 December 2018.
26. Academy of Nutrition and Dietetics. Evidence analysis manual. Chicago (IL), 2016, p. 106.
27. Krebs JD, Elley CR, Parry-Strong A, Lunt H, Drury PL, Bell DA, Robinson E, Moyes SA, Mann JI. 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;55:905–14.
28. Sucher S, Markova M, Hornemann S, Pivovarova O, Rudovich N, Thomann R, Schneeweiss R, Rohn S, Pfeiffer AFH. Comparison of the effects of diets high in animal or plant protein on metabolic and cardiovascular markers in type 2 diabetes: a randomized clinical trial. Diabetes Obes Metab 2017;19:944–52.
29. Gannon MC, Hoover H, Nuttall FQ. Further decrease in glycated hemoglobin following ingestion of a LoBAG30 diet for 10 weeks compared to 5 weeks in people with untreated type 2 diabetes. Nutr Metab (Lond) 2010;7:64.
30. Moosheer SM, Waldschutz W, Itariu BK, Brath H, Stulnig TM. A protein-enriched low glycemic index diet with omega-3 polyunsaturated fatty acid supplementation exerts beneficial effects on metabolic control in type 2 diabetes. Prim Care Diabetes 2014;8:308–14.
31. Von Bibra H, Wulf G, St John Sutton M, Pfutzner A, Schuster T, Heilmeyer P. Low-carbohydrate/high-protein diet improves diastolic cardiac function and the metabolic syndrome in overweight-obese patients with type 2 diabetes. IJC Metab Endocr 2014;2:11–8.
32. Seino Y, Seino S, Ikeda M, Matsukura S, Imura H. Beneficial effects of high protein diet in treatment of mild diabetes. Hum Nutr Appl Nutr 1983;37A:226–30.
33. Gannon MC, Nuttall FQ. Effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. Diabetes 2004;53:2375–82.
34. Gannon MC, Nuttall FQ, Saeed A, Jordan K, Hoover H. An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. Am J Clin Nutr 2003;78:734–41.
35. Nuttall FQ, Schweim K, Hoover H, Gannon MC. Effect of the LoBAG30 diet on blood glucose control in people with type 2 diabetes. Br J Nutr 2008;99:511–9.
36. O'Dea K, Traianedes K, Ireland P, Niall M, Sadler J, Hopper J, De Louise M. The effects of diet differing in fat, carbohydrate, and fiber on carbohydrate and lipid metabolism in type II diabetes. J Am Diet Assoc 1989;89:1076–86.
37. Scott LW, Balasubramanyam A, Kimball KT, Aherns AK, Fordis CM, Jr., Ballantyne CM. Long-term, randomized clinical trial of two diets in the metabolic syndrome and type 2 diabetes. Diabetes Care 2003;26:2481–2.
38. Brinkworth GD, Noakes M, Parker B, Foster P, Clifton PM. 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;47:1677–86.
39. Sargrad KR, Homko C, Mozzoli M, Boden G. Effect of high protein vs high carbohydrate intake on insulin sensitivity, body weight, hemoglobin A1c, and blood pressure in patients with type 2 diabetes mellitus. J Am Diet Assoc 2005;105:573–80.
40. Larsen RN, Mann NJ, Maclean E, Shaw JE. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. Diabetologia 2011;54:731–40.
41. Luger M, Holstein B, Schindler K, Kruschitz R, Ludvik B. 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;121:286–94.
42. Pomerleau J, Verdy M, Garrel DR, Nadeau MH. Effect of protein intake on glycaemic control and renal function in type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1993;36:829–34.
43. Gross JL, Zelmanovitz T, Moulin CC, De Mello V, Perassolo M, Leitao C, Hoefel A, Paggi A, Azevedo MJ. Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: a randomized crossover trial. Diabetes Care 2002;25:645–51.
44. Wheeler ML, Fineberg SE, Fineberg NS, Gibson RG, Hackward LL. Animal versus plant protein meals in individuals with type 2 diabetes and microalbuminuria: effects on renal, glycemic, and lipid parameters. Diabetes Care 2002;25:1277–82.
45. Papakonstantinou E, Triantafillidou D, Panagiotakos DB, Koutsovasilis A, Saliaris M, Manolis A, Melodonis A, Zampelas A. A high-protein low-fat diet is more effective in improving blood pressure and triglycerides in calorie-restricted obese individuals with newly diagnosed type 2 diabetes. Eur J Clin Nutr 2010;64:595–602.
46. Navas-Carretero S, Abete I, Zulet MA, Martinez JA. Chronologically scheduled snacking with high-protein products within the habitual diet in type-2 diabetes patients leads to a fat mass loss: a longitudinal study. Nutr J 2011;10:74.
47. Layman DK, Clifton P, Gannon MC, Krauss RM, Nuttall FQ. Protein in optimal health: heart disease and type 2 diabetes. Am J Clin Nutr 2008;87:1571S–5S.
48. Kamper AL, Strandgaard S. Long-term effects of high-protein diets on renal function. Annu Rev Nutr 2017;37:347–69.
49. Hu FB. Protein, body weight, and cardiovascular health. Am J Clin Nutr 2005;82:242S–7S.
50. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. 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;115:1447–63.