Macronutrients, Food Groups, and Eating Patterns in the Management of Diabetes

A systematic review of the literature, 2010

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The effectiveness of medical nutrition therapy (MNT) in the management of diabetes has been well established (1). Previous reviews have provided comprehensive recommendations for MNT in the management of diabetes (2,3). The goals of MNT are to *1*) attain and maintain optimal blood glucose levels, a lipid and lipoprotein profile that reduces the risk of macrovascular disease, and blood pressure levels that reduce the risk for vascular disease; *2*) prevent and treat the chronic complications of diabetes by modifying nutrient intake and lifestyle; *3*) address individual nutrition needs, taking into account personal and cultural preferences and willingness to change; and *4*) maintain the pleasure of eating by only limiting food choices when indicated by scientific evidence (4).

The literature on nutrition as it relates to diabetes management is vast. We undertook the specific topic of the role of macronutrients, eating patterns, and individual foods in response to continued controversy over independent contributions of specific foods and macronutrients, independent of weight loss, in the management of diabetes. The position of the American Diabetes Association (ADA) on MNT is that each person with diabetes should receive an individualized eating plan (4). ADA has received numerous criticisms because it does not recommend one specific mix of macronutrients for everyone with diabetes. The previous literature review conducted by ADA in 2001 supported the idea that there was not one ideal macronutrient distribution for all people with diabetes. This review focuses on literature that has been published since that 2001 date (5). This systematic review will be one source of information considered when updating the current ADA Nutrition Position Statement (4). Other systematic reviews and key research studies that may not be included in this review will also be considered.

When attempting to tease out the role of macronutrients from other dietary and lifestyle factors, two critical components of MNT—energy balance and a healthful eating pattern—are not addressed. While both are critical components in the management of diabetes as well as the secondary prevention of complications and promotion of health, these topics are beyond the scope of this particular review. The following questions are addressed in this review:

1. What aspects of macronutrient quantity and quality impact glycemic control and cardiovascular disease (CVD) risk in people with diabetes?
2. How do macronutrients combine in whole foods and eating patterns to affect health in people with diabetes?
3. Is there an optimal macronutrient ratio for glycemic management and CVD risk reduction in people with diabetes?
4. What findings and needs should direct future research?

Systematic review procedure—A search of the PubMed database was conducted using the search terms "diabetes" and one of a number of words (low-fat diet, low-carbohydrate diet, Mediterranean diet, Mediterranean eating pattern, vegetarian, vegan, glycemic index (GI), dietary carbohydrates, dietary protein, total fat, dietary fat, saturated fat, omega-3 fatty acid, dietary fiber, meats, legumes, nuts, fruit, vegetables, whole grains, milk) to identify articles published between January 2001 and October 2010. Certain terms relevant to nutrition therapy in the management of diabetes were not included in the search terms. These terms include *trans* fatty acids, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), sucrose, and sugars. The literature search was limited to articles published in English, and multiple publications from the same study were limited to the primary study results article.

Studies included in the systematic review were conducted in people already diagnosed with diabetes; conducted in outpatient ambulatory care settings; contained a sample size of 10 or more participants in each study group; and one of the following study designs: clinical trials (controlled and randomized controlled [RCT]), prospective observational studies, cross-sectional observational studies, or case-control studies. Studies were excluded if they were published before January 2001 or after October 2010; were conducted in acute care or inpatient settings, in women with gestational diabetes, children under 2 years of age, or individuals without diabetes or at risk for diabetes; had less than 10 participants in any study

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group; were studies lasting only 1 or 2 days; or were not in one of the study designs previously listed.

In an effort to expand the research review, studies were not excluded based on retention rates; however, this information is included in Supplementary Table 1 and only studies with a retention rate of >80% are included in the key summary for each topic area. Weight loss is a confounder in some of the studies and is noted in Supplementary Table 1.

Meta-analyses published during the inclusion period of this systematic review were reviewed for studies meeting this systematic review's criteria. This information can be found in Supplementary Table 1.

An initial PubMed database search found 152 studies after excluding by title and abstract review. An additional 18 studies were found from bibliography review. Of these, 72 studies were excluded for not meeting inclusion criteria. The most common reasons for exclusion were for results not applicable to the research question, not published in a major journal, small sample size, review articles, and duplicates.

Challenges in evaluating macronutrient studies in diabetes management—Isolating the effects of dietary macronutrient composition on glycemic control and CVD risk is difficult due to confounding, especially by weight loss and medication changes. Furthermore, altering the level of one macronutrient affects the proportion of other macronutrients, making it difficult to isolate the true exposure. Additional study design issues include the difficulty blinding study participants, investigators, and clinicians. Finally, the lack of standardized definitions for terms such as "low-fat (or high-fat) diet," "low-carbohydrate (or high-carbohydrate) diet," and "low-GI (or high-GI) diet" makes comparisons among study results difficult. These issues were addressed by reporting the entire macronutrient composition of diet approaches and potential confounders when this information was available.

Question 1: What aspects of macronutrient quantity and quality impact glycemic control and CVD risk in people with diabetes?

Carbohydrate amount—There is no consistent definition of "low- (or high-) carbohydrate diets" throughout the literature. Based on the studies in this systematic review, the following definitions are used:

- very-low-carbohydrate diet: 21–70 g/day of carbohydrate
- moderately low–carbohydrate diet: 30 to <40% of kcal as carbohydrate
- moderate-carbohydrate diet: 40–65% of kcal as carbohydrate
- high-carbohydrate diet: >65% of kcal as carbohydrate

These definitions are not all-inclusive (e.g., a 100-g/day carbohydrate diet may be <30% kcal), but they represent the typical definitions used by authors, and all published articles fit in one of these categories.

Many studies use the term "conventional" or "traditional" macronutrient distribution as a comparison group. Based on studies in this review, these terms refer to an energy contribution from the diet of 55–65% carbohydrate, ≤30% fat, and 10–20% protein. It should be noted that people with diabetes have been shown to consume an eating pattern that is about 45% of calories from carbohydrate (6–9). The comparison diets referred to as conventional or traditional throughout this review are higher in carbohydrate than those generally consumed by people with diabetes.

Lower (very low and moderately low) carbohydrate

Glycemic control. Eleven clinical trials examined the effects of lowering total carbohydrate intake on glycemic control in individuals with diabetes. The carbohydrate content goal of the diet was very low in 7 studies (10–16) and moderately low in 4 studies (17–20).

All studies included adults with type 2 diabetes, duration of follow-up ranged from 14 days to 1 year, and sample sizes ranged from 10 to 55 participants per study group. Designs included two feeding trials (one crossover clinical trial and one RCT) (10,18) and nine outpatient nutrition counseling interventions (two single-arm clinical trials, one crossover RCT, and six parallel RCTs) (11–17,19,20). All studies analyzed participants according to treatment assignment, eight studies were randomized (11–13,15–19), and for six studies, completion of follow-up was 80% or higher (10,12,13,17–19).

A1C decreased with a lower-carbohydrate diet in 6 of 10 studies in which it was measured (10,14–17,20). Three RCTs found no statistically significant changes in A1C with a very-low-carbohydrate diet (11–13) and one found no difference with a moderately low–carbohydrate diet (19). Other glycemic parameters such as fasting blood glucose (FBG), 24-h blood glucose, 24-h insulin (10), and fasting insulin levels (18) decreased significantly, and insulin sensitivity increased significantly (10) on the lower-carbohydrate diet. Glucose-lowering medications were decreased for individuals following the lower-carbohydrate diet (10–12,14,17) or were more frequently decreased than in the comparison diet (16).

CVD risk. Each of the 11 clinical trials reported at least one serum lipoprotein. The most notable results were that HDL cholesterol increased significantly more in one very-low-carbohydrate diet group (16) and two moderately low–carbohydrate diet groups (18,20) compared with the higher-carbohydrate control diet. Also, triglycerides (TGs) decreased more in one moderately low–carbohydrate diet group (20) compared with the higher-carbohydrate control diet. Otherwise, mean changes in serum lipoproteins resulting from a lower-carbohydrate diet were typically beneficial but occurred without a comparison arm or were not statistically greater than the comparison arm.

Summary of lower-carbohydrate research since 2002

In studies reducing total carbohydrate intake, markers of glycemic control and insulin sensitivity improved, but studies were small, of short duration, and in some cases were not randomized or had high dropout rates. Serum lipoproteins typically improved with reduction of total carbohydrate intake but, with the exception of HDL cholesterol, were not statistically greater than with the comparison diet. The contribution of weight loss to the results was not clear in some of these studies.

Moderate or high carbohydrate

Glycemic control. Seven clinical trials and two meta-analyses examined the effects of moderate- or high-carbohydrate diets on glycemic control in patients with type 2 diabetes (21–28) or type 1 diabetes (29). Durations of follow-up ranged from 5 to 74 weeks, and sample sizes of participants completing follow-up ranged from 10 to 99. All seven studies were RCTs and analyzed participants according to treatment assignment. Four studies had

completion of follow-up of 80% or higher (21,22,25,26). Only one of the studies blinded participants to diet treatment (22), and none blinded the outcome assessors.

Four studies found no significant differences in glycemic control when comparing moderate- or high-carbohydrate diets with conventional diets (21–24). One RCT found A1C improved with higher carbohydrate (75% of energy intake) compared with conventional carbohydrate (60–70% of energy intake) (21) in secondary analyses that used the observation immediately prior to a participant dropping out or having a diabetes medication change as the final outcome. The intent-to-treat analyses, however, showed no significant differences between groups. In another study, A1C decreased significantly more during 5 weeks on a 40% carbohydrate/30% protein versus a 55% carbohydrate/15% protein diet (25). A1C was not significantly different compared with a conventional diet in two studies examining a moderate-carbohydrate/higher-protein diet (23,24), two studies examining a moderate-carbohydrate/higher-fat (MUFA) diet (22,26), and one study comparing a 55% carbohydrate/25% fat with a 55% carbohydrate/30% fat diet (29).

Regarding other glycemic parameters, 24-h glucose response was lower with a 40% carbohydrate/30% protein diet compared with a 55% carbohydrate/15% protein diet (25); however, plasma glucose (22–24,26), plasma insulin (23,24,26,29), plasma fructosamine (22), and homeostasis model assessment (HOMA) (24) were not significantly different in other diet comparisons.

Two meta-analyses compared lower-carbohydrate diets with conventional carbohydrate diets (27,28). Of the 19 studies reviewed in the article by Kodama et al. (27), only three (18,26,30) were published during the date range for this review, and of the 13 studies in the meta-analysis by Kirk et al. (28), only four (10,14,22,25) were published during the review time period. The seven studies are included in this review.

CVD risk. Six of the seven interventions reviewed above reported lipoproteins. Two (25,26) reported significant reductions in TGs on a 40% carbohydrate diet (vs. 50–55% carbohydrate), whereas one (21) observed a significant reduction in LDL cholesterol on a 75% carbohydrate diet (vs. 60–70% carbohydrate). Three studies (22–24) found no significant differences between comparison diets.

Summary of moderate- and high-carbohydrate research since 2002

RCTs presenting information on moderate- and high-carbohydrate diets are diverse in terms of fat and protein content as well as length of study. Only two RCTs found significant differences in A1C between groups, with one study finding significantly lower A1C with the higher-carbohydrate diet only in a subgroup analysis, and the other study finding significantly lower A1C with the lower-carbohydrate diet. In terms of CVD risk factors, LDL cholesterol improved more with a high-carbohydrate diet in one study, whereas two studies found TGs improved more with a lower-carbohydrate diet.

Carbohydrate type—Studies in this systematic review addressing the type of carbohydrate were those of GI/glycemic load or dietary fiber.

GI

For studies in this review that provided the GI that subjects were able to achieve (end-of-study GI numbers), there was no agreement as to the definition of "low GI" (range 39–77) or "high GI" (range 56–84). The meta-analyses (almost all studies used were published before 2001) found that the average low GI was 65, and the average high GI was 82, but both had wide ranges. This is further complicated by the two bases (glucose or white bread) that have been used to determine GI values for individual foods.

Glycemic control. Five RCTs (19,31–34) compared lower-GI diets with higher-GI diets in individuals with type 2 diabetes. Duration of follow-up ranged from 4 to 6 weeks and sample sizes were small in four studies (12–14 in three of the studies, 45 in the other), whereas the fifth study lasted for 1 year and included 156 subjects in the analysis (19). Completion rates were ≥80% except for 39% in one study (33). Results were mixed with two studies finding A1C was significantly reduced with the lower-GI versus higher-GI diets (32,33) and the others finding no differences in glycemic measures (19,31,34).

Three parallel RCTs (16,35,36) compared a lower-GI diet with diets other than those designated as higher GI (high-fiber diet, traditional diet, very-low-carbohydrate diet) in individuals with type 2 diabetes. Duration of follow-up was 6–12 months, retention rates were <80% in two of the studies (16,35), and sample sizes were moderate (range 40–155). Compared with a higher-fiber diet, the lower-GI diet decreased A1C and FBG significantly (35). When the lower-GI weight-loss diet was compared with a conventional weight-loss diet (36), both groups lowered A1C significantly with no significant differences between groups. The lower-GI diet reduced A1C significantly less than the very-low-carbohydrate diet (16).

A study in youth with type 1 diabetes (37) found that individuals advised to follow a lower-GI diet had significant reductions in A1C compared with individuals advised to follow a carbohydrate-exchange diet, despite the fact that the mean GI for the two diet groups was not significantly different. Two studies indicated that education can change food selection and may (38) or may not (39) affect the GI of the diet.

Three meta-analyses (40–42) evaluated GI. Anderson et al. (41) included no studies meeting this review's criteria; Brand-Miller et al. (40) included one (37); and Thomas and Elliott (42) included three (32,33,37). These three studies from the meta-analyses are included above (32,33,37).

CVD risk. Mixed results were found for the five RCTs comparing low-GI with high-GI diets for lipoprotein measures. Two studies found a significant reduction in total cholesterol (31,32) with one of the two reporting a significant reduction in LDL cholesterol and apolipoprotein (apoB) (32) for the lower-GI diet. The other three studies found no significant changes between groups (19,33,34).

Results were mixed in studies comparing lower GI with other dietary approaches. Significantly increased HDL cholesterol was found with lower GI versus higher-cereal fiber but no significant differences in other measured CVD risk markers (35). Total cholesterol was significantly lowered with both a lower-GI diet and a traditional diet without significant differences between groups; however, LDL cholesterol was significantly higher with the lower-GI diet versus the traditional diet (36). A very-low-carbohydrate diet reduced TGs significantly and increased HDL cholesterol significantly compared with a lower-GI, reduced-calorie diet, with no significant differences in total cholesterol and LDL cholesterol (16).

A cross-sectional study (43) of men with type 2 diabetes described a statistically significant trend toward decreasing

adiponectin with increasing quintiles of GI.

Summary of GI research since 2002

In general, there is little difference in glycemic control and CVD risk factors between low-GI and high-GI or other diets. A slight improvement in glycemia may result from a lower-GI diet; however, confounding by higher fiber (16,33,35) must be accounted for in some of these studies. Furthermore, standardized definitions of low GI need to be developed and low retention rates on lower-GI diets must be addressed (16,33,35).

Dietary fiber

The Institute of Medicine defines dietary fiber as consisting of nondigestible (not digested in the human small intestine) carbohydrates and lignin that are intrinsic and intact in plants (44). Quantification of the dietary fiber in research studies may be on the basis of dietary recommendations, grams per 1,000 kcals, the amount added, or its distribution within the study population. Functional fibers are beyond the scope of this systematic review, and thus functional fiber and total fiber were not included in this review.

Glycemic control. Seven RCTs examined the effects of moderate amounts of fiber supplements (4–19 g/day) on glycemic control in adults with type 2 diabetes (45–51). Durations of follow-up ranged from 4 to 12 weeks, and sample sizes were small (12–60 participants in the fiber intervention). All studies were randomized; all studies analyzed participants according to treatment assignment; completion of follow-up was >80% for two of the studies (46,51); two of the studies blinded participants to diet treatment (48,51); and two were double-blinded (45,46). In general, these studies support the idea that fiber supplements may improve postprandial glycemia; however, little improvement in A1C was observed.

Two dietary counseling RCTs examined the effects of dietary fiber as part of an intervention diet. In the first study, individuals on the low-GI diet showed small but significant improvements in A1C (after controlling for weight loss, fiber, or carbohydrate) and FBG at 6 months compared with those on the high–cereal fiber diet (35). In the second study, individuals on a moderate-carbohydrate (51%), high-fiber (27 g/1,000 kcals), lower-GI, moderate-fat diet had significant decreases in postprandial glucose variability after 4 weeks compared with a lower-carbohydrate (44%), lower-fiber (8 g/1,000 kcal), higher-GI, higher-MUFA diet (52).

Markers of improved insulin sensitivity (adiponectin) or inflammation (C-reactive protein [CRP], tumor necrosis factor-R2 [TNF-R2]) were assessed in three cross-sectional reports (43,53,54). Higher cereal or fruit fiber intakes were associated with higher levels of adiponectin (43,53,54) and lower levels of CRP (53,54) or TNF-R2 (53,54). Another cross-sectional study (55), using a 3-day weighed diet, found that individuals with type 2 diabetes and the metabolic syndrome had significantly lower intakes of total dietary fiber (specifically whole grains and fruits) than those with diabetes but without the metabolic syndrome; however, there were no associations between fiber intake and A1C or FBG in either group.

The time period of the meta-analysis by Anderson et al. (41) is before any of the articles in this systematic review were published, therefore the meta-analysis results are not included here.

CVD risk. All RCTs described above assessed lipoproteins (35,45–52). Four studies found no significant difference between intervention and control groups for these measures (46,48–50). One study found that psyllium (vs. cellulose) supplements (45) significantly improved HDL cholesterol; a second study found that a higher-fiber, lower-fat, and lower-GI diet versus a lower-fiber, higher-fat diet produced significantly lower total cholesterol, LDL cholesterol, and HDL cholesterol (52). In addition, one cross-sectional study found that a diet higher in soluble fiber from whole grains was associated with a lower TG level (55). In contrast, Jenkins et al. (35) found that the lower-GI, high–cereal fiber diet increased HDL cholesterol significantly versus the higher-GI diet, and Ble-Castillo (51) found that native banana starch increased TGs, whereas soy milk decreased TGs.

The Nurses' Health Study (NHS) found lower CVD-specific mortality in women with diabetes associated with bran intake after adjustments for lifestyle and dietary factors (56).

Summary of fiber research since 2002

The majority of the reviewed evidence indicates that adding fiber *supplements* in moderate amounts (4–19 g) to a daily diet leads to little improvement in glycemia and CVD risk markers.

Fat amount

Glycemic management

Eight clinical trials examined low-fat eating patterns (21–23,29,57–60). One trial studied adults with type 1 diabetes (29), whereas the rest studied adults with type 2 diabetes; duration of follow-up ranged from 3 days to 74 weeks, and sample sizes of participants completing follow-up ranged from 10 to 48 participants per study group. All eight trials were outpatient nutrition counseling interventions: one single-arm (57), two crossover RCTs (22,29), and five parallel RCTs. Four trials reduced total fat intake to <25% of daily energy intake (21–23,57), and for the rest, fat intake was 25–30%. All studies analyzed participants according to treatment assignment, and completion of follow-up was ≥80% except in three studies (29,59,60).

A1C decreased with a low-fat diet in one of seven studies in which it was measured (58). In that study (58), intensive dietary advice for a lower-fat, moderate-carbohydrate, higher-fiber diet in adults with poor glycemic control significantly decreased A1C compared with the control group. Insulin sensitivity by euglycemic-hyperinsulinemic clamp improved in the lower-fat diet compared with the conventional diet in one study (29).

Two weight-loss RCTs by the same group compared meal replacements versus conventional diets (59,60) and found significant reductions in FBG over short durations with meal replacements. One study carried out for 12 months showed no persistent difference in FBG between groups, although significantly more subjects in the meal replacement group had reductions in diabetic medications (60).

In addition to the information from the clinical trials, a cross-sectional study (61) found that higher-fat intake correlated with significantly higher A1C.

CVD risk

Of the seven studies that measured CVD risk factors, only one had significant findings. In a small single-arm study (57) comparing 3 days on a low-fat, fiber-rich diet with study participants' baseline higher-fat diet, both total cholesterol and HDL cholesterol decreased significantly.

The cross-sectional study (61) found that higher-fat intake correlated with higher levels of total cholesterol and

LDL cholesterol as well as coronary artery calcium.

Summary of low-fat research since 2002

Lowering total fat intake infrequently improved glycemic control or CVD risk factors in clinical trials involving individuals with diabetes. Lowering fat intake in individuals with diabetes may improve total cholesterol and LDL cholesterol but may also lower HDL cholesterol.

Fat type—For this review, the type of fat refers to the proportion of total energy from a specific fatty acid or fatty acid category. Categorization may be on the basis of the number of, the location of, or the configuration of double bonds. Saturated fatty acids (SFAs) may be assessed based on distribution within the study population or recommended dietary levels. Omega-3 fatty acids are usually evaluated as milligrams per day or as a distribution within the population rather than on the basis of percent of energy intake.

Saturated fatty acids

Glycemic control. One RCT in individuals with type 2 diabetes compared glycemic control outcomes for SFAs versus MUFAs with the total fat remaining equal (62) and did not find a significant difference between diets for postprandial glucose or insulin response.

CVD risk. A 3-week study (62) reported no improvement in postprandial lipid tolerance except for a small but significant reduction in small VLDL TGs when subjects consumed a low SFA diet (8% kcal compared with 17% as SFA).

Summary of SFAs research since 2002

The results from the one study relevant to this topic indicate that the type/amount of fatty acid does not affect postprandial glycemic control so long as the amount of total fat is equivalent. An intriguing idea for future research is that lowering SFA or increasing MUFA may increase glucagon-like peptide-1 activity, thereby reducing postprandial TG.

Omega-3 fatty acids

Glycemic control. Three blinded RCTs in individuals with type 2 diabetes (63–65) found that omega-3 fatty acid supplements may increase FBG by a small but significant amount. However, a fourth blinded RCT (66) observed a significant decrease in A1C with supplementation compared with controls. In the meta-analysis by Hartweg et al. (67), six studies met this systematic review criterion (63–65,68–70) and are included in this section.

CVD risk. Three RCTs using omega-3 fatty acid supplements (4 g/day eicosapentaenoic acid [EPA] or docosahexaenoic acid [DHA]) (64), 2.6 g/day EPA plus DHA (65), or 4 g/day fish oil (68) versus controls of corn or olive oil observed an increase in HDL cholesterol, particularly the HDL-2 and HDL-2b fractions. One of these studies (64) also found a decrease in the HDL-3 fraction with EPA supplementation. Most studies (64,65,68–70) observed significant decreases in TGs with EPA, fish oil, or EPA/DHA combination; however, one (64) showed an increase in TGs with supplementation of DHA alone. A one-armed clinical trial (71) also found a significant increase in HDL cholesterol and a significant decrease in TGs with an EPA/DHA combination.

One study (73) focused on whole-food omega-3 intake in a prospective cohort and found that baseline marine omega-3 fatty acid intake was inversely associated with TG.

Summary of omega-3 fatty acids research since 2002

Overall it appears that supplementation with omega-3 fatty acids does not improve glycemic control but may have beneficial effects on CVD risk biomarkers among individuals with type 2 diabetes by reducing TGs (in some but not all studies). Other benefits (e.g., increasing HDL cholesterol or decreasing LDL cholesterol) are not clearly defined.

Protein—This section reviews studies examining the effects of varying the amount of daily protein intake or the source of protein intake and further distinguishes those studies that included individuals with diabetic kidney disease (DKD).

Amount of protein, individuals without DKD

One metabolic unit-type crossover RCT (25) and two parallel dietary consultation RCTs (23,74) examined the effects of higher protein versus usual protein intake (30% vs. 15% of calories as protein with fat remaining constant at 25–30%) on glycemic control and CVD risk in individuals with type 2 diabetes. Durations of follow-up ranged from 4 to 16 weeks, and sample sizes were small (range 12–29 participants in the higher-protein intervention). All studies analyzed participants according to treatment assignment, completion of follow-up was >80%, and no studies were blinded.

A 5-week weight-maintenance study (25) observed a significant reduction in A1C and 24-h glucose response and significantly lower fasting TGs on the higher- versus lower-protein eating patterns. A study of 8 weeks of weight loss followed by 4 weeks of weight maintenance (74) found no significant differences between higher- and lower-protein groups for A1C; however, significant decreases in serum total cholesterol and LDL cholesterol were observed on the higher- versus lower-protein diets. Another study (23) and a 1-year follow-up of the Parker and colleagues study (24) reported no significant differences between groups in glycemic control or CVD risk factors.

Amount of protein, individuals with DKD

Four parallel RCTs examined the effects of lower versus usual protein intake on glycemic control, CVD risk factors, and renal function markers in individuals with types 1 and 2 diabetes and microalbuminuria (75), macroalbuminuria (76,77), or both (78). Durations of follow-up ranged from 1 to 4 years, sample sizes were small (23–47 participants in the intervention groups), and retention rates were >80% in two studies (76,77). One study blinded physicians to diet treatment (75). Two studies achieved lower protein intakes of 0.86–0.89 g protein/kg/day versus usual protein intakes (1.02–1.24) (76,77), whereas in the other two studies, the lower-protein group had higher actual protein intakes versus the control groups (75,78). None of the studies found significant differences between groups for glycemia, CVD risk factors, or renal function (glomerular filtration rate [GFR], various measures of proteinuria). At the levels of protein achieved, no reduction in serum albumin was noted.

Two meta-analyses addressed protein restriction in people with diabetes and micro- and macroalbuminuria. The meta-analysis by Pan et al. (79) included four studies meeting this review's criteria (75–78), and the Cochrane analysis by Robertson et al. (80) included three studies (75–77). These four studies (75–78) are included above.

Source of protein, individuals with DKD

Four RCTs examined the effects of source of protein intake on glycemic control, CVD risk factors, and renal function in individuals with type 2 diabetes and microalbuminuria (81) or macroalbuminuria (82–84). Durations of follow-up ranged from 4 weeks to 4 years, and sample sizes were small (14–20 participants in the designated source interventions). Two studies had completion rates of >80% (81,83).

The nutrition source focus for two RCTs was soy. HDL cholesterol increased significantly and urinary albumin-to-creatinine ratio decreased significantly with soy powder versus casein powder supplementation (82). The 4-year RCT reported that the replacement of 35% of animal protein with textured soy protein resulted in significant improvements in FBG and total cholesterol, LDL cholesterol, and TGs, but no significant changes in kidney function versus control (83). In two crossover RCTs from the same author group (81,84), the dark chicken meat group significantly improved total cholesterol, TGs, and urinary albumin excretion rate, and the low-protein/vegetables group significantly improved total cholesterol and GFR versus the red meat control group.

Summary of amount and source of protein research since 2002

For individuals without DKD, higher protein eating patterns (30% of calories) may or may not improve A1C; however, they appear to improve one or more CVD risk measures.

For individuals with DKD and either micro- or macroalbuminuria, reducing the amount of protein from normal levels does not appear to alter glycemic measures, CVD risk measures, or the course of GFR. For individuals with DKD and macroalbuminuria, changing the source of protein to be more soy based may improve CVD risk measures but does not appear to alter proteinuria.

Question 2A: How do macronutrients combine in food groups to affect glycemic response and CVD risk reduction in people with diabetes?

Nuts

The high MUFA content of most tree nuts and peanuts and high PUFA content of walnuts and pine nuts lends support to the investigation of potential effects of nuts on glycemic control and CVD risk in individuals with diabetes. Since 2002, three RCTs and two reports from the NHS have been published on this topic (30,85–89). All studies analyzed participants according to treatment assignment, and two studies blinded participants to treatment. Completion of follow-up was greater than 85% for all studies, and two of the three studies controlled for weight change.

Glycemic control. Two RCTs (85–87) tested the effects of walnuts against general advice or advice to consume specific PUFA-rich foods. There were no significant differences among groups for glycemic control. One double-blinded study compared 10% of total calories from fat of almonds or olive/canola oil in the context of either a high-fat (37%) or low-fat (25%) diet and also did not find significant differences in glycemic control (30).

CVD risk. Results relating to measures of CVD risk were mixed. Addition of walnuts led to no significant differences in total cholesterol and LDL cholesterol; however, improved endothelial function was observed (85). In another study (86), the walnut group achieved significant reductions in LDL cholesterol and increases in HDL cholesterol and the ratio of HDL-to-total cholesterol relative to the other treatment groups. However, a third study (30) found that HDL cholesterol was significantly lower in the group receiving almonds (vs. olive/canola oil). These authors concluded that total dietary fat had a greater effect on serum lipids than did fat source (30).

Two cross-sectional studies reported associations between nut consumption and lower-risk CVD risk markers. Nuts, as a part of the Mediterranean-style eating pattern, had an independent effect on adiponectin levels, which were 12% higher in the highest nut intake quintile versus the lowest (88). Consumption of at least five servings per week of nuts or peanut butter was significantly associated with a more favorable lipid profile (lower total cholesterol, LDL cholesterol, and apoB-100). There were no significant associations for inflammatory markers (89).

Summary of nuts research since 2002

Nut-enriched diets do not alter glycemia in individuals with diabetes. The evidence is mixed as to whether they have beneficial effects on serum lipoproteins.

Whole grains

—The 2010 "Dietary Guidelines for Americans" (90) defines whole grains as foods containing the entire grain seed (kernel, bran, germ, and endosperm).

Two single-blinded crossover RCTs compared whole grains to fiber (47,48) in individuals with type 2 diabetes. Duration of follow-up was 5–12 weeks, sample sizes were small (15–20 adults), and retention rates were 74% or not reported (47). Whole-wheat flour products did not change glycemic measures over 5 weeks, while adding fiber (arabinoxylan) to whole-wheat flour products resulted in significantly lower postprandial glucose, insulin, and fructosamine (47). In the second RCT, A1C and FBG were not altered significantly over 12 weeks with Salba (a novel whole grain) or wheat bran (48). Neither study found significant differences in CVD risk markers.

Two cross-sectional analyses from the NHS found that higher intake of whole grains was associated with lower levels of markers of inflammation (CRP and TNF-R2) (54) and with higher adiponectin concentrations (88). One of the RCTs also found CRP was significantly lower in the whole grain versus the wheat bran groups (48).

Summary of whole-grains research since 2002

Whole-grain consumption does not appear to be associated with improved glycemic control in individuals with diabetes. However, diets high in whole grains may reduce systemic inflammation.

Legumes

Soybean-based supplements

Two crossover and four parallel RCTs (50,60,91–95) investigated the effects of soy-based supplements on individuals with type 2 diabetes. One of the above RCTs reported glycemic and CVD information in separate publications (91,92). Durations of follow-up ranged from 6 weeks to 1 year, retention rates were >80% for four (91–95) of the six studies, sample sizes were small (15–38 in the intervention group), and four of the studies were double-blinded (91–95). Five of the six studies found no significant difference in glycemic measures between groups (92,93) (50,94) (60); however, two studies observed improvements in LDL cholesterol (91,93) or total cholesterol (93) versus control. A diet-counseling, randomized crossover trial (52) found that legumes as part of

a moderately high–carbohydrate, high-fiber, and lower-GI diet improved postprandial glucose and CVD risk factors compared with a higher-MUFA diet.

Isolated soy proteins that included isoflavones

Three crossover RCTs compared soy protein for effects on glycemic and CVD risk markers in postmenopausal women with type 2 diabetes (96–98). Duration of follow-up ranged from 4 to 12 weeks, sample sizes were small (16–32), and all studies were double-blinded. Two studies found no significant differences between groups in glycemic control measures or lipoproteins (97,98), and one of these found no difference in CRP or HOMA-insulin resistance (IR) (97). However, the third (96) showed significant reductions in A1C, fasting insulin, HOMA-IR, total cholesterol, and LDL cholesterol in the soy group compared with the control group.

Summary of legumes research since 2002

While the soy-derived supplements in the studies were quite different, most studies did not indicate a significant reduction in glycemic measures or CVD risk factors compared with controls.

Vegetables and fruit—One small short-term RCT addressed vegetable supplements in individuals with type 2 diabetes. At four weeks, garlic powder tablets significantly improved FBG, fructosamine, and TGs (99). Higher-fiber vegetables as part of a moderately high–carbohydrate, high-fiber, and lower-GI diet improved postprandial glucose and CVD risk factors compared with a higher-MUFA diet (52). In women with type 2 diabetes, vegetables and fruit (as a component of the Mediterranean-style eating pattern score) were not associated with adiponectin concentrations (88).

Summary of vegetable and fruit research since 2002

Eating pattern research has not directly addressed the role of vegetables and fruits in people with diabetes. Of the few studies found since 2002, results are mixed.

Dairy—Five RCTs (two crossover and three parallel feeding trials) examined the effects of dairy supplements on glycemic control and CVD risk factors (one RCT reported glycemic and CVD information in separate publications) (91,92). Three studies included adults with type 2 diabetes and one included youths with type 1 diabetes (100). Duration of follow-up ranged from 6 to 52 weeks, and sample sizes ranged from 11 to 59 participants per study group. All studies were randomized, analyzed participants according to treatment assignment, completion of follow-up was >80%, and three were double-blinded (91–94).

One RCT (100) found that adding camel's milk to the usual diets of youth newly diagnosed with type 1 diabetes significantly reduced A1C and mean dose of insulin compared with usual diets alone.

Three RCTs comparing soy to dairy (91–94) found no significant differences between groups in glycemic control. However, two of the studies (91,93) did find LDL cholesterol to be significantly higher for the milk protein isolate (91) and casein (93) groups (vs. the soy groups).

An ancillary report of a weight-loss study (101) found that there was no relationship between dairy calcium and glycemic control or CVD risk markers.

Summary of dairy research since 2002

None of the components of dairy appear to have an effect on glycemic control or CVD risk reduction.

Meats, poultry, and fish—In two crossover RCTs from the same research group (81,84), a usual diet with dark chicken meat replacing red meat was compared with a low-protein/vegetable diet. There were no significant differences among groups for FBG, LDL cholesterol, and HDL cholesterol. Total cholesterol was significantly lower after the chicken and the vegetable protein diet versus the red meat diet, and TGs were significantly lower after the chicken diet versus the red meat diet and the vegetable protein diet. In women with type 2 diabetes in the NHS (102), a high intake of red meat was significantly associated with fatal coronary heart disease, coronary revascularization, and total coronary heart disease. A case-control study (103) indicated that a high intake of fish protein was associated with a decreased risk of micro/macroalbuminuria in youth with type 1 diabetes.

Summary of meat research since 2002

Currently, there is limited evidence to provide conclusive statements relating to the intake of meat, poultry, and fish.

Overall summary of Question 2A

Research involving diabetes and food groups is sparse and does not indicate an advantage for specific foods in improving glycemic control. There is a possibility that certain CVD risk factors could be improved with the consumption of nuts or whey.

Question 2B: How do macronutrients combine in eating patterns to affect glycemic response and CVD risk factors in people with diabetes?

—Eating patterns include—but are not limited to—lower carbohydrate, lower fat, lower GI (see the respective sections in Question 1) as well as Mediterranean and vegetarian.

Mediterranean-style eating pattern

A Mediterranean-style eating pattern, based on the reviewed studies, generally includes more vegetables, whole grains, fruit, legumes, nuts, fish, and MUFA/PUFA; less red meat and SFAs; and some alcohol (wine) compared with a traditional diet.

Summary of reviewed studies

Five RCTs (52,104–107) compared a Mediterranean or modified Mediterranean-style eating pattern to other eating patterns over a period of 4 weeks to 4 years.

A 4-year study (104) compared a weight-reduction/maintenance Mediterranean-style eating pattern to a lower-fat eating pattern. Weight loss was similar, and there were no significant differences in glycemic control between groups. Adiponectin increased similarly with both eating patterns.

De Natale et al. (52) found that a moderately high–carbohydrate, high-fiber, and lower-GI Mediterranean-style eating pattern significantly improved postprandial glucose compared with a higher-MUFA Mediterranean-style eating pattern.

Three RCTs comparing Greek traditional or fast foods found no significant differences between groups for glycemic control and CVD risk factors (105–107).

A cross-sectional study (88) and a case-control study (108) examined the Mediterranean-style eating pattern to address how adherence was related to selected biomarkers. There were no significant differences between adherence tertiles for A1C (88,108), total cholesterol (88,108), or LDL cholesterol (88). HDL cholesterol was significantly higher and TG was significantly lower in the highest tertile of adherence to the Mediterranean-style eating pattern (88); the highest tertile of adherence also was associated with a 56% reduction in risk of peripheral arterial disease (108). The NHS (88)

found that adherence to the Mediterranean-style eating pattern was associated with higher plasma adiponectin concentrations in women with diabetes, and this was attributed mainly to the intake of alcohol, nuts, and whole grains.

An RCT (109) compared 4 oz. of red wine daily to no alcohol. Fasting insulin and HOMA decreased in both groups, with the wine group having a significantly greater decrease. Both groups significantly reduced total cholesterol and LDL cholesterol with no change in TG. HDL cholesterol was significantly increased in the wine group only, whereas markers of inflammation (TNF, CRP, and others) were significantly increased in the control group.

Summary of Mediterranean-style eating pattern research since 2002

There appears to be no advantage in using the Mediterranean-style eating pattern compared with other eating patterns for glycemic control. There are mixed results for CVD risk factors with some studies indicating that the Mediterranean-style eating pattern might improve HDL cholesterol and TG. Individual components of the Mediterranean-style eating pattern (wine, high MUFA/olive oil) do not appear to have independent effects on glycemic control, but may be responsible for improvement in HDL cholesterol.

Vegetarian eating pattern—One RCT (21,110) comparing a low-fat vegan eating pattern and a conventional eating pattern found that weight and A1C decreased in both groups, with no significant difference between groups in the primary analyses. In an ancillary analysis that removed participants who did not complete follow-up or who had medications changed during follow-up, there was a significantly greater decrease in A1C and LDL cholesterol in the vegan group. In a 4-week crossover RCT in individuals with early DKD, a lacto-vegetarian eating pattern did not show significant differences in FBG, HDL cholesterol, or LDL cholesterol; however, total cholesterol significantly decreased compared with the usual eating pattern, and GFR significantly decreased compared with both the usual and chicken diets (81,84).

Summary of vegetarian eating pattern research since 2002

Research is limited regarding vegetarian eating patterns. Because of methodological problems, more research is needed before conclusive remarks can be made about the associations between a vegetarian eating pattern and glycemic control and CVD risk factors.

Overall summary of Question 2B

Studies examining how eating patterns are related to glycemic control and CVD risk markers have varied with respect to macronutrient distribution used to characterize low-fat, Mediterranean, low-GI, vegetarian, and lower-carbohydrate eating patterns. While some research suggests that these eating patterns improve glycemic and cardiovascular outcomes, variability in research methods and definitions have complicated interpretation of findings. Issues that could affect conclusions include retention rates, dietary intervention and assessment methodology, and data analysis approaches.

Question 3: Is there an optimal macronutrient ratio for glycemic management and cardiovascular risk reduction in people with diabetes?

—Variability in study methodology, including measurement of dietary intake, retention rates, and confounding by weight loss, limits comparisons as to how macronutrient distribution independent of weight loss affects outcomes of interest. Although in many instances there were not statistically significant differences between dietary approaches, improvements were often seen from baseline to follow-up in both intervention groups supporting the idea that several different macronutrient distributions may lead to improvements in glycemic and/or CVD risk factors (Supplementary Table 1).

Question 4: What should guide the future directions of research?

—The evidence presented in this review suggests that many different approaches to MNT and eating patterns are effective for the target outcomes of improved glycemic control and reduced CVD risk among individuals with diabetes. However, several gaps in the literature remain that warrant mentioning here.

Most of the studies in the present review examined the relationship of macronutrients and foods to biochemical markers of glycemic control and CVD risk. While research has long explored the mechanisms underlying the relationship between nutrition and glycemia, studies have only just begun examining how nutrition relates to the endocrine functions of fat tissue and other cardiovascular parameters. For example, future studies should address:

- The role of adiponectin, which may be responsive to changes in eating patterns and has been associated with better diabetes-related health outcomes in epidemiological studies
- The relationship between fiber/whole-grain intake and improved insulin sensitivity and markers of inflammation (e.g., CRP and TNF)
- The role of omega-3 fatty acids in relation to adipose tissue inflammation, thrombosis, and lipid metabolism in the context of observations that higher intakes are associated with reduced CVD mortality, particularly sudden cardiac death
- The impact of very-low-carbohydrate and moderately low–carbohydrate eating patterns on long-term complications such as nephropathy
- The impact of postprandial excursions and hyperglycemia on inflammatory response and subsequent CVD risk

In addition to these biochemical mechanisms underlying nutrition-related CVD risk, the interplay between specific nutrients and dietary macronutrient composition has yet to be thoroughly evaluated. The use of technology such as continuous glucose monitors to evaluate the impact of macronutrients in isolation, in the presence of specific nutrients, in the context of a mixed meal, and in overall eating patterns must be elucidated in order to fully understand how diet impacts glycemic control.

Moving forward, it is essential to consider that individuals benefit differently from various nutritional approaches. Studies on gene-diet interactions and the impact of various macronutrient compositions across the continuum of dysglycemia/insulin resistance warrant additional investigation. Related to this tailored approach to MNT, it should be noted that individual adherence to nutrition recommendations is highly variable—and generally suboptimal. Research is needed to develop strategies that enhance adherence and to determine if certain nutritional approaches promote greater adherence than others.

Continued support is needed for large, multicenter trials with clinical event end points. Diabetes care involves monitoring risk factors for both macrovascular

and microvascular complications and therefore the sample size needed to detect multiple biologically and clinically relevant effect sizes requires special consideration. Furthermore, the duration of follow-up needs to be adequate relative to the outcomes of interest, and strategies should be used to improve retention. When dropout and/or missing data are extensive, special analytic strategies may be necessary to reduce the potential for selection bias. Study design and statistical analyses should consider time-varying factors, such as changes in weight and medications, which may independently impact study outcomes, especially in small-scale efficacy trials. Finally, due to the large volume and variety of research regarding diet and diabetes-related health outcomes, rigorous systematic reviews and meta-analyses need to be conducted so that researchers, clinicians, patients, and funding agencies are aware of the most recent research and the direction in which it is heading.

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