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Improving the Scientific Rigor of Nutritional Recommendations for Adults with Type 2 Diabetes:

A Comprehensive Review of the American Diabetes Association Guidelines Recommended Eating Patterns

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Abbreviations:

CPG, Clinical Practice Guidelines; **ADA**, American Diabetes Association; **2018 Standards**, Standards of Medical Care in Diabetes - 2018; **2014 Recommendations,** Nutrition Therapy Recommendations for the Management of Adults with Diabetes - 2014; **2019 Standards,** Standards of Medical Care in Diabetes - 2019; **DASH**, Dietary Approaches to Stop Hypertension; **RCT**, randomized controlled trial; **T2D**, type 2 diabetes; **T1D**, type 1 diabetes; **CVD,** cardiovascular disease; **BMI**, body mass index; **FBG**, fasting blood glucose; **LDL-C,** low-density lipoprotein cholesterol; **HDL-C**, high-density lipoprotein cholesterol; **GI,** Glycemic Index

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INTRODUCTION

Clinical Practice Guidelines (CPG) are not new, but they are growing in number. A modern definition of CPG was set forth in 1992 by the Institute of Medicine and updated in 2011: "Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[1] Rising along with the number of CPGs is concern about the process behind their creation. To ensure that guidelines affecting clinical care are created using the most rigorous and unbiased methods possible, multiple organizations have issued standards for evaluating scientific evidence when creating guidelines (Supplemental Appendix Table [ST 5]). Despite the availability of standards to improve the development of CGAs, there is still wide concern that even the most well-respected guidelines lack sufficient rigor.[2-6]

Over half of adult Americans now have diabetes or prediabetes,[7] and worse, this multifactorial epidemic is now worldwide and shows no signs of slowing, with rates of both diabetes and diabetes-related health complications rising.[8] When advising people with T2D on food choices, many health care providers rely on nutrition guidelines provided by the American Diabetes Association (ADA), and these guidelines influence standard recommendations made around the globe.[9-11] Given these alarming trends, it is paramount to review the treatment guidelines to ensure they are based on rigorous, accepted scientific methods.

The ADA's approach to the evidence in developing its guidelines has been to employ a grading system to rate the strength of evidence. An A rating is given to well-conducted randomized, controlled trials that are adequately powered, as well as to meta-analyses that incorporate quality ratings. B ratings are given to well-conducted cohort studies, C ratings are for poorly controlled trials or uncontrolled studies, and a score of E is for expert consensus or clinical experience. This approach does not follow any of the

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widely accepted standards or "guidelines for guidelines" such as Agree II, Grade, or those from the National Academy of Sciences Engineering and Medicine (ST 5).

Several concerns prompted our review of the evidence cited by the ADA in support of its recommendations for eating patterns in the management of T2D: 1) a strong reliance by the ADA on sources that they rate as B, C, and E;[12,13] 2) the failure to conduct a systematic review to inform source selection; 3) the exclusion of studies that could have been considered; 4) the lack of explanation of how the ADA selected and reviewed cited studies or how the experts weighed various endpoints in forming their opinion; 5) the possibility of bias.

Our review is of the sources cited for currently recommended eating patterns in the ADA's Standards of Medical Care in Diabetes (2018 and 2019 Standards),[12,14] and the ADA's Nutrition Therapy Recommendations for Adults with Diabetes (2014 Recommendations),[13] which helped inform the 2018 Standards. In addition, a comprehensive search was conducted to identify any studies that would have been appropriate to include in a rigorous review. Our review considers the strength of the evidence but does not assign a grade to each study.

After this review was initially conducted, the ADA published the 2019 Standards.[14] In this new document, low-carbohydrate diet has been endorsed as a recommended eating pattern (new in 2019), with specific acknowledgment of the evidence for antiglycemic medication reduction in persons with T2D who adhere to a low-carbohydrate diet. This updated review includes all new citations from the 2019 Standards. Concerns about the rigor of these guidelines remain.

MATERIALS AND METHODS

 doi:10.20944/preprints201812.0187.v2

Our review is of sources cited in the 2014 Recommendations and the 2018 Standards (Table 1), as well as studies newly cited in the 2019 Standards (Supplemental Appendix Tables [ST 1-4]).

First, we sought to determine if each ADA-cited study was appropriate for inclusion in the guidelines, using the following criteria: 1) it was a clinical trial, a systematic review, or a systematic review with meta-analysis of clinical trials; 2) it involved persons with T2D; 3) one of the study arms followed one of the three eating patterns recommended by the 2018 Standards or a low-carbohydrate diet; 4) its reported outcomes included glycemic control; 5) outcomes were reported separately for persons with T2D if there was a T2D subgroup within a larger trial. Adherence to these criteria helps ensure that each included study belongs in the evidence base supporting the "cornerstone" of diabetes management, which the ADA defines as metabolic control. Our exclusion of prospective studies in our criteria was based upon the judgment that such studies, while perhaps appropriate for T2D prevention guidelines, are not appropriate as a basis for treatment guidelines because they do not test a specific therapeutic intervention. In our review, we considered HbA1c to be the primary biomarker for glycemic control; fasting blood glucose (FBG) was considered if HbA1c data were not available. We also reported outcomes data on lipids and lipoproteins, blood pressure, and weight, as these biomarkers are relevant for assessing overall cardiovascular disease (CVD) risk status, a critical component of T2D management.

Second, we searched the literature for other articles that might be appropriate for consideration in the development of dietary guidelines for T2D, following the same criteria by which we appraised studies cited by the ADA. The searches were limited to human studies published in English from January 1, 2000, through May 31, 2018. We employed the following search terms: diabetes, DASH, Dietary Approaches to Stop Hypertension, Mediterranean, vegetarian, vegan, plant-based, low-carbohydrate, carbohydrate-restriction, carbohydrate-restricted, and ketogenic. We found other articles by reviewing

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references cited in relevant studies. A flow diagram for the search can be found in Supplemental Figure I.

Two co-authors independently conducted the searches and evaluated all studies for appropriateness. In cases of disagreement, the two co-authors and a third co-author discussed the findings and reached consensus. All studies deemed appropriate for inclusion are presented in ST 1–4.

Third, we evaluated the evidence from all of the assembled studies, those cited by the ADA (Table 1) as well as those we had identified (ST 1–4). We did not assign a grade to each study but rather, on a prima facie basis, assessed whether or not the cited study provided evidence of benefit.

RESULTS

Dietary Approaches to Stop Hypertension (DASH) Diet

Cited evidence. The 2014 Recommendations and 2018 Standards cite eight studies[15-22] (Table 1) to support claims that the DASH diet is a healthy eating pattern for glycemic control, blood pressure, and other CVD risk factors in persons with T2D. The cited studies include four randomized controlled trials (RCTs); however, the evidence for the DASH diet is limited: Only one[15] of the four RCTs[15, 16,18,19] cited by the ADA was on persons with T2D. This study reported significant improvements in weight, FBG, blood pressure, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and HbA1c, but the trial was short (eight weeks), had a 30% dropout rate,[15] and resulted in a 14.4% increase in triglycerides. Findings of two other ADA-cited RCTs are from the same trial, published in two different journals.[16,19] Neither study provides a sub-analysis on persons with T2D. The other four studies cited are an observational study,[20] a commentary,[22] a non-systematic review,[21] and the 2010 USDA Dietary Guidelines for Americans.[17]

 doi:10.20944/preprints201812.0187.v2

Additional evidence. We identified a post hoc analysis of the ENCORE study and an additional RCT,[23,24] both of which were published prior to the 2018 Standards (ST 1). The post hoc analysis by Blumenthal et al. compared a usual care diet, which allowed ad libitum energy intake, to the DASH diet alone and to a DASH diet with energy restriction and exercise.[23] The DASH diet + exercise did result in significantly greater improvements in FBG, body fat, total cholesterol (total C), LDL-C, and triglycerides compared to usual care, but the DASH diet alone did not have any of these significant outcomes compared to usual care. The study also reported a worsening in diabetes status during the study period in participants without diabetes or prediabetes in the DASH arm, more than with the control and DASH diet + exercise.[23] The RCT by Paula et al. compared the DASH diet + exercise to a diet based on ADA guidelines that did not include exercise. Significance of change from baseline and in a comparison of interventions was mixed; DASH + exercise resulted in a greater reduction in blood pressure but no difference in glycemic control when compared to usual care. However, the effect of the DASH diet without exercise was unknown.[24]

Summary of evidence. To our knowledge, clinical research on the DASH diet that provides outcomes for persons with T2D consists of two RCTs, of four and eight weeks duration, and a post hoc analysis.[15,23,24] Only one of the two trials showed glycemic improvement that can be attributed to the DASH diet alone. According to our evaluation, the rest of the cited sources provided limited to no support for the DASH diet for people with T2D, because of the concerns already cited: that these studies were not clinical trials or systematic reviews, or did not provide outcomes data for persons with T2D. While evidence shows that the DASH diet reduces blood pressure, primarily in non-diabetic patients, the lack of evidence for glycemic control does not support a recommendation for DASH as a healthy eating pattern for the management of diabetes. Additionally, as can be seen in the other eating pattern sections, a decrease in blood pressure (critical for CVD risk management) can be achieved with other eating patterns with more

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robust glycemic control data. In order to corroborate the current ADA recommendation for the DASH diet in management of T2D, more research is needed to closely evaluate the diet on those with T2D; particularly needed is research on glycemic control and CVD risk factors as study endpoints.

Mediterranean Diet

Cited evidence. The ADA documents cite six studies,[25-31] including three RCTs of longer duration,[25-28] to support claims that a Mediterranean diet can improve glycemic control and CVD risk factors and is therefore a healthy eating pattern for people with T2D (Table 1). Two RCTs found that the Mediterranean diet was superior to comparison diets:[25,28] one found that a low-carbohydrate Mediterranean diet resulted in a significantly greater HbA1c reduction compared to the control diet,[28] and the other found at four-year follow-up that the Mediterranean diet resulted in significant HbA1c reduction, sustained improvements in triglycerides and HDL-C, and less medication initiation in persons with newly diagnosed T2D.[25] A third RCT,[26] for which data were reanalyzed with essentially the same results in 2018,[27] reported a significant reduction of major cardiovascular events in both versions of the Mediterranean diet studied, compared with the control. Two systematic reviews[29,30] found limited evidence that the Mediterranean diet is effective for glycemic control, but more robust support for CVD risk reduction. Also cited was a commentary favoring the Mediterranean diet that was based on a non-systematic selection of articles.[31]

Additional evidence. We identified 12 other studies on the Mediterranean diet worthy of consideration: four RCTs, two RCT follow-up studies, and six systematic reviews with meta-analysis (ST 2).[32-43] One RCT found that this diet significantly improved HbA1c and BMI in postmenopausal women with T2D, but the diet was not superior to usual care for improving blood pressure and lipids.[32] A two-year RCT[36] comparing low-fat, low-carbohydrate, and Mediterranean diets in obese patients with T2D, with data available for 36 persons with T2D, found that the Mediterranean diet improved FBG, but not HbA1c,

 doi:10.20944/preprints201812.0187.v2

compared to a low-fat and low carbohydrate diet. Two studies[33,34] followed up Esposito 2009,[25] which was in the ADA-cited evidence (Table 1). Both studies found longer times to medication need in the Mediterranean diet arm compared to a low-fat diet, as well as increased partial remission and improved FBG and CVD risk markers. One of two smaller 12-week RCTs found a statistically significant HbA1c reduction favoring a Mediterranean diet over a typical diet; the other did not find a difference between the Mediterranean diet and a low-fat diet.[35,37] Neither of these trials resulted in between-group statistical significance for CVD risk factor markers including BMI, blood pressure, and lipids, but one found improvement in inflammation markers and flow-mediated dilation in the Mediterranean diet arm only.[35] Four systematic reviews with meta-analysis[38-41] and two with network meta-analysis[42,43] concluded that the Mediterranean diet is superior to other eating patterns for glycemic control, weight loss, lipid profile, and reduced need for diabetes medication.

Summary of evidence. The ADA-cited sources combined with additional ones identified through our search resulted in a total of seven RCTs, two follow-up RCT studies, and seven systematic reviews (including five with meta-analysis) that are appropriate for consideration in developing nutrition guidelines for T2D. Among the included trials are several large-scale studies, one with 3,614 participants[26,27] and one with more than 200 participants.[25,33,34] Longer-term studies include one lasting 12 months,[28] one lasting 24 months,[36] and two lasting longer than four years.[25,26,27,33,34]

As recommended by the ADA guidelines, we found that the Mediterranean eating pattern has demonstrated effectiveness in improving glycemic control[25,28,32-34,38-43] as well as CVD risk factors and even in reducing CVD events.[26,27, 29,30, 33,34, 22,23,38-43] This diet appears to be rightfully considered helpful for T2D management and appropriate for inclusion in the recommended eating patterns. On the other hand, questions remain about which components of the Mediterranean diet contribute to its effectiveness on all of these outcomes. Some studies suggest that it is the diet's more moderate carbohydrate content

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(less than 50% of total energy intake) that accounts for reductions in weight and cardiovascular risk,[44] while others suggest that the high monounsaturated fat content in the diet plays an important role in improving insulin sensitivity, glycemic control, and inflammation.[45,46] Research in these areas will strengthen future nutritional recommendations and provide more in-depth guidance on how the Mediterranean diet can be used for T2D management.

Plant-based Diet

Cited evidence. The ADA documents cite eight studies in support of this diet[47-54] (Table 1) for glycemic control and CVD risk reduction. Of three RCTs,[49,51,53] none found a significant improvement in HbA1c over the control diet, although in all three, the test diet resulted in reductions from baseline for HbA1c as well as diabetes medication use, a significant factor in the diet's overall effectiveness. In one RCT,[51] a low-fat vegan diet resulted in significantly greater FBG reduction than the control diet. Of note is the small study sample (11 total and four in the control arm), as well as the lower energy intake prescribed for the vegan diet. Additionally, the follow-up[54] to the 2006 RCT by Barnard[49] found a substantial decline in benefits occurring between 22 and 74 weeks, with no significant differences in HbA1c and FBG between the low-fat vegan and control diets. However, when the data were analyzed before medication changes, there was a significant between-group reduction in HbA1c observed in the vegan group.[54] In a review by Rinaldi et al.[47] favorable to plant-based diets, six trials did not consistently show improvements in glycemic control, weight loss, or CVD risk factors.[51-53,55,58,59] The ADA also cited a commentary based on a non-systematic review,[48] a cross-sectional study,[52] and an assessment of diets in Barnard 2006.[49] None of these studies is a controlled trial or systematic review.

Additional evidence. We identified nine studies[40,56-62] not included in the ADA review, three of which were published after the 2018 Standards (ST 3). Three RCTs found reductions in HbA1c from baseline;[56,58,59] two found the test diet superior compared to the control diet.[58,59] However, in all three

 doi:10.20944/preprints201812.0187.v2

studies, a slight increase in triglycerides was observed in the intervention arms, with one study reporting a statistically significant change.[59] This study also reported significant decreases in weight, as well as in total C, LDL-C, and HDL-C levels in the intervention arm.[59] A follow-up study[57] to the 2011 Kahleova trial[53] found that the significant improvements (from baseline) in HbA1c had regressed over time, even though the intervention arm maintained a significant weight loss and higher level of antiglycemic medication reduction at 24 months. A single-arm demonstration study[61] found a plant-based diet coupled with digital support was effective for glycemic control, according to patient-reported outcomes on HbA1c, while another non-randomized study found no significant change in glycemic control, compared to both baseline and the control diet.[59] In addition, we found three systematic reviews with meta-analysis. Yokoyama et al.[61] found that the evidence supports plant-based diets for glycemic control, but had left out the follow-up Kahleova study, while Ajala et al.[40] concluded that the evidence is only suggestive of benefit. Lastly, a systematic review with network meta-analysis[43] did not find plant-based diets to be superior to other eating patterns for T2D.

Summary of evidence. In sum, all six known controlled trials[9,51,53,56,58,59] and two follow-up studies[54,57] showed improvements from baseline in HbA1c and FBG with a plant-based diet; however, only two showed significant improvement compared to a control diet.[58,59] Longer-term data, from two follow-up studies at one year and 74 weeks, found no lasting significant benefit.[54,57] All controlled studies but one had fewer than 100 participants. Overall, as recommended by ADA guideline, a plant-based diet may be effective in improving glycemic control for some people with T2D, especially in those with a personal preference for such an eating pattern, at least in the short term. However, some of the studies that showed improvements in glycemic endpoints were restricted in energy intake;[51,53] therefore, it is not clear exactly what generated the beneficial outcomes—the composition of the diet or, rather, the weight loss resulting from energy restriction.[63-65] Further, the decrease in HDL-C[56,59,66,67] and higher

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triglyceride levels[66,67] seen in some studies need to be considered. Whether these changes in CVD risk markers are clinically meaningful or associated with poor CVD outcomes needs to be closely assessed; any worsening in atherogenic dyslipidemia, which has been found to indicate worsening insulin resistance status,[68] needs to be weighed against the improvements in other aspects of the lipid profile. This may allow for individualized recommendations based on values prior to diet initiation and to any changes in the lipid panel in response to a plant-based diet.

Low-Carbohydrate Diet

Cited evidence. The ADA documents cite 19 studies (Table 1) in their review of low-carbohydrate diets.[28,29,36,69-84] Of the 14 RCT trials cited, one[72] was inappropriately included, as noted in Table 1. Of the remaining 13 RCTs, five found a significant between-group advantage for the low-carbohydrate arm for glycemic control.[28,69,71,83,84] Of the eight that did not show a between-group glycemic advantage, all but one found a reduction from baseline, and three had greater reductions in medication use.[73,74,82] Of the seven trials with a duration of one year or more, three showed sustained clinically significant improvements in HbA1c at one year,[28,69,82] and two showed sustained meaningful benefit at two years.[36,78] Another one year study found decreased glucose variability in the low-carbohydrate arm. An isocaloric trial found the low-carbohydrate arm had a significant decrease in insulin and visceral fat accumulation compared to a high-carbohydrate arm.[70]

Of the 10 studies that reported on lipids, five found significant improvements in triglycerides with a low-carbohydrate diet;[74,78,82-84] none resulted in a worsening. Six[28,70,71,73,74,82] of 10 studies reporting HDL-C or total C:HDL-C ratio found that the low-carbohydrate diet resulted in significantly better outcomes than comparison diets; the others found non-significant differences between diets.[75,78,83,84] Seven of eight studies reporting LDL-C found non-significant differences between diets,[71,73,75,78,82-84] while one study found superior improvement with a low-carbohydrate diet.[28] Four systematic reviews

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with meta-analysis cited by the ADA concluded that there is evidence supporting the use of low-carbohydrate diets in patients with T2D,[29,77,79,80] although benefits were found in some cases to decline over time or with higher carbohydrate intake. A fifth non-systematic review, of meta-analyses, by van Wyk concluded that adherence may be the most significant barrier to efficacy with a low-carbohydrate approach to glycemic control.[80]

Additional evidence. We identified 27 additional studies: 10 RCTs (nine new, one follow-up), 12 non-randomized trials (eleven new, one follow-up), and five systematic reviews with meta-analysis. Of these 27 additional evidence sources, 20 were published in time for inclusion in the 2014 Recommendations, and 21 were published prior to the 2018 Standards (ST 4).[85-109] All 27 studies reported outcomes data for persons with T2D and thus were appropriate for consideration in the development of nutritional recommendations for T2D management. Of the 10 RCTs, all of which reported on glycemic control, nine found that a low-carbohydrate diet resulted in a significant change from baseline to end of study;[85,86,88,,89,91-93,95] six also found a superior between-group reduction favoring the low-carbohydrate diet.[85,86,89,91,93,95] While some studies found that the control diet also improved glycemic control significantly from baseline, none found the control diet superior to the low-carbohydrate diet. All 12 single-arm and non-randomized trials found that a low-carbohydrate diet significantly improved glycemic control from baseline to end of study; the two studies that made between-group comparisons found the low-carbohydrate diet superior to the control diet.[98,100] We identified eight longer-term studies (one to three years duration),[85,87,90,92,96-98,104] of which five[85,96,97,98,104] found significant glycemic benefit sustained with a low-carbohydrate diet; these include two two-year trials[96,104] and a three-year trial.[97] Another longer trial also found sustained improvement in glycemic control at 44 weeks.[102]

Of 11 studies that reported on diabetes medication use,[84,87-91,96-,98,102,103,105] eight reported more medication reductions and/or elimination of glycemic control medications in the low-carbohydrate arm.

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Five of six studies that conducted between-group comparisons of medication use found the low-carbohydrate diet to be superior,[85,87,88,90,98] and one study[91] found that both diets reduced usage significantly from baseline with no between-group difference. No study found the control diet to be superior.

Overall a favorable result was seen in triglycerides and HDL-C. No study found the control diet to be superior or that a low-carbohydrate diet significantly worsened triglycerides or HDL. The additional evidence is mixed regarding the low-carbohydrate diet's effects on LDL-C. Seven studies found no significant change from baseline,[86-88,90,92,94,95,105] whereas five other studies found that the diet resulted in significant improvement[100,104,106] or showed superiority to a control diet.[96,97] In another study, the diet improved LDL-C significantly in women but not in men.[101] Two studies found that the diet resulted in significant worsening from baseline.[98,99] However, the Hallberg study reported no change between the test and control diets for measured ApoB—likely more pertinent to CVD risk than the calculated LDL-C value, which is impacted proportionately by the significant rise in HDL-C and decrease in triglycerides that was also seen.[98]

Three of four additional systematic reviews,[40,107,109] including two published since 2017,[40,108] recommended a low-carbohydrate diet for T2D management, while one found no advantage with a low-carbohydrate diet.[108] A fifth systematic review, with network meta-analysis, concluded that a low-carbohydrate diet was superior for HbA1c reduction compared to other eating patterns, but that a Mediterranean diet was superior for reduction of FBG.[43]

Summary of evidence. The studies that we deemed appropriate for consideration in the development of nutritional guidelines in T2D treatment consisted of 18 from the ADA review (one was a follow-up study) and 27 from our search (two were follow-up studies). These 42 separate studies included 22 randomized trials; ten non-randomized trials; and 10 systematic reviews, eight of which included a

 doi:10.20944/preprints201812.0187.v2

meta-analysis. Ten of the trials had more than 100 participants,[28,73,74,76,78,89,90,96,98,100] and 16 provided longer-term data: 10 studies lasting one to two years,[28,69,73,76,84,91,93,98,102,104] five studies lasting two years,[36,78,87,90,96] and one study providing follow-up data at three years. Of six studies lasting two years or longer,[36,78,87,90,96,97] five sustained a clinically meaningful HbA1c reduction (of at least 0.7% from baseline). Three of the four two-year studies reporting on diabetes medication use found significant reductions with a low-carbohydrate diet compared to a control diet;[87,90,96] this includes the one study that did not sustain HbA1c reduction at two years.[87]

Evidence from 30 trials and 10 follow-up studies demonstrates that a low-carbohydrate diet is an effective dietary approach for addressing dyslipidemia. More than half of the studies that reported triglyceride levels found a significant improvement from baseline with a low-carbohydrate diet; eight also showed superiority over a control diet.[28,71,84,90,95,98,100,102] Similarly, the evidence consistently showed significant improvements in HDL-C with a low-carbohydrate diet with ten studies finding a significant increase over control diet.[28,70,71,73,87,88,90,98,100,102] It is also worth again noting that two[98,99] studies showed a significant increase in LDL-C in the low-carbohydrate arm; the rest of the studies found no change or a decrease of LDL-C. Adding a clause in future guidelines on monitoring LDL-C would further guide physicians in recommending this diet for their patients, as individual results may vary.

The authors of the ADA guideline documents, in their evaluation of a low-carbohydrate eating pattern, raise concerns about the quality of evidence that they do not apply to other dietary patterns. For example, regarding low-carbohydrate diets, the 2014 Recommendations state, “many of the studies were small, were of short duration, and/or had low retention rates.” However, these issues could apply to plant-based and DASH eating patterns as well. Another concern, raised in the 2018 Standards, is that there is “not a standard definition” of low-carbohydrate diets. While we agree that this is important, the

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issue—which essentially centers on the question of what an efficaciously low-carbohydrate intake level is—can be evaluated within the currently available literature. This approach was used in the meta-analysis by Snorgaard 2017, which showed that the lower the actual percentage of daily calories consumed as carbohydrate (as reported by research participants), the greater the glycemic control achieved.[79] One of the key limitations observed in most studies on low-carbohydrate diet is the discrepancy between the prescribed and actual carbohydrate intake. Most participants end up consuming more carbohydrate at the end of the intervention than was prescribed, affecting the outcome. This is a limitation that can be seen with any dietary intervention for which the prescribed diet and the diet actually consumed tend to be very different.

SUMMARY

Treatment guidelines must be based on rigorous scientific standards that are consistently applied in order to ensure that guidelines are both reliable and credible. In reviewing the evidence cited in support of the ADA recommendations on eating patterns for T2D management, we found multiple reasons for concern. Although the ADA does provide a rubric for grading studies to include in its evidence review, not apparent in the 2018 or 2019 Standards or the 2014 Recommendations is a description of the process used to guide final selection decisions. Perhaps that is the source of the issues we find concerning; for example, studies were cited as evidence that by the ADA's own rubric were not A-rated sources or that were not on persons with T2D, were not clinical trials, or were not based on a systematic review of the evidence.

Our literature searches added considerably to the body of credible evidence worthy of consideration for a thorough review of the ADA recommendations on eating patterns. We found two additional studies to include on the DASH diet, 12 studies on the Mediterranean diet, nine on plant-based diets, and 27 on

 doi:10.20944/preprints201812.0187.v2

low-carbohydrate diets. Almost all of these additional studies were published prior to the documents reviewed here.

We would like to note several things in the ADA documents that could be interpreted as evidence ofbias, one of which is the inclusion of opinion pieces or reviews favoring the DASH, plant-based, and Mediterranean eating patterns that were not based upon a systematic approach to the literature.[22,47,48] Further, there seemed to be inconsistency in the ADA's determination of what constitutes sufficiently ample and rigorous evidence for its recommendations. For example, regarding glycemic control, the ADA recommends the DASH diet on the basis of a single trial in T2D. For plant-based diets, the ADA recommends on the basis of three trials and one follow-up study, none of which showed superiority of the test diet over the control diet in HbA1c reduction,[49,51,53,54] and despite its conclusion that vegetarian and low-fat vegan studies "did not consistently improve glycemic control or CVD risk factors except when energy intake was restricted, and weight was lost." In contrast, the 2014 Recommendations and both the 2018 and 2019 Standards raise concerns about lack of sustainability with a low-carbohydrate diet over the long term. While adherence is a common behavior change problem, it is not unique to low-carbohydrate diets, and the long-term data on this approach are supportive.

Our review is based only on studies in which glycemic control in persons with T2D is an endpoint, because of its central importance to T2D management. Our aim has been to produce a review and presentation (ST 1,2) of a more complete body of evidence that is objective, fair, and easily accessible to most readers and may prove useful in the creation of future iterations of the ADA guidelines.

Another section of the ADA guidelines on HbA1c target guidance was recently reviewed and assessed by the American College of Physicians when they issued new HbA1c target guidance. Using the Agree II instrument for evaluation, the American College gave a score of 3.7 out of 7 for the ADA guidelines, the second-lowest of six guidelines scored. Additionally, the ADA guidelines scored significantly lower

 doi:10.20944/preprints201812.0187.v2

than all others in "rigor of development." Supplemental Table 6 provides our assessment of the ADA guidelines using the National Academies of Sciences, Engineering, and Medicine's *Clinical Practice Guidelines We Can Trust* evaluation method, along with recommended steps for improving the overall process. Additionally, another review evaluated the evidence for CVD prevention in the 2016 edition of the Standards of Care.[4] The prior two and current reviews of separate sections of the ADA guidelines all raise the same underlying concern regarding the rigor of the guideline development process. Given this, we believe our review is a critically important document that reinforces the need for a process change.

CONCLUSION

In order to change the current global trajectory of diabetes, it is imperative that health organizations be willing to invest resources in creating objective guidelines based on rigorous and unbiased scientific review. Guidance from the ADA is valuable on many fronts. However, our review of the current Standards and Recommendations finds significant shortcomings regarding scientific review methodologies, which are likely to translate to suboptimal clinical care decisions for patients with T2D.

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SJH is an employee and shareholder of Virta Health, a for-profit company that provides remote diabetes care using a low-carbohydrate nutrition intervention, and serves as an advisor for Atkins Corp.

NED is a paid consultant for Virta Health.

JAK serves as medical director of McNair Interests, a private equity group with investments in type 1 diabetes and other chronic illnesses, and is also an advisor for Sanofi and Lexicon.

SJA is an employee and shareholder of Virta Health.

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Table 1
Description of Eating Patterns
as described in 2014 Recommendations

DASH Diet
Emphasizes fruits, vegetables, and low-fat dairy products, including whole grains, poultry, fish, and nuts and is reduced in saturated fat, red meat, sweets, and sugar-containing beverages. The most effective DASH diet was also reduced in sodium.

Mediterranean Diet
Mediterranean style includes abundant plant food (fruits, vegetables, breads, other forms of cereals, beans, nuts and seeds); minimally processed, seasonally fresh, and locally grown foods; fresh fruits as the typical daily dessert and concentrated sugars or honey consumed only for special occasions; olive oil as the principal source of dietary lipids; dairy products (mainly cheese and yogurt) consumed in low to moderate amounts; fewer than 4 eggs/week; red meat consumed in low frequency and amounts; and wine consumption in low to moderate amounts generally with meals.

Plant-based Diet
The two most common ways of defining vegetarian diets in the research are vegan diets (diets devoid of all flesh foods and animal-derived products) and vegetarian diets (diets devoid of all flesh foods but including egg [ovo] and/or dairy [lacto] products). Features of a vegetarian-eating pattern that may reduce risk of chronic disease include lower intakes of saturated fat and cholesterol and higher intakes of fruits, vegetables, whole grains, nuts, soy products, fiber, and phytochemicals.
**More recently have been referred to as plant-based diets but defined as vegetarian and vegan in the 2014 Recommendations

Low-Carbohydrate
Focuses on eating foods higher in protein (meat, poultry, fish, shellfish, eggs, cheese, nuts and seeds), fats (oils, butter, olives, avocado), and vegetables low in carbohydrate (salad greens, cucumbers, broccoli, summer squash). The amount of carbohydrate allowed varies with most plans allowing fruit (e.g., berries) and higher carbohydrate vegetables; however, sugar-containing foods and grain products such as pasta, rice, and bread are generally avoided. There is no consistent definition of “low” carbohydrate. In research studies, definitions have ranged from very low-carbohydrate diet (21–70 g/day of carbohydrates) to moderately low-carbohydrate diet (30 to 40% of calories from carbohydrates).
**More widely understood that this diet is not high in protein.

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Table 2 Summary of evaluation of studies on different eating patterns cited in the ADA 2018 guidelines and 2014 Nutrition Recommendations

Study #	ADA Statement/ Recommendation	Citation	Study Type	Description	Subjects	Duration	Findings for Test Diet	Comments
DASH DIET								
1	"A variety of eating patterns (combinations of different foods or food groups) are acceptable for the management of diabetes. ...In one small study in people with type 2 diabetes, the DASH eating plan ... improved A1c, blood pressure, and other cardiovascular risk factors." (46, ADA 2014)	Azadbakht L, 2011 [ref 46, ADA 2014][15]	Randomized crossover	Compared DASH diet to control diet. Calorie and macronutrient distribution same in both.	n=44 persons with T2D 31 (70%) completed study	8 weeks each diet	♦ **HbA1c** AR ↓1.7% (↓22.1%) BG SS ♦ **FBG** AR ↓29.4mg/dL (↓18.3%) BG SS ♦ **Weight** AR ↓5.0kg (↓6.8%) BG SS ♦ **HDL** AI ↑4.3mg/dl (↑10.4%) BG SS ♦ **SBP** AR ↓13.6mmHg (↓10.1%); **DBP** AR ↓9.5mmHg (↓11.6%) BG SS ♦ **TRG** AI ↑14.4mg/dl (↑8.4%) BG SS unknown	**Should be included in a review of the evidence.** Supports the ADA Statement. *Error in reporting and analysis of triglycerides
2	"The blood pressure benefits are thought to be due to the total eating pattern, including the reduction in sodium and other foods and nutrients that have been shown to influence blood pressure." (99, 105, ADA 2014)	Harsha DW, 1999 [ref 99, ADA 2014][16]	RCT	Multi-center DASH trial. Compared control diet (typical fat content for Americans); diet rich in fruit and vegetables; DASH (fruit, vegetables, low fat).	n=459 persons with SBP <160mmHg, DBP80-95mmHg 354 (77%) completed study	8 weeks	No data on persons with diabetes **Differences between DASH and control:** ♦ **SBP** ↓ 5.5mmHg BG SS ♦ **DBP** ↓3.0mmHg BG SS	**Should not be included in review of evidence.** This study excluded subjects with T2D.

3		US HHS, USDA Dietary Guidelines for Americans, 2010 [ref 105, ADA 2014][17]	Health policy report	Diet recommendations for the general population; includes sodium limit for blood pressure control.				**Should not be included in a review of the evidence.** DGAs are not intended for persons with diabetes.
4	"In people without diabetes, the DASH eating plan has been shown to help control blood pressure and lower risk for CVD and is frequently recommended as a healthful eating pattern for the general population (104–106, ADA, 2014). ... Limited evidence exists on the effects of the DASH eating plan on health outcomes specifically in individuals with diabetes; however, one would expect similar results to other studies using the DASH eating plan." (46, ADA 2014)	Sacks FM, 2001 [ref 104, ADA 2014][18]	RCT	Compared DASH and control diets (typical US diet). Within each group, participants ate foods with high, mid, and low sodium for 30 days each, in random order.	n=412 persons with SBP 120-159mmHg DBP 80-95mmHg 390 (95%) completed study	8 weeks	**Differences between DASH and control for 3 Na levels:** ♦ High Na-intake group: **SBP** ↓5.9mmHg; **DBP** AR↓ 2.9 BG SS ♦ Mid Na-intake group: **SBP** ↓5.0mmHg; **DBP** ↓ 2.5mmHg BG SS ♦ Low Na-intake group: **SBP** ↓2.2mmHg; **DBP** ↓1.0mmHg BG SS	**Should not be included in a review of the evidence.** Study does not include separate analysis of subjects with T2D.
5		Appel L, 1997 [ref 106, ADA 2014][19]	RCT	Compared effects of 3 dietary patterns [control, typical diet; diet rich in fruits and vegetables; in DASH (fruit + veg, low-fat)]. Sodium levels same for all diets.	n=459 persons with SBP <160mmHg; DBP 80-95mmHg ~97% across groups completed study	8 weeks	No data on persons with diabetes **Differences between DASH and control:** ♦ **SBP** ↓5.5mmHg BG SS	**Should not be included in review of evidence.** Study does not include analysis of subjects with T2D.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

							♦ **DBP** ↓3.0mmHg BG SS	
6	The DASH diet is an example "of healthful eating patterns that have shown positive results in research." (56-58, ADA 2018)	Cespedes EM, 2016 [ref 56, ADA 2018][20]	Observational data analysis from an RCT (Women's Health Initiative)	Investigated incidence of T2D in adherents of 4 dietary patterns including DASH.	n=101,504 postmenopausal women without T2D		♦ Lowest incidence of T2D associated with adherence to DASH.	**Should not be included in review of evidence.** This may belong in the prevention section but not appropriate in the management section.
7		Ley SH, 2014 [ref 57, ADA 2018][21]	Non-systematic review	Cites 2 prospective studies on DASH on food intake and T2D incidence for diabetes prevention and Azadbakht, 2011 trial on diabetes management.			♦ DASH associated with lower T2D risk.	**Should not be included in review of evidence.** It is not a systematic review.
8		Campbell AP, 2017 [ref 58, ADA 2018][22]	Commentary	Presents basics of DASH diet. Cites one RCT on DASH in persons with T2D.				**Should not be included in a review of the evidence.** This was a commentary not based on a systematic review. Cites only one study on DASH in persons with T2D.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

MEDITERRANEAN DIET								
1	The Mediterranean-style eating pattern … has been observed to improve cardiovascular risk factors (i.e., lipids, blood pressure, triglycerides) in individuals with diabetes… (11, 72, 88, 100, ADA 2014) Individuals following an energy-restricted Mediterranean-style eating pattern also achieve improvements in glycemic control." (88, ADA 2014).	Esposito, 2009 [ref 72, ADA 2014; ref 54, ADA 2018][25]	RCT	Tests diet for efficacy in delay of medication initiation in patients newly diagnosed with T2D. Med "low carb" diet (<50%E CHO) vs. control diet (<30%E fat). Both diets were E-restricted.	n = 215 overweight persons newly diagnosed with T2D 195 (91%) completed study	4 years	♦ **HbA1c** Y4: AR ↓0.9 (↓11.6%) **BG SS** ♦ **Weight** Superior to control, **BG SS** at Yr 1 but nSS at Yr 4 ♦ **TRG** Y4: AR ↓0.28mmol/L (↓14.7%) **BG SS** ♦ **HDL** Y4**:** AI ↑0.09mmol/L (↑8.2%) **BG SS** ♦ **% requiring meds at Y4:** Med diet: 44% Control: 70% BG SS	**Should be included in a review of the evidence.** Supports the ADA Statement with limitations: Some benefits not sustained. 44% required medication by end of study.
2	"The Mediterranean-style eating pattern … has been observed to lower combined end points for CVD events and stroke when supplemented with mixed nuts ... or olive oil." (83, ADA 2014).	Estruch, 2013 [ref 83 ADA 2014] [26] replaced by Estruch 2018 after re-analyses[27]	RCT PREDIMED study	CV events was main outcome of interest. Compared 2 versions of Med diet to low-fat control diet. Not E-restricted.	n=3,614 persons with T2D	4.8 years	♦ The two Med diets reduced the incidence of major CVD events (composite of myocardial infarction, stroke and death from cardiovascular causes). ♦ **Overall study population** Med diet with olive oil: HR=0.69 Med diet with nuts: HR=0.74	**Should be included in a review of the evidence**. Supports the ADA Statement in regard to CVD risk.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

3		Elhayany, 2010 [ref 100, ADA 2014][28]	RCT	Compared low-carbohydrate Med diet, traditional Med diet, and 2003 ADA diet. Limited to 20 calories/kg body weight in all study groups. Main outcomes: HbA1c, FBG, TRG..	n=259 persons with T2D 194 (75%) completed study	12 months	♦ **HbA1c** Low-carb Med AR ↓2.0% (↓24.1%) BG SS (vs. ADA diet); Trad Med AR ↓1.8% (↓21.7%) BG SS (vs ADA diet) ♦ **Weight loss** Low-carb Med AR↓8.9kg (↓10.3%) BG nSS Trad Med AR ↓7.4kg (↓8.7%) BG nSS but WG SS ♦ **HDL** Low-carb Med AI↑ 0.13mmol/L (↑12.0%) BG SS (vs ADA and Trad Med diets) ♦ **TRG** Low-carb Med AR ↓1.52mmol/L (↓47.8%) BG SS (vs ADA diet); Trad Med AR↓1.46mmol/L (↓48.0%) BG SS (vs ADA diet) ♦ **LDL** Low-carb Med AR ↓.61mmol/L (↓20.0%) BG SS (vs ADA diet); Trad Med AR↓ .55mmol/L (↓17.3%) BG nSS	**Should be included in a review of the evidence**. Supports the ADA Statement.
4		Wheeler, 2013 [ref 88, ADA 2014][29]	Systematic review	2001-2010 review on diet and diabetes; cites 7 studies on Med diet.		4 weeks to 4 years	"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	**Should be included in a review of the evidence.** Does not strongly support the ADA Statement.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

							eating pattern might improve HDL cholesterol and TG."	
5		Franz, 2010 [ref 11, ADA 2014][30]	Systematic review	Reviews the evidence for the ADA's nutrition practice guidelines. In section on treatment for CVD, cited are studies on Med diet that include 2 RCTS; 2 cross-sectional and 1 case-control study.	Persons with diabetes or other CVD risk factors		Notes that the Med diet has shown benefit for endothelial health, blood pressure and lipid levels, but concludes that "a clearer understanding is needed" of the diet's "protective mechanisms and role in diabetes management."	**Should be included in a review of the evidence.** Does not strongly support the ADA Statement.
6	"A variety of eating patterns are acceptable for persons with diabetes." The Mediterranean diet is an example. (54 Esposito, above; 55, ADA 2018)	Boucher, 2018 [ref 55, ADA 2018][31]	Commentary based on non-systematic review	Discussions of select studies on the Med diet in diabetes.				**Should not be included in a review of the evidence.** This was a commentary that was not based on a systematic review.
PLANT-BASED DIET								
1	"A variety of eating patterns are acceptable for the management of diabetes." Plant-based diets are an example of a healthy eating pattern. (59, 60, ADA 2018)	Rinaldi S, 2015 [ref 59, ADA 2018][47]	A non-systematic review	Lit search thru March 2015. Reviewed 13 studies (5 RCTs, 4 observational, 3 FU or ancillary to cited RCTs, 1 meta-analysis) on glycemic control,			Results mixed on efficacy of PBD for glycemic control, weight loss, CVD risk improvement	**Should not be included in a review of the evidence.** Not a systematic review.

				CVD risk, other health measures.				Limitations: Of 5 RCTs, 2 had n < 20, short duration (4, 12 weeks).
2		Pawlak R, 2017 [ref 60, ADA 2018][48]	Commentary based on non-systematic review	Reviews observational studies on diabetes.				**Should not be included in a review of the evidence.** This was a commentary not based on a systematic review.
3	Six plant-based diets reviewed found inconsistent results for glycemic control and weight loss. "Diets often did result in weight loss." (36, 93, 101-103,131, ADA 2014).	Barnard N, 2006 [ref 36, ADA 2014][49]	RCT	Compared low-fat vegan diet to ADA diet for glycemic control and CVD risk. Only the control diet was E-restricted.	n=99 persons with T2D 88 (88%) completed study	22 weeks	**For vegan diet:** ♦ **HbA1c** AR ↓0.96% (↓12.0%) WG SS; BG nSS ♦ **FBG** AR ↓35.5mg/dL (↓21.7%) WG SS, BG nSS ♦ **Weight** AR ↓5.8kg (↓6.0%) WG SS, BG nSS ♦ **Diabetic meds** ↓43% **BG SS** ♦ **HDL↑ LDL↓ VLDL↓ TRG↓** All WG SS. All BG nSS	**Should be included in a review of the evidence.** Supports the ADA Statement.
4		Turner-	Nutritional assessment of diets tested in	Ancillary study to 22-wk. trial (Barnard, 2006).			The vegan diet group increased intakes of carb, fiber, some micronutrients and	**Should not be included in a**

		McGrievy, 2008 [ref 93, ADA 2014][50]	Barnard, 2006 trial	Assessed changes from baseline of nutrient intake and diet quality of participants in vegan diet group vs. ADA diet, using AHEI metric based on the US DGA			improved its AHEI score; the ADA diet group AHEI score stayed same.	**review of the evidence.** This study is not germane to glycemic control or weight loss (see ADA Statement)**.**
5		Nicholson A, 1999 [ref 101, ADA, 2014][51]	RCT	Compared non-isocaloric low-fat vegan and low-fat diets on glycemic control and CVD risk factors. LFV prepared meals lower in E than those for LF meals.	n=13 with T2D 11 (85%) completed study	12 weeks	**For the vegan diet:** ♦ **HbA1c** AR↓1.4% (↓16.9%) BG nSS ♦ **FBG** AR↓ 54.0mg/dL (↓27.8%) BG SS ♦ **Weight** AR↓ 7.2kg **(**7.4%) BG SS ♦ **Lipids** all nSS**.**	**Should be included in a review of the evidence.** Supports the ADA Statement. Note: 11 completed study (control group n=4).
6		Tonstad S, 2009 [ref 102, ADA 2009] [52]	Cross sectional	Assessed prevalence of T2D in the Adventist Health Study cohort for different types of vegetarian diets	1,007 in sub-group analysis of health measures		♦ **T2D prevalence** Vegans 2.9% Nonvegetarians 7.6% ♦ **Diabetes risk (OR)**	**Should not be included in a review of the evidence** Observational studies cannot provide evidence

				and in nonvegetarians.			Vegans .51 (vs nonvegetarians, 1.0) ♦ **BMI** Vegans 23.6 (lowest of all diet types) Nonvegetarians 28.8	for treatment efficacy. This study is not germane to glycemic control or weight loss (see ADA Statement)**.**
7		Kahleova H, 2011 [ref 103, ADA 2014][53]	RCT	Compared E-restricted vegetarian and conventional diabetic diets on body fat, IS, oxidative stress. No exercise for first 12 weeks and then exercise added in second 12 weeks.	n=74 persons with T2D 62 (84%) completed study	24 weeks	**For vegetarian diet:** ♦ **HbA1c** AR ↓0.65% (↓8.6%) WG SS BG nSS ♦ **Weight** AR ↓6.2kg (↓6.1%) BG SS ♦ **Medication** ↓43% BG SS ♦ **LDL** AR ↓0.17mmol/L (↓6.7%) WG SS, BG nSS ♦ **Oxidative stress markers** improved SS more with vegetarian diet. ♦ **HDL, TRG** BG nSS	**Should be included in a review of the evidence.** Supports the ADA Statement.
8		Barnard N, 2009 [ref 131, ADA, 2013][54]	Follow-up to RCT Barnard 2006	Compared low-fat vegan and ADA diets for glycemic control and CVD risk. 74-week FU to 22-week RCT (Barnard, 2006)	n=99 with T2D 87 (88%) completed study	74 weeks	**For vegan diet:** ♦ **HbA1c** AR ↓0.34% (↓4.2%) WG, BG nSS **Weight** AR ↓4.4kg (↓4.5%) WG SS, BG nSS	**Should be included in a review of the evidence.** Support for the ADA Statement is

 doi:10.20944/preprints201812.0187.v2

							LDL↓ VLDL↓ TRG↓ All WG SS in low-fat vegan, BG nSS ♦ **HbA1c before medication adjustment AR** ↓0.40% (before any medication changes) WG, BG SS	limited.
LOW-CARBOHYDRATE STUDIES								
1	1. "Some published studies comparing lower levels of carbohydrate intake (ranging from 21 g daily up to 40% daily energy intake) to higher carbohydrate intake levels indicated improved markers of glycemic control and insulin sensitivity with lower carbohydrate intakes." (92, 100, 107-111, ADA 2014) 2. "Many of these studies were small, were of short duration, and/or had low retention rates." (92,107, 109,110,112,113, ADA 2014) 3. "Some studies comparing lower levels of carbohydrate intake to higher carbohydrate intake levels revealed improvements in serum lipid/lipoprotein	Stern L, 2004 [ref 92, ADA 2014] 69	Follow-up to RCT Samaha 2003	1-yr FU to 6-mo RCT in which patients followed either low-carbohydrate diet or E-restricted low-fat diet.	n=54 obese persons with T2D(subgroup of larger study cohort). 34 (63%) of T2D sub-group completed study	1 year	**For low carbohydrate diet:** ♦ **HBA1c** AR ↓0.7% (↓10.8%) BG SS after adjustment and remained SS after weight loss was added to model ♦ **FBG** AR↓1.55mmol/L (↓16.8%) BG nSS ♦ **Insulin sensitivity** BG nSS ♦ Lipid levels and weight change not reported for T2D subgroup.	**Should be included in a review of the evidence.** Supports ADA Statement 1, but not Statement 3 (data not available for T2D). Partial support for ADA Statement 2. Note 1 year duration.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

	measures, including improved triglycerides, VLDL triglyceride, and VLDL cholesterol, total cholesterol, and HDL cholesterol levels (71,92,100,107,109,111, 112, 115)." 4. "Four RCTs indicated no significant difference in glycemic markers with a lower-carbohydrate diet compared with higher carbohydrate intake levels." (71, 112-114, ADA 2014)." 5. "A few studies found no significant difference in lipids and lipoproteins with a lower-carbohydrate diet compared with higher carbohydrate intake levels. It should be noted that these studies had low retention rates, which may lead to loss of statistical power and biased results (110,113,116, ADA)."							
2		Elhayany A, 2010 [ref 100	RCT	Compared low-carbohydrate Med	n=259 overweight or	1 year	♦ **HbA1c** Low-carb Med AR ↓2.0% (↓24.1%) BG SS (vs	**Should be included in a**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

		in ADA 2014][28]		diet, traditional Med diet, and 2003 ADA diet. All diets were E-restricted.All diets restricted calories to 20/kg. of body weight.	obese persons with T2D 194 (75%) completed study		ADA diet) ♦ **Weight loss** Low-carb Med AR↓10.1kg (↓10.3%) WG SS, BG nSS ♦ **HDL** Low-carb Med AI↑ 0.13mmol/L (↑12.0%) BG SS with (vs ADA and Trad Med diets) ♦ **TRG** Low-carb Med AR ↓1.52mmol/L (↓47.8%) BG SS with (vs ADA diet) ♦ **LDL** Low-carb Med AR ↓.61mmol/L (↓20.0%) BG SS (vs ADA diet)	**review of the evidence.** Supports ADA Statements 1 and 3.
3		Miyashita Y, 2004 [ref 107, ADA 2014][70]	RCT	Compared effects, of isocaloric low-carbohydrate diet vs. high-carbohydrate diet, on glucose and lipid metabolism, and visceral fat accumulation.	n=22 obese adults with T2D n completed unknown	4 weeks	**For low carbohydrate diet:** ♦ **Fasting insulin (**↓30%) BG SS ♦ **FBG** AR ↓103mg/dL (↓50.0%) BG nSS ♦ **HDL** ↑15% BG SS ♦ **TRG** BG nSS ♦ **FBG** AR ↓98mg/dL ↓50.0% BG nSS ♦ **Weight loss** AR ↓9kg ↓12.3% BG nSS	**Should be included in a review of the evidence**. Supports ADA Statements 1, 2, and 3. Limitations: carb intake unknown; n completed unknown.

							♦ **Visceral fat accumulation** BG SS favored low carb -40 cm(2) versus -10 cm(2)	
4		Shai I, 2008 [ref 108, ADA 2014][36]	RCT	Compared safety and effectiveness of 3 diets (low-fat, restricted-E; Mediterranean, restricted-E; low-carbohydrate, not restricted-E) in obese persons, some with T2D.	322 obese adults, n with T2D=46 (14%) for 36 included in analysis (low-carb n=12, Med n=13, low-fat n=11).	2 years	♦ **HbA1c**: Low-fat decrease 0.4 Mediterranean decrease 0.5% Low-carb AR↓ 0.9% WG SS only for low-carb, BG nSS ♦ **FBG, HOMA-IR, fasting insulin** nSS for low-carb	**Should be included in a review of the evidence.** Supports ADA Statement 1.
5		Jonsson T, 2009 [ref 109, ADA 2014][71]	RCT crossover	Compared Paleolithic diet vs. ADA diabetes diet for improving CVD risk.	**n=17** adults with T2D; 13 (76%) completed study	3 months on each diet	**Differences between Paleo and ADA:** ♦ **HbA1c** ↓0.4% BG SS ♦ **TRG** ↓0.4mmol/L BG SS ♦ **LDL** BG nSS ♦ **DBP** ↓4mmHg BG SS ♦ **HDL** ↑0.08mmol/L BG SS	**Should be included in a review of the evidence.** Supports ADA Statement 1, 2, and 3.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

							♦ **Weight** ↓3kg BG SS	
6		Khoo J, 2011 [ref 110, ADA 2014][72]	RCT	Compared effects of two diets (low-calorie vs. low-calorie/high protein/low-fat) on weight loss, sexual and endothelial function, lower urinary track symptoms, and inflammatory markers in obese men.	31 obese men with T2D n completed unknown	8 weeks	**See Comments**	**Should not be included in a review of the evidence.** Not relevant: Compares two restricted-E diets. No evidence that the test diet was low-carb (i.e., no data provided on protocol diet carb content or reported dietary intake)
7		Davis NJ, 2009 [ref 71, ADA 2014][73]	RCT	Compared the effects on weight loss and glycemic control of a low-carbohydrate diet vs. low-fat diet in adults with T2D.	n=105 overweight adults with T2D 91 (87%) completed study	1 year	**For low carbohydrate diet:** ♦ **HbA1C** At 3 mos. AR ↓0.64% (↓8.5%); at 1 year returned to baseline. BG nSS ♦ **HDL** AI ↑0.16mmol/L (↑12.3%) BG SS ♦ **TRG, LDL** BG nSS ♦ **Weight** Both groups lost: AR ↓3.1kg (↓3.4%) at 1 yr.	**Should be included in a review of the evidence.** Does not support ADA Statement 3. Does Support Statement 4.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

							♦ **SBP, DBP, LDL, HDL, TRG:** no SS results. ♦ **Insulin use:** reduced in low-carb arm and increased in control	
8		Daly ME, 2006 [ref 112, ADA 2014][74]	RCT	Compared low-carbohydrate diet vs. reduced-portion, low-fat diet.	**n =**102 obese adults with poorly controlled T2D 79 (78%) completed study.	3 months	**For low carbohydrate diet:** ♦ **HbA1c AR** ↓0.55% (↓6.1%) BG nSS ♦ **Weight** AR ↓3.55kg (↓3.5%) BG SS ♦ **Total C:HDL ratio** AR ↓0.48 (↓11.9%) BG SS ♦ **TRG** AR ↓0.67mmol/L (↓27.0%) BG nSS ♦ **Diabetes medication use:** reduced more in low-carb arm vs control: (insulin use ↓85% vs 22%)	**Should be included in a review of the evidence.** Partial support for ADA Statements 2, 3, and 4. Note medication use.
9		Dyson PA, 2007 [ref 113, ADA 2014][75]	RCT	Assessed the impacts on body weight, HbA1c, ketone and lipid levels in diabetic and non-diabetic subjects, comparing low-	n=13 overweight or obese adults with T2D and 13 adults without T2D	3 months	**For low carbohydrate diet:** ♦ **HbA1c** AR ↓0.4% ↓**5.5%** BG nSS ♦ **Weight** AR ↓8.0kg	**Should be included in a review of the evidence.**

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

				carb diet vs. an E-restricted diet based on UK diabetes diet.	12 (92%) with T2D completed study.		BG SS ♦ **HDL, total C, LDL, TRG** BG nSS	Supports ADA Statements 2, 4, and 5.
10		Wolever TM 2008 [ref 114, ADA 2014][76]	RCT	Aim was to compare the effects of altering the GI or the amt of carb on HbA1c, FBG, and other biomarkers. Compared 3 diets: high-carb/high GI; high-carb/low GI Lower-carb/high monounsat-fat (39%carb)	162 adults with T2D 130 (80%) completed	1 year	**HbA1c** At 1 year, was identical for the 3 diet groups.	**Should be included in a review of the evidence.** Supports ADA Statement 4.
11		Kirk JK, 2008 [ref 115, ADA 2014][77]	Systematic review/ meta-analysis	Reviewed 13 studies on carbohydrate-restricted diets for adults with T2D (RCT, crossover; RCT parallel; non-randomized two-arm; single-arm pre-post).	Adults with T2D. Study n range: 8-52.	1 week to 26 weeks	**HbA1c** 1 study ↑2.7%; 1 study 0% change; 9 studies ↓3.7%-22.4%. Of 6 studies with data for both low-carb and high-carb, low-carb performed better in 4.	**Should be included in a review of the evidence.** Some support for ADA Statement 3.
12		Iqbal N, 2010 [ref 116, ADA 2014][78]	RCT	Compared effects of low-carbohydrate diet (30gr) vs. low-fat, calorie-restricted diet with low-intensity intervention	n=144 OB adults with T2D 68 (47%) completed study	2 years	**HbA1c** ♦ At 6 mos AR ↓0.5% (↓6.3%) BG SS At 2 years AR ↓0.1% (↓2.6%) BG nSS ♦ **FBG** At 2 years AR ↓1.8mg/dL (↓1.3%)	**Should be included in a review of the evidence.** Supports ADA Statement 5.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

							BG nSS ♦ **Weight** At 2 years AR ↓1.5kg ↓1.3% BG nSS ♦ **TRG** AR ↓26 mg/dl (16.8%) BG nSS All other lipids nSS	
13	"The role of low-carbohydrate diets in patients with diabetes remains unclear (72, ADA 2018)."	Wheeler ML, 2012 [ref 72, ADA 2018][29]	Systematic review	2001-2010 review on diet and diabetes; included 11 studies on low-carbohydrate diets.	n range=10-55 per study group	2 weeks to 1 year	♦ **HbA1c** decreased with a low-carb diet in 6 of 10 studies. ♦ **FBG, 24-hour insulin, fasting insulin and insulin sensitivity** improved "significantly on the lower-carbohydrate diet." ♦ **Need for diabetes medication** lower with lower-carb diets. ♦ **Lipids** Some studies showed lower-carb diets improved lipid levels, mainly HDL and TRG. **Conclusion:** Evidence mixed and of not high quality due to study size, duration, dropout rates, or lack of randomization in some cases.	**Should be included in a review** Partial support for ADA Statement Note: Three of the reviewed studies reported carb consumption at <70g/day; they attained a SS improvement in HbA1c of -6.8% to -17%.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

14	"While benefits to low-carbohydrate diets have been described, improvements tend to be in the short term and, over time, these effects are not maintained." (74-77, ADA 2018)	Snorgaard O, 2017 [ref# 74, ADA 2018][79]	Systematic review and meta-analysis	Review/analysis of 10 RCTs to address the question: Is there an ideal amount of dietary carbohydrate for individuals with T2D? Analyzed association of reported carbohydrate intake with reduction in HbA1c.	pooled n=1376 adults with T2D	varied	**Conclusion**: ♦ The ideal amount of carbohydrates in the diet in the management of T2D is unclear. ♦ Low-carb and moderate-carb diets have greater glucose-lowering effect compared with high-carb diets. ♦ The greater the carb restriction, the greater glucose lowering. ♦ Apart from improvements in HbA1c over the short term, low-carb is not superior to high-carb for glycemic control or weight.	**Should be included in a review of the evidence**. Supports ADA Statement.
15		van Wyk HJ, 2016 [ref 75, ADA 2018][80]	Review	Aimed to better understand efficacy of low-carb diets for glycemic control as well as the reasons for different conclusions among 9 meta-analysis on the subject. Reviewed were 12 RCTs that were ≥4	Adults with T2D	≥ 4 wks	**Conclusions:** Variability in study design and subject characteristics, as well as reported carb intake, may account for differences in studies' findings; total E intake is the best predictor of body weight; low-carb diets perform no better than high-carb diets to improve metabolic markers; very low-carb diets may not be sustainable, as carb intake	**Should be included in a review of the evidence, but with clarification:** Supports the ADA Statement 9. Note: It was likely adherence, not the low-carb diet

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 March 2019 doi:10.20944/preprints201812.0187.v2

				weeks and which tested low-carb diets of ≤ 45g/day,			often returns to a more moderate level over time.	per se, that determined outcomes. Reported carb intake at end of study for low-carb arms, for the 12 studies, was 132-228 g/day.
16		Meng Y, 2017 [ref 76, ADA 2018][81]	Systematic review and meta-analysis	Reviewed 9 RCTs; aimed to assess the efficacy of low-carb diets compared to normal/higher-carb, low-fat diets in T2D.	Pooled n=734 adults with T2D	3-24 months	♦ Superior benefit for HbA1c, TRG, HDL, and short-term weight loss, but not LDL, total cholesterol, FBG or long-term weight loss, when compared to control diet.	**Should be included in a review of the evidence.** Supports ADA Statement. **Limitation:** Analysis did not consider reported carb intake of study diets but only target levels.
17		Tay J, 2015 [ref 77, ADA 2018] [82]	RCT	Compared effects of a very low-carb, high-unsaturated fat/low-saturated fat diet vs. a high-carb, low-fat diet on glycemic control and CVD risk factors in T2D. Both study arms E-restricted.	n=115 overweight or obese adults with T2D 78 (68%) completed study.	1 year	♦ **HbA1c** AR ↓1.0% (↓13.6%) BG nSS ♦ **FBG** AR ↓0.7mmol/L (↓9.0%) BG nSS ♦ **Weight** loss AR ↓9.8kg (↓9.6%) BG nSS ♦ **HDL** AI ↑0.1mmol/L(↑8.3%) BG SS	**Should be included in a review of the evidence.**

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							♦ LDL AR ↓0.1mmol/L BG nSS ♦ **TRG** AR ↓0.4mmol/L (↓25%) BG SS ♦ **Blood glucose stability** SS improved with low-carb diet. **Diabetes medication use:** Reduced more with low-carb diet. BG SS Participants in the low carb arm spend more time in euglycemic range than hyperglycemic range versus the one in high carb arm	
18	"While some studies have shown modest benefits of very low-carbohydrate or ketogenic diets (less than 50-g carbohydrate per day (78,79), this approach may only be appropriate for short-term implementation (up to 3-4 months) if desired by the patient, as there is little long-term research citing benefits or harm." (ADA 2018)	Goday A, 2016 [ref 78, ADA 2018][83]	RCT	Evaluated the short-term safety and tolerability of a very low-carb, ketogenic diet (<50g/day) in a weight loss/lifestyle modification program for adults with T2D. VLCK group ate commercial weight-loss products and natural foods. Restricted-E	n=89 obese adults with T2D 76 (85%) completed study.	4 months	**Safety** No SS differences in safety parameters were found between the two study groups, including: **Efficacy** ♦ **HbA1c** AR ↓0.9% (↓13.0%) BG SS ♦ **FBG** AR ↓28.0mg/dL (↓20.5%) WG SS BG nSS ♦ **HOMA-IR** AR ↓3.4 (↓49.3%) WG BG nSS	**Should be included in a review of the evidence.** Supports ADA Statement in part. However, other studies (see Table 8) provide safety and efficacy data

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				control diet was based on ADA guidelines.			♦ **TRG** AR ↓35.9mg/dL (↓23.9%) WG SS BG SS ♦ **HDL, LDL** no SS changes ♦ **Weight** AR ↓14.7kg (↓16.1%) BG SS ♦ **Medications** significant decrease in low carbohydrate arm only although no specific details on which medications were given.	from longer studies.
19.		Saslow L, 2017 [ref 79, ADA 2018][84]	RCT	Compared effects on glycemic control and other outcomes of 2 online interventions (ad libitum very low-carb with behavioral support vs. ADA's "Create Your Plate" diet.	n=25 overweight adults with T2D 18 (72%) completed study.	32 weeks	♦ **HbA1c** AR ↓0.8% (↓11.3%) BG SS ♦ **Weight** AR ↓12.7kg (↓11.6%) BG SS ♦ **TRG** AR↓ 60.1mg/dL (↓34.5%) BG SS ♦ **HDL, LDL** no SS changes	**Should be included in a review of the evidence.** Supports ADA Statement in part. s However, other studies (see Table 8) provide safety and efficacy data from longer studies.