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Special Article

Diabetes Canada Position Statement on Low-Carbohydrate Diets for Adults With Diabetes: A Rapid Review

Purpose and Background

Carbohydrates (CHO) are biomolecules that are available in the form of starches, sugars and fibre. Evidence suggests that excess calorie intake and over-consumption of refined CHO are major drivers of the epidemic of obesity and type 2 diabetes, while obesity is emerging as a challenge for people with type 1 diabetes. The *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* (CPG) emphasise the importance of nutritionally balanced, calorie reduced diets to achieve and maintain a healthier body weight, which can be achieved by several dietary patterns based on individual preferences and treatment goals (1). In the absence of specific evidence on macronutrient distribution, Diabetes Canada recommendations aligned with those of Health Canada for the general population (45% to 60% CHO of total energy).

Diabetes Canada's consensus recommendation (45-60% CHO) was not intended to restrict the choices of individuals with diabetes to follow dietary patterns below this level, nor their access to support from health-care practitioners. Rather, it reflected the absence of convincing evidence for superiority of any particular dietary patterns for all adults with type 2 diabetes, but did indicate that for people with type 1 diabetes, small, short-term studies demonstrated that lower-CHO diets could be an option (2).

Since the completion of our last literature review (September 15, 2017), organizations, such as Diabetes Australia, Diabetes UK, and the American Diabetes Association in conjunction with the European Association for the Study of Diabetes, have developed position statements and recommendations regarding lower-CHO diets for people with diabetes (3,4,5). Several consistent themes have emerged. All have concluded that low-CHO diets (<130g or <45% energy CHO/day), especially very low-CHO diets (<50 g CHO/day) can be safe and effective in managing weight and lowering A1C in people with type 2 diabetes over the short term (<3 months), however, these diets may not have a long-term advantage. Overall, it has been suggested that an individualized approach to reducing CHO intake may be integrated into a variety of eating patterns.

Diabetes Canada develops position statements to address issues that are important for people living with diabetes and/or health-care providers when there is insufficient data to perform a systematic review or there is no high level evidence. This position statement has been developed in response to emerging evidence, a shift in international consensus regarding lower-CHO diets, and to provide important clarification for people living with diabetes and health-care providers. In particular, we hope that this update will facilitate effective engagement with multi-disciplinary teams, avoid interprofessional tensions, and clearly identify key safety issues and clinical monitoring requirements.

Purpose

1. To summarize the evidence for the role of low-CHO (50-130g/day) or very low-CHO (<50g/day) diets in the management of people diagnosed with type 1 and type 2 diabetes.[1]
2. To provide practical recommendations to patients and practitioners regarding the utilization of low-CHO dietary patterns.

Methods

Leveraging the search methods used for the 2018 CPG, this position statement utilized a targeted approach from existing databases, using keywords such as, but not limited to, "low-carb" and "keto" from searches developed by health science librarians from the McMaster Evidence Review and Synthesis Team (MERST). They systematically searched across databases and reviewed all relevant citations at title and abstract, and full-text levels published since the previous search for the 2018 CPG. All selected full-text citations were critically appraised by a methodologist from MERST and critical appraisal reports were provided to the position statement authors. Additional citations were identified by reviewing references of identified articles.

The data collected from the included studies were abstracted and summarized to be presented as an overview of the available evidence. Given the paucity of high quality evidence, only consensus recommendations could be made and thus there was no formal grading or independent methods review process.

Summary of Evidence

A. Type 1 Diabetes

Low Carbohydrate Diets: Two small studies examined the use of low-CHO diets (target <75 g/day) in people with type 1 diabetes (6,7). One small (n=10), 12 week, pilot randomized controlled trial (RCT) conducted in individuals using multiple daily injections with modern insulin analogs found reductions in A1C (63 to 55 mmol/mol or 7.9% pre-intervention to 7.2% post intervention), $p<0.05$), insulin use (reduction from 64.4 to 44.2 units/day post intervention, $p<0.05$) with no change in body weight (83.2 vs.78.0 kg, p=ns), respectively, in the low-CHO group while these parameters were unchanged in the standard CHO counting diet group (6). There were no changes in blood

[1] Various studies classify low-CHO and very low-CHO differently. For the purposes of this paper, we have summarized the evidence in this way based on the majority of the literature reviewed.

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pressure, creatinine or lipid profile, continuous glucose monitoring (CGM), or quality of life, in either group (6).

Nielson and colleagues (7) performed a retrospective chart review that evaluated the outcomes after individuals with type 1 diabetes participated in an educational program describing a low-CHO dietary pattern (n=48). The outcomes of interest were both A1C changes and individual self-reported adherence. Compared with baseline, A1C was lower after 4 years for the whole group (decrease in A1C 0.7 +/- 1.1; p<0.001). The adherence rate at 4 years was 48%. A1C was no different from baseline among subjects who did not adhere to the dietary pattern, but was lower among those that did adhere (decrease in A1C 1.3 ± 0.9%; p<0.001) (7).

Very Low Carbohydrate Diets: The only data on very low-CHO diets in type 1 diabetes are observational. An online social media survey conducted in both adults and children with type 1 diabetes who followed very low-CHO diets (≤30 g/day) was reported by Lennerz et al. The adult participants achieved a mean change in A1C from pre to post very low-CHO diet of -1.45% and it was reported that the rate of adverse events was low (8). Mean A1C post intervention was 5.7% with low glycemic variability (glucose sd of 1.56 mmol/L). Of 300 participants, 2% reported hospitalizations in the past 12 months, 1% had 4 hospitalizations (0.01 per person per year) for diabetic ketoacidosis (DKA), and 2% had 9 hospitalizations (0.03 per person per year) for other reasons (8). Symptomatic hypoglycemia within the past month was reported by 69% of participants, with 55% having 1 to 5 episodes per month. Rates of severe hypoglycemia were low, with 2% reporting hypoglycemia with seizure or coma and 4% requiring glucagon in the past year (8). Of note, participants reported high levels of overall health and satisfaction with diabetes management but not with their professional diabetes care (8). Of those who did discuss their diet, only 49% agreed or strongly agreed that their diabetes care providers were supportive.

A small (n=11), observational study of adults consuming mean 28.9g CHO/day and 65% daily energy intake from fat, resulted in a mean A1C of 5.3 ± 0.4% and low glucose variability (sd 1.5 mmol/L) using blinded CGM. Participants in this study had high LDL (5.5 ± 1.7 mmol/L) and spent 3.6% time with blood glucose <3.0 mmol/L although reporting only 0.4 ± 0.7 episodes of hypoglycemia per week (9).

B. Type 2 Diabetes

Low Carbohydrate Diets: Several meta-analyses of RCTs comparing diets with different CHO and their role in the management of type 2 diabetes content have been performed. However, several of these combined studies of very low-, low- and moderate-CHO interventions (10,11,12).

Two meta-analyses published in 2018 and 2019 sought to examine RCTs of very low (<50 g per day) and low-CHO diets (50-130 g per day) separately from RCTs where the intervention was moderate-CHO diets (130 - 225 g per day) (13, 14). Low-CHO diets showed greater A1C and weight reductions than control diets in trial duration of up to 6 months while moderate-CHO dietary interventions showed no statistically significant difference from control diets in either A1C or weight (14).

An observational 12-month evaluation of people who had completed a 10-week digitally delivered low-CHO diet program showed statistically significant changes in A1C (-1.17%) and significant reductions in body weight (-7.0%) (15). It should be noted that last observation carried forward was used to impute data for 29% of subjects who were lost to follow up, which is a significant limitation and may overestimate the benefit of the intervention. Among completers, there were statistically significant reductions in the use of anti-hyperglycemic medications (15).

Very Low Carbohydrate Diets: Six studies assessed the effect of very low-CHO diets on glycemic control and body weight in adults with type 2 diabetes with overweight or obesity (16, 17-20). Very low-CHO diets were defined in different studies with a range of 20–50g/day of CHO (≤10% of total daily energy). Four of the included studies were RCT (16,17,19,20). Three studies followed participants for ≥12 months (16,17,21), with shorter follow up in the others (12-32 weeks) (18-20). Five of six studies reported greater reductions in A1C and greater weight loss with very low-CHO diets compared to control diets with higher CHO content (17-21).

Tay et al. reported equal efficacy for A1C and weight loss for very low-CHO diet compared with an energy matched control diet. The very low-CHO diet, however, demonstrated greater reductions in glycemic variability and lower use of glucose lowering medications (16).

Not all studies compared isocaloric diets and may not have controlled for weight change, a potential mediating variable, in their analysis of changes in A1C. Additional interventions, including counselling, may not have been provided to control groups (19). It should be noted that additional interventions, including counselling, exercise and sleep advice in extended contact with study personnel, as well as consistent professional and peer support, may have contributed to the positive outcome (21).

Thus far, meta-analyses of RCTs comparing very-low CHO diet have not provided clear evidence of superiority. Sainsbury combined very-low and low-CHO diet trials (to try and ensure adequate power) and found CHO restriction was superior for A1C and weight (13). McCardle found greater A1C lowering (although the difference was not statistically significant) when only RCTs of very-low CHO diet were examined but did not show any difference in weight loss versus control diets (14).

Davis et al. examined diabetes-specific quality of life (QOL) after a very low-CHO diet versus a low-fat diet, and reported improvement in QOL scores related to sexual function, energy and mobility domains for all participants, but these were independent of the dietary approach used (22). No differences in cognitive function were observed in an RCT of very low-CHO, high-fat diet versus a high-CHO, low-fat diet on cognitive function over a 12-month period, although weight loss (independent of diet pattern) was associated with improvement in one aspect of cognitive function (23).

Non-randomised, short-term studies of very low-CHO diets have demonstrated significant reductions in A1C levels (-1.0%), weight (-7.2%) and triglycerides (20%) after 10 weeks while permitting anti-hyperglycemic medications to be reduced or discontinued in one-half of participants (24).

Uncertainties

It is unclear what the precise mechanisms underlying the benefits of low or very low-CHO diets for lowering A1C, reducing weight and need for antihyperglycemic therapies are since it is difficult to design well-controlled studies which are easily translated into real world settings. Lack of persistence, high discontinuation rates and missing data are common challenges in dietary studies.

Because of the limitation of short-term data, it is uncertain whether improvements in glycemic control and weight seen with these dietary approaches will be maintained long-term or will translate into reductions in diabetes complications, cardiovascular disease or mortality. Sustainability is another question since lack of persistence has been reported. In Van Wyk et al.'s meta-analysis, it was reported that success in maintaining low-CHO diets within studies often decreased over time, suggesting that low-CHO diets may not be sustainable over a medium or longer term (25). These

limitations are not confined to studies of low- and very low-CHO diets, however, and apply to other dietary patterns. Many individuals will need support if they are to maintain such long-term, significant changes to dietary patterns.

Cautions and Safety

Antihyperglycemic Therapies

Reductions in antihyperglycemic therapies were reported in both type 1 (6) and type 2 diabetes (13,15,16,26) with CHO restriction. Thus, insulin and/or sulphonylurea doses may need to be reduced or discontinued to avoid hypoglycemia. SGLT2 inhibitor therapy may increase the risk of ketoacidosis in individuals following low-CHO diets (27). A small RCT found that luseogliflozin significantly increased ketone bodies in the low-CHO diet group compared to the high-CHO diet group, providing a mechanistic link between low-CHO intake, SGLT2 inhibitor therapy and ketonemia (28).

Hypoglycemia

Some additional cautions may be needed around the detection and treatment of hypoglycemia. It is possible that ketonemia resulting from very low-CHO diets may impair awareness of hypoglycemia since some studies have described reduced hormonal responses to experimental hypoglycemia possibly as a result of changes in cerebral fuel utilisation (29). Another concern is related to the reduced effectiveness of glucagon in the treatment of hypoglycemia because of inadequate hepatic glycogen stores (30). Thus, individuals using insulin and following a low-CHO diet need alternative strategies (including extra glucose monitoring) to safely detect and manage severe hypoglycemia (29).

Healthy Nutrition

Healthy eating is much broader than simply macronutrient composition and healthy weight. It may be difficult to achieve adequate dietary fibre in carbohydrate-restricted diets. Individual studies and a meta-analysis report lower fibre consumption (11,12,16). Very little is known about changes in micronutrients in people with diabetes following low-CHO diets, but it may be worth noting that decreases in vitamin A and magnesium were observed in children with epilepsy treated with a very low-CHO diet (31). Attention to the quality of fats and proteins replacing carbohydrates in low- or very low-CHO may mitigate concerns regarding fibre and micronutrients. In the DIETFITS study, individuals living with obesity without diabetes were counselled on achieving high diet quality in both low-CHO and high-CHO groups. However, at 12-months follow-up, fibre intake was still significantly lower in the low-CHO (18.6 +/- 0.5 g/day) than the high-CHO group (23.0 +/- 0.6 g/day) (32).

Conclusion

The aim of this position statement was to examine and appraise the current literature in order to identify a rational and safe approach to the use of low-CHO diets in people with diabetes, informed by current evidence, and to provide practical recommendations to patients and their health-care providers. This comprehensive literature search and study selection resulted in 33 relevant articles examining the role of very low-CHO and low-CHO diets in the management of type 1 and type 2 diabetes.

For people living with type 1 diabetes:

- There are very little reliable data and major evidence gaps which make it difficult to make general recommendations with any confidence.
- Significant improvements in outcomes important to persons with diabetes (lower A1C, reduced insulin requirements, less glucose variability, weight loss) have been reported by individuals who have chosen to follow a low- or very low-CHO diet.
- There are very few studies investigating the long-term effectiveness of low-CHO diets for people with type 1 diabetes, furthermore, the few small studies available are of poor methodological quality and provide insufficient evidence to make a general recommendation for low-CHO diets to all people with type 1 diabetes.

For people living with type 2 diabetes:

- This current review indicates a low-CHO diet may be effective for weight loss and improved glycemic control with a reduction in need for antihyperglycemic therapies. Other comparator dietary approaches may also be effective for weight loss and improved glycemic control, but have not achieved this while also reducing the need for antihyperglycemic therapies, which is a meaningful outcome.
- The review further suggests that very low-CHO diets may be superior to comparator (higher-CHO) diets for improving glycemic control, body weight and can reduce the need for medications in the short term (up to 12 months), but evidence regarding longer-term benefits is limited.
- With current data, we are unable to determine whether the benefits of very low-CHO diets (on weight loss and A1C) are specific to the macronutrient composition or associated differences in calorie intake.
- Several methodological limitations exist in the published literature to date, including non-adjustment for confounders in observational studies, short-term follow-up of small-sized RCTs, along with relatively high rates of poor persistence to the assigned dietary approach.

Future Directions

- While long-term studies of the safety and efficacy of low- and very low-CHO diets are desirable, they may be difficult to perform. Future research comparing dietary approaches should include people living with type 1 diabetes and people with type 2 diabetes irrespective of weight.
- In addition to delineating the role of very low-CHO diets and low-CHO diets in the management of people diagnosed with type 1 and type 2 diabetes, more research is urgently required to examine the role of low-CHO diets in people at high risk for developing diabetes to delay progression to diabetes.
- In the absence of clear trial evidence to support generalised recommendations and the positive results experienced by people following low- and very low-CHO diets, health-care providers will need to work as partners with individuals seeking to identify an optimal and sustainable dietary pattern that fits with their individual preferences. Health-care providers will need to recognize that diverse approaches are required to address the complex challenges of diabetes and obesity. Health-care providers should strive to engage with patients in supportive relationships which respect shared decision making.

Recommendations

1. Individuals with diabetes should be supported to choose healthy eating patterns that are consistent with the individual's values, goals and preferences.
2. Healthy* low- or very-low-CHO diets can be considered as one healthy eating pattern for individuals living with type 1 and

type 2 diabetes for weight loss, improved glycemic control and/or to reduce the need for antihyperglycemic therapies. Individuals should consult with their health-care provider to define goals and reduce the likelihood of adverse effects.
3. Health-care providers can support people with diabetes who wish to follow a low-CHO diet by recommending enhanced blood glucose monitoring, adjusting medications that may cause hypoglycemia (sulfonylureas and insulin), or increase risk for DKA (SGLT2 inhibitors, underdosing insulin in those with insulin deficiency), and to ensure adequate intake of fibre and nutrients.
4. Individuals and their health-care providers should be educated about the risk of euglycemic DKA while using SGLT2 inhibitors and low-CHO diet, and further educated about the strategies to mitigate this risk (33).[2]
5. People with diabetes who begin a low-CHO diet should seek support from a dietitian who can help create a culturally appropriate, enjoyable and sustainable plan. A dietitian can propose ways to modify CHO intake that best aligns with an individual's values, preferences, needs and treatment goals as people transition to or from a low-CHO eating pattern.

*Canadians, with and without diabetes, who prefer to adopt a low- or very low-CHO dietary pattern, should be encouraged to consume a variety of foods recommended in Canada's Food Guide. Regular or frequent consumption of high energy foods that have limited nutritional value, and those that are high in sugar, saturated fat or salt, including processed foods and sugary drinks, should be discouraged.

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[2] See Table 1: Antihyperglycemic agents for use in type 2 diabetes in the "Pharmacologic Glycemic Management of Type 2 Diabetes in Adults" chapter in the 2018 CPG.

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