Low-Carbohydrate Diets for Type 1 Diabetes Mellitus

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None.

Conflicts of interest
Dr. Kieron Rooney has given talks for "Low Carb Down Under" on the biochemistry of low carbohydrate diets and has been a collaborator on primary research investigating the effect of lower carbohydrate diets for weight loss. A full disclosure of previous funding and published research is available at http://sydney.edu.au/health-sciences/about/people/profiles/kieron.rooney.php.

Background

Description of the condition

Type 1 Diabetes Mellitus (T1D) is an auto-immune condition characterised by the destruction of pancreatic beta cells and absolute insulin deficiency. Affected individuals have impaired glucose metabolism and are prone to acute complications from hypoglycemia and ketoacidosis, as well as chronic complications from hyperglycemia. The standard treatment consists of daily injections of insulin and diet flexibility is encouraged.

The strongest predictor of diabetes complications is glycemic control and achieving normal haemoglobin A1c (HbA1c ≤ 7.0%) is considered the primary target in T1D management (1-4). However, data from T1D registries across 19 countries in Australasia, Europe and North America (n = 324,501) showed that 84% of patients with T1D exhibited HbA1c above this target (5). It appears that current therapies are lacking in effect and adjunctive strategies require consideration.

Description of the intervention

Low-carbohydrate diets are defined according to the American Diabetes Association (ADA) classifications of less than 130 grams or 26% total energy from carbohydrate per day. However, in Australia, there is no clear definition and any diet below the Acceptable Macronutrient Distribution Range (AMDR) for carbohydrate (45-65% total energy) may be termed low-carbohydrate. Prior to the discovery of insulin, strict low-carbohydrate diets were the original method for treating diabetes and severe carbohydrate restriction (≤10 grams of carbohydrate per day (g/d)) or water-fasting was prescribed until glycosuria was eliminated (6). Complementary to more recent evidence, this practice suggests that levels of carbohydrate tolerance varies within-persons across time and between individuals (4).

How the intervention might work

It is well-accepted that dietary carbohydrate has the greatest impact on blood glucose excursions. In Type 2 Diabetes, carbohydrate restriction shows the greatest reduction in postprandial and overall glucose concentrations as well as HbA1c (7-15). In Type 1 Diabetes specifically, blood glucose excursions are a function of the input of glucose from food, mainly carbohydrates (starch and sugars), and insulin from subcutaneous insulin stores (16). By reducing dietary carbohydrate, the error rate in determining insulin needs to match it is reduced and blood glucose fluctuations minimised (4). This results in less frequent and
severe hyperglycaemic and hypoglycaemic episodes, as well as an overall reduced requirement for medication (16, 17).

**Why it is important to do this review**

Concerns regarding development of ketoacidosis are a barrier to the widespread use of this dietary strategy being recommended today (18). Two recent cases for example, report ketoacidosis occurring in individuals following carbohydrate-restricted diets (19, 20). Another barrier to exploring low-carbohydrate diets is the continued emphasis on low-fat intake for cardiovascular disease (CVD) prevention. This recommendation continues to resonate in dietary guidelines and clinical practice despite the accumulation of high-quality systematic reviews deeming the evidence linking total and saturated fat intake to CVD as inconclusive (21-23).

In accordance with the National Health and Medical Research Council (NHMRC) recommendations for the management of T1D, patients are advised to consume carbohydrates to the level of 45-65% total energy intake as per the general population (18, 24). Approaches that promote dietary flexibility, such as Dose Adjustment For Normal Eating (DAFNE), are encouraged by health professionals. However, such regimens rely heavily on carbohydrate counting and insulin to carbohydrate ratios. A recent systematic review has shown carbohydrate counting to be ineffective for Type 1 Diabetes, suggesting a requirement for complementary dietary strategies (25). In addition, a qualitative review of participants who had undergone the DAFNE course highlights how flexible insulin therapy led some patients to severely restrict carbohydrate by choice as they found that large amounts of carbohydrate coupled with large insulin doses led to unpredictable blood glucose results (26).

Scientific evidence for carbohydrate restriction in Type 1 Diabetes is promising. For example, O’Neill et al. restricted carbohydrate to 30 g/d in participants with diabetes (27). Mean HbA1c decreased from 7.9% to 5.7% over 21 months (P < 0.001), and participants with T1D reduced their daily insulin dosage from 47.0 to 30.0 units. Similarly, Vernon and colleagues restricted carbohydrate intake to less than 20 g/d before incrementally increasing this by 5 g per week until individual carbohydrate threshold was determined (28). Mean HbA1c reduced from 10.0% at baseline to 5.9% over 8 months (p < 0.001) and insulin was discontinued or reduced by 50%.
The underlying conflict between the literature and professional practice, as well as a sheer lack of specific dietary recommendations for patients with T1D, demands a thorough review of the literature to determine the effect of low-carbohydrate diets in the management of T1D.

**Aim**

We will conduct a systematic review to evaluate the effect of all low-carbohydrate diets on Type 1 Diabetes Mellitus (T1D).

**Objectives**

To determine whether:

- Significant differences in results (i.e., effect size) for T1D management outcomes exist between low-carbohydrate diets and higher-carbohydrate comparators.
- Primary nutrition studies of very low-carbohydrate, ketogenic diets (<50 g/d) (VLCKD), true low-carbohydrate diets (50-130 g/d) (TLCD) and false low-carbohydrate diets (>130 g/d) (FLCD) have different levels of effect in the treatment of T1D.

**Methods**

**Criteria for Considering Studies for this Review**

**Inclusion Criteria:**

*Population*

- Adults and/or children with Type 1 Diabetes Mellitus and BMI $\geq 18.5$ kg/m$^2$ and $<40$kg/m$^2$ and that are otherwise healthy.

*Intervention*

- Low-carbohydrate diet ($<45\%$ total energy as dietary carbohydrate) in combination with appropriate standard care (i.e., insulin therapy, carbohydrate counting, education, etc.). If carbohydrate intake is only given in grams and no information on total energy intake is provided, then $<230$ grams per day will be used (based on a person’s intake of 8700 KJ per day).
- The duration of the intervention is equal to or more than 2 weeks.
We will include all low-carbohydrate diets below the AMDR for carbohydrate (<45% total energy) and will classify interventions as very low-carbohydrate, ketogenic diets (VLCKD), true low-carbohydrate diets (TLCD) or false low-carbohydrate diets (FLCD) according to the amounts of total carbohydrate prescribed in grams. VLCKD studies are those in which the intervention prescription is <50 grams of total carbohydrate per day. TLCD studies are those in which the intervention prescription is 50-130 grams of total carbohydrate per day. FLCD studies are those in which the intervention prescription is below the AMDR for carbohydrate (i.e., <45% total energy) but does not meet the ADA criteria for a low-carbohydrate diet (i.e., <130 grams of total carbohydrate per day or <26% total energy as carbohydrate).

**Comparator**

- Carbohydrate not restricted (i.e., ≥45% of total energy) or any other dietary intervention that is significantly higher in carbohydrate than the low-carbohydrate dietary intervention, in combination with appropriate standard care (i.e., insulin therapy, carbohydrate counting, education, etc.).

As insulin therapy is dependent upon diet, appropriate standard care for the comparator will not be equivalent to that of the intervention, but should be comparable. For example, one group may require more educational sessions to help adjust insulin therapy to their specific dietary regime.

For studies investigating different levels of carbohydrate restriction, including VLCKD versus TLCD or TLCD versus FLCD, the lowest level of prescribed dietary carbohydrate will be considered the intervention and the highest level will be considered the comparator/control.

**Study Type / Context**

- Primary research studies only – including randomised controlled trials, non-randomised controlled trials, cohort and case control studies.
- Research letters, clinical audits, case series and case reports will be included if they include a methods section.
- In the case of multiple reports from the same study, we will use the most complete and/or recently reported data.
- The study quantitatively measures the effects of low-carbohydrate diets therapy in humans.
• The study evaluates one or more primary and/or secondary outcomes relating to T1D management [see ‘Outcomes’].

**Exclusion Criteria:**

**Population**

• Only people with a BMI <18.5 kg/m² or ≥40 kg/m².
• Only elderly people (≥70 years old).
• Only people with co-morbidities related to T1D (i.e., diabetes “end-points”) (e.g. cardiovascular diseases, chronic kidney disease, etc.) or other chronic complications requiring specific treatment (e.g. epilepsy).

**Intervention**

• The intervention is within or exceeds the AMDR for carbohydrate (i.e., ≥45% total energy).
• Mixed interventions other than standard care (e.g. nutrition and non-standard pharmaceuticals) whereby data related to the low-carbohydrate diet used in combination with standard care are not reported separately or cannot be obtained from the authors.
• The duration of the intervention is less than 2 weeks.

**Comparator**

• Mixed interventions other than standard care (e.g. nutrition and non-standard pharmaceuticals) whereby data related to the diet used in combination with standard care are not reported separately or cannot be obtained from the authors.
• Carbohydrate intake is not significantly different from the intervention.

**Study Type / Context**

• Cross-sectional studies, conference abstracts, reviews and meta-analysis, letters to the editor, commentaries.
• No primary and/or secondary outcomes relating to T1D [see ‘Outcomes’] are measured.

**Outcomes**

For this study, we will use various clinical and surrogate outcomes for evaluating the effect of dietary interventions on T1D management. These outcomes were selected and prioritised in consultation with a previous Vice-President of the International Diabetes Federation.
Primary Outcomes

1. HbA1c (%)
2. Severe hypoglycaemia (frequency/week)
3. Insulin dosage (units/day)

Secondary Outcomes

1. BMI (kg/m2)
2. Quality of life (Audit of Diabetes Dependent Quality of Life score)
3. Mean glucose from a continuous glucose monitor (mmol/L)

Searches

We will search the following databases from inception until 28 March 2017: Ovid MEDLINE; CINAHL; Cochrane Library; and EMBASE. The search strategy is shown in Appendix 1 for Ovid MEDLINE, and will be adapted for the other databases. The search strategy combines terms relating to or describing the population with those relating to or describing the intervention. The search will be restricted to include only human studies that are published in English. Reference lists of studies included from the full-text screen will also be searched.

Data Management

All included and excluded studies identified from the search strategy will be stored in EndNote 7. A secure hard-drive will be used for the storing of all data to be extracted from the included studies. Secure back-ups of all data will be saved fortnightly.

Data Extraction (Selection and Coding)

Two investigators (JT & KR) will independently screen the titles and abstracts of all retrieved records for obvious exclusions. Two investigators (JT & KR) will then assess the remaining papers based on full text, applying aforementioned inclusion criteria for included studies. Agreement will be reached on any discrepancies by consensus between the two assessors. If agreement cannot be reached, a third assessor (AR) will make a decision. Two reviewers (JT & KR) will independently extract data (see 'Data Items’) and assess each study for all outcomes. If agreement cannot be reached on extraction of data, an additional investigator (AR) will adjudicate the outcome. If any relevant data are missing from the included papers, an investigator (JT) will contact the authors to attempt to retrieve the missing data.
Data Items

Data from each included study on the population, intervention, comparator and outcome/s will be reported in a 'Characteristics of Included Studies' table. The specific data items to be extracted include:

a) Journal Name
b) Title of the paper
c) Year of publication
d) Location (country)
e) Study design
   1. RCT/cluster RCT
   2. Controlled trial/pseudo-randomized
   3. Cohort
   4. Clinical audit
   5. Case-control
   6. Research letter
   7. Case Series
   8. Case Report
f) Sample size of study
g) Sex of participants
h) Age of participants (mean and range)
i) Intervention or observation period
j) Primary aim of the study (verbatim)
k) Intended intervention prescription / level of exposure
   1. How the study defined the intervention (verbatim)
   2. How the study delivered the intervention (verbatim), including details on methods such as food provision, meal replacements, diet books, dietary counselling, etc.
   3. Daily intake of total dietary carbohydrate (grams)
   4. Daily intake of total dietary carbohydrate (percent total energy)
   5. Daily intake of dietary protein (grams)
   6. Daily intake of dietary protein (percent total energy)
   7. Total daily energy intake: (i) replete (ad libitum) (ii) restricted
   8. Total daily energy intake (mean) (kcal and kJ)
   9. Classification of intended intervention: (i) VLCKD (ii) TLCD (iii) FLCD
l) Comparison
   Type of Comparison
   1. Low-carbohydrate diet vs low-carbohydrate diet (different doses)
   2. Low-carbohydrate diet vs high-carbohydrate diet
   3. Low-carbohydrate diet vs control / usual diet
   4. Low-carbohydrate diet vs other dietary intervention
   5. Other (mixed intervention)

Details of Comparator
   6. How the study defined the comparator (verbatim)
   7. How the study delivered the comparator (verbatim), including details on methods such as food provision, meal replacements, diet books, dietary counselling, etc.
   8. Daily intake of total dietary carbohydrate (grams)
   9. Daily intake of total dietary carbohydrate (percent total energy)
   10. Daily intake of dietary protein (grams)
   11. Daily intake of dietary protein (percent total energy)
   12. Total daily energy intake: (i) replete (ad libitum) (ii) restricted
   13. Total daily energy intake (kcal or kJ)

m) Primary/secondary outcome measures
   1. Effect size
   2. Level of significance (p-value or 95% confidence interval)
   3. Direction of result: (i) favours intervention (ii) favours comparator

n) Actual intervention and level of exposure
   1. Mean daily intake of total dietary carbohydrate (grams)
   2. Mean daily intake of total dietary carbohydrate (percent total energy)
   3. Mean daily intake of dietary protein (grams)
   4. Mean daily intake of dietary protein (percent total energy)
   5. Mean total daily energy intake (kcal or kJ)
   6. Classification of actual intervention: (i) VLCKD (ii) TLCD (iii) FLCD

o) Compliance to Intervention
   1. Yes (mean daily intake of total carbohydrate [l] is within +20% of [i])
   2. No (mean daily intake of total carbohydrate [l] exceeds [i] by >20%)

p) Drop-outs
1. Yes: (i) number of drop-outs (ii) reason/s (verbatim)

2. No

q) Sponsorship / Funding (verbatim)

Assessment of Risk of Bias in Included Studies

Two reviewers will independently conduct risk of bias assessments for methodological quality using Cochrane Risk of Bias tools and The Joanna Briggs Institute Critical Appraisal tools (JT & KR). For experimental trials (randomised controlled trials and controlled trials), we will use the Cochrane Risk of Bias tool for randomised studies (29). This tool assesses bias across 7 domains which will be reported separately as ‘low risk’, ‘high risk’ or ‘unclear risk’. For cohort studies, we will use the ROBINS-E tool for non-randomised studies (30). This tool also assesses bias across 7 domains which will be reported separately as ‘low risk’, ‘moderate risk’, ‘serious risk’, ‘critical risk’ or ‘no information’. These results will also be used to determine an overall risk of bias judgement for each non-randomised study. This tool is currently under development and our review, along with others (31), will help contribute recommendations for its refinement. For case-control studies, case series and case reports, we will use the corresponding critical appraisal checklist from the Joanna Briggs Institute (32). These checklists are a series of eight to ten questions which will help form an overall appraisal for each study assessed. The available options are ‘yes’, ‘no’, ‘unclear’ and ‘not applicable’. For standardisation, we will consider ‘yes’ as low risk of bias, ‘no’ as high risk of bias, and ‘unclear’ as unclear risk of bias. If agreement cannot be reached on bias assessments, an additional investigator (AR) will adjudicate the outcome.

Measures of Treatment Effect

Effect sizes and levels of significance will be taken for all primary and secondary outcomes measured in the study. For each outcome, results will be considered conclusive if statistical significance was reached ($p < 0.05$ or 95% confidence interval [CI] excludes null value) and inconclusive if statistical significance was not reached ($p \geq 0.05$ or 95% confidence interval [CI] includes null value). A direction (favours intervention or favours comparator) will be assigned to conclusive results.

Data Synthesis

If sufficient data are available we will use meta-analysis and or meta-regression to compare the statistical significance of results and magnitude of effect (i.e., effect sizes) of all low-carbohydrate diets. We will attempt to compare the effect estimates between groups for our continuous outcome measures by pooling homogeneous studies and measuring the mean difference from baseline measures. We will assess
heterogeneity using I-squared and use a random-effects model when statistical heterogeneity is substantial, defined as an I-squared > 50%.

We will perform a subgroup analyses by level of carbohydrate restriction. Results will be analysed according to our classification of the intended intervention (VLCKD, TLCD and FLCD). If Compliance to Intervention is significantly low (<50% ‘Yes’) then a second subgroup analyses will be performed. Results will be analysed according to our classification of the actual intervention.

Quality of Evidence
The GRADE approach will be used to grade the quality of the body of evidence for each individual outcome in this review (33). This involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. The GRADE approach specifies four levels of quality; 'high', 'moderate', 'low' and 'very low'. Quality of Evidence (GRADE) results will be presented by outcome in a 'Summary of Findings' table.

Significance of Results
Given that there are no specific dietary recommendations for patients with T1D, we need to identify whether low-carbohydrate diets are effective in improving T1D management outcomes. We must also identify the different levels of carbohydrate restriction being used in primary research studies evaluating low-carbohydrate diets, including any differences in results.

Type 1 Diabetes Mellitus is a chronic disease with severe complications for its mismanagement. To strengthen patient-centered care and better individual capacity for problem solving and self-management, patients with T1D should be presented with all effective management strategies and empowered to make their own health decisions with expert support. Failure to do so may have deleterious effects on the long-term health of people with T1D and lead to a divide between health professionals responsible for managing individuals with Type 1 and the Diabetic community themselves.
Bibliography


Appendix 1. Search Strategy

OVID Medline: Type 1 Diabetes Mellitus, Low-Carbohydrate Diets

1. Diabetes Mellitus, Type 1/
2. (Diabet* adj3 (type 1? or type I? or T1? or juvenile or insulin dependent or autoimmune or sudden onset)).mp.
3. (absolute adj3 insulin adj3 deficien*).mp.
4. (insulin adj3 therap*).mp.
5. (insulin adj3 inject*).mp.
6. (T1D or T1DM or IDDM or IDD).mp.
7. or/1-6
8. ((carb or carbs or carbohydrate*) adj3 (reduc* or restrict* or low* or limit* or deficien*)).mp.
9. ((ketone or ketosis or ketogenic or ketotic) adj3 (produc* or diet* or nutrition*)).mp.
10. ((diet or protocol) adj3 (CSIRO or south beach or atkins or protein power or dukan or LCHF or zero carb or sugar busters or bernstein* or paleo* or zone)).mp.
11. (high* adj3 fat adj3 diet*).mp.
12. Diet, Carbohydrate-Restricted/
13. Ketogenic Diet/
14. 8 or 9 or 10 or 11 or 12 or 13
15. 7 and 14
16. limit 15 to humans