The Association between a Low Carbohydrate Diet, Quality of Life and Glycemic Control in Australian Adults living with Type 1 Diabetes: A Pilot Study Protocol

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Abstract

Background: Globally, the prevalence of type 1 diabetes (T1DM) is rising. In 2020, 124,652 Australians had T1DM. Maintaining optimal glycemic control [HbA1c ?7.0% (?53 mmol/mol)] on a standard carbohydrate diet can be a challenge for people living with T1DM. The Diabetes Complications and Control Trial established that macrovascular and microvascular complications could be reduced by improving glycemic control. Recent studies have found that a very low or low carbohydrate diet can improve glycemic control. However, the overall evidence relating to an association between a very low or low carbohydrate diet and glycemic control in people living with T1DM is both limited and mixed. In addition, research has suggested that poor quality of life (QoL) due to anxiety and depression adversely influences glycemic control. Despite a potential link between a very low or low carbohydrate diet and good glycemic control, no research to our knowledge has examined an association between a very low or low carbohydrate diet, QoL and glycemic control, making this study unique in its approach.

Objective: The study aims to: 1) develop a validated diabetes specific quality of life questionnaire for use in Australian adults with T1DM and 2) determine if an association exists between a low carbohydrate diet, quality of life and glycemic control in Australian adults living with T1DM.

Methods: This cross-sectional study will be conducted in a tertiary hospital outpatient setting and will consist of three phases. Phase 1, online Australian diabetes specific quality of life questionnaire development and piloting (n=25-30 T1DM adults); Phase 2, questionnaire validation (n=364 T1DM adults) and Phase 3, a 12-week dietary intervention to determine if an association exists between a low carbohydrate diet, QoL and glycemic control in adults with T1DM (n=16-23 T1DM adults). The validation of the study developed Australian diabetes specific quality of life questionnaire and change in HbA1c and QoL in adults with T1DM while undertaking a low carbohydrate diet over 12 weeks will be the primary outcomes of this study.

Results: Study phase 1 is currently open for recruitment and has recruited 12 participants to date. It is anticipated that the first results will be submitted for publication in November 2021. Presently, no results are available.

Conclusions: This study is the first of its kind and will firstly generate a new validated instrument, which could be used in evidence-based practice and research to understand T1DM adults QoL. Secondly, the low carbohydrate dietary intervention outcomes could be used to inform clinicians about an alternative approach to assist T1DM Australian adults to improve their QoL and glycemic control. Finally, this study could warrant the development of an evidence based low carbohydrate dietary guideline for adults living with T1DM with the potential to have a profound impact on this population. Clinical Trial: ClinicalTrials.gov NCT04213300; https://www.clinicaltrials.gov/ct2/show/NCT04213300

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JMIR RESEARCH PROTOCOL

The Association between a Low Carbohydrate Diet, Quality of Life and Glycemic Control in Australian Adults living with Type 1 Diabetes: A Pilot Study Protocol

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Abstract

Background: Globally, the prevalence of type 1 diabetes (T1DM) is rising. In 2020, 124,652 Australians had T1DM. Maintaining optimal glycemic control [HbA1c ≤7.0% (≤53 mmol/mol)] on a standard carbohydrate diet can be a challenge for people living with T1DM. The Diabetes Complications and Control Trial established that macrovascular and microvascular complications could be reduced by improving glycemic control. Recent studies have found that a very low or low carbohydrate diet can improve glycemic control. However, the overall evidence relating to an association between a very low or low carbohydrate diet and glycemic control in people living with T1DM is both limited and mixed. In addition, research has suggested that a reduced quality of life (QoL) due to anxiety and depression adversely influences glycemic control. Despite a potential link between a very low or low carbohydrate diet and optimal glycemic control, no research to our knowledge has examined an association between a low carbohydrate diet, QoL and glycemic control, making this study unique in its approach.

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Trial Registration: ClinicalTrials.gov NCT04213300; https://clinicaltrials.gov/ct2/show/NCT04213300

Keywords: Type 1 diabetes; diet; low carbohydrate; HbA1c; adults; quality of life

Introduction

There are more than 420 million people worldwide aged 20 to 79 years, living with type 1 diabetes mellitus (T1DM) [1]. In 2020, 124,652 Australians had T1DM [2]. As the number of people with this autoimmune condition increases, so does the prevalence of those with suboptimal glycemic control [3].

Glycemic control is evaluated by glycated hemoglobin (HbA1c), which provides an average blood glucose level over a two to three month period [4]. The target for optimal glycemic control for people with T1DM is ≤7.0% (≤53 mmol/mol) [5]. In 2015, data from T1DM registries from 19 countries across Europe, North America and Australasia (n=324,501) found that only 46% of adults (aged ≥25 years) with T1DM achieved the HbA1c target of <7.0% [6].

Suboptimal glycemic control increases the risk of developing and/or progression of various diabetes related complications including hypoglycemia, diabetic ketoacidosis (DKA) neuropathy, nephropathy, retinopathy and cardiovascular disease [1].

The Diabetes Control and Complications Trial aimed to determine the long-term frequency and severity of chronic complications in individuals living with T1DM using intensive insulin therapy (INT) with the goal of maintaining blood glucose levels (BGLs) as close to normal range as possible. This seminal work convincingly demonstrated the effectiveness of INT in reducing the long-term complications of T1DM and improving the prospects for a healthy life span for individuals living with T1DM. This landmark study, established the glycemic control guidelines used today [7].

A recent systematic review reported the incidence and prevalence of DKA in adults with T1DM from

three continents [8]. Nineteen studies (one randomized control trial (RCT) and 18 cross-sectional) containing similar numbers of males and females, were included. Over 80% of participants were Caucasian. The review found that adults aged 18 to 25 years had the highest prevalence of DKA (100–120 cases per 1,000 in studies with 12 months recall) compared to those >65 years who had the lowest prevalence of DKA (38–60 cases per 1,000 in studies with 12 month recall) [8].

Traditionally, it has been recommended that people living with T1DM consume 45% to 60% of total energy intake from carbohydrate sources [9]. Dietary approaches commonly used to manage glycemic control includes carbohydrate counting, which matches insulin to carbohydrate intake, and/ or a low glycemic index diet [10, 11].

Recently, there has been a growing focus on the utility of a low carbohydrate diet to manage glycemic control in individuals living with T1DM [12, 13]. This dietary management strategy has been thoroughly investigated in people living with type 2 diabetes (T2DM) [14, 15]. However, there is a paucity of evidence regarding T1DM.

A very low carbohydrate diet is defined as 0-50g per day or <10% of the total daily energy intake [16] and a low carbohydrate diet is defined as <130g per day or <26% of total daily energy intake [16, 17]. Schmidt et al. (2019) conducted a randomized cross-over study to examine the effects of a low carbohydrate diet (LCD <100g carbohydrate/day) compared to a high carbohydrate diet (HCD >250g carbohydrate/day) on glycemic control. Participants baseline characteristics included Caucasian adults [(males n=6 (43%) and females n=8 (57%)] with T1DM (n=14), aged 44±12 years from Denmark. Participant median diabetes duration was 19 (13-32) years and HbA1c was 7.5% (7.2%-7.6%). Participants undertook two, 12-week interventions separated by a 12 week “washout” period [12]. Ten of the 14 participants completed the study. The study found that a LCD compared to a HCD did not significantly improve HbA1c, but stabilized glucose variability and reduced hypoglycemia frequency (P<.001) [12].

There is only one systematic review that has examined the association between very low and low carbohydrate diets and glycemic control in people living with T1DM [18]. It included a total of nine original studies: 2/9 RCT [19, 20], 2/9 quasi pre/post cross-sectional [21, 22], 4/9 case series [23-26], and 1/9 case reports [27] with participants ranging from 14 to 65 years of age residing in either the UK, USA, Europe, Australia or New Zealand. Less than half of the studies 3/9 reported a significant

improvement in HbA1c (0.7% to 2.4%, *P*<.05) [18]. The difference in sample sizes, study methodologies and participant baseline characteristics (age, gender, ethnicity and diabetes duration) may account for these non-significant results. Despite a paucity of evidence, associations have been observed between very low and low carbohydrate diets, and good glycemic control in individuals living with T1DM [13, 19, 23-26]. However, these findings are relatively mixed [12, 13, 19, 21, 23-26, 28-31].

Very little research has been conducted in the area of a low carbohydrate diet and quality of life (QoL) in adults living with T1DM. Additional research is needed to determine if there is a link between these two variables because T1DM has been reported to be the cause of a reduced QoL [32]. Roy and Lloyd (2012) conducted a systematic review to examine the evidence for rates of depression within the diabetes population. The authors reported the prevalence of depression to be three-times higher in people living with T1DM when compared to those without it (12% vs. 3%). In Australia, it has been divulged that 41% of adults (>18 years old) living with T1DM experience diabetes related anxiety, depression and stress [33]. In turn, these psychological issues have been linked with suboptimal glycemic control and diabetes complications thus contributing to diminished QoL.

There is no agreed explanation of QoL [35, 36] as demonstrated by the numerous existing definitions reported in the literature [36-40]. There is however, universal agreement that QoL is a multi-dimensional, subjective construct that includes at least three domains (physical e.g. pain, psychological e.g. body image and social well-being e.g. relationships) [35-37, 41-44]. Common QoL definitions don't appear to take a holistic lifestyle approach failing to consider dietary well-being, a key aspect of QoL for individuals living with T1DM [45].

QoL is commonly assessed in T2DM populations [46, 47] however rarely in adults living with T1DM [48]. Pereira et al. (2020) conducted a systematic review to determine the relationship between QoL and HbA1c in those living with T1DM. The review included 110 studies (78 observational and 32 interventional) from countries in North America and Europe, which consisted of 69 T1DM studies, 35 T2DM studies, and six studies including both T1DM and T2DM [47]. All studies included approximately a 1:1 male to female participant ratio, with an age range from 5 to 70 years and a diabetes duration from 2 to 29 years. QoL instruments used included the Diabetes Quality of Life Measure (DQOL) [49] and the Diabetes Quality of Life for Youths Measure (DQOLY) [50]. Baseline HbA1c for T1DM interventional and observational studies ranged from

6.1% to 11.0% and 7.0% to 12.2% respectively. Endpoint HbA1c ranges for interventional and observational studies reduced to 5.9% to 9.5% and 7.1% to 9.6% respectively. Despite a reduction in HbA1c, only 41% of participants reported an improvement in QoL suggesting people living with T1DM generally perceive this as unsatisfactory [47].

The Diabetes Specific Quality of Life scale is the only validated QoL instrument for adults living with T1DM [48]. Nevertheless, it is not suitable for assessing the dietary well-being of Australian adults because the instrument fails to consider carbohydrate counting, which is a fundamental skill, used by those living with T1DM in Australia to manage insulin and BGLs [51]. The instrument also neglects to assess food intake satisfaction, which is another important aspect of dietary well-being [45]. These factors are likely to influence QoL outcomes therefore, the development of a new T1DM specific QoL instrument, that includes four domains, physical, psychological, social and dietary well-being, is being proposed.

To address the identified gaps in the literature our study aims to:
1. Develop and validate a diabetes specific quality of life questionnaire for use in Australian T1DM adults and,
2. Determine if an association exists between a low carbohydrate diet, quality of life and glycemic control.

Methods

Study Design and Ethics

This cross-sectional study will be conducted in three phases:

- Study phase 1: online Australian Diabetes specific quality of life questionnaire development and piloting.
- Study phase 2: Australian Diabetes specific quality of life questionnaire validation:
    - Study sub-phase 2a: Initial validation: Online Diabetes specific quality of life questionnaire and
    - Study sub-phase 2b: Online questionnaire validation of the Australian Diabetes specific quality of life questionnaire, SF-36, DQOL and PAID-20 questionnaires.
- Study phase 3: Intervention: to determine if an association exists between a low carbohydrate diet, quality of life and glycemic control in adults living with T1DM.

Ethics approval has been obtained from the Gold Coast Hospital and Health Service (GCHHS) Human Research Ethics Committee (HREC) and the University of Canberra Human Research Ethics

Committee. Ethics approval numbers as follows:

- Study phase 1 and 2: HREC/2019/QGC/54049 and HREC/2019/UC/2223.
- Study phase 3: HREC/2019/QGC/60717 and HREC/2020/UC/4691.

The study was registered at ClinicalTrials.gov (NCT04213300).

Participant Recruitment

Participant recruitment for each study phase will be facilitated by both face to face and online (such as social media and email) approaches. Information posters will be placed across the GCHHS patient waiting areas containing the Principal Investigator (PI) contact details (email, phone number) and a questionnaire QR code. A flow chart for each study phase is shown below.

GCHHS HREC and University of Canberra HREC, approval received.

Study phase 1: Online Australian diabetes specific quality of life questionnaire: Development and Piloting:

- Participants: 25-30 T1DM adults (≥18 years old).
- Data collection duration: 1 month.
- Method: online questionnaire followed by a face to face or online interview.
- Online questionnaire duration: 10-15 minutes.
- Face to face or online interview location: Gold Coast University Hospital, Outpatient Department, Diabetes Resource Centre or Zoom online platform (the participant may choose their preferred interview method).
- Face to face/online interview duration: 20-30 minutes.
- Interview data will be audio recorded, transcribed verbatim, coded and common themes identified. A summary of key suggestions for revising the online questionnaire, to be used in study sub-phases 2a and 2b will be produced.

Study phase 2a: Initial validation: Online Australian diabetes specific quality of life questionnaire:

- Participants: 364 adults (≥18 years old) with T1DM.
- Data collection duration: 3 months.
- Participant questionnaire access duration: 2 weeks (where a questionnaire link expires, the participant may request a new link by contacting the PI).
- Estimated online questionnaire completion time: 10-12 minutes.

Study phase 2b: Subsequent validation: Online Questionnaire Validation of the Australian diabetes specific quality of life questionnaire, SF-36, DQOL and PAID-20 questionnaires:

Three months after the study sub-phase 2a is completed, study sub-phase 2b will commence. Participants from study sub-phase 2a will be invited by email to complete the

same online questionnaire for a second time. In addition, they will be asked to complete the following:

- MOS 36-item Short Form Health Survey (SF-36) [52],
- Diabetes Quality of Life (DQOL) [49] and
- Problem areas in diabetes scale (PAID) [53].
- Responses will be analysed to determine the statistical reliability and validity of the Australian diabetes specific quality of life questionnaire.
- Participants: 100 adults (≥18 years old) with T1DM.
- Data collection duration: 3 months.
- Participant questionnaire access duration: 2 weeks (where the questionnaire link expires, the participant may request a new link by contacting the PI).
- Estimated online questionnaires completion time: 15-18 minutes.

Study phase 3: Intervention: to determine if an association exists between a low carbohydrate diet, quality of life and glycemic control in adults living with T1DM:

Study design: cross-sectional cohort study.

Participants: 16-23 adults (≥18 years old) with T1DM.

Study phase 3: Pre-intervention, Intervention, Post intervention

Pre-intervention: One week prior to commencing the intervention, participants will attend the study hospital for approximately three hours to:

- Complete the study consent form (hard copy), if not already completed.
- Discuss the intervention process ensuring they have a clear understanding of what is required during all phases of the intervention.
- Receive an information kit containing:
    - The study procedure;
    - The research team contact details (endocrinologist, CDE and diabetes dietitian) and Gold Coast Hospital Emergency Department;
    - A food diary;
    - A sick day management plan and
    - Support services (in case any psychological distress is experienced during the study).
- Complete the online Australian Diabetes specific quality of life questionnaire.
- Have weight (kg), height (cm) and HbA1c recorded.
- Receive CGMS education and supply of CGMS equipment.
- Apply the CGM sensor to their abdominal wall, attach the transmitter and establish a connection between the transmitter and their own compatible smart device, for recording and displaying of their glucose levels.
- Participants will be instructed to continue with their usual, daily routine however, they will be asked to commence recording what they eat and drink via a food diary.

The day prior to commencing the intervention, participants will receive by email their individualized meal plans.

Intervention: Setting: In the participants own environment: Duration: 12 weeks

- Follow the low carbohydrate dietary plan (dietary composition CHO 20% (<100g)

protein 25% and fat 55%) as prescribed by a diabetes dietitian.
- Complete a daily food diary.
- Test blood ketone levels weekly (at fasting).
- Participate in a weekly endocrinologist appointment to discuss BGLs and insulin adjustments by telephone and diabetes dietitian appointment to discuss any concerns with the dietary plan by telephone.
- Contact the CDE if having problems with the CGMS.
- Change the CGM sensor every 10 days.

Post intervention: The day after the intervention has been completed participants will attend the study hospital for up to 90 minutes for the following:

- To record weight (kg) and HbA1c by the CDE.
- To complete the online Diabetes specific quality of life questionnaire and online patient global impression change questionnaire.
- Participation in a face to face CGMS experience interview with the PI.

Participants Eligibility Criteria

Inclusion criteria

Study participants for each phase will self-identify against the following eligibility criteria: 1) aged ≥18 years; 2) living with T1DM and 3) T1DM diagnosis for ≥1 year. Study phase 3 includes five additional eligibility criteria that participants must meet: 1) use of multiple daily injections for insulin administration; 2) experienced at least one hypoglycemic episode since diagnosis; 3) knowledge of hypoglycemic management; 4) ability to test for blood ketones and 5) knowledge of blood ketone management.

Exclusion criteria

Ineligible participants include: 1) people living with T2DM; 2) people living with gestational diabetes mellitus; 3) people who administer insulin using a continuous subcutaneous insulin infusion; 4) those living with a known food allergy; 5) those with a history of an eating disorder; 6) having a BMI <18.5kg/m^2; 7) aged <18 years; 8) those who are pregnant or planning to conceive; 9) those taking prescription medications such as phentermine or corticosteroids; 10) individuals with an active medical problem that may hinder their ability to take part or potentially affect study outcomes such as a recent myocardial infarction, stroke or peripheral re-vascularization (within 3 months), active treatment of diabetic retinopathy, recent serious infection (requiring in-hospital treatment or prolonged antibiotic therapy); 11) those for whom written materials may be unsuitable i.e. vision impaired/illiterate individuals; 12) those unable to understand English and 13) those who fail to sign the participant consent form.

Sample Size

Study phase 1: Online Australian diabetes specific quality of life questionnaire development and piloting

Sample size data will be collected from approximately 25-30 adult participants with T1DM. This sample size is based on previous research [54] which has been deemed as sufficient to facilitate in-

depth face-to-face interviews [55].

Study phase 2: Online Australian diabetes specific quality of life questionnaire validation: compromises of two sub-phases 2a and 2b:

Study sub-phase 2a: Initial validation: online Australian diabetes specific quality of life questionnaire: will require 364 adult participants with T1DM. This sample size has been calculated using the participant to item ratio method [56].

Study sub-phase 2b: Subsequent validation: online Australian diabetes specific quality of life questionnaire, SF-36, DQOL and PAID-20 questionnaires: will need 100 responses to be collected for test re-test, convergent and divergent validity statistical analysis. This sample size (n=100) is based on biostatistician advice and other studies that have validated QoL instruments [49, 57-59].

Study phase 3: The low carbohydrate dietary intervention

Sample size (n=16) is calculated with a 0.05 significance level and power of 0.8 to detect a significant clinical difference of 1.0% in HbA1c. A 1.0% change in HbA1c will be used because dietary changes alone have shown to improve HbA1c by 1.0% [60]. To complete the study 16 participants are required. To account for a 40% attrition rate [12], 23 participants will be the maximum number recruited.

Data privacy and confidentiality

Confidentiality and privacy of participant data will be restricted to the PI. The strategy for identification, coding and de-identification of participant data will involve recording the participants' name, email address and contact phone number in an electronic master list stored at the hospital and retained for archiving purposes. All questionnaires in this study will be delivered using an online encrypted questionnaire platform to ensure participant responses are secure and confidential.

Data Collection

Study phase 1: Online Australian diabetes specific quality of life questionnaire development and piloting

Volunteering participants will consent to completing both the online questionnaire and a face to face interview. Table 1 outlines each questionnaire section and provides a brief description of what is included. The participants' pilot questionnaire link will be active for two weeks. A courtesy email reminder will be sent to those who have not completed or have partially completed the pilot questionnaire after seven days. It is anticipated that the questionnaire will take 10-15 minutes. Once

the pilot questionnaire is completed, the participant will be contacted via phone to arrange a suitable time for either a face to face interview at the study hospital or an online interview. It is estimated that the duration of interview will be 20-30 minutes. Interviews will be undertaken by the PI with the aid of a question guide to ensure a consistent approach is followed. Each interview will be audio-recorded then transcribed verbatim. Common participant feedback will be documented then reviewed by the research team. As a result, this feedback will be used to modify specific items identified as needing improved clarity and conciseness or removed due to irrelevance. The revised version of the online questionnaire will be used in study phase 2, sub-phases 2a and 2b.

Table 1: Study Phase 1: Online Australian diabetes specific quality of life questionnaire completed by adults with type 1 diabetes mellitus (n=25-30)

Questionnaire section	Items Brief Description	Source
Section 1: Information sheet[a]	Overview of the study.	NA
Section 2: Screening questions[b]	Assessment of study eligibility.	NA
Section 3: Consent form[a]	Signed by participant.	NA
Section 4: Australian Diabetes specific quality of life questions[c]	A 28-item questionnaire containing four constructs measuring diabetes quality of life using a 10-point Likert scale “very strongly disagree to “very strongly agree”.	Adapted from [48, 57]
Section 5: Sociodemographic covariates	Data collection: gender, age, height, weight, diabetes duration, occupation, level of education etc.	Adapted from [61-63]

[a]Participant Information and Consent form - completed online.
[b]Screening questions - completed online. Response to each question is yes or no. The questions include:

1. I have type 1 diabetes mellitus;
2. I am 18 years or older and
3. I have had type 1 diabetes mellitus for one year or longer.

[c]Australian diabetes specific quality of life questions developed using previously validated questionnaires [48, 57], input received from the research team and through one to one participant interviews.

Study phase 2: Online Australian diabetes specific quality of life questionnaire validation

Study phase 2 has been split into two sub-phases 2a and 2b:

Study sub-phase 2a: Initial validation: Online Australian diabetes specific quality of life questionnaire

Data will be collected from 364 participants to support the statistical validation of the questionnaire. These 364 participants will be different to those who participated in Study phase 1. Table 2 shows each questionnaire section and a brief description of the section. After seven days, one reminder email will be sent to those participants who have not commenced or have only partially complete the questionnaire. It is anticipated that the questionnaire will take 10-15 minutes to complete.

Study sub-phase 2b: Subsequent validation: Online Australian diabetes specific quality of life questionnaire and SF-36, DQOL and PAID-20 questionnaires

All participants (n=364) from study sub-phase 2a will receive an email three months after completing the initial online questionnaire requesting the completion of the questionnaire for a second time. This email will also request the participant to complete online the MOS 36-item Short Form Health Survey (SF-36) [52], Diabetes Quality of Life (DQOL) [49] and Problem Areas In Diabetes Scale (PAID) [53]. Participants will be supplied with one link for access to all four questionnaires. Of the 364 participants, 100 participants will be needed to complete the questionnaire to establish test re-test validity, convergent and divergent validity. Table 3 outlines the questionnaires to be completed as part of the subsequent validation process.

Table 2: Study phase 2a: Initial validation: Online Australian diabetes specific quality of life questionnaire completed by adults with type 1 diabetes mellitus (n=364)

Questionnaire section	Items Brief Description	Source
Section 1: Information sheet[a]	Overview of the study.	NA
Section 2: Screening questions[b]	Assessment of study eligibility.	NA
Section 3: Consent form[a]	Signed by participant.	NA
Section 4: Australian diabetes specific quality of life questionnaire	A 28-item questionnaire containing four constructs measuring diabetes quality of life using a 10-point Likert scale “very strongly disagree” to “very strongly agree”.	Adapted from [48, 57]
Section 5: Sociodemographic covariates	Data collection: gender, age, height, weight, diabetes duration, occupation, level of education etc.	Adapted from [61-63]

[a]Participant Information and Consent form - completed online.

[b]Screening questions - completed online. Response to each question is yes or no. The questions include:

1. I have type 1 diabetes mellitus;
2. I am 18 years or older and
3. I have had type 1 diabetes mellitus for one year or longer.

Table 3: Study Phase 2b: Subsequent validation: Online Australian diabetes specific quality of life questionnaire, SF-36, DQOL and PAID-20 completed by adults with type 1 diabetes mellitus (n=100)

Questionnaire section	Items Brief Description	Source
Section 1: Information sheet[a]	Overview of the study.	NA
Section 2: Screening questions[b]	Assessment of study eligibility.	NA
Section 3: Consent form[a]	Signed by participant.	NA
Section 4: Australian diabetes specific quality of life questionnaire	A 28-item questionnaire containing four constructs measuring diabetes quality of life using a 10-point Likert scale “very strongly disagree” to “very strongly agree”.	Adapted from [48, 57]
Section 5: MOS SF-36	Measures physical and psychological constructs of general well-being. Response scales vary.	[52]
Section 6: Diabetes Quality of Life (DQOL)	A 43-item instrument consisting of four constructs (satisfaction, impact, worry: social/vocational and worry: diabetes related. A Likert response format “very satisfied” to “not satisfied” for the satisfaction construct and “never” to “always” for the other constructs.	[49]
Section 7: Problems areas in diabetes (PAID-20)	A 20-item questionnaire that measures diabetes-related distress. Each item addresses a different issue associated with diabetes. A 5-point response scale is used “Not a problem to “Serious problem”.	[53]
Section 8: Sociodemographic covariates	Data collection: gender, age, height, weight, diabetes duration, occupation, level of education etc.	Adapted from [61-63]

[a]Participant Information and Consent form - completed online.

[b]Screening questions - completed online. Response to each question is yes or no. The questions include:

1. I have type 1 diabetes mellitus;
2. I am 18 years or older and

3. I have had type 1 diabetes mellitus for one year or longer.

Phase 3 The low carbohydrate dietary intervention

Phase 3 is planned to commence in February 2021. Potential participants will volunteer to participate in the study by responding to the PI contact details on information flyers in the hospital patient waiting areas or provided to them by an endocrinologist or credentialled diabetes educator (CDE). Potential study participants may include those who participated in study phase 1 or 2 but may not necessarily have participated in any of the previous study phases. Potential participants who contact the PI regarding study participation will have a verbal discussion to ensure they meet the inclusion criteria and, the study requirements will be explained. These include: the requirement to follow a low carbohydrate diet for 12 weeks, use a CGMS for 12 weeks, test blood ketones weekly, complete a daily food diary, participate in two in-person study hospital appointments, participate in weekly diabetes dietitian and endocrinologist telephone appointments. If the participant provides verbal consent to be included in the study, a pre-intervention appointment date and time will be organized with the participant to attend the study hospital one week prior to commencing the intervention. The participant will be sent an email to confirm the appointment date and time as well as a participant information and consent form. The consent form may be completed and returned to the PI by email prior to or at the pre-intervention appointment. Two days prior to the pre-intervention appointment, the PI will telephone the participant as a courtesy reminder of the appointment date and time.

Pre-Intervention Procedure

The pre-intervention appointment will be conducted by a CDE at the study hospital. The CDE will ensure the participant consent form has been completed before commencing the pre-intervention appointment. The CDE will discuss the study procedure to ensure the participant understands what is required during all phases of the intervention. The CDE will record the participants' weight(kg) and height(cm) using a seca® 763 electronic measuring station. This information will be recorded on a participant data collection form which will be used pre and post intervention. A HbA1c test will be undertaken using a SIEMENS DCA Vantage® Analyzer. Participants will complete the online Australian Diabetes Specific Quality of Life questionnaire using a hospital computer. The CDE will provide each participant with a Dexcom® G6 continuous glucose monitoring system (CGMS) kit. The kit includes a transmitter, sensors and a sensor applicator, provided by Dexcom®. Novice CGMS participants will be taught how to use the device. During this appointment, the participant will apply the CGM sensor to their abdominal wall, attach the transmitter and establish a connection between the transmitter and their own compatible smart device, for recording and displaying of their

glucose levels. Participants glucose levels will then record and display via the Dexcom® G6 application which the participant will install onto their compatible smart device. The Dexcom® G6 CMS kit will be retained by the participant at the completion of the study. Participants will not use their own personal glucose monitor during the study to test BGLs. However, the participant will use it weekly to test blood ketones. The participant will also be required to use their own blood ketone strips for this test.

Participants will continue with their usual, daily routine however, they will commence recording food and fluid consumption in a food diary. Participants will be required to complete the daily food diary commencing for one week prior to commencing the intervention and for the 12 weeks of the intervention. The participant will email this information to the diabetes dietitian weekly to ensure these records are being maintained as the information will be used in the final data analysis stage. Participant individualized meal plans will be emailed to each participant the day prior to commencing the intervention. Each participant will also be provided with digital kitchen scales and measuring cups/spoons to assist with weighing and measuring foods and fluids to ensure accuracy of quantities consumed. These instruments have been supplied by the GCHHS Study, Education and Research Trust Account.

Intervention

All participants will follow a prescribed meal plan to meet their estimated energy needs as per the Schofield formula [64]. Meal plan macronutrient distribution will be 20% for carbohydrate, 25% for protein and 55% for fat based on the Australian "*CSIRO low-carb diet*" [65]. The meal plan contains no more than 100g per day of dietary carbohydrate making this intervention, a low carbohydrate dietary regimen as per Feinman et al., 2015 definition [16]. Alcohol influences BGLs, food and fluid choices plus quantities consumed [66]. For this reason, participants are strongly advised to abstain from alcohol consumption during the 12-week intervention. Weekly telephone follow up will be conducted by the diabetes dietitian to discuss any concerns or questions participants may have. Follow-up by telephone has been shown to an effective method to monitor medical nutrition therapy [67, 68]. Weekly telephone appointments will also be conducted by the research teams' endocrinologist to discuss BGLs management and adjust insulin doses as needed.

Any hypoglycemia treatment will be recorded in the food diary in relation when, what and how much carbohydrate was used to treat the hypoglycemic event. If any hypoglycemic events occur, the endocrinologist

will discuss this with the participant during the weekly telephone appointment and advice will be provided to avoid future occurrences. Participants will check blood ketones once a week, the morning after an overnight fast to avoid diabetic ketoacidosis. If blood ketones are present (>0.6mmol/l), participants will follow a "sick day" management plan and if unsure what to do, will contact the research teams' endocrinologist for advice. Participants will be encouraged to follow their usual exercise habits as no exercise advise will be given [69]. This study is unique and if a participant feels they are unable to complete the 12-week intervention, they may withdraw at any time.

Post intervention procedure

At the completion of the intervention, the participant's weight(kg) will be recorded. A HbA1c test will be performed by the research teams' CDE. The online diabetes specific quality of life questionnaire will be re-administered. An online patient global impression of change (PGIC) questionnaire will be administered to determine the participants' perception of the degree of change following the intervention relating to glycemic control and QoL [70]. This PGIC questionnaire will consist of two questions using a seven-point scale ("no change/has got worse" to "a great deal better/ considerable improvement"). Finally, each participant will be asked in an individual interview, five questions regarding the CGMS experience relating to its acceptability, perception, benefits and barriers. An interview question guide will be used to facilitate the interview. Data will be transcribed, coded and common themes identified for inclusion in a publication.

Potential adverse events

Hypoglycemia, hyperglycemia, blood ketones and diabetic ketoacidosis (DKA) episodes

All adverse events will be discussed between the research teams' endocrinologist and participant and a plan will be put in place to prevent any future occurrences. Furthermore, adverse events are not envisaged due to the safety alerts thresholds that will be set up on the CGM as recommended by the CGM use guidelines [71].

Outcomes

The primary outcomes:

1) Study phase 1 will develop and pilot the new Australian diabetes specific quality of life questionnaire, primary outcome 1 (PO1);
2) Study phase 2 will validate the study developed questionnaire (PO2) and
3) Study phase 3: will result in three sub-deliverables that will:

3.1) Examine the association between a low carbohydrate diet and glycemic control in adults with T1DM (PO3.1)

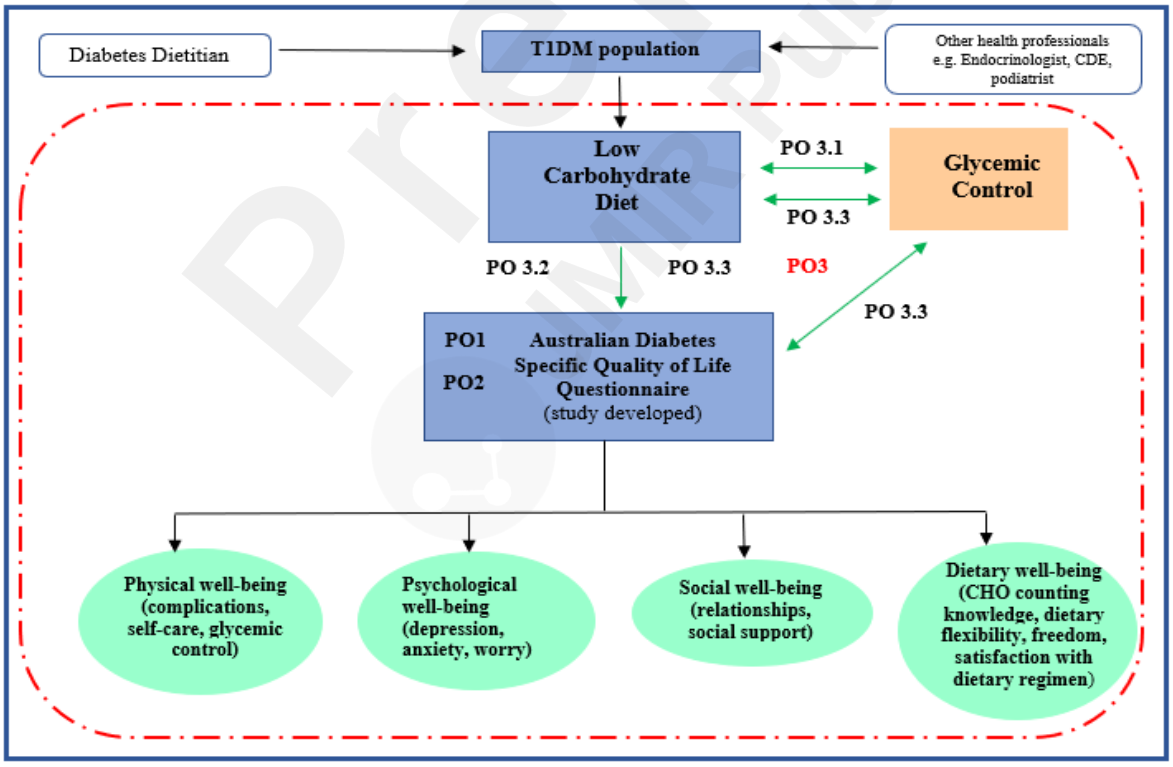
3.2) Examine the association between a low carbohydrate and quality of life in adults with T1DM (PO3.2);

3.3) Investigate whether a low carbohydrate diet mediates the relationship between quality of life and glycemic control in adults with T1DM (PO3.3).

There are no secondary study outcomes.

Figure 1 schematically shows the relationship between the study objectives. The association between quality of life, low carbohydrate diet and glycemic control variables have been represented with double headed arrows. This indicates that the direction of the association is unclear and may be bidirectional in nature as each variable has the potential to influence the other [13, 19, 30].

Figure 1: The association between adults living with type 1 diabetes mellitus, quality of life and glycemic control



Study phase 1: Australian diabetes specific quality of life questionnaire development and piloting

A qualitative approach will be implemented to analyze data collected from audio-recorded participant interviews. Coding will be undertaken using an interview question guide as a framework. The question guide includes the following categories: 1) technical aspects; 2) formatting and layout; 3) participant understanding of the questionnaire aim and purpose; 4) interpretation of the questions; 5) time taken to complete the questionnaire and 6) any other feedback to improve the usefulness of the questionnaire. In addition, divergence and concordance of participant opinion will be noted. Following this process, data will be cross-checked by a second CDE (trained coder). Any discrepancies will be resolved by a round table discussion with the study team, and questionnaire items to be revised will be determined at this forum.

Study phase 2: Online Australian diabetes specific quality of life questionnaire validation and Study phase 3: The low carbohydrate dietary intervention

Data will be coded, entered into a password protected database and checked by the PI followed by a cross check by the same CDE (trained coder) from study phase 1. Descriptive statistics will be reported using mean and standard deviations (SDs). Study phase 2 (includes subphases 2a and 2b) and 3 data will be analyzed using R statistical software (version 3.6.1) or later [72]. Statistical significance will be $P<.05$.

Statistical Plan

Table 4 outlines a brief summary of the study objectives, the independent and dependent variables relating to each objective and the planned statistical analysis to be conducted.

Table 4: Brief statistical plan

Statistical objectives	IV	DV	Statistical analysis
To develop and pilot the Australian Diabetes Specific Quality of Life Questionnaire	Australian Diabetes Specific Quality of Life Questionnaire	N/A	Transcribe, code, identify common themes of interview data
To validate the Australian Diabetes Specific Quality of Life Questionnaire (study developed)	Australian Diabetes Specific Quality of Life Questionnaire	Factorial validation indicators: Root mean square error of approximation, Comparative fit	Exploratory Factor Analysis, Confirmatory Factor Analysis, Structural

		index, Tucker-Lewis Index, Root mean square error of approximation	Equation Modelling
To examine the association between a low carbohydrate diet and glycemic	Low carbohydrate diet	Glycemic control	Bivariate: ANOVA, correlations Multivariate: hierarchical regression controlling for sociodemographic covariates
To examine the association between QoL and a low carbohydrate	Low carbohydrate diet	QoL	Bivariate: ANOVA, correlations Multivariate: hierarchical regression controlling for sociodemographic covariates
To investigate whether a low carbohydrate diet mediates the relationship between QoL and glycemic control	Low carbohydrate diet	Glycemic control QoL	Bivariate: ANOVA, correlations Multivariate: hierarchical regression controlling for sociodemographic covariates

Results

To date, 12 participants have been recruited into phase 1 of this study. The anticipated data collection completion date for all study phases is March 2022. At present, no study results are available.

Discussion

This study is the first of its kind by examining the association between a low carbohydrate diet, QoL and glycemic control. This cross-sectional study protocol aims to 1) develop, pilot and validate a diabetes specific QoL questionnaire and 2) determine if an association exists between QoL and glycemic control while using a low carbohydrate dietary intervention in Australian adults living with T1DM.

The strengths of this study are that, to our knowledge, no previous published research has evaluated a low carbohydrate diet and its influence on QoL and glycemic control in Australian adults living with T1DM. Moreover, this is the first study to develop and validate an Australian T1DM specific QoL questionnaire Therefore, these strengths make this study unique in its approach.

Potential limitations of this study include firstly, the Australian diabetes specific QoL questionnaire is not available to those who are vision impaired, intellectually impaired or have any other type of diabetes such as T2DM and gestational diabetes mellitus. Future studies could develop resources to include these populations. Secondly, in study phases 1 and 2, questionnaire data will be self-reported and may have the potential to result in social desirability bias [73]. However, self-reported data is the most feasible option for this pilot study in order for the sample size (n=364) and statistical validation of the questionnaire to be achieved. Thirdly, study phase 3 has been designed as a non-randomized intervention group pilot study, that will inform the design and feasibility of a potential larger randomized control trial. Finally, in study phase 3, there is potential selection bias. Individuals who are highly motivated to improve glycemic control are more likely to participate [25].

The Australian diabetes specific QoL questionnaire will be a useful instrument for health care professionals (HCPs) such as general practitioners, diabetes dietitians and diabetes educators. This instrument will support HCPs to gain a better understanding of Australian T1DM adults' QoL perception relating to physical, psychological, social and dietary well-being. To-date, studies that have investigated the influence of a very low or low carbohydrate diet and glycemic control in adults living with T1DM, have not examined QoL using a validated instrument in tandem with participants undertaking the dietary regimen [12, 13, 19, 21, 23-31]. Consequently, a validated QoL instrument is needed for clinical practice and future research to identify Australian T1DM adults QoL as no validated instrument currently exists.

It is recommended that people living with T1DM follow the general population healthy eating dietary guidelines [3]. However, this study's dietary intervention outcomes could provide an alternative approach. Additionally, the study findings could warrant the development of a specific dietary guideline for using a low carbohydrate diet to support glycemic management and improve QoL in adults living with T1DM.

This study will generate a new validated QoL instrument which could be used in evidence-based practice and research to understand T1DM adults QoL. It will also investigate the association of a low carbohydrate diet, QoL and glycemic control in Australian adults living with T1DM. If successful, this study has the potential to have a profound impact on those living with T1DM.

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Author's Contributions
All authors contributed to the development of the study concept. JP authored the first version of this article, reviewed by RJ, PD and CKA and further revisions made by JP.

Conflicts of Interest
None declared.

Abbreviations
BGLs: blood glucose levels

CDE: credentialled diabetes educator

CHO: carbohydrate

CGM: continuous glucose monitor

CGMS: continuous glucose monitoring system

cm: centimeter

DQOL: Diabetes quality of life

DV: dependent variable

GCHHS: Gold Coast Hospital and Health Service

HbA1c: glycated hemoglobin

HCPs: health care professionals

HREC: human research ethics committee

INT: intensive insulin therapy

IV: Independent variable

kg: kilogram

PAID: Problem areas in diabetes

PGIC: Patient global impression of change;

PI: Principal investigator

PO: primary outcome

QoL: quality of life

RCT: randomized control trial

SERTA: Study, Education and Research Trust Account

SF-36: MOS 36-item short form health survey

T1DM: type 1 diabetes mellitus

UC: University of Canberra

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Supplementary Files

Figures

The association between adults living with type 1 diabetes mellitus, quality of life and glycemic control.