PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Randomized controlled trial of a web-based low carbohydrate diet intervention for adults with type 2 diabetes: The T2Diet study protocol
AUTHORS	Dening, Jedha; George, Elena; Ball, Kylie; Mohebbi, Mohammadreza; Shariful Islam, Sheikh Mohammed

VERSION 1 – REVIEW

REVIEWER	Brinkworth, Grant D CSIRO, CSIRO human nutrition
REVIEW RETURNED	11-Aug-2021

GENERAL COMMENTS	This paper represents a study protocol of a randomised trial that aims to compare a web-based low carb diet intervention with standard care to standard care only for 16-week in 100 adults with type 2 diabetes. It is a well prepared manuscript and well-designed study that will appropriately test the proposed aim and hypothesis. A few minor comments were noted for consideration: Abstract: Page 5, Line 14: The statement that this is the first web-based study to evaluate the effects of a low-carb diet should be checked for accuracy. There a several other web-based low carb diet programs currently available that have been evaluated with formal publications in the mainstream literature. The paper listed is an example: Laura R Saslow 1, Charlotte Summers 2, James E Aikens 3, David J Unwin 4 Outcomes of a Digitally Delivered Low-Carbohydrate Type 2 Diabetes Self-Management Program: 1-Year Results of a Single-Arm Longitudinal Study. JMIR Diabetes. 2018 Aug 3;3(3):e12. doi: 10.2196/diabetes.9333. Do the authors mean the first RCT to examine a web-based low-carb intervention? Methods: Please provide additional information of how T2D diagnosis will be confirmed? Will patients that have been previously diagnosed with T2D, using diabetes medications but with a HA1c <7.0% be excluded? Whilst glycaemic control is the primary target for diabetes management, type 2 diabetes is closely associated with other cardiometabolic risk factors that are closely interrelated and routinely monitored in patients with type 2 diabetes that are both positively (Triglycerides and HDL-c levels) and negatively (LDL-C level) impacted by a low carbohydrate diet. Has any consideration

	been given to assessing these routine health markers n T2D management. If not, this could limit the translatability of the intervention and research outcomes into clinical practice. Will participants in the intervention group pay for the online intervention? If not, unless this is provided free of charge in clinical practice this maybe a confounder in the translation of the results into the real-world. This should be made clear and acknowledged. Will any instructions of physical activity be provided or measure of physical activity be assessed?

REVIEWER	Lowe, JM The University of Newcastle, University of Newcastle
REVIEW RETURNED	06-Sep-2021

GENERAL COMMENTS	This is an interesting trial and if successful will be of particular benefit during COVID19 restrictions. It will also help people with diabetes in rural and remote areas. I have some concerns about the failure to involve the patients' GPs in any way- if only to notify them that their patient is in the study, as they or their practice nurse may be giving the patient contradictory advice and causing confusion. In a larger and longer study it would be of benefit to have access to other laboratory results that GPs may be checking such as lipids. I would liek to see the role of GPs (who are delivering the standard care) better acknowledged. A limitation is the short-term nature of the study as almost any intervention improves control in a six month time period but it is maintainance of better glycaemic control long term that is hard to achieve.

REVIEWER	Finucane, Francis Galway University Hospital, HRB Clinical Research Facility
REVIEW RETURNED	27-Sep-2021

GENERAL COMMENTS	BMJO 2021 054594 reviewer comments: This protocol describes a randomised controlled trial in adults with insulin naïve type 2 diabetes and a HbA1c above 53 mmol/mol of a low carbohydrate online intervention compared to usual care, on HbA1c after 16 weeks. The study population of 100 patients, with randomisation stratified by age and sex and with anticipated dropout of 20% is modest. The anticipated effect size of 5 mmol/mol in the primary outcome after just 16 weeks seems very large. The authors present a power analysis suggesting that recruiting 100 patients will be adequate. This is an interesting and timely study and the authors cover most of te important issues well. In the abstract introduction, I would like to see more of an emphasis on defining the study population better and on recognising the role of the MDT, not just the physician. Also the controversy around carbohydrate restriction needs to be embraced and acknowledged. I'm not sure that measuring the confounding effects of things like medication usage is necessary or sound in an RCT. The authors mention allocation concealment and blinding, two major issues that are considered inadequately in many similar studies. Why is there a need for a specified lower limit of CHO intake? Will the authors measure hunger and satiety?

REVIEWER	Gluud, Lise Copenhagen University Hospital, Gastro Unit Copenhagen University Hospital - Hvidovre
REVIEW RETURNED	07-Oct-2021

GENERAL COMMENTS	This is an interesting trial and very clinically relevant. The primary outcome is well-defined and justified. I have very few comments. It is an important first step towards web-based interventions, longer follow up would provide important information although the justification for the 16-week intervention is provided. My main question is regarding the sample size calculation where the power and estimated difference is described but not eg sd or alpha. Likewise, the planned methods that will be used in the analyses are not clearly described, e.g., the handling of missing outcomes. The methods that will be used to blind outcome assessors were not clear to me.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Grant D Brinkworth, CSIRO
Comments to the Author:
This paper represents a study protocol of a randomised trial that aims to compare a web-based low carb diet intervention with standard care to standard care only for 16-week in 100 adults with type 2 diabetes.

It is a well prepared manuscript and well-designed study that will appropriately test the proposed aim and hypothesis.

A few minor comments were noted for consideration:

Abstract:
Page 5, Line 14: The statement that this is the first web-based study to evaluate the effects of a low-carb diet should be checked for accuracy. There a several other web-based low carb diet programs currently available that have been evaluated with formal publications in the mainstream literature. The paper listed is an example: Laura R Saslow 1, Charlotte Summers 2, James E Aikens 3, David J Unwin 4 Outcomes of a Digitally Delivered Low-Carbohydrate Type 2 Diabetes Self-Management Program: 1-Year Results of a Single-Arm Longitudinal Study. JMIR Diabetes. 2018 Aug 3;3(3):e12. doi: 10.2196/diabetes.9333. Do the authors mean the first RCT to examine a web-based low-carb intervention?

RESPONSE: Thank you for correcting this inaccuracy. We are aware of other web-based low carbohydrate diet programs and extend our apologies that this was an error in the text. The manuscript was meant to state the first RCT and has been updated on page 3 of the manuscript:
“To the best of our knowledge, this is the first RCT to evaluate the effectiveness of a web-based low carbohydrate diet (10-<26% energy intake) intervention on glycemic control in adults with type 2 diabetes.”
Methods:
Please provide additional information of how T2D diagnosis will be confirmed? Will patients that have

been previously diagnosed with T2D, using diabetes medications but with a HA1c <7.0% be excluded?
RESPONSE: T2D diagnosis will be self-reported. This has been updated on page 5 of the manuscript.
“Inclusion criteria will be adults aged 40-89 years, the most highly affected demographic for T2D in Australia [26], with self-reported non-insulin-dependent T2D and self-reported HbA1c levels ≥7.0% within the previous six months”
At recruitment, the participants HbA1c levels will be self-reported within the previous six months, therefore, it will be expected that participants HbA1c levels may be below 7.0 due to adhering to their diabetes medication requirements, or other factors. For this study, it will not be feasible to exclude participants if their baseline levels return a lower HbA1c result. However, if their baseline report returns as normal ≤5.6%, as defined by the American Diabetes Association, they will be excluded. Thus, to clarify, we have added the following on page 5 of the manuscript:
“All eligible participants with self-reported HbA1c levels ≥7.0% within the previous six months will be included in the study, once baseline HbA1c measurements are conducted
any reports returned as normal ≤5.6% [2] will result in participants being excluded.”

Reference

- American Diabetes Association, Standards of Medical Care in Diabetes—2021. Diabetes Care, 2021. 44: p. S1-S232. https://doi.org/10.2337/dc21-in01

Whilst glycaemic control is the primary target for diabetes management, type 2 diabetes is closely associated with other cardiometabolic risk factors that are closely interrelated and routinely monitored in patients with type 2 diabetes that are both positively (Triglycerides and HDL-c levels) and negatively (LDL-C level) impacted by a low carbohydrate diet. Has any consideration been given to assessing these routine health markers n T2D management. If not, this could limit the translatability of the intervention and research outcomes into clinical practice.
RESPONSE: We recognize the importance of monitoring cardiometabolic risk factors. Consideration of these factors was discussed among the research team. However, due to limited funding and feasibility, we were unable to include any additional biomarkers in this trial. In addition, adding additional biomarkers may have prohibited a completely remote trial, which was necessary to conduct this study during Covid-19. Furthermore, a fully remote trial will enable greater reach in terms of enrolling participants from rural and remote areas. We have added a section to the manuscript on page 16-17 ‘Limitations and strengths’ where we have added the following:
“One limitation is this study will not collect biomarkers related to cardiometabolic risk, which was beyond the scope of this trial. While more research is needed in this area, the overall evidence suggests LCDs may be associated with cardiovascular benefits, as commonla reduction in triglycerides and an increase in HDL cholesterol are observed [6, 8, 13, 68, 69]. For LDL cholesterol, the evidence remains unclear due to mixed reports [9, 75-77]. In addition, blood pressure can be influenced by LCDs [78]. Given this web-based dietary intervention will be provided in conjunction with standard care, biomarkers such as lipid profiles and blood pressure would continue to be routinely monitored by the participants’ GP or healthcare team.…
This study also has significant strengths. While only one primary biomarker will be included, it will enable this research to be conducted remotely. This makes the study highly feasible during COVID-19 when restrictions of movement and face-to-face contact can be limited. In addition, remote delivery will increase the capacity to include participants from wide geographical locations, which will be of benefit given support for people with T2D in rural and remote areas is less accessible [79].”

Will participants in the intervention group pay for the online intervention? If not, unless this is provided free of charge in clinical practice this maybe a confounder in the translation of the results into the real-world. This should be made clear and acknowledged.
RESPONSE: Study participants in the intervention group have no cost to participate in the web-based intervention. At this stage there is no plan for the web-based intervention beyond the study.

Will any instructions of physical activity be provided or measure of physical activity be assessed?
RESPONSE: A measure of physical activity was considered by the research team, however, no instructions or measures for physical activity will be given or collected for this trial. A measure of physical activity was not included for the following three reasons: 1) our objective was to place minimal burden on participants; 2) the intervention did not aim to impact physical activity; 3) the RCT design would account for potential differences in physical activity among participants. In relation to this, we have added the following update to the manuscript under 'Limitations and strengths' on page 16-17:
"Another potential limitation is the study will not measure other lifestyle-related factors such as physical activity or psychological well-being [2]. The intervention was not designed to influence these outcomes, and any differences should be adequately addressed through random distribution in an RCT design."

Reviewer: 2
Dr. JM Lowe, The University of Newcastle, Sunnybrook Health Sciences Centre
Comments to the Author:
This is an interesting trial and if successful will be of particular benefit during COVID19 restrictions. It will also help people with diabetes in rural and remote areas.

I have some concerns about the failure to involve the patients' GPs in any way- if only to notify them that their patient is in the study, as they or their practice nurse may be giving the patient contradictory advice and causing confusion.

RESPONSE: Thank you for highlighting this concern and we acknowledge this is a matter that was not sufficiently explained in the submitted manuscript. To clarify, participants will be encouraged to consult with their general practice physician (GP) and/or healthcare team to discuss their participation in the study. Discussion with their GP and healthcare team is encouraged for all participants, and emphasized for participants taking medications such as sulfonylureas and sodium glucose transport 2 inhibitor medications, which have cautions in relation to LCDs.

A section has been added to the manuscript on page 8 to describe the process that will be used:

"Intervention group follow-up
Approximately three days after being provided with login details for the study website, intervention group participants will be followed up by email or phone to draw their attention to the potential adverse effects of carbohydrate reduction, cautions regarding medications, and to encourage participants to discuss their participation in the study with their GP and healthcare team. Intervention participants will be able to download a study information letter they can give to their GP or healthcare team."

In a larger and longer study it would be of benefit to have access to other laboratory results that GPs may be checking such as lipids.

RESPONSE: This will be the first RCT of a web-based LCD intervention; therefore, there were limitations on what was feasible for this study. However, we acknowledge that in a larger and longer study it could be beneficial to look at dlivering such a web-based intervention through primary care recommendations, where engagement with the patients' GP and healthcare team could be optimized and monitoring of a wider range of health parameters could be implemented.

I would liek to see the role of GPs (who are delivering the standard care) better acknowledged.

RESPONSE: We acknowledge the central role of GPs and would like to highlight that the participants will be taking the web-based intervention, in conjunction with their standard care. To better reflect this, we have updated the manuscript with a number of alterations:

On page 2, Abstract introduction:

“Type 2 diabetes (T2D) management frequently involves a multidisciplinary care team. However, standard care for T2D patients is the central role of the general practice physician, and consists of routine appointments to monitor glycemic status and overall health. Dietary modification is an essential component of T2D management. Evidence suggests a low carbohydrate diet (LCD) provides better clinical outcomes for people with T2D compared to other diets. However, providing dietary support in face-to-face settings is challenged by issues of availability and accessibility. Provided in conjunction with standard care, digital interventions can help bridge this gap.”

On page 3, the Introduction:

“Management of T2D frequently involves engagement of a multidisciplinary healthcare team to ensure the needs of individuals are met comprehensively. However, the general practice physician (GP) plays the central role in providing standard care for T2D management [4].”

On page 4, the Introduction:
“Provided in conjunction with standard care, web-based interventions can help bridge this gap, offering the potential for greater reach and accessibility, with the advantage of being convenient and on-demand to participants when required [19].”

In addition, please view the previous response where we note that participants will be encouraged to discuss their participation in the study with their GP and healthcare team.

A limitation is the short-term nature of the study as almost any intervention improves control in a six month time period but it is maintainance of better glycaemic control long term that is hard to achieve.

RESPONSE: We acknowledge the short-term nature of the study, however, as noted above, a longer study was not feasible for this trial. The duration of this trial was justified in the manuscript on page 5. In summary, a period of 16 weeks was chosen as previous web-based dietary interventions demonstrated significant improvements in glycemic control could be achieved within this timeframe (Dening et al. 2020). As suggested above, being this is the first RCT of a web-based LCD intervention, a larger-scale study with additional biomarkers and longer follow-up would be the logical next step in this research. To address this, we have added the following to the manuscript ‘Limitations and strengths’ on page 16:

“The short duration of this trial is also a potential limitation. However, the duration was justified based on previous web-based dietary interventions [23], and given this will be the first RCT of a web-based LCD intervention, determining effectiveness prior to allocating additional time and resources will be important.”

References

- Dening, J, Islam, SMS, George, E, et al., Web-Based Interventions for Dietary Behavior in Adults With Type 2 Diabetes: Systematic Review of Randomized Controlled Trials. J Med Internet Res, 2020. 22(8): p. e16437. https://doi.org/10.2196/16437.

Reviewer: 3
Dr. Francis Finucane, Galway University Hospital
Comments to the Author:
BMJO 2021 054594 reviewer comments:

This protocol describes a randomised controlled trial in adults with insulin naïve type 2 diabetes and a HbA1c above 53 mmol/mol of a low carbohydrate online intervention compared to usual care, on HbA1c after 16 weeks.

The study population of 100 patients, with randomisation stratified by age and sex and with anticipated dropout of 20% is modest. The anticipated effect size of 5 mmol/mol in the primary outcome after just 16 weeks seems very large. The authors present a power analysis suggesting that recruiting 100 patients will be adequate.

RESPONSE: We acknowledge the concerns regarding the sample size and would like to present further clarification and justification. The dropout rate reflects what we considered reasonable compared to other LCD that had indicated low dropout rates (<10%; Sato et al. 2017, Jonasson et al. 2014) and other web-based dietary studies where average dropout rates were approximately 22% (Dening et al. 2020). The effect size may seem large, although it is similar to what other LCD studies have achieved. The authors Sato et al. (2017), Jonasson et al. (2014), Yamada et al. (2014) conducted LCD RCT studies of 6-month duration with smaller sample sizes ranging from 24 to 72 participants, achieving an average HbA1c reduction of 0.6%. The manuscript, page 12, indicated that the sample size calculation was conducted by an independent statistician using Stata's power twomeans command. We have updated the manuscript on page 12, to include the following for the selected effect size and dropout rate, further justifying the power calculation:

"The effect size of 0.5% was chosen as it is considered a clinically meaningful HbA1c reduction [64]. This may seem large for a relatively short intervention. However, it is not vastly different to previous LCD stuies in people with T2D, where 6-month durations with smaller sample sizes demonstrated reductions in HbA1c of approximately 0.6% [59, 60, 65]. Previous LCD studies have indicated low dropout rates (<10%) [60, 65] and the average dropout across five web-based dietary interventions in people with T2D was approximately 22% [23]. Therefore, a 20% dropout was considered reasonable for this study."

References

- Yamada, Y, Uchida, J, Izumi, H, et al., A Non-calorie-restricted Low-carbohydrate Diet is Effective as an Alternative Therapy for Patients with Type 2 Diabetes. Internal Medicine, 2014. 53(1): p. 13-19. https://doi.org/10.2169/internalmedicine.53.0861.
- Jonasson, L, Guldbrand, H, Lundberg, AK, et al., Advice to follow a low-carbohydrate diet has a favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. Ann Med, 2014. 46(3): p. 182-7. https://doi.org/10.3109/07853890.2014.894286.
- Sato, J, Kanazawa, A, Makita, S, et al., A randomized controlled trial of 130 g/day low-carbohydrate diet in type 2 diabetes with poor glycemic control. Clin Nutr, 2017. 36(4): p. 992-1000. https://doi.org/10.1016/j.clnu.2016.07.003.

- Dening, J, Islam, SMS, George, E, et al., Web-Based Interventions for Dietary Behavior in Adults With Type 2 Diabetes: Systematic Review of Randomized Controlled Trials. J Med Internet Res, 2020. 22(8): p. e16437. https://doi.org/10.2196/16437.

This is an interesting and timely study and the authors cover most of the important issues well. In the abstract introduction, I would like to see more of an emphasis on defining the study population better and on recognising the role of the MDT, not just the physician.

RESPONSE: In response to these comments, we have updated the manuscript:

On page 2, Abstract:

“Type 2 diabetes (T2D) management frequently involves a multidisciplinary care team.”

“100 adults with non-insulin-dependent T2D aged between 40-89 years”

On page 3, Introduction:

“Management of T2D frequently involves engagement of a multidisciplinary healthcare team to ensure the needs of individuals are met comprehensively.”

Also the controversy around carbohydrate restriction needs to be embraced and acknowledged.

RESPONSE: We recognize the historical controversy around carbohydrate restriction, although in recent years LCDs have been accepted by international diabetes care guidelines and have also been successfully implemented through primary care. To reflect this, we have updated the manuscript on page 4 Introduction:

“LCDs had previously been viewed as controversial. However, the growing body of evidence has prompted updates across international diabetes care guidelines, which have acknowledged LCDs as a safe and viable dietary option for people with T2D [2, 10-12]. Systematic reviews and meta-analyses of LCDs in people with T2D have consistently demonstrated greater improvements in glycemic control, increases in HDL cholesterol, decreases in triglycerides, reduced medication requirements [6, 8, 9, 13, 14], and potential for diabetes remission [9]. In addition, significant improvements have been demonstrated in people with T2D provided with LCD recommendations through routine clinical care [15].”

I’m not sure that measuring the confounding effects of things like medication usage is necessary or sound in an RCT.
RESPONSE: We apologize that the justification for the collection of anti-diabetes medication and dosages was inadequate in the submitted manuscript. As such, the manuscript has been updated on page 14:
“Reductions in anti-diabetes medication are commonly reported in LCD studies in people with T2D [8, 13, 14]. It has been noted that this reflects an underestimation in the overall benefits of LCDs [68, 69]. Thus, consideration of the influence of medication requirements needs to be taken into account. The Medication Effect Score will be used to quantify and summarize the changes in anti-diabetes medication [70].”
In addition, after further review of the literature and discussion among the research team, anti-diabetes medications and dosages were described in the manuscript as a secondary outcome and not a confounder. This was revised on page 11, within Table 1, and on page 10:

“Anti-diabetes medication and dosages and diabetes-related comorbidities [4] will be collected to assess changes.”

The authors mention allocation concealment and blinding, two major issues that are considered inadequately in many similar studies.

RESPONSE: Thank you for this positive feedback. We have added a short note on this in the manuscript on page 17 ‘Limitations and strengths’:

“Furthermore, the RCT design, allocation concealment and blinding are key strengths that will minimize bias and maximize the validity of the study findings.”

Why is there a need for a specified lower limit of CHO intake? Will the authors measure hunger and satiety?

RESPONSE: Evidence suggests that a low carbohydrate intake, defined as 10-<26% total energy intake, has a higher rate of adherence compared to very low carbohydrate ketogenic diets, defined as <10% total energy intake (<50g), which is why a lower limit of carbohydrate was applied in the context of this study (Huntriss et al. 2018, Goldenberg et al. 2021). The carbohydrate goal and definition for the intervention was provided on page 6-7. In summary, we stated that the overall goal of this intervention was to achieve a low carbohydrate intake, defined as 10-<26% total energy intake.

We will not be measuring hunger or satiety in this trial and have added this consideration to the ‘Limitations and strengths’ section on page 17:

“In addition, improvements related to hunger and satiety have been previously noted in LCD studies [68, 69], though will not be collected for this trial.”

References

- Huntriss, R, Campbell, M, and Bedwell, C, The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Eur J Clin Nutr, 2018. 72(3): p. 311-325. https://doi.org/10.1038/s41430-017-0019-4.
- Goldenberg, JZ, Day, A, Brinkworth, GD, et al., Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. BMJ, 2021. 372: p. m4743. https://doi.org/10.1136/bmj.m4743.

Reviewer: 4
Dr. Lise Gluud, Copenhagen University Hospital
Comments to the Author:
This is an interesting trial and very clinically relevant. The primary outcome is well-defined and justified. I have very few comments. It is an important first step towards web-based interventions, longer follow up would provide important information although the justification for the 16-week intervention is provided.

My main question is regarding the sample size calculation where the power and estimated difference is described but not eg sd or alpha.

RESPONSE: The standard deviation and alpha was described in the submitted manuscript. Please refer to the manuscript, page 12. In summary, a total of 100 participants (50 per group) will provide

80% power at type I error of 0.05 to detect a between-group difference of 0.5% on HbA1c (primary outcome). The sample size is based on the following assumptions: a standard deviation of 0.9 HbA1c, a pre-post intervention correlation of 0.5 [61], and a dropout rate of 20%.

Likewise, the planned methods that will be used in the analyses are not clearly described, e.g., the handling of missing outcomes.

RESPONSE: The handling of missing outcomes was described in the submitted manuscript. Please refer to the manuscript pages 14 and 15. In summary, multiple imputation techniques with missing at random assumption will be used to impute missing data due to dropouts or withdrawals to comply with the intention-to-treat approach. Sensitivity analysis will be performed to evaluate missing at random assumption for missing observation pattern. Subgroup analysis will be conducted with the duration of diabetes and gender.

The methods that will be used to blind outcome assessors were not clear to me.

RESPONSE: To clarify the blinding of outcome assessors, the manuscript has been updated on page 13:

“Post intervention outcomes, except the primary outcome, will be assessed via participant self-report. Primary outcome assessment will be blinded as HbA1c samples are assessed by the pathology lab with no disclosure of group allocation.”

VERSION 2 – REVIEW

REVIEWER	Brinkworth, Grant D CSIRO, CSIRO human nutrition
REVIEW RETURNED	22-Nov-2021

GENERAL COMMENTS	Thank you to the authors for addressing the reviewer comments comprehensively. No further comments are suggested.

REVIEWER	Lowe, JM The University of Newcastle, University of Newcastle
REVIEW RETURNED	09-Nov-2021

GENERAL COMMENTS	Thank you for your revisions. My only suggestion is to add something to the effect that it is necessary to demonstrate short term efficacy before trialling an intervention for long term effectiveness.

REVIEWER	Finucane, Francis Galway University Hospital, HRB Clinical Research Facility
REVIEW RETURNED	08-Nov-2021

GENERAL COMMENTS	This is an excellent proposal. I hope the trial is successful.