

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Mediterranean Diet and Time-Restricted Eating as a Cardiac Rehabilitation Approach for Patients with Coronary Heart Disease and Prediabetes: The DIABEPIC-1 Protocol of a Feasibility Trial
AUTHORS	Iglesies-Grau, Josep; Dionne, Valérie; Latour, Élise; Gayda, Mathieu; Besnier, Florent; Gagnon, Daniel; Debray, Amélie; Gagnon, Christine; Pelletier, Véronique; Nigam, Anil; L'Allier, Philippe L.; Juneau, Martin; Bouabdallaoui, Nadia; Bherer, Louis

VERSION 1 – REVIEW

REVIEWER	Vázquez-Ruiz, Zenaida University of Navarra
REVIEW RETURNED	19-Jun-2023

GENERAL COMMENTS	<p>The DIABEPIC 1 pilot study protocol aims to determine whether an intensive and up-to-date multidisciplinary cardiac rehabilitation program, combining dietary counseling, physical training, and health education, can successfully reverse prediabetes in patients with coronary heart disease. The implementation of intermittent fasting and the reduction of ultra-processed food consumption as an additional tool to the Mediterranean diet intervention is novel and it will be of interest to observe its potential to reverse prediabetes. The objectives of the study in each phase of the intervention are thoroughly explained and well planned; Table 1 provides a well-organized schedule of the intervention.</p> <p>Concerning the carbohydrate restriction (Line 16), it would be necessary to complete what it refers to, I understand that it is <40% of total energy intake but should be specified. I wonder how the dietitians control that participants do not exceed this limit of carbohydrate intake since they will not be on a portion-controlled diet.</p> <p>Will there be specific recommendations on servings of carbohydrate-rich foods or on the glycemic index of foods? Which carbohydrate-rich foods will be reduced?</p> <p>Did you consider recommending whole-grain versions of carbohydrate-rich foods instead of reducing carbohydrate intake? Why was that option not chosen?</p> <p>The reference number 8 must be completed with the web url .</p> <p>It will be interesting to see the results of this pilot study and to see whether this intervention would be feasible in a randomized trial, as well as whether the reversal of diabetes is sustained over time if patients stop intermittent fasting.</p>
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REVIEWER	Taylor, Roy University of Newcastle
REVIEW RETURNED	15-Jul-2023

GENERAL COMMENTS	<p>This protocol paper addresses an important question. However, describing the intervention 'unique' is incorrect. Several major matters require attention.</p> <ol style="list-style-type: none"> 1. Abstract: First sentence appears to ignore current national programmes of proven efficacy such as the NHS Diabetes Prevention Programme and the Type 2 Diabetes Path to Remission Programme. Similarly the second sentence overlooks current cardiac rehab programmes. Both sentences require to be rephrased. 2. P9 – What training will the nurses have? That is surely an essential study factor to state. 3. P11 – Surely the 'feasibility'/applicability depends largely upon resource available to deploy in routine clinical practice, and for the study itself upon the costed time for the personnel delivering the intervention. 4. P13 – The list of cognitive tests is long and potentially adverse for retention in the study. 5. The flow mediated assessment appears out of place in this preliminary single arm feasibility study. 6. P18, para 2 – 'Exploratory' is curious. The strict dependence of type 2 diabetes remission upon adequate loss of weight has been clearly demonstrated. The inclusion of exercise will blunt the achieved weight loss but the overall effect depends upon intensity as shown by the x study. 7. P20 para 2 – The sentence 'Despite the prevalence of prediabetes there are currently limited options...' is incorrect in view of the well described approaches. Later in the same para, it is curious to read that 'there is no currently agreed-upon terminology...' as pre-diabetes is defined simply in terms of HbA1c, so reversion to normal will be defined by re-entry into the normal range. Claiming that this pilot feasibility study will provide an evidence base for definitions is inaccurate. 8. P21- Quoting ref 17 is inadequate. The ADA/EASD/DUK consensus statement on the definition of T2D remission was published simultaneously in 3 journals in 2021. The authors appear to be out of date with currently accepted norms, and reference 20 provides more detailed information on this point. 9. P25- Attempting to evaluate any relationship between cognitive performance and pre-diabetes is unrealistic on the timescale of the study.
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1 (Comments for the Author):

The DIABEPIC 1 pilot study protocol aims to determine whether an intensive and up-to-date multidisciplinary cardiac rehabilitation program, combining dietary counseling, physical training, and health education, can successfully reverse prediabetes in patients with coronary heart disease. The implementation of intermittent fasting and the reduction of ultra-processed food consumption as an additional tool to the Mediterranean diet intervention is novel and it will be of interest to observe its potential to reverse prediabetes. The objectives of the study in each phase of the intervention are

thoroughly explained and well planned; Table 1 provides a well-organized schedule of the intervention.

Response: We would like to thank Reviewer #1 for his/her thoughtful feedback.

Concerning the carbohydrate restriction (Line 16), it would be necessary to complete what it refers to, I understand that it is <40% of total energy intake but should be specified. I wonder how the dietitians control that participants do not exceed this limit of carbohydrate intake since they will not be on a portion-controlled diet.

Will there be specific recommendations on servings of carbohydrate-rich foods or on the glycemic index of foods? Which carbohydrate-rich foods will be reduced?

Did you consider recommending whole-grain versions of carbohydrate-rich foods instead of reducing carbohydrate intake? Why was that option not chosen?

Response: Thank you for bringing up this important topic. One of the nutritional interventions planned for this feasibility study is to evaluate whether specific dietary instructions can lead to a reduction in carbohydrate consumption to an average of 40% of total calorie intake. To assess participants' dietary habits, they will be asked to complete a 3-day nutritional diary using the Keenoa artificial intelligence tool before the start of the project. The adherence to the Mediterranean Diet will be also evaluated using the Predimed score, which consists of 14 items. This second assessment will provide insights into participants' nutrient intake and their adherence to the Mediterranean Diet in clinical practice. However, it is important to note that this questionnaire does not include an assessment of the number of servings of whole grains consumed by participants for instance, although it is a question regularly asked by the registered dietitian (R.D.).

The initial assessment, which includes objective data from the Keenoa App and subjective information from the Predimed questionnaire, will inform the registered dietitian (RD) about participants' carbohydrate intake, simple sugar intake, fiber intake, net carbohydrate intake, and the proportion of different macronutrient sources. The RD will also have access to pictures of meals consumed by the participants and registered in the application during the 3-day diary. Based on previous studies using the Keenoa app on similar populations from Canada (PMC9723975) and data on calorie consumption from ultra-processed foods in the Canadian population (source: <https://www.heartandstroke.ca/-/media/pdf-files/canada/media-centre/hs-report-upp-moubarac-dec-5-2017.pdf?rev=c844895571d0415cb2e0ab96e3512a46>), we estimate that participants will initially have a mean carbohydrate intake proportion of around 40-50%, with a significant amount of total intake coming from simple sugars.

During the first 3-month intervention, the nutritional advice will be general and will focus on the following: 1) Educating participants on identifying processed and ultra-processed foods according to the NOVA classification, with advice to reduce consumption of Group 2 and 3 products and avoid Group 4 products. This intervention is expected to reduce carbohydrate intake and, particularly, the intake of simple sugars to approximately 40%. 2) The Mediterranean Diet Pyramid will guide participants in adapting to the new dietary pattern. They will be advised to consume a predominantly plant-based diet consisting of vegetables, legumes, fruits, whole grains, nuts, and seeds. As mentioned by the reviewer, the RD will provide personalized one-on-one interventions, identifying carbohydrate-rich foods and recommending quality whole-grain alternatives. For example, during breakfast, participants will be advised to switch from commercial bread to whole-grain bread.

It is assumed (and will be studied) that the reduction in total carbohydrate intake and possible calorie reduction will be a consequence of the step-wise nutritional counseling approach. Although no portion-controlled diet will be specifically implemented, and no specific calorie reduction targets will be set, the results are expected to provide valuable insights into whether general recommendations

based on nutrient quality and dietary patterns can lead to a reduction in total carbohydrate intake, an increase in fiber intake, and a decrease in simple sugar intake, total carbohydrate intake, and overall calorie consumption.

Following the suggestion, we have now provided additional information in the text (in page 8) clarifying that the 40% refers to the proportion relative to the total energy intake.

The reference number 8 must be completed with the web url.

Response: Thank you for bringing up this point. We have now provided complete information for this reference.

It will be interesting to see the results of this pilot study and to see whether this intervention would be feasible in a randomized trial, as well as whether the reversal of diabetes is sustained over time if patients stop intermittent fasting.

Response: Thank you for all of your comments and feedback. We appreciate it. We have taken note of this suggestion to analyze the occurrences during the clinical follow-up of participants in terms of prediabetes reversal or relapse, specifically in relation to changes in adherence to time-restricted eating.

Reviewer #2 (Comments for the Author):

This protocol paper addresses an important question. However, describing the intervention 'unique' is incorrect. Several major matters require attention.

Response: We sincerely appreciate the thoughtful consideration and the valuable, detailed comments provided by Reviewer #2 regarding our manuscript. We have made all the necessary modifications to enhance the quality of the manuscript.

1. Abstract: First sentence appears to ignore current national programmes of proven efficacy such as the NHS Diabetes Prevention Programme and the Type 2 Diabetes Path to Remission Programme. Similarly, the second sentence overlooks current cardiac rehab programmes. Both sentences require to be rephrased.

Response: Thank you very much for providing this valuable feedback. The study is conducted in Canada, where no specific program for achieving remission of type 2 diabetes or prediabetes existed at the time of conceiving this feasibility study protocol in 2021, especially for patients with coronary artery disease in the setting of a cardiac rehabilitation program. Since the conception of the protocol, significant developments have taken place:

- We have published the initial results of a T2D remission clinic in Montreal (PubMed: 36402709).
- The Canadian Guidelines for T2D remission, along with the associated practice guidelines, have been published, which include low-calorie diets as a primary recommendation.
- The RESET protocol for T2D remission, a study conducted at McGill University and led by Dr. Dasgupta (PubMed: 36130753), has also been published.

Considering this dynamic landscape, we have revised the initial sentences to emphasize the potential value of exploring new approaches for achieving prediabetes remission in patients with coronary heart disease, particularly within the context of existing 3-month cardiac rehabilitation programs worldwide. However, it is important to note that these programs do not specifically address the reversal of risk factors, such as prediabetes.

During the conception of the study protocol, the Centre ÉPIC had no prior experience with low-calorie diets. Although the clinic and the study draw inspiration from the DPP and the Direct studies, we made the decision to develop a new protocol to investigate the feasibility of a step-wise mixed exercise training and nutritional intervention aimed at enhancing the existing structured cardiac rehabilitation program. This program presents an excellent opportunity to promote lifestyle interventions in patients with ASCVD.

As a result, our protocol is implemented in a cardiac rehabilitation center and focuses primarily on assessing the feasibility of achieving prediabetes remission.

The final proposed sentence for the abstract thus, reads as follows: “Despite proven programs, implementing lifestyle interventions for prediabetes and type 2 diabetes is challenging. Cardiac rehabilitation programs provide a valuable opportunity to promote the adoption of healthy lifestyle behaviors for patients with atherosclerotic cardiovascular disease (ASCVD). However, only a limited number of studies have explored the potential for reversing the underlying causes of ASCVD in this setting”.

Thank you once again for your valuable feedback.

2. P9 – What training will the nurses have? That is surely an essential study factor to state.

Response: Thank you for raising this question and giving us the opportunity to provide clarification. The nurses involved in the project are research nurses from the Centre ÉPIC of the Montreal Heart Institute. They have extensive experience in cardiac rehabilitation programs and have completed a motivational interviewing skills course. Their expertise includes educating patients with coronary heart disease on various aspects, such as managing risk factors, understanding the root causes of ASCVD, the Mediterranean Diet, exercise training concepts, intermittent fasting, and the challenges patients face when adopting a healthy lifestyle.

To ensure we stay updated with the latest scientific knowledge, we actively participate in multidisciplinary team meetings where we collectively review and discuss the most recent research findings. Additionally, the nurses have thoroughly familiarized themselves with the primary guidelines for T2D remission, including those outlined by ADA/EASD/DUK and Diabetes Canada.

Throughout the project, they will meet with the participants three times for individualized 1-hour sessions at 0, 3, and 6 months.

3. P11 – Surely the ‘feasibility’/applicability depends largely upon resource available to deploy in routine clinical practice, and for the study itself upon the costed time for the personnel delivering the intervention.

Response: Thank you for raising an important point. Indeed, the feasibility and applicability of any intervention depend significantly on the available resources for implementation in routine clinical practice. In the context of our study, we fully recognize that the cost and time required for personnel to deliver the intervention are crucial considerations.

In our research design, we have taken these practical aspects into account to ensure that the intervention can be realistically implemented within the available resources, particularly in other cardiac rehabilitation centers that already offer similar programs based on exercise training and nutrition interventions.

The novelty of our protocol lies in three main aspects, with a particular focus on nutrition and cost-efficiency, especially considering that some cardiac rehab programs may not have registered dietitians (RD) on their staff. These aspects include:

- Education on reducing consumption of ultra-processed foods, including an introduction to the NOVA classification.
- Recommendation of a primarily Mediterranean Diet pattern.
- Introduction of time-restricted eating in an enhanced fashion at the end of the standard 3-month cardiac rehab program.
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In cases where RD are not available, the general advices on nutrition can be easily implemented by nurses, kinesiologists, or doctors, all of whom are typically involved in standard cardiac rehab programs.

By taking into consideration the available resources and the time commitment for personnel, our aim is to provide valuable insights into the potential implementation of the intervention in real-world settings.

4. P13 – The list of cognitive tests is long and potentially adverse for retention in the study.

Response: Thank you for your valuable feedback regarding the list of cognitive tests in our study. We acknowledge that the inclusion of a lengthy set of cognitive tests has the potential to impact participant retention in the study. Additionally, we understand that the repeated administration of these tests three times throughout the study protocol may pose further challenges to participant adherence.

To address this concern, we have made provisions in the study design. The study will take place in a cardiac rehab center with extensive experience in cognitive research. This ensures that the assessments can be conducted efficiently and accurately by trained research neuropsychologists who have successfully administered the same tests in other research protocols, resulting in good participant retention.

Our aim is to strike a balance between collecting valuable cognitive data for our research objectives while ensuring a positive participant experience and high retention rates. We will closely study and account for any complications that may arise from the cognitive testing process to ensure the overall success of the study.

5. The flow mediated assessment appears out of place in this preliminary single arm feasibility study.

Response: Thank you for raising the concern regarding the inclusion of flow-mediated dilatation assessment in our preliminary single-arm feasibility study. We appreciate your suggestions, and we acknowledge that these measures may seem unusual for a small study like the DIABEPIC-1 protocol. However, we would like to provide a few reasons for their inclusion.

One of the main reasons for including these measures is that they are routinely assessed by one of the research labs at the Centre ÉPIC, specializing in studying vascular health in cardiac patients. We

believed that gathering preliminary data on changes in vascular health among participants could provide valuable insights for designing a future randomized controlled study, particularly if achieving remission of prediabetes correlates with improved vascular function.

Furthermore, it is important to highlight that we have made participation in these measurements completely optional. We have taken great care to clearly communicate and outline this information in the consent form. Participants have the autonomy to choose whether they want to opt-in or opt-out of these specific assessments, prioritizing their comfort and individual preferences throughout the study. This approach aims to ensure high retention rates by accommodating their needs and preferences.

6. P18, para 2 – ‘Exploratory’ is curious. The strict dependence of type 2 diabetes remission upon adequate loss of weight has been clearly demonstrated. The inclusion of exercise will blunt the achieved weight loss but the overall effect depends upon intensity as shown by the x study.

Response: We appreciate the reviewer's comment regarding the use of the term "exploratory" in our study description. We agree that the term might not accurately reflect the established understanding that weight loss is a critical factor for achieving remission in type 2 diabetes (T2D).

Our intention was to emphasize that, although this feasibility study may not have the scale or design to comprehensively examine the impact of various factors on remission, we will approach the analysis in an investigative manner. We plan to perform regressions to assess the relationship between body mass loss and the achievement of prediabetes remission. Additionally, we would like to highlight that our study utilizes the SÉCA bioimpedance balance to assess body composition. This measurement tool will enable us to evaluate changes in various components such as fat mass loss, visceral fat loss, and muscle mass changes. By assessing these specific components, we aim to gain insights into their individual contributions to achieving remission in an exploratory manner.

We anticipate that our study will make a valuable contribution to the existing literature and offer additional insights into the potential influence of using a body composition balance on patients' journeys toward lifestyle changes. We genuinely appreciate the reviewer's feedback, and we have made the necessary adjustments to the text to ensure clarity and eliminate any potential confusion.

7. P20 para 2 – The sentence ‘Despite the prevalence of prediabetes there are currently limited options...’ is incorrect in view of the well described approaches. Later in the same para, it is curious to read that ‘there is no currently agreed-upon terminology...’ as pre-diabetes is defined simply in terms of HbA1c, so reversion to normal will be defined by re-entry into the normal range. Claiming that this pilot feasibility study will provide an evidence base for definitions is inaccurate.

Response: Thank you for your insightful comment. We genuinely acknowledge that there are several scientifically proven approaches to achieve type 2 diabetes (T2D) remission. However, we also recognize that these methods are not widely implemented in clinical practice as much as we would hope, particularly outside of the UK where significant advancements have been made and serve as an inspiration for others.

In our specific context in Canada, the adoption of T2D remission guidelines has only recently taken place, and their implementation in clinical practice is still in its early stages, as far as our knowledge goes. We wanted to emphasize this point to express our understanding of the current landscape.

Furthermore, we also wanted to address the lack of a clear rationale for promoting prediabetes remission in cardiac patients. How does it impact their overall health? Does it reduce the occurrence of major adverse cardiovascular events (MACE)? With the results of this small trial, we aim to

contribute to the existing body of evidence and shed light on the potential benefits of pursuing prediabetes remission within the context of cardiac rehabilitation programs.

We genuinely appreciate the feedback provided by the reviewer #2, and we have carefully adapted the paragraph (page #20) accordingly. Your valuable input has helped us refine our work and enhances the overall quality of the study.

8. P21- Quoting ref 17 is inadequate. The ADA/EASD/DUK consensus statement on the definition of T2D remission was published simultaneously in 3 journals in 2021. The authors appear to be out of date with currently accepted norms, and reference 20 provides more detailed information on this point.

Response: We thank the reviewer #2 for bringing up this point, letting us clarify.

The authors would like to clarify that there was initially a misinterpretation of the ADA/EASD/DUK guidelines regarding prediabetes remission. This misinterpretation stemmed from the absence of a specific paragraph or statement addressing prediabetes remission in those guidelines. After personally contacting Dr. Matthew C. Riddle to discuss this matter, he confirmed that "you're correct in noting that there is currently no agreed-upon terminology for describing a remission from prediabetes to normal glucose levels, and there is also no clear rationale for pursuing this endpoint at the moment. Your current approach to describing this process appears as logical as possible at present. Your work will eventually contribute to establishing an evidence-based definition of terms and goals." Dr. Riddle's words and guidance served as personal inspiration to continue pursuing this endpoint and provided the foundation for developing the research protocol for this prediabetes remission trial, as well as the ongoing DIABEPIC-2 protocol for T2D remission in our center.

It should be noted that the work of Dr. Riddle and Dr. Taylor has been a continuous source of inspiration from the very beginning, and the authors have thoroughly considered all the published work.

Accordingly, we have updated the manuscript (page #21) to include references to the guidelines on T2D remission published by the ADA/EASD/DUK consensus report, as well as the most recent Canadian guidelines. We sincerely appreciate the opportunity to clarify this significant issue.

9. P25- Attempting to evaluate any relationship between cognitive performance and pre-diabetes is unrealistic on the timescale of the study.

Response: Thank you for your question. We appreciate the reviewer's comment regarding the timescale of our study and the evaluation of the relationship between cognitive performance and prediabetes. We understand that the timeline of our study may limit our ability to draw definitive conclusions on this complex relationship. However, we believe that our study can still provide valuable insights and contribute to the existing literature in several ways:

Short-term effects and identifying trends: Even within a relatively short timeframe, it is possible to observe short-term effects on cognitive function in individuals with risk factors (PubMed: 37215433). Our team has a long experience in this domain and evidence from our group and others support the notion that cognitive performance can be improved within 3-6 month lifestyle intervention. By employing repeated measures of cognitive tests, we can capture immediate changes or fluctuations in cognitive performance following the lifestyle intervention. While a longer-term study would be necessary to establish a definitive relationship, our study can still help identify trends or preliminary

associations between prediabetes remission and cognitive function. These preliminary findings can guide future research and hypothesis generation.

Clinical implications: Despite the limited timescale, our study can have potential clinical implications. If we observe any significant short-term improvements in cognitive function associated with prediabetes remission, it could suggest the importance of early interventions to prevent cognitive decline and promote optimal metabolic health.

In summary, while we acknowledge the limitations imposed by the timescale of our study, we believe that our research can provide valuable preliminary insights into the association between prediabetes remission and cognitive function. We appreciate the reviewer's comment and will consider it in the discussion section of our future manuscript, emphasizing the need for further long-term investigations in this area.