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Mediterranean Diet and Time-Restricted Eating as a Cardiac Rehabilitation Approach for Patients with Coronary Heart Disease and Prediabetes: The DIABEPIC-1 Clinical Trial Rationale and Design

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Running title: Feasibility and impact of an intensive team-based intervention on prediabetes remission in patients with coronary heart disease

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ABSTRACT

Background: Effective implementation of lifestyle interventions as a first-line treatment for prediabetes and type 2 diabetes (T2D) is rarely seen in routine clinical care. A cardiac rehabilitation program after an acute cardiovascular event offers a unique opportunity to influence the underlying causes of cardiovascular disease and adopt healthy lifestyle behaviors.

Objectives: The DIABEPIC1 study is an ongoing single-arm lifestyle clinical trial to assess the feasibility of an upgraded 6-month intensive cardiac rehabilitation program combining an innovative diet assignment with exercise training to reverse newly onset prediabetes (HbA1c 5.7% to 6.4%) to normal glucose concentrations in patients with coronary heart disease.

Methods: 36 patients referred from the Montreal Heart Institute for cardiac rehabilitation, aged ≥ 40 years with a recent diagnosis of prediabetes in the last six months, will be offered to participate in the upgraded program. Interventions will include four sessions of nutritional counseling on ultra-processed foods intake reduction and a moderate-carbohydrate (< 40%) *ad libitum* Mediterranean diet coupled with 36 1-hour sessions of supervised exercise training (continuous and interval aerobic training, and resistance training) and educational intervention. Phase 2 will continue the same interventions adding 8:16 hour time-restricting eating (TRE) at least five days per week. During this second phase, exercise training will be performed with autonomy. **The primary objectives** will be to evaluate the recruitment rate, the completion rates at 3 and 6 months, and the compliance of participants. **The secondary objectives** will be to assess the proportion of prediabetic participants in remission of prediabetes at the program's end and to characterize the factors associated with remission.

Conclusions: The DIABEPIC1 trial will examine the feasibility and effectiveness of an enhanced cardiac rehabilitation program combining exercise training with an ultra-processed food reduction intervention, a Mediterranean Diet, and TRE counseling to remit prediabetes to normal glucose concentrations. (Identifier: NCT05459987).

Keywords: Cardiovascular Disease, Risk Factors, Prediabetes, Remission, Cardiac Rehabilitation, Mediterranean Diet, Time-restricting Eating

Strengths and limitations of this study

Strengths:

- Addresses the issue of effective implementation of lifestyle interventions as a first-line treatment for prediabetes, which is rarely seen in routine clinical care.

- Offers a unique opportunity to influence the underlying causes of cardiovascular disease and adopt healthy lifestyle behaviors through an upgraded 6-month intensive cardiac rehabilitation program.

- Combines multiple proven interventions, including nutritional counseling, exercise training, and time-restricted eating, to achieve remission of prediabetes and improve metabolic health.

Limitations:

- The study population is relatively small (36 participants), and it is limited to patients with coronary heart disease referred for cardiac rehabilitation, which may not be representative of the general population with prediabetes.

- The study duration is limited to six months, which may not be sufficient to observe sustained changes in lifestyle behaviors and metabolic health.

Abbreviations' list by order of appearance

T2D = Type 2 diabetes mellitus

CVD = Cardiovascular disease

TRE = Time-restricted eating

Centre ÉPIC = Cardiovascular Prevention and Rehabilitation Center of the Montreal Heart Institute

HbA1c = Glycated hemoglobin

FMD = Flow-mediated dilatation

ACSM = American College of Sports Medicine

RPE = Rate of perceived exertion

HIIT = High-Intensity Interval Training

MICT = Moderate Intensity Continuous Training program

1-RM = one-repetition maximum

INTRODUCTION

Prediabetes and Type 2 diabetes (T2D) are major risk factors for cardiovascular disease (CVD) and a significant burden for patients and healthcare systems. In Canada, the estimated prevalence of T2D is 3.4 million (9% of the population), and 5.7 million (15% of the population) are living with prediabetes, most of them unaware of their condition (1). Despite current optimal treatments, cardiovascular events remain high in individuals with prediabetes and T2D, and it is predicted that the number of people living with these conditions will continue to increase (2).

Early diagnosis and intensive interventions, such as adequate weight loss through physical exercise, distinct dietary interventions, and intermittent fasting modalities like time-restricted eating (TRE), have been shown to prevent, improve, and even reverse these conditions (3). Unfortunately, these lifestyle interventions are only sometimes effectively implemented in routine clinical practice, likely due to obstacles such as healthcare resources, infrastructure, and personal barriers. Therefore, innovative ways to effectively implement and maintain lifestyle changes are needed. One potential solution is to use a cardiac rehabilitation program after an acute cardiovascular event as an opportunity to influence the underlying causes of cardiovascular disease and adopt healthy lifestyle behaviors.

The DIABEPIC1 study is a single-arm lifestyle clinical trial that will assess the feasibility of an intensive lifestyle program to reverse newly onset prediabetes (HbA1c 5.7% to 6.4%) to normal glucose concentrations in patients with a recent acute cardiovascular event that would otherwise start a standard cardiac rehabilitation program of 12 weeks. The patients will be offered an upgraded 6-month intensive team-based multidisciplinary stepwise program combining diet assignment (ultra-processed foods reduction, Mediterranean Diet and TRE) with exercise training (continuous/interval aerobic training and resistance training) and educational intervention to remit prediabetes.

The study's primary aim is to assess the feasibility of the enhanced program to devise and iteratively improve participant recruitment and adherence strategies for a possible future randomized controlled trial.

The study also aims at studying the factors associated with metabolic improvements and prediabetes remission to contribute to a clear rationale for seeking this endpoint. Finally, the study also intends to better understand the distinct lifestyle interventions' benefits by characterizing baseline and intervention-related changes in anthropometric measures, blood analysis, a 3-day nutritional diary registered by the *Keenoa* artificial intelligence *App*, vascular function measured by flow-mediated dilatation and central arterial stiffness, and cognitive performance evaluated by a short neuropsychological battery targeting executive functions, processing speed, and episodic memory.

The DIABEPIC1 trial will examine the feasibility and effectiveness of an enhanced cardiac rehabilitation program combining exercise training with a Mediterranean Diet and TRE counseling to remit prediabetes to normal glucose concentrations. The potential impact of the results of this intervention on the delivery of cardiac rehabilitation programs for patients with prediabetes is significant. If proven feasible, it could improve cardiovascular function after an acute coronary event, reverse a causal risk factor, and enhance metabolic health.

METHODS

Study design overview and setting

The study will take place at the Cardiovascular Prevention and Rehabilitation Centre of the Montreal Heart Institute (Centre ÉPIC). The study duration will be 24 weeks (6 months) with two distinct 3-month interventions: Phase 1 (Intensive Cardiac Rehabilitation Program) will consist of a synchronous intensive nutritional intervention (4 sessions of counseling on ultra-processed foods intake reduction and moderate-carbohydrate (< 40%) *ad libitum* Mediterranean diet) coupled with 36 1-hour sessions of supervised exercise training (continuous and interval aerobic training, and resistance training) and educational intervention. Phase 2 (Autonomy period) will continue the same interventions adding 8:16 hour time-restricting eating (TRE) at least five days per week. Exercise training will continue in autonomy.

Nurses will deliver the educational intervention throughout the project in individualized 1-hour meetings at 0, 3, and 6 months. Topics addressed will be as follows: the concepts of insulin resistance, prediabetes, and T2D; the main reasons behind the development of the disease; and the scientifically proven ways to reverse these conditions. Sessions will be tailored to the specific needs of the patients and will involve motivational interviewing to build intrinsic motivation for lifestyle modifications.

Anthropometric measures, blood analysis, a 3-day nutritional diary registered by the *Keenoa* artificial intelligence *App*, and cognitive performance evaluated by a short neuropsychological battery will be performed at baseline, after three months of the intensive intervention, and at three months. Vascular function measurements by flow-mediated dilatation and central arterial stiffness will be optional, and measures will take place at baseline and six months. A visual illustration of the DIABEPIC1 interventional study is depicted in **Figure 1**.

Institutional Review Board Statement

The study protocol has been approved by the Research Ethics Board of the Montreal Heart Institute (Project Number ICM 2022-3005). It is reported per the Standard Protocol Items-Recommendations for Interventional Trials guidelines (SPIRIT). The study has also been prospectively registered on Clinicaltrials.gov (Identifier: NCT05459987). The study complies with International Conference on Harmonization for Good Clinical Practice (ICH-GCP) guidelines and all regulatory requirements.

Participant selection

Participants will be recruited among those referred for a cardiac rehabilitation program from the Montreal Heart Institute because of stable angina, after an acute coronary heart event (with or without ST-segment elevation), after coronary revascularization (primary or elective), or after bypass surgery. Potentially eligible patients recently diagnosed with prediabetes (< 6 months) based on the American Diabetes Association cut-off criteria of glycated hemoglobin (Hb1Ac) between 5.7% to 6.4% (4) will be identified by the researchers before their first scheduled cardiac rehabilitation medical visit based on the results of their routine blood analysis typically performed one week in advance that includes: complete blood count, kidney function, a lipid profile, fasting glycemia, insulin, and HbA1c. They will be contacted and explained the possibility of participating in the study. They will be comprehensively informed and provided with an informed consent form if interested. Following this first call, the participant will have their first medical appointment, including a maximal exercise test to screen for potential contraindications and securely follow prescribed exercise training. This visit will also serve as the enrollment visit, where the participant will have another opportunity to discuss the project, clarify any doubts, and, if wished, be enrolled. Participants who refuse to participate in the present study will continue as scheduled and participate in the standard 3-month cardiac rehabilitation program. Subjects will be eligible to participate if all inclusion criteria are met, and none of the exclusion criteria are met. All study procedures, including the signature of informed consent, will be conducted at the Centre ÉPIC, providing all required settings, including material, trained nurses, registered dietitians and kinesiologists in clinical research, trained research assistants, and administrative assistant. Detailed inclusion and exclusion criteria are shown in **Table 1**.

Study outcomes

Primary objective: To assess the feasibility of an intensive, multidisciplinary cardiac rehabilitation program based on lifestyle changes in coronary heart disease patients recently diagnosed with prediabetes that are referred to the Centre ÉPIC. Currently, the Centre ÉPIC receives up to 550 new coronary heart disease patients annually (approximately 50 per month) to participate in its cardiac rehabilitation program. Of these patients, between 20-30% are diagnosed with T2D, and around 15-20% fulfill the criteria for prediabetes (HbA1c 5.7% to 6.4%). Based on these numbers, four parameters are considered to assess the feasibility of our study:

1) Total Recruitment: Number of participants screened compared to final enrollments. Hypothesis: At least 50% of patients living with prediabetes and referred to the Centre ÉPIC for the cardiac rehabilitation program will find the study interesting and accept participation.

2) Recruitment rate: Number of participants that can be recruited monthly. Hypothesis: At least two participants can be enrolled weekly, eight per month.

3) Completion rate at 3 and 6 months: Number of participants that complete the intervention at three and six months compared to the enrolled participants. Hypothesis: At least 70% of the participants will finish the 3-month and 6-month programs (i.e., dropout rate $\leq$ 30%).

4) Compliance: Total number of appointments attended (nutritional, exercise training and educational interventions) compared to the maximum possible. Hypothesis: Participants will attend at least 80% of all proposed sessions.

To summarize, the full-scale study will be feasible if we can recruit at least eight subjects per month on average, if the completion rate is at least 70% at six months, and if compliance with all protocol interventions is at least 80%. From here, all other collected data during the study will serve only for an exploratory purpose (see below secondary and tertiary endpoints).

Secondary objectives include assessing the proportion of participants with prediabetes at the start of the program (HbA1c 5.7% to 6.4%) in complete remission of prediabetes, defined by the following three criteria: A HbA1c <5.7% at three months of intervention (metabolic criteria), which is maintained at six months (duration criteria), without the use of glucose-lowering agents (pharmacological measures). Partial remission of diabetes will be defined if the metabolic criteria (HbA1c <5.7%) is reached six months following the study's second phase. This will allow researchers to examine how long it takes some participants to remission of prediabetes and the effect of the TRE intervention on metabolic changes. Hypothesis: At least 50% of participants will fulfill one of the remission criteria definitions at the end of the follow-up.

Tertiary objectives will characterize baseline and intervention-related changes in distinct anthropometric, physical, blood analysis, cognitive, vascular function, and questionnaire measures detailed in **Table 2**. Incidence of cardiovascular events will also be recorded and reported as a five-point composite of major adverse cardiovascular events (MACE) including cardiovascular death, myocardial infarction, unstable angina, ischemic stroke, and hospitalization for heart failure.

Detailed study interventions and timelines

A complete illustration of the study enrolment and evaluation assessments can be found in **Table 3**.

Pre-intervention evaluation (over one week): Upon signing the informed consent form, participants will have several pre-intervention assessments, including baseline missing blood analysis parameters and total anthropometric measurements by bioimpedance (mBCA 515, SECA). A visit with the nurse in which the patient will be involved in a motivational interviewing to assess personal objectives. In this visit, participants will also be offered expert educational and nutritional information about the concepts of insulin resistance, prediabetes, and T2D, the main reasons behind the development of the disease, and the scientifically proven ways to reverse these conditions. The patient will also be informed on how to use the

Keenoa application to collect a 3-day nutritional diary. The 3-month scheduled intervention program will be reviewed with the participant to clarify any remaining questions.

Cognitive Function Assessment. A short cognitive assessment will be performed by a neuropsychologist or by trained research assistants. The tests will target general cognitive functioning, executive functions, processing speed, and episodic memory: Montreal Cognitive Assessment (MoCA; general cognitive functioning), Rey Auditory Verbal Learning Test (episodic memory), Coding (WAIS-IV) (processing speed), Stroop (D-KEFS) (executive functions), Trail Making Test (executive functions), Verbal fluency (D-KEFS) (executive functions). Neuropsychological testing will be conducted in person or by videoconference; the aforementioned tests are adequate for remote administration (5). Moreover, all tests have all been validated for an adult population.

Vascular Function Assessment. Flow-mediated dilatation (FMD) change to measure endothelial function and carotid-femoral pulse wave velocity to measure central arterial stiffness will be optional. For FMD measurement, brachial artery blood velocity and diameter will be measured with a high-resolution ultrasound device (uSmart3300, Terason) and a linear bar probe (5-12 MHz) before and after 5 minutes of forearm ischemia. A cuff downstream of the ultrasound probe will be inflated to a pressure of 250 mmHg to induce ischemia. After the cuff is released, the brachial artery blood velocity and diameter increase will be measured continuously for 3 minutes. An analysis program (FMD studio, Quipu srl) will independently determine peak diameter and shear rate. FMD will be quantified as the change in diameter from rest to peak, corrected by the shear stimulus and the baseline diameter. This measurement will be performed per current guidelines (6). Central arterial stiffness will be measured via carotid-femoral pulse wave velocity. The pulse wave will be recorded continuously over the carotid and femoral arteries by a non-invasive surface tonometer (Millar Inc). The pressure waveforms will be recorded for a minimum of 10 consecutive cardiac cycles. Distance traveled by the pulse wave will be measured, in triplicate, as the direct distance between the two measurement sites with a correction factor of 0.8, as per current guidelines (7).

Phase 1 (3 months): Intensive Cardiac Rehabilitation Program

Nutritional Intervention: Once a 3-day food diary is collected, registered dieticians will perform four personalized 1-hour visits stepwise throughout the first three months. *Step 1*: During the first visit, participants will be informed about how to read nutritional information of food products, how to identify processed and ultra-processed foods following the NOVA classification (8), and will be advised to reduce Group 2 and 3 products and avoid Group 4 products. *Step 2*: After this first visit, patients will have two personalized nutritional visits in which a Mediterranean Diet moderate in carbohydrates (<40%) will be explained and proposed to them. The Mediterranean Diet Pyramid will guide participants in adapting to the new pattern. As part of the diet, participants will be advised to consume a diet predominately plant-based made up of vegetables, legumes, fruits, whole grains, nuts, and seeds. Fish will be the primary source of protein, and olive oil will be the primary source of fat in the recommendations. There will not be specific calorie reduction targets. During these visits, efforts will be made to progressively adjust and improve, resolve doubts, and teach cooking techniques if necessary. *Step 3*: During the last two weeks of Phase 1, the participant will have one last visit to be informed about the concepts of intermittent fasting and time-restricted eating to be prepared for Phase 2 and informed to introduce an 8:16 hour TRE at least for five days a week, starting the second phase.

Exercise Training Intervention: The exercise training intervention for Phase 1 will consist of 1-hour / three sessions per week of in-patient supervised endurance and strength training for twelve weeks (a total of 36 sessions). One session per week will be allowed at home if the participant wishes to accommodate preferences and prepare participants for Phase 2 (training in autonomy). In-person sessions will be encouraged and supervised by a certified kinesiologist at the Centre ÉPIC, who will also organize the exercise-training sessions designed to be performed at home. The aerobic and resistance training prescriptions will be programmed according to the recent American College of Sports Medicine (ACSM) Guidelines for Exercise Training and Prescription, Eleventh Edition, 2021 (9). The rate of perceived exertion (RPE) during the exercise sessions will be assessed on the BORG scale from 6-20.

Furthermore, participants will be encouraged to engage in their activities at home, like walking or cycling, following the 2020 WHO recommendations of at least 150 to 300 minutes of moderate-intensity aerobic exercise per week (10). All the characteristics of the activities will be recorded (type of activity, intensity, heart rate, duration) with the Polar Beat application and the heart rate sensor Polar H10.

The first two weeks will progressively introduce participants to all the exercise techniques, get familiar with all materials, and assess different muscular-group strengths. During these first two weeks, continuous moderate exercise sessions and high-intensity interval training will be proposed to facilitate acquaintance with all participants. The endurance exercise program will be performed on a bicycle ergometer, treadmill, or elliptical. The intensity will start at 50% of maximal aerobic power or 11-12 of the Borg RPE during the first week and gradually increase to 60-70%. If needed, the intensity of the training will be adjusted according to the heart rate reserve of each patient.

After these first two introductory weeks, alternating high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) sessions will be proposed in a 2:1 fashion; 2 HIIT sessions and 1 MICT session per week. The endurance sessions will include 5 to 10 minutes of warm-up and 5 minutes of cool-down. In the case of MICT sessions, the intensity will be between 60-70% of maximal aerobic power at a RPE, starting at 12 and progressively increasing to 14. During the HIIT, exercises (2 to 3 blocks of 10 minutes) will be composed of 1 to 3 minutes intervals at 80-100% of the maximal aerobic power interspersed with an active recovery of the same duration. The RPE for the HIIT sessions will start at 15 and gradually increase to 17 through the exercise training program (11).

All training sessions will include 20 to 30 minutes of strength training that will take place using machines, free weights, or elastic bands depending on the program phase. Strength training will be programmed according to the recent ACSM guidelines with a gradual progression of higher intensities and/or numbers of sets/repetitions. Intensities will be prescribed at a RPE from 12 to 15, which corresponds to 40 to 70% of the one-repetition maximum (1-RM), with 6 exercises involving major muscle groups. The number of

sets will be from 1 to 3, and the number of repetitions will be from 6 to 15. The gradual assumption of autonomy towards Phase 2 will be encouraged throughout this first phase of cardiac rehabilitation as, at the end of the three months, all participants should be able to follow personalized endurance and strength autonomous training.

Mid-intervention evaluation: At the end of the 3-month program, participants will be offered to repeat a maximal effort test on a treadmill, a medical visit and examination, complete blood analysis, and anthropomorphic assessment. Participants will also be asked to redo all questionnaires, a 3-day food diary with the application *Keenoa* and the cognitive tests.

Phase 2 (3 months): Time-restricted eating and exercise training in autonomy.

Nutritional Intervention: After the mid-term assessments, participants will be asked to maintain all healthy lifestyle changes introduced during the first three months and to start an 8:16 hour TRE pattern at least five days a week, meaning an 8-hour window in which the participant will be allowed to eat and 16-hour window in which the participant will be asked to restrict from ingestion. General advice will be given to practice TRE successfully, such as to plan meals, eat consistently, gradually adjust the eating window, choose nutrient-dense foods, stay hydrated, and avoid snacking outside the designated eating window. This period will include two additional nutritional consultations to resolve doubts.

Exercise Intervention: During the study's second phase and following the 2020 WHO guidelines of physical activity, all patients will be given personalized aerobic and strength exercise training to be performed without supervision at a gym or at home. Only remote follow-ups will be offered to resolve doubts and adjust if needed.

Post-intervention evaluation (over one week): At the end of the program, participants will have a last medical visit that will include a maximal effort test on a treadmill, a medical visit and examination, complete blood analysis, and an anthropomorphic assessment. Participants will also be asked to redo all questionnaires and cognitive tests and collect a 3-day food diary with the application *Keenoa*. Vascular

function measures will again be optional for patients who have consented and attended their first appointment.

Statistical considerations

Sample Size calculation: Primary outcome measures for this study are feasibility criteria to inform any future randomized controlled trial powered to detect an intervention effect. Therefore, a sample size for this study was calculated to allow the estimation of a completion and compliance rate with reasonable precision. Assuming that the completion rate will be around 70%, a sample size of 25 would allow estimating this rate with an accuracy of ± 18.0% using a two-sided 95% confidence interval. For a compliance rate of around 80%, a sample size of 30 subjects would assure a precision of ± 15.7% for estimating this rate. Assuming a 30% loss rate to follow-up, approximately 36 patients will be recruited.

Statistical analysis will be mainly descriptive with, when appropriate, the presentation of 95% confidence intervals. They will be computed for baseline characteristics and follow-up assessments at three and six months. They will be presented as mean and standard deviation for continuous variables and frequencies and percentages for categorical variables.

The number of participants that can be recruited monthly and the number of participants screened will be summarized. The total recruitment and monthly rates will be presented with a 95% confidence interval. The number of participants that complete the intervention at three months, the number of participants that attend their 6-month follow-up appointment, and the total number of appointments attended (nutritional intervention (up to 6), exercise training intervention (up to 36) and educational intervention (up to 3) will be summarized. Completion/retention rate at 3 and 6 months and compliance rate will be presented with a 95% confidence interval.

For illustrative purposes (because this pilot study is not powered to detect statistically significant findings), all analyses of this pilot study, including both secondary and tertiary endpoints, will be the assessments that could be considered as efficacy parameters in the large, full-scale study. For the analysis of change in

continuous secondary and tertiary endpoints, i.e., anthropometric measures, exercise-derived measurements, blood analysis measures, and scores from questionnaires, a one-way repeated-measures ANOVA model will be used to compare differences between intervention (pre, per, post) periods, with mean differences and 95% confidence intervals and with effect sizes (Cohen's d) when appropriate. The assumptions underlying the planned models will be checked, and if they are not tenable, data transformation or non-parametric analyses may be used if necessary.

In an exploratory manner, the adjusted impact of the different factors associated with remission of prediabetes (e.g., mass loss, fat mass loss) will be evaluated. For this analysis, univariable and multivariable logistic regression models will be created for the categorical outcome of remission of prediabetes: yes/no, accordingly to the definition previously mentioned. Covariates will be selected a priori based on their described association with remission (clinical plausibility) or as a potential confounding effect according to the rules proposed by Kleinbaum and colleagues using the user-written Stata command "confound" (ref). The practical and clinical interpretation will be presented with measures of association (odds ratio, OR). Statistical significance will be defined as a p-value < 0.05. Statistical analyses will be performed using STATA (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

Data management, ethics and dissemination

Hard copy files will be stored in a locked filing cabinet at the clinic site at Centre ÉPIC. After the study, all hard copy files containing the participant data will be anonymized and stored in a password-protected secured storage system accessed by approved personnel only.

The DIABEPIC1 results will be communicated through an internal committee's thorough review and editing process to ensure the scientific accuracy and authorship of the publication and abstracts. No interim analysis is planned. The authorship of the publication and ancillary studies will be determined per the guidelines of the International Committee of Medical Journal Editors. The results will also be shared with participants, staff of the Centre ÉPIC, and the broader medical community. Additionally, the complete and

anonymous dataset will be made available for sharing by the principal investigator upon request no later than three years after the end of the study.

DISCUSSION

The DIABEPIC 1 study aims to investigate the effectiveness of an upgraded, intensive multi-disciplinary program for cardiac rehabilitation in reversing prediabetes in patients with coronary heart disease. The program, which will last six months, will include a combination of dietary intervention, exercise training, and education. The rationale behind this project is to address the growing issue of prediabetes as the unaddressed underlying cause of cardiovascular disease (12) and propose an enhanced cardiac rehabilitation program following an acute cardiovascular event to promote healthy lifestyle behaviors and reverse this condition to normal glucose concentrations.

Why is it important?

A substantial gradient of cardiovascular risk is observed across HbA1c levels from as low as HbA1c $\geq$ 5.4%, way below the threshold for diabetes (13). It is often reported that approximately 1 in 3 Americans have prediabetes and that 90% are not aware of their condition. Furthermore, about 25% of individuals with prediabetes will develop T2D within 3 to 5 years, and as many as 70% will develop the disease during their lifetime (14). Despite the prevalence of prediabetes, there are currently limited options for halting or reversing the condition in clinical practice. Despite its relationship with an increased risk of CVD, there is no currently agreed-upon terminology for describing a remission from prediabetes to normal glucose levels. As such, there is not yet an entirely clear rationale for seeking this endpoint. The results of the DIABEPIC1 study can eventually provide the evidence base for a complete definition of terms and goals.

What is known?

Although remission of prediabetes and T2D in the community have been described, they have been historically understudied (15). For decades, T2D has been regarded as a progressive and irreversible condition requiring increasing numbers of oral glucose-lowering agents and insulin.

Nevertheless, remission has been recently identified as a top priority by people with prediabetes and T2D (16), and only in the past decade, at least 178 studies with over 100 participants (11 of which were randomized controlled trials) have been published focusing on the possibility of reversing T2D and prediabetes (17). Among them, surgical interventions were the focus of 164 (93%) studies compared to 8 (4%) pharmacological and 5 (2%) lifestyle interventions.

Reversion to normoglycemia is associated with positive health benefits beyond T2D prevention or delay. A 1% absolute decrease in HbA1c was associated with a 14-27% decrease in major CV events and a 37% reduction in microvascular complications in a cohort from the United Kingdom (18). The risk of cardiovascular disease and all-cause mortality was also reduced in a Chinese cohort of patients with prediabetes who reverted to normoglycemia within two years compared to those who progressed to T2D over nearly nine years of follow-up. The odds of developing microvascular disease (retinopathy, nephropathy, and neuropathy) were also reduced (19). Most of these studies have a common strategy: to improve insulin sensitivity and reverse insulin resistance, individuals need to shift to burning fat as their primary energy source to reduce fat mass. This can be achieved by lowering insulin levels (fasting, restrictive diets, reducing consumption of ultra-processed foods, metabolic surgery, or oral drugs) or increasing energy expenditure through endurance and resistance training. However, it is important to note that the combination of both strategies - lowering insulin levels and increasing energy expenditure - can have a synergistic effect, leading to greater improvements in insulin sensitivity and reductions in fat mass. A comprehensive narrative review of the evidence can be found elsewhere (20).

What is new in this interventional study?

An intensive synchronous intervention in the setting of cardiac rehabilitation. A Mediterranean diet, TRE, educational interventions, and regular exercise training have provided positive health benefits for improving metabolic parameters in healthy individuals and/or patients with prediabetes and T2D . However, there is limited evidence on the effect of multiple synchronous lifestyle interventions in patients with

prediabetes combining these approaches in a synchronous stepwise intervention to attain remission, particularly in cardiac rehabilitation. The enhanced insulin resistance reversal program aims to improve patients' glucose regulation and overall cardiovascular health by targeting various risk factors associated with prediabetes and cardiovascular disease. The proposed program seeks to address this gap by providing a comprehensive and intensive approach to cardiac rehabilitation that includes not only traditional exercise training but also education on the concepts of insulin resistance, prediabetes, and T2D, the main reasons behind the development of the disease, and the scientifically proven ways to reverse these conditions as well as an innovative dietary intervention including ultra-processed food reduction, a moderate-carbohydrate ad libitum Mediterranean Diet and the inclusion of TRE.

A reduction of ultra-processed foods as the starting point. The consumption of ultra-processed foods is associated with excess calorie intake and weight gain (21), metabolic syndrome (22), coronary heart disease, cerebrovascular disease (23), and cancer (24). These foods have also been shown to cause an elevated glycemic response, disrupt satiety signals, promote inflammation, and the occurrence of diabetes (25). Processed and ultra-processed foods are probably one of the main drivers of ad libitum dietary habits and today's global epidemic. In this context, the DIABEPIC1 study will start the nutritional intervention by teaching how to identify these foods and an intervention to reduce ultra-processed foods consumption. This strategy is a consequence of most weight-reducing diets that intrinsically exclude these types of products but is barely studied as a specific starting-point education strategy at the roots of the problem, which can lead to weight loss and a decrease in glycemic spikes. Still, it can also be important in rebalancing satiety signals and promoting adherence to subsequent nutritional recommendations.

A Mediterranean diet with moderate carbohydrate consumption as a diet assignment. The Mediterranean diet is well known for its various health benefits in healthy individuals, cardiovascular diseases, and cancer (26). It reduces the incidence of T2D among non-diabetics with high cardiovascular risk (27). In insulin-resistant individuals, it improves glycemic control, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and triglycerides. In addition to its high nutritional quality,

it also carries relatively easy long-term compliance (28), data lacking for most all other dietary interventions. For these reasons, the proposed interventions will be focused on a Mediterranean diet pattern.

Some randomized controlled trials show that low-carbohydrate diets prevent body weight more effectively than low-fat diets (29,30). For instance, blood glucose, HbA1c, and glycemic control are improved by low-carbohydrate in comparison with low-fat diets (31,32), and ApoB is improved in a moderate-carbohydrate diet (26-45% carbohydrate) compared to a high-carbohydrate diet (49-65% carbohydrate) (33). Thus, our nutritional program includes instructions to reduce carbohydrate consumption to an average of 40% of calories consumed.

Time-restricted eating in a cardiac rehabilitation setting as a new approach. Not only what we eat but also when we eat could affect health. A reduced food consumption window of 10 hours/day (14 hours of fasting) promotes weight loss in patients with metabolic syndrome, prediabetes, and T2D. It decreases waist circumference, visceral fat, blood pressure, atherogenic lipoproteins, and glycated hemoglobin (34). A daily food consumption window reduced to 4h or 6h/day (20h or 18h of fasting) resulted in a 3.2% loss of body weight while improving fasting insulin levels, insulin resistance, and oxidative stress (35). Nonetheless, there is little evidence of the added effects of TRE in patients with prediabetes or T2D. It has not been evaluated in the context of a Mediterranean Diet intervention, particularly in the cardiac rehabilitation setting. The DIABEPIC1 trial will propose and study a Mediterranean diet assigning moderate carbohydrate consumption with the addition of a TRE 16:8 pattern during the study's second phase. This will allow assessing the impact of adding this nutritional intervention separately from the effects of the first three months of synchronous dietary and exercise training intervention.

The use of the *Keenoa* Application to assess participants' food intake and personalized approach to lifestyle intervention. The DIABEPIC1 study will use data collected from the novel Canadian diet application *Keenoa*™ at 0, 3, and 6 months. The validity and usability of this smartphone image-based dietary assessment app compared to 1-day and 3-day food diaries have been previously assessed (36,37).

Its use offers several potential advantages: real-time data collection, which reduces the delay between intervention delivery and data collection; convenience as participants can access the application from their mobile devices; a more collaborative and personalized approach to lifestyle intervention between participants and healthcare providers, and improved data quality helping reduce errors and biases associated with manual data collection and increases the accuracy of data collection. The feasibility of its use and adherence will be reported.

Multicomponent anthropometric measurements by bioelectrical impedance as an innovation. Visceral adipose tissue and visceral fat mass loss are critical players in the pathogenesis of insulin resistance. The likelihood of prediabetes and T2D remission increases when substantial weight loss is achieved (38). Despite the nature of lifestyle or pharmacological interventions, most studies utilize total weight loss as a marker or endpoint, thus neglecting the impact of individual body components. Therefore, to gain a better understanding of the factors leading to remission, there is a need to improve data on the specific impact of different body components.

One of the particularities of this study will be the systematic use of the SECA-mBCA 515 balance to measure different components of body composition by bioelectrical impedance analysis, which will allow observing the absolute and proportional change in body mass, fat mass, visceral fat, lean body mass, and skeletal muscle that participants will present through the different phases of the intervention. These will also allow exploratory assessment of the adjusted impact of the other factors associated with remission of prediabetes.

Vascular function to assess changes in endothelial function and central arterial stiffness and their relationship with remission. Vascular dysfunction plays a significant role in the development and progression of diabetes-related micro- and macrovascular complications. Lifestyle modification can improve vascular function. However, most studies performed to date have been within the context of mitigating changes in vascular function that occur with aging. Similar evidence is lacking for interventions

combing multiple lifestyle modifications, in patients with coronary heart disease and prediabetes. The DIABEPIC1 trial will offer participants the possibility of measuring both flow-mediated dilatation and central arterial stiffness at baseline and at the end of the intervention. The results will determine if an intensive lifestyle intervention combining exercise training and TRE improves endothelial vascular function in adults with prediabetes. Furthermore, this study will also allow us to investigate the relationship between achieving prediabetes remission and changes in vascular function.

Exploring the relationship between prediabetes remission and cognitive performance. The presence of prediabetes and T2D increases the risk of cerebrovascular diseases, cognitive deficits, and neurodegenerative diseases such as Alzheimer's (39). T2D and Alzheimer's disease are associated with cerebral insulin resistance, linked to cognitive and mood dysfunction (40). Indeed, cerebral insulin resistance alters energy metabolism and essential synaptic and immune functions. T2D is associated with impaired cognitive function, specifically decreased verbal memory and verbal fluency, and can impact functional capacity and patients' quality of life. Cardiac Rehabilitation programs that include nutritional counseling and physical exercise have improved cognition (41). Still, the association between reaching the remission criteria and changes in cognitive function has not been documented.

Conclusions

Healthy lifestyles are the cornerstone of CV prevention and can reverse the physiopathology of underlying causes of cardiovascular disease. In this regard, the cardiac rehabilitation setting offers a unique opportunity to study the effectiveness of implementing intensive lifestyles to attain remission. The DIABEPIC1 trial will address this gap by providing a comprehensive and intensive approach that includes not only traditional exercise training but also specific education and innovative dietary intervention in real-world settings and provide evidence for reversing prediabetes in patients with coronary heart disease. Ultimately, the findings from this study could significantly impact the management and prevention of prediabetes and cardiovascular disease, offering a new and improved approach to enhance patient outcomes.

Declaration of competing interest: All authors declare no competing interest.

Authors' contributions: All authors have participated in the conceptualization of the study and design**.** J.I.G. wrote the first version of the manuscript. V.D. contributed equally to the development of this study. V.D, E.L., M.G., F.B., D.G., A.D., C.G., A.N., P.L., and M.J. revised and contributed to the writing of the first version. N.B., L.B. supervised the conceptualization of the study and design and revised the final version of the manuscript.

TABLES

Table 1. Detailed inclusion and exclusion criteria of DIABEPIC1 Trial.

Inclusion criteria
- Coronary heart disease patients referred from the Montreal Heart Institute. - Aged ≥ 40 years. - Recently diagnosed prediabetes (HbA1c 5.7% to 6.4%) in the last six months. - Referred to Centre ÉPIC for stable angina, acute coronary syndrome (with or without ST elevation), after coronary revascularization (primary or elective), or bypass surgery. - Able to perform a maximal exercise test and exercise training program by current cardiovascular rehabilitation recommendations. - Able to use a smartphone application or to complete an adherence/compliance diary. - Able to read, understand and sign the information and consent form.
Exclusion criteria
- Absolute and relative contraindications to exercise testing and/or exercise training. - Patients with previously known type 2 diabetes (HbA1c ≥ 6.5%) or patients with an HbA1c value of 5.7% to 6.4% but with the help of oral hypoglycemic agents.

- Taking psychotropic medications that may induce mass gain (tricyclic antidepressants, mirtazapine, paroxetine, lithium, valproate, clozapine, olanzapine) or other medications known to promote mass gain (cortisone).
- Taking recently introduced weight-loss medications (ex: semaglutide).
- Unintentional mass loss of more than 10 kg in the past year.
- Pregnant or nursing women.

Table 2. Detailed baseline and intervention-related changes will be measured at 0, 3, and 6 months of the study.

Anthropometric measures assessed non-invasively by the SECA-mBCA 515
- Total body mass (kg) and body mass index (kg/m2). - Waist circumference (cm). - Fat mass (kg), lean mass (kg), skeletal muscle mass (kg), the proportion of total body mass, and indexes (kg/m2). - Visceral fat (L) - Change in different anthropometric measures after interventions such as proportion of visceral fat mass and skeletal muscle mass change. - Energy expenditure at rest (kcal/day). - Proportion of patients with >5% of body mass loss and >10% of body mass loss.
Physical measures measured on the day of the maximum effort test
- Systolic and diastolic blood pressure at rest and maximal effort (mmHg), - Resting heart rate, maximal heart rate, heart rate reserve, and heart rate recovery at 1 minute. - VO2 peak (ml/kg/min) and METs estimated by the FRIEND Formula (42). - Upper and lower-body 1-RM strength test on leg press and horizontal row.
Blood analysis measures
- Fasting glucose and fasting insulin. - Lipid profile including total cholesterol, LDL-C, HDL-C, triglycerides, and Apo-B. - Inflammation parameters including hs-CRP, fibrinogen, ferritin, albumin, and uric acid. - Hepatic liver enzymes: AST/ALT to calculate non-alcoholic fatty liver disease scores, % of liver fat and % of non-alcohol fatty liver disease. - Cardiac damage enzymes including troponins (cardiac injury) and pro-BNP (cardiac strain).
Cognitive scores

- Montreal Cognitive Assessment (MoCA) total score, Rey Auditory Verbal Learning Test, Coding (WAIS-IV), Stroop (D-KEFS), Trail Making Test, Verbal fluency (D-KEFS).
Vascular function measures
- Change in brachial artery flow-mediated dilatation - Central arterial stiffness
Questionnaires measures
- Nutritional Scores: Adherence to a Mediterranean Diet score (PREDIMED Test). The Food Craving Questionnaire Trait reduced (FCQ-T-r) measures food craving. Food matrix, total calories, the proportion of macronutrients, and hours spent eating and fasting collected by a 3-day journal with the application *Keenoa*. - Physical Activity Scores: International Physical Activity Questionnaire (IPAQ) score. - Psycho-emotional status: Depression, Anxiety, and Stress Scale (EDAS21)

Table 2 summarizes the distinct anthropometric, physical, blood analysis, cognitive performance, peripheral vascular function, and questionnaire measures that will be studied at baseline and repeated at 3 and 6 months of the study. Kg: kilogram, kg/m2: kilogram per square meter, cm: centimeter, L: liter, mmHg: millimeters of mercury, METs: metabolic equivalents, VO2: maximal oxygen uptake, 1-RM: one-rep max, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, Apo-B: apolipoprotein B, hs-CRP: high-sensitivity C-reactive protein, AST: aspartate aminotransferase, ALT: alanine transaminase, pro-BNP: pro-BNP: B-type natriuretic peptide.

Table 3. DIABEPIC1 schedule of enrolment and assessments.

	Cardiovascular Prevention and Rehabilitation Center of the Montreal Heart Institute (Centre ÉPIC)									
	Pre-intervention Evaluations (T0)				Mid-intervention evaluations (T3)			Post-intervention evaluations (T6)		
		Visit 1	Visit 2	Visit 3 (optional)	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
Duration (6 months)	90 min	120 min	60 min	90 min	60 min	120 min	60 min	60 min	120 min	60 / 150 min
Procedures										
Explanation of the project	X									
Consent to participate	X									
Medical visit	X				X			X		
Maximum effort test	X				X			X		
Blood test		X				X			X	
Body composition		X				X			X	
Food Diary (appl. *Keenoa*)			X				X			X
Cognitive tests		X				X			X	
Educational intervention			X				X			X
Questionnaires	X				X			X		
Vascular measurements (optional)				X						X

FIGURES

Figure 1. Central illustration summarizing the study synchronous interventions. After inclusion and baseline assessment, coronary heart patients with recently diagnosed prediabetes status defined by an HbA1c $\geq$ 5.7% to 6.4% will follow a 3-arm synchronous nutritional, exercise training, and education intervention. They will then be reassessed after three months of the intervention and again three months after the autonomy and time-restricted eating period. HbA1c: glycated hemoglobin, MedDiet: Mediterranean Diet, TRE: Time-restricted feeding, HIIT: High-intensity interval training.

REFERENCES

1. P S, I P, P S, B M, S K, N U, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9 th edition. Diabetes Res Clin Pract [Internet]. 2019 Nov 1 [cited 2021 Jul 28];157. Available from: https://pubmed.ncbi.nlm.nih.gov/31518657/

2. C B, V S, E H, J MG, R A, T B, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. Diabetes Care. 2018 May;41(5):963–70.

3. MacKay D, Chan C, Dasgupta K, Dominy C, Gagner M, Jin S, et al. Remission of Type 2 Diabetes: Diabetes Canada Clinical Practice Guidelines Expert Working Group: Can J Diabetes [Internet]. 2022 Dec 1 [cited 2023 Feb 22];46(8):753-761.e8. Available from: http://www.canadianjournalofdiabetes.com/article/S1499267122004038/fulltext

4. Committee ADAPP. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care [Internet]. 2022 Jan 1 [cited 2023 Feb 22];45(Supplement_1):S17–38. Available from: https://diabetesjournals.org/care/article/45/Supplement_1/S17/138925/2-Classification-and-Diagnosis-of-Diabetes

5. Gagnon C, Olmand M, Dupuy EG, Besnier F, Vincent T, Grégoire CA, et al. Videoconference version of the Montreal Cognitive Assessment: normative data for Quebec-French people aged 50 years and older. Aging Clin Exp Res. 2022 Jul;34(7):1627–33.

6. DHJ T, RM B, ACCM van M, SM H, F F, A G, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J. 2019 Aug 7;40(30):2534–47.

7. RR T, IB W, EL S, AP A, JA C, JR C, et al. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension. 2015 Sep 14;66(3):698–722.

8. The NOVA Food Classification System.

9. ACSMs Guidelines for Exercise Testing and Prescription [Internet]. [cited 2021 Jul 29]. Available from: https://www.acsm.org/read-research/books/acsms-guidelines-for-exercise-testing-and-prescription

10. Physical activity [Internet]. [cited 2021 Jul 29]. Available from: https://www.who.int/news-room/fact-sheets/detail/physical-activity

11. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, et al. Exercise/Physical Activity in Individuals with Type 2 Diabetes: A Consensus Statement from the American College of Sports Medicine. Med Sci Sports Exerc [Internet]. 2022 Feb 1 [cited 2023 Mar 8];54(2):353–68. Available from: https://pubmed.ncbi.nlm.nih.gov/35029593/

12. Mutie PM, Pomares-Millan H, Atabaki-Pasdar N, Jordan N, Adams R, Daly NL, et al. An investigation of causal relationships between prediabetes and vascular complications. Nature Communications 2020 11:1 [Internet]. 2020 Sep 14 [cited 2023 Feb 22];11(1):1–11. Available from: https://www.nature.com/articles/s41467-020-18386-9

13. Honigberg MC, Zekavat SM, Pirruccello JP, Natarajan P, Vaduganathan M. Cardiovascular and Kidney Outcomes across the Glycemic Spectrum: Insights from the UK Biobank. J Am Coll Cardiol. 2021 Aug;

14. Hostalek U. Global epidemiology of prediabetes - present and future perspectives. Clinical Diabetes and Endocrinology 2019 5:1 [Internet]. 2019 May 9 [cited 2023 Feb 22];5(1):1–5. Available from: https://clindiabetesendo.biomedcentral.com/articles/10.1186/s40842-019-0080-0

15. Karter AJ, Nundy S, Parker MM, Moffet HH, Huang ES. Incidence of Remission in Adults With Type 2 Diabetes: The Diabetes & Aging Study. Diabetes Care. 2014 Dec 1;37(12):3188.

16. S F, P R, K C, A D, E R, A F. Top ten research priorities for type 2 diabetes: results from the Diabetes UK-James Lind Alliance Priority Setting Partnership. Lancet Diabetes Endocrinol. 2017 Dec 1;5(12):935–6.

17. Captieux M, Prigge R, Wild S, Guthrie B. Defining remission of type 2 diabetes in research studies: A systematic scoping review. PLoS Med. 2020 Oct 28;17(10):e1003396.

18. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000 Aug 12;321(7258):405–12.

19. Liu X, Wu S, Song Q, Wang X. Reversion From Pre–Diabetes Mellitus to Normoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality in a Chinese Population: A Prospective Cohort Study. J Am Heart Assoc. 2021 Feb 2;10(3):1–9.

20. Hallberg SJ, Gershuni VM, Hazbun TL, Athinarayanan SJ. Reversing Type 2 Diabetes: A Narrative Review of the Evidence. Nutrients. 2019 Apr 1;11(4):1–16.

21. KD H, A A, R B, H C, T C, KY C, et al. Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake. Cell Metab. 2019 Jul 2;30(1):67-77.e3.

22. Sandoval-Insausti H, Jiménez-Onsurbe M, Donat-Vargas C, Rey-García J, Banegas JR, Rodríguez-Artalejo F, et al. Ultra-Processed Food Consumption Is Associated with Abdominal Obesity: A Prospective Cohort Study in Older Adults. Nutrients 2020, Vol 12, Page 2368. 2020 Aug 7;12(8):2368.

23. Montero-Salazar H, Donat-Vargas C, Moreno-Franco B, Sandoval-Insausti H, Civeira F, Laclaustra M, et al. High consumption of ultra-processed food may double the risk of subclinical coronary atherosclerosis: the Aragon Workers' Health Study (AWHS). BMC Medicine 2020 18:1. 2020 Aug 13;18(1):1–11.

24. T F, B S, L S, E KG, B A, C M, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. BMJ. 2018;360.

25. RJ de S, A M, A M, AI C, V H, T K, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ. 2015 Aug 12;351.

26. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. https://doi.org/101056/NEJMoa1800389. 2018 Jun 13;378(25):e34.

27. J SS, M B, N B, MÁ MG, N IJ, J B, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care. 2011;34(1):14–9.

28. Estruch R, Sacanella E, Ros E. Should we all go pesco-vegetarian? Eur Heart J. 2021 Mar 21;42(12):1144–6.

29. CD G, JF T, LC DG, ME H, J R, JPA I, et al. Effect of Low-Fat vs Low-Carbohydrate Diet on 12-Month Weight Loss in Overweight Adults and the Association With Genotype Pattern or Insulin Secretion: The DIETFITS Randomized Clinical Trial. JAMA. 2018 Feb 20;319(7):667–79.

30. H S, M R. Low Carbohydrate and Low-Fat Diets: What We Don't Know and Why we Should Know It. Nutrients. 2019 Nov 1;11(11).

31. S BA, I HB, D S, I S. Dietary strategies for patients with type 2 diabetes in the era of multi-approaches; review and results from the Dietary Intervention Randomized Controlled Trial (DIRECT). Diabetes Res Clin Pract. 2009 Dec;86 Suppl 1(SUPLL.1).

32. M H, C R, U K, A W, J B. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. Obes Rev. 2009 Jan;10(1):36–50.

33. V L, A S, M F. Nutritional management of hyperapoB. Nutr Res Rev. 2016 Dec 1;29(2):202–33.

34. MJ W, ENC M, A Z, H L, S F, A S, et al. Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome. Cell Metab. 2020 Jan 7;31(1):92-104.e5.

35. S C, K G, F K, M E, E W, V P, et al. Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity. Cell Metab. 2020 Sep 1;32(3):366-378.e3.

36. Ji Y, Plourde H, Bouzo V, Kilgour RD, Cohen TR. Validity and Usability of a Smartphone Image-Based Dietary Assessment App Compared to 3-Day Food Diaries in Assessing Dietary Intake Among Canadian Adults: Randomized Controlled Trial. JMIR Mhealth Uhealth [Internet]. 2020 Sep 1 [cited 2023 Feb 22];8(9). Available from: https://pubmed.ncbi.nlm.nih.gov/32902389/

37. Moyen A, Rappaport AI, Fleurent-Grégoire C, Tessier AJ, Brazeau AS, Chevalier S. Relative Validation of an Artificial Intelligence–Enhanced, Image-Assisted Mobile App for Dietary Assessment in Adults: Randomized Crossover Study. J Med Internet Res 2022;24(11):e40449 https://www.jmir.org/2022/11/e40449 [Internet]. 2022 Nov 21 [cited 2023 Mar 8];24(11):e40449. Available from: https://www.jmir.org/2022/11/e40449

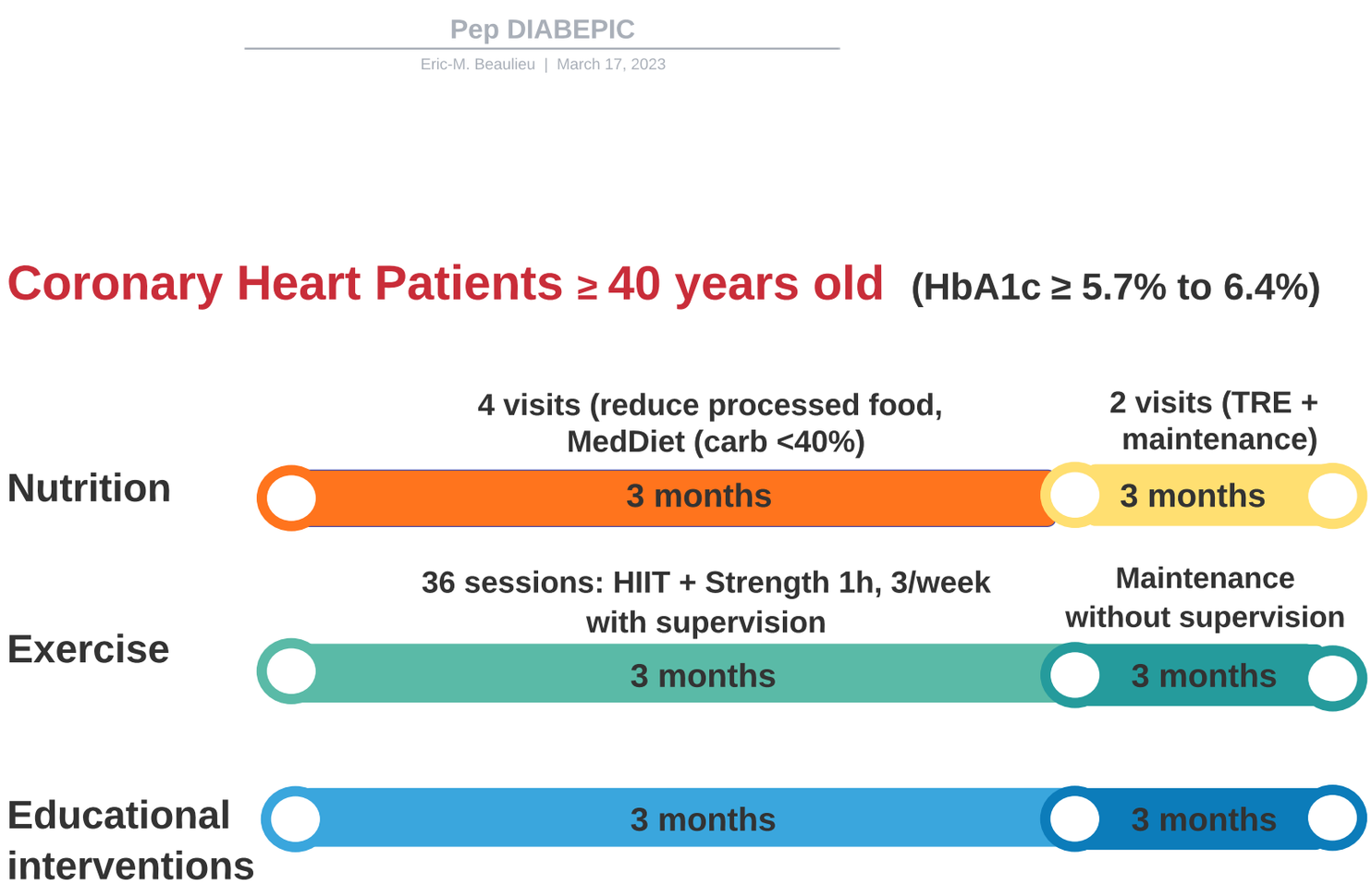
38. Taylor R. Type 2 diabetes and remission: practical management guided by pathophysiology. J Intern Med [Internet]. 2021 Jun 1 [cited 2023 Feb 22];289(6):754–70. Available from: https://pubmed.ncbi.nlm.nih.gov/33289165/

39. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nature Reviews Neurology 2018 14:3. 2018 Jan 29;14(3):168–81.

40. LD B, DJ C, S M, D B, GS W, S C. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol. 2011 Jan;68(1):51–7.

41. N D, M J, BA M. Effects of cardiac rehabilitation on cognitive impairments in patients with cardiovascular diseases: a systematic review. Int J Neurosci. 2020;

42. P K, LA K, R A, J Z, J M. New Generalized Equation for Predicting Maximal Oxygen Uptake (from the Fitness Registry and the Importance of Exercise National Database). Am J Cardiol. 2017 Aug 15;120(4):688–92.


Pep DIABEPIC
Eric-M. Beaulieu | March 17, 2023
Coronary Heart Patients ≥ 40 years old (HbA1c ≥ 5.7% to 6.4%)
Nutrition
4 visits (reduce processed food, MedDiet (carb <40%)
3 months
2 visits (TRE + maintenance)
3 months
Exercise
36 sessions: HIIT + Strength 1h, 3/week with supervision
3 months
Maintenance without supervision
3 months
Educational interventions
3 months
3 months

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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

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Running title: Feasibility and impact of an intensive team-based intervention on prediabetes remission in patients with coronary heart disease

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ABSTRACT

Introduction: Despite proven programs, implementing lifestyle interventions for prediabetes and type 2 diabetes is challenging. Cardiac rehabilitation, 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.

Objectives: The DIABEPIC1 study is an ongoing single-arm lifestyle clinical trial to assess the feasibility of an upgraded 6-month intensive cardiac rehabilitation program combining an innovative diet assignment with exercise training to reverse newly onset prediabetes (HbA1c 5.7% to 6.4%) to normal glucose concentrations in patients with coronary heart disease.

Methods and analysis: 36 patients referred from the Montreal Heart Institute for cardiac rehabilitation, aged ≥ 40 years with a recent diagnosis of prediabetes in the last six months, will be offered to participate in the upgraded program. Interventions will include four sessions of nutritional counseling on ultra-processed foods intake reduction and a moderate-carbohydrate (< 40%) *ad libitum* Mediterranean diet coupled with 36 1-hour sessions of supervised exercise training (continuous and interval aerobic training, and resistance training) and educational intervention. Phase 2 will continue the same interventions adding 8:16 hour time-restricting eating (TRE) at least five days per week. During this second phase, exercise training will be performed with autonomy. **The primary objectives** will be to evaluate the recruitment rate, the completion rates at 3 and 6 months, and the compliance of participants. **The secondary objectives** will be to assess the proportion of prediabetic participants in remission of prediabetes at the program's end and to characterize the factors associated with remission.

Ethics and dissemination: The DIABEPIC1 feasibility study is approved by the Research Ethics Board of the Montreal Heart Institute (Project Number ICM 2022-3005). Written informed consent will be obtained from each participant prior to inclusion. Results will be available through research articles and conferences.

Conclusions: The DIABEPIC1 trial will examine the feasibility and effectiveness of an enhanced cardiac rehabilitation program combining exercise training with an ultra-processed food reduction intervention, a Mediterranean Diet, and TRE counseling to remit prediabetes to normal glucose concentrations.

Trial registration number: ClinicalTrials.gov Identifier: NCT05459987

Strengths and limitations of this feasibility study

Strengths:

- Addresses the issue of effective implementation of lifestyle interventions as a first-line treatment for prediabetes, which is rarely seen in routine clinical care.

- Offers a unique opportunity to influence the underlying causes of cardiovascular disease and adopt healthy lifestyle behaviors through an upgraded 6-month intensive cardiac rehabilitation program.

- Combines multiple proven interventions, including nutritional counseling, exercise training, and time-restricted eating, to achieve remission of prediabetes and improve metabolic health.

Limitations:

- The study population is relatively small (36 participants), and it is limited to patients with coronary heart disease referred for cardiac rehabilitation, which may not be representative of the general population with prediabetes.

- The study duration is limited to six months, which may not be sufficient to observe sustained changes in lifestyle behaviors and metabolic health.

Abbreviations' list by order of appearance

T2D = Type 2 diabetes mellitus

ASCVD = Atherosclerotic cardiovascular disease

TRE = Time-restricted eating

Centre ÉPIC = Cardiovascular Prevention and Rehabilitation Center of the Montreal Heart Institute

HbA1c = Glycated hemoglobin

FMD = Flow-mediated dilatation

ACSM = American College of Sports Medicine

RPE = Rate of perceived exertion

HIIT = High-Intensity Interval Training

MICT = Moderate Intensity Continuous Training program

1-RM = one-repetition maximum

INTRODUCTION

Prediabetes and Type 2 diabetes (T2D) are major risk factors for cardiovascular disease (ASCVD) and a significant burden for patients and healthcare systems. In Canada, the estimated prevalence of T2D is 3.4 million (9% of the population), and 5.7 million (15% of the population) are living with prediabetes, most of them unaware of their condition (1). Despite current optimal treatments, cardiovascular events remain high in individuals with prediabetes and T2D, and it is predicted that the number of people living with these conditions will continue to increase (2).

Early diagnosis and intensive interventions, such as adequate weight loss through physical exercise, distinct dietary interventions, and intermittent fasting modalities like time-restricted eating (TRE), have been shown to prevent, improve, and even reverse these conditions (3). Unfortunately, these lifestyle interventions are only sometimes effectively implemented in routine clinical practice, likely due to obstacles such as healthcare resources, infrastructure, and personal barriers. Therefore, innovative ways to effectively implement and maintain lifestyle changes are needed. One potential solution is to use a cardiac rehabilitation program after an acute cardiovascular event as an opportunity to influence the underlying causes of cardiovascular disease and adopt healthy lifestyle behaviors.

The DIABEPIC1 study is a single-arm lifestyle clinical trial that will assess the feasibility of an intensive lifestyle program to reverse newly onset prediabetes (HbA1c 5.7% to 6.4%) to normal glucose concentrations in patients with a recent acute cardiovascular event that would otherwise start a standard cardiac rehabilitation program of 12 weeks. The patients will be offered an upgraded 6-month intensive team-based multidisciplinary stepwise program combining diet assignment (ultra-processed foods reduction, Mediterranean Diet and TRE) with exercise training (continuous/interval aerobic training and resistance training) and educational intervention to remit prediabetes.

The study's primary aim is to assess the feasibility of the enhanced program to devise and iteratively improve participant recruitment and adherence strategies for a possible future randomized controlled trial.

The study also aims at studying the factors associated with metabolic improvements and prediabetes remission to contribute to a clear rationale for seeking this endpoint. Finally, the study also intends to better understand the distinct lifestyle interventions' benefits by characterizing baseline and intervention-related changes in anthropometric measures, blood analysis, a 3-day nutritional diary registered by the *Keenoa* artificial intelligence *App*, vascular function measured by flow-mediated dilatation and central arterial stiffness, and cognitive performance evaluated by a short neuropsychological battery targeting executive functions, processing speed, and episodic memory.

The DIABEPIC1 trial will examine the feasibility and effectiveness of an enhanced cardiac rehabilitation program combining exercise training with a Mediterranean Diet and TRE counseling to remit prediabetes to normal glucose concentrations. The potential impact of the results of this intervention on the delivery of cardiac rehabilitation programs for patients with prediabetes is significant. If proven feasible, it could improve cardiovascular function after an acute coronary event, reverse a causal risk factor, and enhance metabolic health.

METHODS

Study design overview and setting

The feasibility study will take place at the Cardiovascular Prevention and Rehabilitation Centre of the Montreal Heart Institute (Centre ÉPIC). The study duration will be 24 weeks (6 months) with two distinct 3-month interventions: Phase 1 (Intensive Cardiac Rehabilitation Program) will consist of a synchronous intensive nutritional intervention (4 sessions of counseling on ultra-processed foods intake reduction and moderate-carbohydrate (< 40% of total energy intake) *ad libitum* Mediterranean diet) coupled with 36 1-hour sessions of supervised exercise training (continuous and interval aerobic training, and resistance training) and educational intervention. Phase 2 (Autonomy period) will continue the same interventions adding 8:16 hour time-restricting eating (TRE) at least five days per week. Exercise training will continue in autonomy.

Nurses will deliver the educational intervention throughout the project in individualized 1-hour meetings at 0, 3, and 6 months. Topics addressed will be as follows: the concepts of insulin resistance, prediabetes, and T2D; the main reasons behind the development of the disease; and the scientifically proven ways to reverse these conditions. Sessions will be tailored to the specific needs of the patients and will involve motivational interviewing to build intrinsic motivation for lifestyle modifications.

Anthropometric measures, blood analysis, a 3-day nutritional diary registered by the *Keenoa* artificial intelligence *App*, and cognitive performance evaluated by a short neuropsychological battery will be performed at baseline, after three months of the intensive intervention, and at three months. Vascular function measurements by flow-mediated dilatation and central arterial stiffness will be optional, and measures will take place at baseline and six months. A visual illustration of the DIABEPIC1 interventional study is depicted in **Figure 1**.

Ethics and Dissemination

The study protocol has been approved by the Research Ethics Board of the Montreal Heart Institute (Project Number ICM 2022-3005). It is reported per the Standard Protocol Items-Recommendations for Interventional Trials guidelines (SPIRIT). The study has also been registered on Clinicaltrials.gov (Identifier: NCT05459987). The study complies with International Conference on Harmonization for Good Clinical Practice (ICH-GCP) guidelines and all regulatory requirements. Written informed consent will be obtained from each participant prior to inclusion.

Hard copy files will be stored in a locked filing cabinet at the clinic site at Centre ÉPIC. After the study, all hard copy files containing the participant data will be anonymized and stored in a password-protected secured storage system accessed by approved personnel only.

The DIABEPIC1 results will be communicated through an internal committee's thorough review and editing process to ensure the scientific accuracy and authorship of the publication and abstracts. No interim analysis is planned. The authorship of the publication and ancillary studies will be determined per the guidelines of the International Committee of Medical Journal Editors. The results will also be shared with participants, staff of the Centre ÉPIC, and the broader medical community through research articles and conferences. Additionally, the complete and anonymous dataset will be made available for sharing by the principal investigator upon request no later than three years after the end of the study.

Patient and public involvement: No patient involved

Participant selection

Participants will be recruited among those referred for a cardiac rehabilitation program from the Montreal Heart Institute because of stable angina, after an acute coronary heart event (with or without ST-segment elevation), after coronary revascularization (primary or elective), or after bypass surgery. Starting recruiting date will be in March 2022. Potentially eligible patients recently diagnosed with prediabetes (< 6 months) based on the American Diabetes Association cut-off criteria of glycated hemoglobin (Hb1Ac) between 5.7% to 6.4% (4) will be identified by the researchers before their first scheduled cardiac rehabilitation medical visit based on the results of their routine blood analysis typically performed one week in advance

that includes: complete blood count, kidney function, a lipid profile, fasting glycemia, insulin, and HbA1c. They will be contacted and explained the possibility of participating in the study. They will be comprehensively informed and provided with an informed consent form if interested. Following this first call, the participant will have their first medical appointment, including a maximal exercise test to screen for potential contraindications and securely follow prescribed exercise training. This visit will also serve as the enrollment visit, where the participant will have another opportunity to discuss the project, clarify any doubts, and, if wished, be enrolled. Participants who refuse to participate in the present study will continue as scheduled and participate in the standard 3-month cardiac rehabilitation program. Participants will be eligible to participate if all inclusion criteria are met, and none of the exclusion criteria are met. All study procedures, including the signature of informed consent, will be conducted at the Centre ÉPIC, providing all required settings, including material, trained nurses, registered dietitians and kinesiologists in clinical research, trained research assistants, and administrative assistant. Detailed inclusion and exclusion criteria are shown in **Table 1**.

Study outcomes

Primary objective: To assess the feasibility of an intensive, multidisciplinary cardiac rehabilitation program based on lifestyle changes in coronary heart disease patients recently diagnosed with prediabetes that are referred to the Centre ÉPIC. Currently, the Centre ÉPIC receives up to 550 new coronary heart disease patients annually (approximately 50 per month) to participate in its cardiac rehabilitation program. Of these patients, between 20-30% are diagnosed with T2D, and around 15-20% fulfill the criteria for prediabetes (HbA1c 5.7% to 6.4%). Based on these numbers, four parameters are considered to assess the feasibility of our study:

1) Total Recruitment: Number of participants screened compared to final enrollments. Hypothesis: At least 50% of patients living with prediabetes and referred to the Centre ÉPIC for the cardiac rehabilitation program will find the study interesting and accept participation.

2) Recruitment rate: Number of participants that can be recruited monthly. Hypothesis: At least two participants can be enrolled weekly, eight per month.

3) Completion rate at 3 and 6 months: Number of participants that complete the intervention at three and six months compared to the enrolled participants. Hypothesis: At least 70% of the participants will finish the 3-month and 6-month programs (i.e., dropout rate ≤ 30%).

4) Compliance: Total number of appointments attended (nutritional, exercise training, and educational interventions) compared to the maximum possible. Hypothesis: Participants will attend at least 80% of all proposed sessions.

To summarize, the full-scale study will be feasible if we can recruit at least eight participants per month on average, if the completion rate is at least 70% at six months, and if compliance with all protocol interventions is at least 80%. From here, all other collected data during the study will serve only for an exploratory purpose (see below secondary and tertiary endpoints).

Secondary objectives include assessing the proportion of participants with prediabetes at the start of the program (HbA1c 5.7% to 6.4%) in complete remission of prediabetes, defined by the following three criteria: A HbA1c <5.7% at three months of intervention (metabolic criteria), which is maintained at six months (duration criteria), without the use of glucose-lowering agents (pharmacological measures). Partial remission of prediabetes will be defined if the metabolic criteria (HbA1c <5.7%) is reached at six months, the end of the study's second phase. This will allow researchers to examine how long it takes some participants to remission of prediabetes and the effect of the TRE intervention on metabolic changes. Hypothesis: At least 50% of participants will fulfill one of the remission criteria definitions at the end of the follow-up.

Tertiary objectives will characterize baseline and intervention-related changes in distinct anthropometric, physical, blood analysis, cognitive, vascular function, and questionnaire measures detailed in **Table 2**. Incidence of cardiovascular events will also be recorded and reported as a five-point composite of major

adverse cardiovascular events (MACE) including cardiovascular death, myocardial infarction, unstable angina, ischemic stroke, and hospitalization for heart failure.

Detailed study interventions and timelines

A complete illustration of the study enrolment and evaluation assessments can be found in Supplementary **Table1**.

Pre-intervention evaluation (over one week): Upon signing the informed consent form, participants will have several pre-intervention assessments, including baseline missing blood analysis parameters and total anthropometric measurements by bioimpedance (mBCA 515, SECA). A visit with the nurse in which the patient will be involved in a motivational interviewing to assess personal objectives. In this visit, participants will also be offered expert educational and nutritional information about the concepts of insulin resistance, prediabetes, and T2D, the main reasons behind the development of the disease, and the scientifically proven ways to reverse these conditions. The patient will also be informed on how to use the *Keenoa* application to collect a 3-day nutritional diary. The 3-month scheduled intervention program will be reviewed with the participant to clarify any remaining questions.

Cognitive Function Assessment. A short cognitive assessment will be performed by a neuropsychologist or by trained research assistants. The tests will target general cognitive functioning, executive functions, processing speed, and episodic memory: Montreal Cognitive Assessment (MoCA; general cognitive functioning), Rey Auditory Verbal Learning Test (episodic memory), Coding (WAIS-IV) (processing speed), Stroop (D-KEFS) (executive functions), Trail Making Test (executive functions), Verbal fluency (D-KEFS) (executive functions). Neuropsychological testing will be conducted in person or by videoconference; the aforementioned tests are adequate for remote administration (5). Moreover, all tests have been validated for an adult population.

Vascular Function Assessment. Flow-mediated dilatation (FMD) change to measure endothelial function and carotid-femoral pulse wave velocity to measure central arterial stiffness will be optional. For FMD measurement, brachial artery blood velocity and diameter will be measured with a high-resolution ultrasound device (uSmart3300, Terason) and a linear bar probe (5-12 MHz) before and after 5 minutes of forearm ischemia. A cuff downstream of the ultrasound probe will be inflated to a pressure of 250 mmHg to induce ischemia. After the cuff is released, the brachial artery blood velocity and diameter increase will be measured continuously for 3 minutes. An analysis program (FMD studio, Quipu srl) will independently determine peak diameter and shear rate. FMD will be quantified as the change in diameter from rest to peak, corrected by the shear stimulus and the baseline diameter. This measurement will be performed per current guidelines (6). Central arterial stiffness will be measured via carotid-femoral pulse wave velocity. The pulse wave will be recorded continuously over the carotid and femoral arteries by a non-invasive surface tonometer (Millar Inc). The pressure waveforms will be recorded for a minimum of 10 consecutive cardiac cycles. Distance traveled by the pulse wave will be measured, in triplicate, as the direct distance between the two measurement sites with a correction factor of 0.8, as per current guidelines (7).

Phase 1 (3 months): Intensive Cardiac Rehabilitation Program

Nutritional Intervention: Once a 3-day food diary is collected, registered dieticians will perform four personalized 1-hour visits stepwise throughout the first three months. *Step 1*: During the first visit, participants will be informed about how to read nutritional information of food products, how to identify processed and ultra-processed foods following the NOVA classification (8), and will be advised to reduce Group 2 and 3 products and avoid Group 4 products. *Step 2*: After this first visit, patients will have two personalized nutritional visits in which a Mediterranean Diet moderate in carbohydrates (<40%) will be explained and proposed to them. The Mediterranean Diet Pyramid will guide participants in adapting to the new pattern. As part of the diet, participants will be advised to consume a diet predominately plant-based made up of vegetables, legumes, fruits, whole grains, nuts, and seeds. Fish will be the primary source of protein, and olive oil will be the primary source of fat in the recommendations. There will not be specific

calorie reduction targets. During these visits, efforts will be made to progressively adjust and improve, resolve doubts, and teach cooking techniques if necessary. *Step 3*: During the last two weeks of Phase 1, the participant will have one last visit to be informed about the concepts of intermittent fasting and time-restricted eating to be prepared for Phase 2 and informed to introduce an 8:16 hour TRE at least for five days a week, starting the second phase.

Exercise Training Intervention: The exercise training intervention for Phase 1 will consist of 1-hour / three sessions per week of in-patient supervised endurance and strength training for twelve weeks (a total of 36 sessions). One session per week will be allowed at home if the participant wishes to accommodate preferences and prepare participants for Phase 2 (training in autonomy). In-person sessions will be encouraged and supervised by a certified kinesiologist at the Centre ÉPIC, who will also organize the exercise-training sessions designed to be performed at home. The aerobic and resistance training prescriptions will be programmed according to the recent American College of Sports Medicine (ACSM) Guidelines for Exercise Training and Prescription, Eleventh Edition, 2021 (9). The rate of perceived exertion (RPE) during the exercise sessions will be assessed on the BORG scale from 6-20.

Furthermore, participants will be encouraged to engage in their activities at home, like walking or cycling, following the 2020 WHO recommendations of at least 150 to 300 minutes of moderate-intensity aerobic exercise per week (10). All the characteristics of the activities will be recorded (type of activity, intensity, heart rate, duration) with the Polar Beat application and the heart rate sensor Polar H10.

The first two weeks will progressively introduce participants to all the exercise techniques, get familiar with all materials, and assess different muscular-group strengths. During these first two weeks, continuous moderate exercise sessions and high-intensity interval training will be proposed to facilitate acquaintance with all participants. The endurance exercise program will be performed on a bicycle ergometer, treadmill, or elliptical. The intensity will start at 50% of maximal aerobic power or 11-12 of the Borg RPE during the

first week and gradually increase to 60-70%. If needed, the intensity of the training will be adjusted according to the heart rate reserve of each patient.

After these first two introductory weeks, alternating high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) sessions will be proposed in a 2:1 fashion; 2 HIIT sessions and 1 MICT session per week. The endurance sessions will include 5 to 10 minutes of warm-up and 5 minutes of cool-down. In the case of MICT sessions, the intensity will be between 60-70% of maximal aerobic power at a RPE, starting at 12 and progressively increasing to 14. During the HIIT, exercises (2 to 3 blocks of 10 minutes) will be composed of 1 to 3 minutes intervals at 80-100% of the maximal aerobic power interspersed with an active recovery of the same duration. The RPE for the HIIT sessions will start at 15 and gradually increase to 17 through the exercise training program (11).

All training sessions will include 20 to 30 minutes of strength training that will take place using machines, free weights, or elastic bands depending on the program phase. Strength training will be programmed according to the recent ACSM guidelines with a gradual progression of higher intensities and/or numbers of sets/repetitions. Intensities will be prescribed at a RPE from 12 to 15, which corresponds to 40 to 70% of the one-repetition maximum (1-RM), with 6 exercises involving major muscle groups. The number of sets will be from 1 to 3, and the number of repetitions will be from 6 to 15. The gradual assumption of autonomy towards Phase 2 will be encouraged throughout this first phase of cardiac rehabilitation as, at the end of the three months, all participants should be able to follow personalized endurance and strength autonomous training.

Mid-intervention evaluation: At the end of the 3-month program, participants will be offered to repeat a maximal effort test on a treadmill, a medical visit and examination, complete blood analysis, and anthropomorphic assessment. Participants will also be asked to redo all questionnaires, a 3-day food diary with the application *Keenoa* and the cognitive tests.

Phase 2 (3 months): Time-restricted eating and exercise training in autonomy.

Nutritional Intervention: After the mid-term assessments, participants will be asked to maintain all healthy lifestyle changes introduced during the first three months and to start an 8:16 hour TRE pattern at least five days a week, meaning an 8-hour window in which the participant will be allowed to eat and 16-hour window in which the participant will be asked to restrict from ingestion. General advice will be given to practice TRE successfully, such as to plan meals, eat consistently, gradually adjust the eating window, choose nutrient-dense foods, stay hydrated, and avoid snacking outside the designated eating window. This period will include two additional nutritional consultations to resolve doubts.

Exercise Intervention: During the study's second phase and following the 2020 WHO guidelines of physical activity, all patients will be given personalized aerobic and strength exercise training to be performed without supervision at a gym or at home. Only remote follow-ups will be offered to resolve doubts and adjust if needed.

Post-intervention evaluation (over one week): At the end of the program, participants will have a last medical visit that will include a maximal effort test on a treadmill, a medical visit and examination, complete blood analysis, and an anthropomorphic assessment. Participants will also be asked to redo all questionnaires and cognitive tests and collect a 3-day food diary with the application *Keenoa*. Vascular function measures will again be optional for patients who have consented and attended their first appointment. The last 6-month evaluation for the latest participant enrolled is scheduled for May 2023. Following that, we will proceed with a 12-month follow-up to assess the long-term sustainability of remission and the metabolic progression of all participants. This follow-up is planned to finish in December 2023.

Statistical considerations

Sample Size calculation: Primary outcome measures for this study are feasibility criteria to inform any future randomized controlled trial powered to detect an intervention effect. Therefore, a sample size for this study was calculated to allow the estimation of a completion and compliance rate with reasonable precision.

Assuming that the completion rate will be around 70%, a sample size of 25 would allow estimating this rate with an accuracy of ± 18.0% using a two-sided 95% confidence interval. For a compliance rate of around 80%, a sample size of 30 participants would assure a precision of ± 15.7% for estimating this rate. Assuming a 30% loss rate to follow-up, approximately 36 patients will be recruited.

Statistical analysis will be mainly descriptive with, when appropriate, the presentation of 95% confidence intervals. They will be computed for baseline characteristics and follow-up assessments at three and six months. They will be presented as mean and standard deviation for continuous variables and frequencies and percentages for categorical variables.

The number of participants that can be recruited monthly and the number of participants screened will be summarized. The total recruitment and monthly rates will be presented with a 95% confidence interval. The number of participants that complete the intervention at three months, the number of participants that attend their 6-month follow-up appointment, and the total number of appointments attended (nutritional intervention (up to 6), exercise training intervention (up to 36) and educational intervention (up to 3) will be summarized. Completion/retention rate at 3 and 6 months and compliance rate will be presented with a 95% confidence interval.

For illustrative purposes (because this pilot study is not powered to detect statistically significant findings), all analyses of this pilot study, including both secondary and tertiary endpoints, will be the assessments that could be considered as efficacy parameters in the large, full-scale study. For the analysis of change in continuous secondary and tertiary endpoints, i.e., anthropometric measures, exercise-derived measurements, blood analysis measures, and scores from questionnaires, a one-way repeated-measures ANOVA model will be used to compare differences between intervention (pre, per, post) periods, with mean differences and 95% confidence intervals and with effect sizes (Cohen's d) when appropriate. The assumptions underlying the planned models will be checked, and if they are not tenable, data transformation or non-parametric analyses may be used if necessary.

The adjusted impact of the different factors associated with remission of prediabetes (e.g., mass loss, fat mass loss, visceral fat loss) will be evaluated. For this analysis, univariable and multivariable logistic regression models will be created for the categorical outcome of remission of prediabetes: yes/no, accordingly to the definition previously mentioned. Covariates will be selected a priori based on their described association with remission (clinical plausibility) or as a potential confounding effect according to the rules proposed by Kleinbaum and colleagues using the user-written Stata command "confound" (ref). The practical and clinical interpretation will be presented with measures of association (odds ratio, OR). Statistical significance will be defined as a p-value < 0.05. Statistical analyses will be performed using STATA (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

DISCUSSION

The DIABEPIC 1 study aims to investigate the feasibility and effectiveness of an upgraded, intensive multi-disciplinary program for cardiac rehabilitation in reversing prediabetes in patients with coronary heart disease. The program, which will last six months, will include a combination of dietary intervention, exercise training, and education. The rationale behind this project is to address the growing issue of prediabetes as the unaddressed underlying cause of cardiovascular disease (12) and propose an enhanced cardiac rehabilitation program following an acute cardiovascular event to promote healthy lifestyle behaviors and reverse this condition to normal glucose concentrations.

Why is it important?

A substantial gradient of cardiovascular risk is observed across HbA1c levels from as low as HbA1c $\geq$ 5.4%, way below the threshold for diabetes (13). It is often reported that approximately 1 in 3 Americans have prediabetes and that 90% are not aware of their condition. Furthermore, about 25% of individuals with prediabetes will develop T2D within 3 to 5 years, and as many as 70% will develop the disease during their lifetime (14). Despite the high prevalence of prediabetes and the existence of proven effective programs, there are currently limited options available in current clinical practice, especially in Canada, to halt or reverse this condition. Additionally, despite its relationship with an increased risk of ASCVD, there is not yet an entirely clear rationale for seeking the endpoint of prediabetes remission. The results of the DIABEPIC1 study can eventually contribute to provide valuable evidence toward clarifying this goal.

What is known?

Although remission of prediabetes and T2D in the community have been described, they have been historically understudied (15). For decades, T2D has been regarded as a progressive and irreversible condition requiring increasing numbers of oral glucose-lowering agents and insulin.

Nevertheless, remission has been recently identified as a top priority by people with prediabetes and T2D (16), and only in the past decade, at least 178 studies with over 100 participants (11 of which were randomized controlled trials) have been published focusing on the possibility of reversing T2D and prediabetes (17). Among them, surgical interventions were the focus of 164 (93%) studies compared to 8 (4%) pharmacological and 5 (2%) lifestyle interventions. In 2021, the ADA/EASD/DUK consensus statement on the definition of T2D remission was published, providing important guidance in this area. Additionally, more recently, the Diabetes Canada Remission of T2D Guidelines and User's Guide have also been published, further contributing to the understanding and management of T2D remission (18,19).

Reversion to normoglycemia is associated with positive health benefits beyond T2D prevention or delay. A 1% absolute decrease in HbA1c was associated with a 14-27% decrease in major CV events and a 37% reduction in microvascular complications in a cohort from the United Kingdom (20). The risk of cardiovascular disease and all-cause mortality was also reduced in a Chinese cohort of patients with prediabetes who reverted to normoglycemia within two years compared to those who progressed to T2D over nearly nine years of follow-up. The odds of developing microvascular disease (retinopathy, nephropathy, and neuropathy) were also reduced (21). Most of these studies have a common strategy: to improve insulin sensitivity and reverse insulin resistance, individuals need to shift to burning fat as their primary energy source to reduce fat mass. This can be achieved by lowering insulin levels (fasting, restrictive diets, reducing consumption of ultra-processed foods, metabolic surgery, or oral drugs) or increasing energy expenditure through endurance and resistance training. However, it is important to note that the combination of both strategies - lowering insulin levels and increasing energy expenditure - can have a synergistic effect, leading to greater improvements in insulin sensitivity and reductions in fat mass. A comprehensive narrative review of the evidence can be found elsewhere (22).

What is new in this interventional study?

An intensive synchronous intervention in the setting of cardiac rehabilitation. A Mediterranean diet, TRE, educational interventions, and regular exercise training have provided positive health benefits for improving metabolic parameters in healthy individuals and/or patients with prediabetes and T2D . However, there is limited evidence on the effect of multiple synchronous lifestyle interventions in patients with prediabetes combining these approaches in a synchronous stepwise intervention to attain remission, particularly in cardiac rehabilitation. The enhanced insulin resistance reversal program aims to improve patients' glucose regulation and overall cardiovascular health by targeting various risk factors associated with prediabetes and cardiovascular disease. The proposed program seeks to address this gap by providing a comprehensive and intensive approach to cardiac rehabilitation that includes not only traditional exercise training but also education on the concepts of insulin resistance, prediabetes, and T2D, the main reasons behind the development of the disease, and the scientifically proven ways to reverse these conditions as well as an innovative dietary intervention including ultra-processed food reduction, a moderate-carbohydrate ad libitum Mediterranean Diet and the inclusion of TRE.

A reduction of ultra-processed foods as the starting point. The consumption of ultra-processed foods is associated with excess calorie intake and weight gain (23), metabolic syndrome (24), coronary heart disease, cerebrovascular disease (25), and cancer (26). These foods have also been shown to cause an elevated glycemic response, disrupt satiety signals, promote inflammation, and the occurrence of diabetes (27). Processed and ultra-processed foods are probably one of the main drivers of ad libitum dietary habits and today's global epidemic. In this context, the DIABEPIC1 study will start the nutritional intervention by teaching how to identify these foods and an intervention to reduce ultra-processed foods consumption. This strategy is a consequence of most weight-reducing diets that intrinsically exclude these types of products but is barely studied as a specific starting-point education strategy at the roots of the problem, which can lead to weight loss and a decrease in glycemic spikes. Still, it can also be important in rebalancing satiety signals and promoting adherence to subsequent nutritional recommendations.

A Mediterranean diet with moderate carbohydrate consumption as a diet assignment. The Mediterranean diet is well known for its various health benefits in healthy individuals, cardiovascular diseases, and cancer (28). It reduces the incidence of T2D among non-diabetics with high cardiovascular risk (29). In insulin-resistant individuals, it improves glycemic control, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and triglycerides. In addition to its high nutritional quality, it also carries relatively easy long-term compliance (30), data lacking for most all other dietary interventions. For these reasons, the proposed interventions will be focused on a Mediterranean diet pattern.

Some randomized controlled trials show that low-carbohydrate diets prevent body weight more effectively than low-fat diets (31,32). For instance, blood glucose, HbA1c, and glycemic control are improved by low-carbohydrate in comparison with low-fat diets (33,34), and ApoB is improved in a moderate-carbohydrate diet (26-45% carbohydrate) compared to a high-carbohydrate diet (49-65% carbohydrate) (35). Thus, our nutritional program includes instructions to reduce carbohydrate consumption to an average of 40% of calories consumed.

Time-restricted eating in a cardiac rehabilitation setting as a new approach. Not only what we eat but also when we eat could affect health. A reduced food consumption window of 10 hours/day (14 hours of fasting) promotes weight loss in patients with metabolic syndrome, prediabetes, and T2D. It decreases waist circumference, visceral fat, blood pressure, atherogenic lipoproteins, and glycated hemoglobin (36). A daily food consumption window reduced to 4h or 6h/day (20h or 18h of fasting) resulted in a 3.2% loss of body weight while improving fasting insulin levels, insulin resistance, and oxidative stress (37). Nonetheless, there is little evidence of the added effects of TRE in patients with prediabetes or T2D. It has not been evaluated in the context of a Mediterranean Diet intervention, particularly in the cardiac rehabilitation setting. The DIABEPIC1 trial will propose and study a Mediterranean diet assigning moderate carbohydrate consumption with the addition of a TRE 16:8 pattern during the study's second phase. This will allow

assessing the impact of adding this nutritional intervention separately from the effects of the first three months of synchronous dietary and exercise training intervention.

The use of the *Keenoa* Application to assess participants' food intake and personalized approach to lifestyle intervention. The DIABEPIC1 study will use data collected from the novel Canadian diet application *Keenoa*™ at 0, 3, and 6 months. The validity and usability of this smartphone image-based dietary assessment app compared to 1-day and 3-day food diaries have been previously assessed (38,39). Its use offers several potential advantages: real-time data collection, which reduces the delay between intervention delivery and data collection; convenience as participants can access the application from their mobile devices; a more collaborative and personalized approach to lifestyle intervention between participants and healthcare providers, and improved data quality helping reduce errors and biases associated with manual data collection and increases the accuracy of data collection. The feasibility of its use and adherence will be reported.

Multicomponent anthropometric measurements by bioelectrical impedance as an innovation. Visceral adipose tissue and visceral fat mass loss are critical players in the pathogenesis of insulin resistance. The likelihood of prediabetes and T2D remission increases when substantial weight loss is achieved (40). Despite the nature of lifestyle or pharmacological interventions, most studies utilize total weight loss as a marker or endpoint, thus neglecting the impact of individual body components. Therefore, to gain a better understanding of the factors leading to remission, there is a need to improve data on the specific impact of different body components.

One of the particularities of this study will be the systematic use of the SECA-mBCA 515 balance to measure different components of body composition by bioelectrical impedance analysis, which will allow observing the absolute and proportional change in body mass, fat mass, visceral fat, lean body mass, and skeletal muscle that participants will present through the different phases of the intervention. These will

also allow exploratory assessment of the adjusted impact of the other factors associated with remission of prediabetes.

Vascular function to assess changes in endothelial function and central arterial stiffness and their relationship with remission. Vascular dysfunction plays a significant role in the development and progression of diabetes-related micro- and macrovascular complications. Lifestyle modification can improve vascular function. However, most studies performed to date have been within the context of mitigating changes in vascular function that occur with aging. Similar evidence is lacking for interventions combing multiple lifestyle modifications, in patients with coronary heart disease and prediabetes. The DIABEPIC1 trial will offer participants the possibility of measuring both flow-mediated dilatation and central arterial stiffness at baseline and at the end of the intervention. The results will determine if an intensive lifestyle intervention combining exercise training and TRE improves endothelial vascular function in adults with prediabetes. Furthermore, this study will also allow us to investigate the relationship between achieving prediabetes remission and changes in vascular function.

Exploring the relationship between prediabetes remission and cognitive performance. The presence of prediabetes and T2D increases the risk of cerebrovascular diseases, cognitive deficits, and neurodegenerative diseases such as Alzheimer's (41). T2D and Alzheimer's disease are associated with cerebral insulin resistance, linked to cognitive and mood dysfunction (42). Indeed, cerebral insulin resistance alters energy metabolism and essential synaptic and immune functions. T2D is associated with impaired cognitive function, specifically decreased verbal memory and verbal fluency, and can impact functional capacity and patients' quality of life. Cardiac Rehabilitation programs that include nutritional counseling and physical exercise have improved cognition (43). Still, the association between reaching the remission criteria and changes in cognitive function has not been documented.

Strengths and Limitations

This feasibility study, exhibits several strengths and limitations. Strengths include its focus on the implementation of lifestyle interventions as a first-line treatment for prediabetes, which is often overlooked in routine clinical care. It offers a unique opportunity to influence the underlying causes of cardiovascular disease through an upgraded 6-month intensive cardiac rehabilitation program. Additionally, the study combines multiple proven interventions, including nutritional counseling, exercise training, and time-restricted eating, to achieve prediabetes remission and improve metabolic health. However, the study's limitations include a relatively small sample size of 36 participants, which may not be representative of the general population with prediabetes. The study's six-month duration might not be sufficient to observe sustained changes in lifestyle behaviors and metabolic health. Acknowledging these strengths and limitations is important for a comprehensive evaluation of the study's potential impact and to guide future research improvements.

Conclusions

Healthy lifestyles are the cornerstone of CV prevention and can reverse the physiopathology of underlying causes of cardiovascular disease. In this regard, the cardiac rehabilitation setting offers a unique opportunity to study the effectiveness of implementing intensive lifestyles to attain remission. The DIABEPIC1 feasibility trial will address this gap by providing a comprehensive and intensive approach that includes not only traditional exercise training but also specific education and innovative dietary intervention in real-world settings and provide evidence for reversing prediabetes in patients with coronary heart disease. Ultimately, the findings from this study could significantly impact the management and prevention of prediabetes and cardiovascular disease, offering a new and improved approach to enhance patient outcomes.

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TABLES

Table 1. Detailed inclusion and exclusion criteria of DIABEPIC1 Trial.

Inclusion criteria
- Coronary heart disease patients referred from the Montreal Heart Institute. - Aged ≥ 40 years. - Recently diagnosed prediabetes (HbA1c 5.7% to 6.4%) in the last six months. - Referred to Centre ÉPIC for stable angina, acute coronary syndrome (with or without ST elevation), after coronary revascularization (primary or elective), or bypass surgery. - Able to perform a maximal exercise test and exercise training program by current cardiovascular rehabilitation recommendations. - Able to use a smartphone application or to complete an adherence/compliance diary. - Able to read, understand and sign the information and consent form.
Exclusion criteria
- Absolute and relative contraindications to exercise testing and/or exercise training. - Patients with previously known type 2 diabetes (HbA1c ≥ 6.5%) or patients with an HbA1c value of 5.7% to 6.4% but with the help of oral hypoglycemic agents. - Taking psychotropic medications that may induce mass gain (tricyclic antidepressants, mirtazapine, paroxetine, lithium, valproate, clozapine, olanzapine) or other medications known to promote mass gain (cortisone). - Taking recently introduced weight-loss medications (ex: semaglutide). - Unintentional mass loss of more than 10 kg in the past year. - Pregnant or nursing women.

Table 2. Detailed baseline and intervention-related changes will be measured at 0, 3, and 6 months of the study.

Anthropometric measures assessed non-invasively by the SECA-mBCA 515
- Total body mass (kg) and body mass index (kg/m2). - Waist circumference (cm). - Fat mass (kg), lean mass (kg), skeletal muscle mass (kg), the proportion of total body mass, and indexes (kg/m2). - Visceral fat (L) - Change in different anthropometric measures after interventions such as proportion of visceral fat mass and skeletal muscle mass change. - Energy expenditure at rest (kcal/day). - Proportion of patients with >5% of body mass loss and >10% of body mass loss.
Physical measures measured on the day of the maximum effort test
- Systolic and diastolic blood pressure at rest and maximal effort (mmHg), - Resting heart rate, maximal heart rate, heart rate reserve, and heart rate recovery at 1 minute. - VO2 peak (ml/kg/min) and METs estimated by the FRIEND Formula (44). - Upper and lower-body 1-RM strength test on leg press and horizontal row.
Blood analysis measures
- Fasting glucose and fasting insulin. - Lipid profile including total cholesterol, LDL-C, HDL-C, triglycerides, and Apo-B. - Inflammation parameters including hs-CRP, fibrinogen, ferritin, albumin, and uric acid. - Hepatic liver enzymes: AST/ALT to calculate non-alcoholic fatty liver disease scores, % of liver fat and % of non-alcohol fatty liver disease. - Cardiac damage enzymes including troponins (cardiac injury) and pro-BNP (cardiac strain).
Cognitive scores
- Montreal Cognitive Assessment (MoCA) total score, Rey Auditory Verbal Learning Test, Coding (WAIS-IV), Stroop (D-KEFS), Trail Making Test, Verbal fluency (D-KEFS).

Vascular function measures
- Change in brachial artery flow-mediated dilatation - Central arterial stiffness
Questionnaires measures
- Nutritional Scores: Adherence to a Mediterranean Diet score (PREDIMED Test). The Food Craving Questionnaire Trait reduced (FCQ-T-r) measures food craving. Food matrix, total calories, the proportion of macronutrients, and hours spent eating and fasting collected by a 3-day journal with the application *Keenoa*. - Physical Activity Scores: International Physical Activity Questionnaire (IPAQ) score. - Psycho-emotional status: Depression, Anxiety, and Stress Scale (EDAS21)

Table 2 summarizes the distinct anthropometric, physical, blood analysis, cognitive performance, peripheral vascular function, and questionnaire measures that will be studied at baseline and repeated at 3 and 6 months of the study. Kg: kilogram, kg/m2: kilogram per square meter, cm: centimeter, L: liter, mmHg: millimeters of mercury, METs: metabolic equivalents, VO2: maximal oxygen uptake, 1-RM: one-rep max, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, Apo-B: apolipoprotein B, hs-CRP: high-sensitivity C-reactive protein, AST: aspartate aminotransferase, ALT: alanine transaminase, pro-BNP: pro-BNP: B-type natriuretic peptide.

FIGURES

Figure 1. Central illustration summarizing the study synchronous interventions. After inclusion and baseline assessment, coronary heart patients with recently diagnosed prediabetes status defined by an HbA1c $\geq$ 5.7% to 6.4% will follow a 3-arm synchronous nutritional, exercise training, and education intervention. They will then be reassessed after three months of the intervention and again three months after the autonomy and time-restricted eating period. HbA1c: glycated hemoglobin, MedDiet: Mediterranean Diet, TRE: Time-restricted feeding, HIIT: High-intensity interval training.

REFERENCES

1. P S, I P, P S, B M, S K, N U, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9 th edition. Diabetes Res Clin Pract [Internet]. 2019 Nov 1 [cited 2021 Jul 28];157. Available from: https://pubmed.ncbi.nlm.nih.gov/31518657/

2. C B, V S, E H, J MG, R A, T B, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. Diabetes Care. 2018 May;41(5):963–70.

3. MacKay D, Chan C, Dasgupta K, Dominy C, Gagner M, Jin S, et al. Remission of Type 2 Diabetes: Diabetes Canada Clinical Practice Guidelines Expert Working Group: Can J Diabetes [Internet]. 2022 Dec 1 [cited 2023 Feb 22];46(8):753-761.e8. Available from: http://www.canadianjournalofdiabetes.com/article/S1499267122004038/fulltext

4. Committee ADAPP. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care [Internet]. 2022 Jan 1 [cited 2023 Feb 22];45(Supplement_1):S17–38. Available from: https://diabetesjournals.org/care/article/45/Supplement_1/S17/138925/2-Classification-and-Diagnosis-of-Diabetes

5. Gagnon C, Olmand M, Dupuy EG, Besnier F, Vincent T, Grégoire CA, et al. Videoconference version of the Montreal Cognitive Assessment: normative data for Quebec-French people aged 50 years and older. Aging Clin Exp Res. 2022 Jul;34(7):1627–33.

6. DHJ T, RM B, ACCM van M, SM H, F F, A G, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. Eur Heart J. 2019 Aug 7;40(30):2534–47.

7. RR T, IB W, EL S, AP A, JA C, JR C, et al. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension. 2015 Sep 14;66(3):698–722.

8. Monteiro CA, Levy RB, Claro RM, de Castro IRR, Cannon G. A new classification of foods based on the extent and purpose of their processing. Cad Saude Publica [Internet]. 2010;26(11):2039–49. Available from: https://pubmed.ncbi.nlm.nih.gov/21180977/

9. ACSMs Guidelines for Exercise Testing and Prescription [Internet]. [cited 2021 Jul 29]. Available from: https://www.acsm.org/read-research/books/acsms-guidelines-for-exercise-testing-and-prescription

10. Physical activity [Internet]. [cited 2021 Jul 29]. Available from: https://www.who.int/news-room/fact-sheets/detail/physical-activity

11. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, et al. Exercise/Physical Activity in Individuals with Type 2 Diabetes: A Consensus Statement from the American College of

Sports Medicine. Med Sci Sports Exerc [Internet]. 2022 Feb 1 [cited 2023 Mar 8];54(2):353–68. Available from: https://pubmed.ncbi.nlm.nih.gov/35029593/

12. Mutie PM, Pomares-Millan H, Atabaki-Pasdar N, Jordan N, Adams R, Daly NL, et al. An investigation of causal relationships between prediabetes and vascular complications. Nature Communications 2020 11:1 [Internet]. 2020 Sep 14 [cited 2023 Feb 22];11(1):1–11. Available from: https://www.nature.com/articles/s41467-020-18386-9

13. Honigberg MC, Zekavat SM, Pirruccello JP, Natarajan P, Vaduganathan M. Cardiovascular and Kidney Outcomes across the Glycemic Spectrum: Insights from the UK Biobank. J Am Coll Cardiol. 2021 Aug;

14. Hostalek U. Global epidemiology of prediabetes - present and future perspectives. Clinical Diabetes and Endocrinology 2019 5:1 [Internet]. 2019 May 9 [cited 2023 Feb 22];5(1):1–5. Available from: https://clindiabetesendo.biomedcentral.com/articles/10.1186/s40842-019-0080-0

15. Karter AJ, Nundy S, Parker MM, Moffet HH, Huang ES. Incidence of Remission in Adults With Type 2 Diabetes: The Diabetes & Aging Study. Diabetes Care. 2014 Dec 1;37(12):3188.

16. S F, P R, K C, A D, E R, A F. Top ten research priorities for type 2 diabetes: results from the Diabetes UK-James Lind Alliance Priority Setting Partnership. Lancet Diabetes Endocrinol. 2017 Dec 1;5(12):935–6.

17. Captieux M, Prigge R, Wild S, Guthrie B. Defining remission of type 2 diabetes in research studies: A systematic scoping review. PLoS Med. 2020 Oct 28;17(10):e1003396.

18. Riddle MC, Cefalu WT, Evans PH, Gerstein HC, Nauck MA, Oh WK, et al. Consensus report: definition and interpretation of remission in type 2 diabetes. Diabetologia. 2021 Nov 1;64(11):2359–66. Available from: https://link.springer.com/article/10.1007/s00125-021-05542-z

19. MacKay D, Chan C, Dasgupta K, Dominy C, Gagner M, Jin S, et al. Remission of Type 2 Diabetes: Diabetes Canada Clinical Practice Guidelines Expert Working Group. Can J Diabetes. 2022 Dec 1;46(8):753-761.e8. Available from: https://pubmed.ncbi.nlm.nih.gov/36567079/

20. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000 Aug 12;321(7258):405–12.

21. Liu X, Wu S, Song Q, Wang X. Reversion From Pre–Diabetes Mellitus to Normoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality in a Chinese Population: A Prospective Cohort Study. J Am Heart Assoc. 2021 Feb 2;10(3):1–9.

22. Hallberg SJ, Gershuni VM, Hazbun TL, Athinarayanan SJ. Reversing Type 2 Diabetes: A Narrative Review of the Evidence. Nutrients. 2019 Apr 1;11(4):1–16.

23. KD H, A A, R B, H C, T C, KY C, et al. Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake. Cell Metab. 2019 Jul 2;30(1):67-77.e3.

24. Sandoval-Insausti H, Jiménez-Onsurbe M, Donat-Vargas C, Rey-García J, Banegas JR, Rodríguez-Artalejo F, et al. Ultra-Processed Food Consumption Is Associated with Abdominal Obesity: A Prospective Cohort Study in Older Adults. Nutrients 2020, Vol 12, Page 2368. 2020 Aug 7;12(8):2368.

25. Montero-Salazar H, Donat-Vargas C, Moreno-Franco B, Sandoval-Insausti H, Civeira F, Laclaustra M, et al. High consumption of ultra-processed food may double the risk of subclinical coronary atherosclerosis: the Aragon Workers' Health Study (AWHS). BMC Medicine 2020 18:1. 2020 Aug 13;18(1):1–11.

26. T F, B S, L S, E KG, B A, C M, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. BMJ. 2018;360.

27. RJ de S, A M, A M, AI C, V H, T K, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ. 2015 Aug 12;351.

28. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. https://doi.org/101056/NEJMoa1800389. 2018 Jun 13;378(25):e34.

29. J SS, M B, N B, MÁ MG, N IJ, J B, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care. 2011;34(1):14–9.

30. Estruch R, Sacanella E, Ros E. Should we all go pesco-vegetarian? Eur Heart J. 2021 Mar 21;42(12):1144–6.

31. CD G, JF T, LC DG, ME H, J R, JPA I, et al. Effect of Low-Fat vs Low-Carbohydrate Diet on 12-Month Weight Loss in Overweight Adults and the Association With Genotype Pattern or Insulin Secretion: The DIETFITS Randomized Clinical Trial. JAMA. 2018 Feb 20;319(7):667–79.

32. H S, M R. Low Carbohydrate and Low-Fat Diets: What We Don't Know and Why we Should Know It. Nutrients. 2019 Nov 1;11(11).

33. S BA, I HB, D S, I S. Dietary strategies for patients with type 2 diabetes in the era of multi-approaches; review and results from the Dietary Intervention Randomized Controlled Trial (DIRECT). Diabetes Res Clin Pract. 2009 Dec;86 Suppl 1(SUPLL.1).

34. M H, C R, U K, A W, J B. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. Obes Rev. 2009 Jan;10(1):36–50.

35. V L, A S, M F. Nutritional management of hyperapoB. Nutr Res Rev. 2016 Dec 1;29(2):202–33.

36. MJ W, ENC M, A Z, H L, S F, A S, et al. Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome. Cell Metab. 2020 Jan 7;31(1):92-104.e5.

37. S C, K G, F K, M E, E W, V P, et al. Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity. Cell Metab. 2020 Sep 1;32(3):366-378.e3.

38. Ji Y, Plourde H, Bouzo V, Kilgour RD, Cohen TR. Validity and Usability of a Smartphone Image-Based Dietary Assessment App Compared to 3-Day Food Diaries in Assessing Dietary Intake Among Canadian Adults: Randomized Controlled Trial. JMIR Mhealth Uhealth [Internet]. 2020 Sep 1 [cited 2023 Feb 22];8(9). Available from: https://pubmed.ncbi.nlm.nih.gov/32902389/

39. Moyen A, Rappaport AI, Fleurent-Grégoire C, Tessier AJ, Brazeau AS, Chevalier S. Relative Validation of an Artificial Intelligence–Enhanced, Image-Assisted Mobile App for Dietary Assessment in Adults: Randomized Crossover Study. J Med Internet Res 2022;24(11):e40449 https://www.jmir.org/2022/11/e40449 [Internet]. 2022 Nov 21 [cited 2023 Mar 8];24(11):e40449. Available from: https://www.jmir.org/2022/11/e40449

40. Taylor R. Type 2 diabetes and remission: practical management guided by pathophysiology. J Intern Med [Internet]. 2021 Jun 1 [cited 2023 Feb 22];289(6):754–70. Available from: https://pubmed.ncbi.nlm.nih.gov/33289165/

41. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nature Reviews Neurology 2018 14:3. 2018 Jan 29;14(3):168–81.

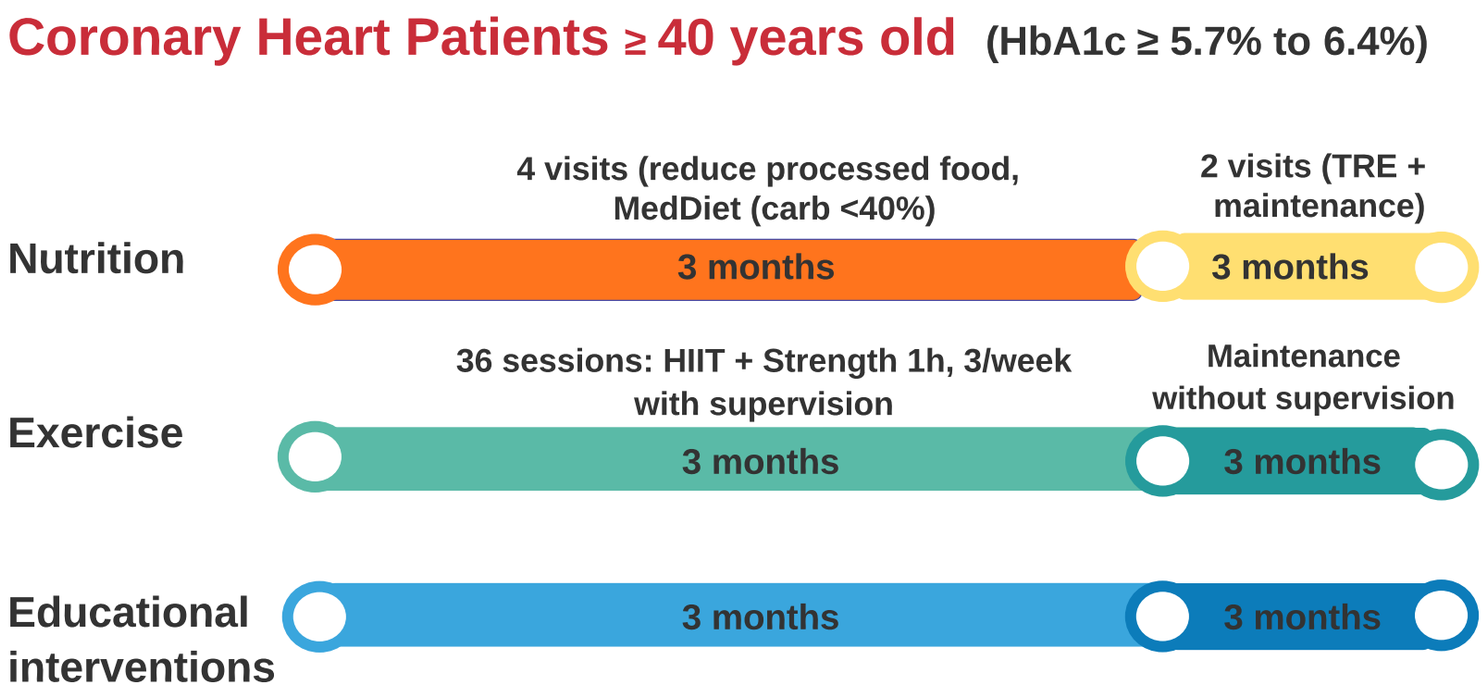
42. LD B, DJ C, S M, D B, GS W, S C. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol. 2011 Jan;68(1):51–7.

43. N D, M J, BA M. Effects of cardiac rehabilitation on cognitive impairments in patients with cardiovascular diseases: a systematic review. Int J Neurosci. 2020;

44. P K, LA K, R A, J Z, J M. New Generalized Equation for Predicting Maximal Oxygen Uptake (from the Fitness Registry and the Importance of Exercise National Database). Am J Cardiol. 2017 Aug 15;120(4):688–92.

Pep DIABEPIC

Eric-M. Beaulieu | March 17, 2023



Supplementary Table 1. DIABEPIC1 schedule of enrolment and assessments.

	Cardiovascular Prevention and Rehabilitation Center of the Montreal Heart Institute (Centre ÉPIC)									
	Pre-intervention Evaluations (T0)				**Mid-intervention evaluations (T3)**			**Post-intervention evaluations (T6)**		
		Visit 1	**Visit 2**	**Visit 3** (optional)	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 1**	**Visit 2**	**Visit 3**
Duration (6 months)	90 min	120 min	60 min	90 min	60 min	120 min	60 min	60 min	120 min	60 / 150 min
Procedures										
Explanation of the project	X									
Consent to participate	X									
Medical visit	X				X			X		
Maximum effort test	X				X			X		
Blood test		X				X			X	
Body composition		X				X			X	
Food Diary (appl. *Keenoa*)			X				X			X
Cognitive tests		X				X			X	
Educational intervention			X				X			X
Questionnaires	X				X			X		
Vascular measurements (optional)				X						X