The effect of physical activity and dietary measures in prediabetic patients: a study protocol.

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Abstract

Introductie

De toenemende prevalentie van type 2 diabetes mellitus (DM2) wereldwijd blijft aanzienlijke gevolgen hebben voor morbiditeit, mortaliteit en zorgkosten. Een systematische review door Poncelet M. en Schutyser D. benadrukt het potentieel van dieet en lichaamsbeweging om de progressie van prediabetes naar DM2 te voorkomen of uit te stellen, waarbij gewichtsverlies waarschijnlijk een sleutelrol speelt. Desalniettemin is verder onderzoek nodig om deze conservatieve behandelingen effectief te integreren in de routinematige klinische praktijk. Het voornaamste doel van dit protocol is het opzetten van een gerandomiseerde gecontroleerde studie (RCT) gericht op het implementeren van leefstijlaanpassingen voor mensen met prediabetes. Dit initiatief streeft ernaar duurzame leefstijlveranderingen te introduceren, met nadruk op betaalbaarheid, lange termijn levensvatbaarheid en integratie in de eerstelijnszorg.

Methode

Een uitgebreid plan voor een RCT gericht op het bestuderen van de effectiviteit van interventiestrategieën bij het voorkomen van de progressie van prediabetes naar DM2 in het Nederlandstalige deel van België (Vlaanderen).

De studie volgt de CONSORT- en SPIRIT-richtlijnen en maakt gebruik van een RCT-ontwerp met twee groepen: een conservatieve groep die basisadvies krijgt over dieet en lichaamsbeweging, en een interventiegroep die meer uitgebreide begeleiding en follow-up ontvangt. Vanwege de aard van de interventie is blindering niet haalbaar. De proef duurt 3 jaar, waarbij patiënten gedurende 1 jaar kunnen worden gescreend en ingeschreven.

De berekening van de steekproefgrootte is gebaseerd op eerdere vergelijkbare RCT's met als doel een totaal van 267 personen met prediabetes, rekening houdend met uitval en conversies naar DM2. De statistische analyse zal worden uitgevoerd met behulp van SPSS, waarbij een intention-to-treat benadering wordt toegepast. Primaire uitkomstanalyse zal gebruik maken van het Cox-proportionele risicomodel, terwijl secundaire uitkomsten zullen worden beoordeeld met behulp van chi-kwadraat tests en t-toetsen.

Er zal gebruik worden gemaakt van eenvoudige randomisatie voor toewijzing van proefpersonen, vanwege de aard van de interventie is blindering niet haalbaar. Inclusiecriteria omvatten personen van 30 jaar en ouder met gestoorde bloedglucosewaarden of HbA1c-niveaus binnen specifieke bereiken. Uitsluitingscriteria omvatten verschillende medische aandoeningen, medicatiegebruik en andere factoren die van invloed kunnen zijn op de studieparticipatie of uitkomsten.

Over het algemeen beoogt deze studie waardevolle inzichten te bieden in de effectiviteit van leefstijlinterventies bij het voorkomen van de progressie naar DM2 bij personen met prediabetes in Vlaanderen. De grondige planning en naleving van vastgestelde richtlijnen versterken de degelijkheid en geldigheid van de bevindingen van de studie.

Discussie

Ondanks uitdagingen biedt prediabetes-screening en op maat gemaakte interventiestrategieën via eerstelijnskanalen veelbelovende perspectieven. Gunstige resultaten van de RCT zouden de basis kunnen leggen voor de integratie van prediabetes-screening en DM2-preventie in initiatieven voor eerstelijnsgezondheidszorg in Vlaanderen, België. Deze aanpak zou economisch haalbare interventies bieden met blijvende gezondheidsvoordelen.

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1. Introduction

Worldwide, there is an increasing prevalence of type 2 diabetes mellitus (DM2), currently affecting more than 400 million people (1). In Belgium, approximately 8% of the population (600,000 individuals) are estimated to have DM2, with around 6.5% (490,000 individuals) having prediabetes. Projections suggest these numbers will rise to approximately 10% (760,000 individuals) for DM2 and 7.5% (570,000 individuals) for prediabetes (2).

The prevalence of DM2 rises with age. Between the ages of 40 to 75, men are more represented in the statistics. However, in the group of people older than 75 years, there is a shift in prevalence towards women. The morbidity, mortality, and cost associated with DM2 are predicted to further increase with the aging population (1).

Individuals of Arabic, Asian, or African descent have a higher risk of developing DM2. Despite the higher prevalence within certain ethnic groups, there are no differences in treatment guidelines (3).

In addition to the aging population, two lifestyle factors play a significant role in the rise of DM2: dietary choices and lack of exercise. Multiple studies have shown that a plant-based diet and/or moderate exercise can improve the comorbidities and mortality associated with DM2 (4).

The causes of DM2 are both genetic and environmental. Its development is characterized by two phenomena: decreased insulin secretion due to pancreatic beta cell dysfunction and insulin resistance in the liver, muscle, and fat tissue.

Insulin resistance is also known as metabolic syndrome, which includes central fat storage, high blood pressure, elevated blood glucose and insulin levels, high triglycerides, and low HDL levels. Central fat storage and insulin resistance are also linked to fat accumulation in different organs and the negative consequences this has on their function.

Various hormones (incretins) play a role in the pathophysiology of DM2, with important ones including glucagon-like peptide 1 (GLP-1) and glucagon-dependent insulinotropic peptide (GIP). These hormones stimulate insulin secretion and inhibit glucagon production. However, in DM2, there is less secretion of GLP-1 and resistance to GIP, leading to inadequate insulin secretion and failure to inhibit glucagon production, resulting in hyperglycemia (5).

DM2 is known for its macrovascular complications, which are associated with the cardiovascular burden of the disease. Diabetic retinopathy, nephropathy, and neuropathy are the most significant microvascular complications of DM2. In addition to the medical burden, DM2 is associated with significant economic costs (6).

Therefore, it is important to manage DM2 rigorously, although it is even more beneficial if it can be prevented altogether.

The diagnosis of DM2 can be achieved through various methods, including two fasting blood samples with glucose values of 126 mg/dL or higher, an HbA1c level of 6.6% or higher (though this method is not recommended), and a random plasma glucose of >200 mg/dL combined with symptoms of

hyperglycemia. An oral glucose tolerance test (OGTT) showing glucose values of 200 mg/dL or higher at 2 hours is also indicative of DM2 (7).

Certain individuals should undergo screening for DM2 (8):

- Fasting blood plasma glucose should be measured in individuals experiencing symptoms or conditions associated with DM2, such as thirst, polyuria, weight loss, recurrent urinary infections, balanitis, mononeuropathy, or sensory disorders.
- Individuals aged over 45 years and meeting at least one of the following criteria: BMI of 27 kg/m2 or higher, first-degree relatives with DM2, hypertension, hypercholesterolemia, hypertriglyceridemia, risk of cardiovascular disease, or of Arabic or Asian descent. Those with negative screening results require follow-up every 3 years.
- Women with a history of pregnancy-related diabetes should be screened for the first five years postpartum and thereafter every 3 years.

The treatment of DM2 is multifaceted. In addition to addressing hyperglycemia, it is essential to prevent and treat micro- and macrovascular complications. Due to the increased cardiovascular risk associated with DM2, cholesterol and blood pressure levels must be monitored and managed effectively (9).

A decline in kidney function or the presence of albuminuria increases the risk of cardiovascular morbidity, end-stage kidney failure, and mortality. Kidney function also influences medication selection and dosage.

Prevention and treatment of retinopathy require annual visits to an ophthalmologist. Complicated foot ulcers are a significant risk for individuals with DM2 due to polyneuropathy and peripheral vascular disease. Proper foot positioning and appropriate footwear are essential in reducing this risk.

Autonomic neuropathy may lead to stomach, gut, and bladder dysfunction, sexual problems, and orthostatic hypotension (6).

Management of DM2 should involve discussions with the patient, emphasizing education about the disease and its implications. Patients play a crucial role in managing DM2, and lifestyle considerations should align with their needs, capabilities, and habits. Websites such as 'Thuisarts.nl' provide valuable information based on the latest guidelines (10).

The treatment goal is to ensure the best possible quality of life for as long as possible, considering the negative impact DM2 can have on the patient. Efforts should be made to minimize the burden of treatment, recognizing that achieving target values for glucose, blood pressure, and lipids may not always be feasible for every patient (11).

Obesity and lack of exercise are significant contributors to the development and progression of DM2. A healthy lifestyle forms the foundation of treatment and remains crucial throughout the course of DM2. For recently diagnosed patients with mild to moderate increases in blood sugar levels and no complications, it may be prudent to observe the effects of lifestyle improvements for the first few months before considering medication (12).

Lifestyle advice for patients with DM2 is generally similar to recommendations for the general population: quitting smoking, engaging in regular physical exercise, consuming a healthy diet, and achieving weight loss for those who are overweight. It is essential to discuss these recommendations with the patient to determine what is feasible for them. Goals, timelines, and guidance should be discussed as needed (13).

In recent years, there has been increasing focus on lifestyle changes for the remission of DM2. However, there is insufficient evidence to support the complete remission of DM2 at a population level solely through lifestyle interventions without medication. Nonetheless, there are many indications of favorable effects on glycemic regulation with lifestyle modifications (14).

Medical treatment is needed when lifestyle changes aren't sufficient to lower glucose levels to a normal value.
Generalized patients can be divided into 2 categories (7):
a) Patients with chronic kidney disease, heart failure or having a high risk for a cardiac event who aren't fragile with a life expectancy over five years and an eGFR > 10 mL/min/1.73 m^2. First line treatment with these patients is metformin, step 2 is a SGLT-inhibitor, step 3 a GLP1-receptor agonist and step 4 is insulin.
b) With other patients step 1 is metformin, step 2 a sulfonylurea derivate, step 3: DPP4 inhibitor or GLP1 agonist and step 4 is a long acting insulin.

The target HbA1c value for patients under 70 years of age is 7% or lower. For patients aged 70 and above, the target value is also 7% if only metformin is taken. If the patient is on multiple medications, a target HbA1c of 7.5% (for those diagnosed with DM2 for less than 10 years) or 8% (for those diagnosed with DM2 for 10 years or more) is considered satisfactory (7).

In frail patients with a short life expectancy, achieving a low HbA1c may not be beneficial. The primary focus should be on avoiding symptomatic hypo- or hyperglycemia. Therefore, a target HbA1c of 8.5% may suffice in such cases.

The target HbA1c value should be discussed with the patient, taking into account the presence of micro- or macrovascular complications (indicating a need for a lower HbA1c), comorbidities, the risk of hypoglycemia, and the patient's motivation (7).

Prediabetes is the stage preceding DM2, characterized by fasting plasma glucose levels between 100 and 125 mg/dL. At this stage, the body begins to experience difficulty in processing blood sugar, which may lead to significant problems over time. Untreated prediabetes can progress to DM2 at a rate of 5 to 10% per year and also increases the risk of cardiovascular disease .

Several risk factors are associated with the development of prediabetes, including obesity (especially visceral), age (starting from 40 to 45 years), genetic predisposition (first and second degree within the family), high blood pressure, unhealthy diet high in fat and sugar with inadequate fruit and vegetable intake, lack of exercise, smoking, excessive alcohol consumption, and previous high blood sugar values (e.g., pregnancy-related diabetes).

Routine testing for prediabetes is recommended for individuals older than 45 years and those younger than 45 with other risk factors for DM2, such as high blood pressure, genetic predisposition, and high cholesterol levels. After a diagnosis of prediabetes, it is advisable to monitor blood plasma glucose every 6 months (15).

There are three main methods for screening for prediabetes (15):

1. **Fasting Blood Sample**: This involves fasting for 8 hours before the test. A blood sample is taken, and if the glucose level falls between 100 and 125 mg/dL, it indicates prediabetes. This test is non-invasive and cost-effective. However, non-fasting glucose tests and glucose meters are not recommended due to their significant error range.

2. **HbA1c Measurement**: HbA1c can be measured without fasting. A value between 5.7% and 6.5% is considered indicative of prediabetes. While this test is less influenced by stress or illness, it is less reliable in individuals with conditions such as anemia or recent blood loss. It's important to note that in Belgium, there is no reimbursement for this test, and the cost is borne entirely by the patient.

3. **Oral Glucose Tolerance Test (OGTT)**: This test requires fasting for 8 hours, followed by consuming a glucose solution. After 2 hours, plasma glucose is measured. Values between 140 and 199 mg/dL indicate prediabetes, while values above this range indicate DM2. The OGTT is a sensitive test but is complex, requiring standardization and replication.

The prevalence of DM2 continues to rise, leading to personal and societal impacts. Preventing the disease is preferable to treating it, and the concept of prediabetes offers a pathway for prevention.

Randomized controlled trials (RCTs) have demonstrated the benefits of exercise and diet in managing DM2. Physical exercise, including aerobic and resistance exercises, improves glycemic control, muscle microvascular blood flow, muscle strength, and quality of life. On a dietary level, increasing fiber, vegetable, and fruit intake, while reducing fat and fast sugars and maintaining a caloric deficit, are crucial.

For obese patients, weight loss can be particularly beneficial. Even a 5% decrease in body weight can reduce the risk of DM2 by 30% overall, in addition to benefiting cardiovascular health.

Overall, lifestyle modifications through exercise and diet play a pivotal role in managing DM2 and preventing its progression (16).

The systematic review conducted by Poncelet M. and Schutyser D. suggests that diet and physical activity may play a crucial role in preventing or delaying the progression of prediabetes to DM2, with weight reduction likely serving as the underlying factor. However, further research is needed to effectively integrate these conservative treatments into daily clinical practice (17).

This review underscores the importance of lifestyle interventions, such as dietary modifications and increased physical activity, in managing prediabetes and potentially preventing the onset of DM2. Weight reduction, in particular, appears to be a significant contributor to the positive outcomes observed in these interventions.

Despite the promising findings, the implementation of these conservative treatments into routine clinical care requires additional research and practical strategies. This may involve developing tailored intervention programs, establishing guidelines for healthcare providers, and addressing barriers to adherence among patients.

In summary, while the systematic review provides valuable insights into the role of diet, physical activity, and weight reduction in preventing or delaying the progression of prediabetes to DM2, further investigation and practical implementation strategies are necessary to translate these findings into effective clinical practice.

The primary objective of this protocol is to develop an RCT aimed at implementing lifestyle changes for individuals with prediabetes. One of the major challenges encountered in studies focusing on lifestyle modifications is the high dropout rate among participants. To address this issue, this protocol emphasizes the implementation of realistic changes that have the potential to be sustained over a lifetime at an affordable cost.

The RCT will be conducted within the primary medical care setting in the region of Flanders, Belgium. By involving primary care providers, the trial aims to ensure that the interventions are accessible and integrated into routine healthcare delivery.

Key components of the trial design include:

1. **Realistic Lifestyle Changes**: The interventions proposed in the trial will be designed to be practical, feasible, and sustainable for participants in their daily lives. Emphasis will be placed on lifestyle modifications that can be maintained over the long term, thereby reducing the likelihood of dropout.

2. **Affordability**: Recognizing the importance of cost-effectiveness, interventions will be designed to be affordable for participants. This may involve leveraging existing resources and infrastructure within the healthcare system.

3. **Long-term Sustainability**: The trial will focus on interventions that have the potential to yield lasting benefits for participants, promoting long-term health outcomes and reducing the risk of disease progression.

4. **Primary Care Integration**: By conducting the trial in the primary care setting, the interventions can be seamlessly integrated into routine healthcare delivery. This ensures that participants receive ongoing support and monitoring from their healthcare providers.

Overall, this protocol aims to overcome the challenges associated with implementing lifestyle changes in individuals with prediabetes by designing an RCT that prioritizes realistic, sustainable interventions within the primary care setting. Through this approach, the trial seeks to improve health outcomes and reduce the burden of disease in individuals at risk of developing type 2 diabetes mellitus.

2. Method

After conducting a follow-up search for articles published between September 2019 and October 2023 using the same search terms and criteria as Poncelet M. and Schutyser D., a total of 1293 articles were identified. Upon initial screening of the titles and/or abstracts, 9 articles were retained. Subsequently, upon full-text review, only 1 article met the selection criteria outlined in the systematic review (18).

This three-arm study compares different intervention approaches for individuals with prediabetes. The control group received usual care, while one intervention group received theory-based lifestyle sessions, and the other intervention group received theory-based lifestyle sessions supplemented by the assistance of diabetes prevention managers. Significant reductions in the transition to DM2 were observed in both intervention groups compared to the control group. Specifically, the odds ratio (OR) for the theory-based intervention group versus control was 0.54 (95% CI, 0.34-0.85; P = .01), and for the theory-based plus prevention manager intervention group versus control was 0.61 (95% CI, 0.39-0.96; P = .03). When the two intervention groups were combined, the OR was 0.57 (95% CI, 0.38-0.87; P = .01). This corresponds to a relative reduction in the transition to DM2 of between 36% and 42%.

Overall, the study provides valuable insights into the effectiveness of theory-based lifestyle interventions, with or without the support of diabetes prevention managers, in reducing the risk of progression to DM2 among individuals with prediabetes.

2.1. Methods: Participants, interventions, and outcomes

2.1.1. Trial objectives and design

In developing the protocol for this study, we adhered to the CONSORT statement guidelines and SPIRIT 2013 checklist. The study will be an RCT consisting of two arms: a conservative group receiving advice about diet and exercise, and an intervention group receiving guidance and follow-up. The study will be conducted in the Dutch-speaking region of Belgium (Flanders) (19,20, 21, 22, 23, 24, 25, 26, 27, 28).

Due to the nature of the intervention, blinding is not feasible. Patients will participate in the RCT for a duration of 3 years, with each patient starting the study at a different time immediately after enrollment. Enrollment of patients will occur over a period of 1 year.

General practitioners (GPs) are invited to participate by receiving a letter outlining the objectives of the study. Those interested can contact the central committee of the RCT via mail or phone for further information and to express their interest in participation.

Starting on a specified date, all participating GP practices are encouraged to review their patient databases and identify individuals who meet the following criteria for a screening visit:

- Age 30 years or older
- Presence of at least one of the following risk factors:
    - Family history of type 2 diabetes (parent, sibling, or child)
    - History of gestational diabetes
    - History of atherosclerosis
    - BMI ≥ 30 kg/m2
    - Impaired plasma glucose levels of 90 mg/dL to 125 mg/dL or HbA1c levels between 5.5 and 6.5%

During the medical history review, the GP will identify and exclude potential candidates who meet the exclusion criteria.

At the screening visit, fasting plasma glucose levels and HbA1c will be tested. Patients with blood plasma glucose values between 100mg/dL and 125 mg/dL and/or HbA1c between 5.7 and 6.5% will be considered eligible for the study. However, if the fasting plasma glucose is >125 mg/dL, the patient will be excluded from the study.

Following the screening visit, eligible patients will be invited for a first initial visit. During this visit, the exclusion criteria will be discussed with the patients, and they will be asked to sign a written informed consent. Patients will be informed that they can withdraw from the study at any time.

At the initial visit, the following measures will be taken:

- A new blood sample will be collected for baseline measures. In addition to fasting plasma glucose and HbA1c, the following data will be checked: hemoglobin (MCV, MCH, MCHC), white cell count and differentiation, thyroid (TSH), liver (AST, ALT, Gamma-GT, alkaline phosphatase), kidney (creatin), eGFR), lipid profile, iron, folic acid, vitamin B12, and vitamin D.
- A urine sample will be collected to check for glucosuria and proteinuria.
- Weight, height, and BMI will be measured.
- Blood pressure will be taken.
- Waist circumference will be measured.
- The EQ-5D questionnaire will be administered to quantify the quality of life.

After the first initial visit and assessment by the GP, along with the signing of the informed consent, the patient's information will be forwarded to the central committee of the study. The central committee

will conduct a final review to ensure that the patients meet the inclusion and exclusion criteria before randomization.

Once approved and randomized, the study for a particular patient begins, and they will be assigned to either the conservative or the intervention group.

Patients in the conservative group will receive basic information about prediabetes and the benefits of physical exercise and diet. They may be given a standardized letter with further information, but there will be no follow-up, except for the control visits as described below.

On the other hand, patients in the intervention group will receive routine follow-up and guidance for physical exercise and diet. The main participants in this group will be the patient, the GP, physiotherapist, and dietician. Although a coach can be acquired, it is not mandatory, as will be described later.

Patients are requested to return for the second initial visit after randomization, during which the full study will be discussed and initiated, marking the beginning of the follow-up period.

Table 1 outlines the proposed schedule for follow-up visits and measurements with the GP. The RCT concludes at 36 months with final measurements, including a blood sample and questionnaire.

	Screening visit	Initial visit	Initial visit 2	Month 3,15,27	Month 6,18,30	Month 9,21,33	Month 12,24,36
Eligibility	X						
Informed consent		X					
Medical history	X	X		X[1]	X[1]	X[1]	X[1]
Start of the study			X				
Baseline measures							
Fasting plasma glucose and HbA1c	X				X		X
Full blood sample[2]		X			X		X
BMI		X		X	X	X	X
Blood pressure		X		X	X	X	X
Waist circum-ference		X		X	X	X	X
EQ-5D		X			X		X

Table 1: scheme of follow up visits and measurements during the 3 year RCT.

1: New medical developments will routinely be asked about.

2: Plasma insulin, hemoglobin (MCV, MCH, MCHC), white cell count and differentiation, thyroid (TSH), liver (AST, ALT, Gamma-GT, alkaline phosphatase) , kidney (creatin, eGFR), lipid profile, iron, folic acid, vitamin B 12 and vitamin D.

The primary objective is to observe a statistically significant difference in the progression toward DM2 within the intervention group compared to the conservative group. Secondary objectives may include assessing factors such as weight loss, improvements in quality of life (measured by EQ-5D), reductions in waist circumference, decreases in blood pressure, and monitoring cardiovascular morbidity, among others.

While weight loss is not the primary focus of this study, it is often a beneficial outcome of exercise and dietary changes. Weight loss is associated with improved glycemic management, partially addressing two key metabolic abnormalities in DM2: insulin resistance and impaired insulin secretion. Therefore, weight loss can play a supportive role in overall management.

2.1.2. Trial Population

The inclusion criteria for initial screening by the GP are as follows:

- Age 30 years or older
- Presence of at least one of the following risk factors:
    - Family history of DM2 (parent, sibling, or child)
    - History of gestational diabetes
    - History of atherosclerosis
    - BMI ≥ 30 kg/m2
    - Impaired plasma glucose levels: 90 mg/dL to 125 mg/dL
    - HbA1c levels between 5.5% and 6.5%

Patients meeting these criteria will receive an invitation to undergo screening at their GP's office, where fasting blood plasma glucose and HbA1c tests will be conducted. Inclusion in the study will be based on blood plasma glucose levels ranging from 100 mg/dL to 125 mg/dL and/or HbA1c levels ranging from 5.7% to 6.5%.

During the screening and initial visit, the GP will conduct a medical history review to determine if the patient meets any of the exclusion criteria, which would result in their exclusion from the RCT.

After the initial visit, the central committee double-checks the inclusion and exclusion criteria to ensure accuracy and consistency in participant selection.

Exclusion criteria include:

- Terminal illness
- Age under 30 or diagnosed with DM1
- Diagnosis of DM2
- Taking medication used for DM2
- Antipsychotic medication usage
- Oral steroid usage in the last year
- Known malignancy

- Pregnancy or lactation
- Stage 4 renal failure
- Stage 4 NYHA cardiac failure
- Patients unwilling to register with their GP
- Inability to give informed consent or comply with interventions due to mental health or cognitive impairment
- Enrollment in another research study involving lifestyle change intervention
- Close relation to someone already included in the study
- Neurological or musculoskeletal disease limiting physical exercise ability
- COPD or asthma limiting physical exercise ability
- Inability to speak and understand Dutch

2.2. Methods: Assignment of interventions

2.2.1. Data handling

Simple randomization will be employed, akin to tossing a coin for each study subject. While not optimal for smaller trials, the sample sizes in this RCT should be sufficiently large. Various programs such as SAS, RANNOR, or RANBIN can be utilized for this purpose (29).

Due to the nature of the intervention in this RCT, blinding the patient or therapist is not feasible.

2.3. Methods: Data collection, management, and analysis

2.3.1. Sample size determination

Using G Power 3.1, we calculated the sample size required for the RCT. Previous similar RCTs have shown an effect size of around 0.4. Setting the power at 0.80 (1-beta) and alpha at 0.05, we determined the sample size to be 78. However, factoring in a 20% dropout rate and a 35% conversion rate to DM2 over 3 years, we adjusted the equation to: 100 / 35 x 78 x 1.20 = 267. Thus, we would need a total sample population of 267 individuals with prediabetes (17, 21, 22, 23, 24, 25, 26, 27, 28, 30).

2.3.2. Statistical analysis

SPSS will be utilized for statistical analysis, employing an intention-to-treat approach. The comparison of the two arms will be conducted using the chi-squared test for binary outcomes and the t-test for continuous outcomes.

The primary outcome, progression to DM2, will be analyzed using a Cox proportional hazards regression model.

Secondary outcomes include weight loss, decreased waist circumference, decreased blood pressure, cardiovascular morbidity, quality of life, and subjective level of fitness.

2.4. Methods: Monitoring

Throughout the trial, data collection occurs at predetermined intervals, encompassing various elements gathered by the GP. This includes vital data such as blood samples, medical history assessments, and administration of questionnaires such as the EQ-5D.

After gathering data, thorough care is taken in its recording and organization. The information is entered into a database for safe storage and management by the central committee.

To maintain the quality and reliability of the data, continuous monitoring and quality control measures are enacted. Regular assessments are carried out to confirm the precision, comprehensiveness, and uniformity of the data, thus ensuring its integrity for further analysis.

Adverse events with over the course of the trial will be reported to the GP who contacts the central committee. The severity, causality, and anticipated nature of each reported adverse event will be evaluated. Transparent communication among study participants and investigators regarding adverse event reporting and management will be established.

2.5. Ethics and dissemination

2.5.1. Ethics approval

In pursuit of ethical approval, the RCT will undergo review by the Ethics Committee of KU Leuven, which will provide recommendations as needed.

Aligned with ethical approval guidelines, participants have the autonomy to withdraw from the program at any juncture, without the necessity of providing reasons for their decision. Those opting to withdraw are offered the choice to discontinue all further involvement or to consent to continued contact solely for time point blood sampling as outlined in the protocol, without further intervention. Additionally, participants who reach a predetermined endpoint of a new DM2 diagnosis will exit the program and transition to standard primary care services for ongoing management.

2.5.2. Consent, security and confidentiality

The participants receive comprehensive information regarding the objectives, procedures, potential risks, and benefits of the screening and intervention program. There will be consent forms provided detailing study objectives, procedures, confidentiality measures, and participants' rights. Written consent from participants will be taken at the first initial visit. Patients are encouraged to ask questions and seek clarification about any aspect of the program.

Security measures will be implemented to safeguard participants' personal and health information, utilizing secure data storage systems and encryption methods to protect electronic records. Access to participant data will be limited to authorized personnel exclusively. All participant staff will be provided training on data security protocols and confidentiality obligations.

Unauthorized disclosure of participants' personal or health information will be avoided. De-identification techniques will be used when sharing data for research or reporting purposes. Clear protocols will be made for managing and disposing of participant records and data in compliance with data protection regulations.

2.5.3. Cost effectiveness

The cost-effectiveness of the intervention arm will be evaluated by comparing it to the control arm. This evaluation will involve estimating the costs associated with the resources and consultations with health professionals (including GPs, dieticians, physiotherapists, etc.) that are involved in the intervention. Additionally, the quality-adjusted life years (QALYs) will be calculated using the EQ-5D questionnaire and used as the outcome measure for the economic evaluation.

To determine the incremental cost-effectiveness ratio (ICER), the incremental costs of the intervention arm will be divided by the incremental QALYs gained compared to the control arm. This ratio will then be compared to established cost-effectiveness thresholds to assess the cost-effectiveness of the intervention.

2.6. Physical activity

Regular physical exercise is highly beneficial in the prevention of DM2, and there is evidence suggesting its effectiveness independent of weight loss. Physical activity improves glycemic management by enhancing insulin responsiveness and may also slow the progression from impaired glucose tolerance to DM2 (31,32,33,34).

However, a major challenge with lifestyle interventions such as physical exercise is a high dropout rate. Therefore, it's crucial to design interventions that are affordable, accessible, and tailored to individual needs.

Time constraints are often cited as a barrier to incorporating physical exercise into daily life. Like dietary changes, lifestyle modification is emphasized, with patients and therapists collaborating to determine feasible goals. The aim is for patients to develop sustainable habits that extend beyond the study period.

Before initiating physical exercise, patients should undergo a medical consultation with their GP to assess medical history, familial history, cardiac risk factors, and any limitations to physical activity, such as musculoskeletal problems. A comprehensive clinical examination should include heart and lung auscultation, blood pressure measurement, routine blood tests (including hemoglobin, thyroid, liver, kidney, lipid profile, iron, folic acid, vitamin B12, and vitamin D), and urine testing for proteinuria.

Cardiac risk assessment is essential, and any identified risk factors should be addressed. Maximal treadmill exercise testing is not recommended before the study due to the relatively low risk of cardiovascular disease and the more moderate exercise plan envisaged. However, consultation with the general practitioner regarding acute coronary syndrome and alarm symptoms is advised.

If cardiac assessment yields concerning results, referral to a cardiologist for further evaluation, such as echocardiography or coronary angiography, may be necessary.

Since patients with prediabetes are not taking medication that predisposes them to hypoglycemia, additional sugar intake is not encouraged.

At the second initial visit, the GP will administer a questionnaire to gather pertinent information for designing a tailored physical activity program. The questionnaire includes the following questions:

1. Did you ever participate in competitive sports? If so, how many hours per week did you train?
2. What sports have you previously engaged in, and for how many hours per week?
3. How physically demanding is your current job?
4. Do you have any limitations or injuries that may affect your ability to engage in physical activity? (e.g., injuries, swimming ability, ownership of a bike)
5. How much time do you have available for exercise? On which days of the week, and for how many hours?
6. Do you follow a regular routine during the week?
7. Do you have a potential exercise partner?
8. Are you willing to use a step counter (smartphone/watch)?
9. Would you consider joining a gym?
10. How many alcoholic drinks do you consume weekly?
11. Do you smoke?
12. How much movement do you typically engage in throughout the day?

13. Are you willing to dedicate a few hours each week to exercise?
14. Would you consider joining a sports club?
15. Are you open to visiting a physiotherapist?
16. Have you ever visited a gym before?
17. Do you have experience with resistance training?
18. Can you provide information about your footwear and any preventive measures you take to avoid orthopedic problems?

Based on the responses provided, suitable sports activities will be identified, and a basic exercise program will be established to meet the individual's needs and preferences.

In Flanders, there is an option known as "exercise by reference," where GPs can refer patients to certified coaches to assist them in becoming more physically active. However, for this study, we have opted for guidance by a physiotherapist, which may be somewhat less expensive and allows for longer personal guidance. While "exercise by reference" offers the advantage of potentially lower costs and extended guidance when conducted in groups, our study prioritizes individualization. Although "exercise by reference" is a valuable initiative, it is not widely recognized or utilized at this time and may not be ideal for this trial.

2.6.1. Aerobic exercise

Aerobic exercise is a cornerstone in reducing the risk of developing DM2, and this RCT emphasizes this by encouraging regular physical activity of up to 30 minutes per day. Patients are encouraged to engage in physical exercise as much as possible, ideally aiming for 5 days a week with a minimum of 30 minutes each session, which can be divided throughout the day to suit individual schedules.

The intensity of aerobic exercise should be moderate, including activities such as biking, walking at a gentle pace, jogging, swimming, or ice skating. Patients are encouraged to experiment and discover their preferred activities.

Progressive overload is essential for effective aerobic exercise. Patients may begin at 40% of their maximum heart rate (calculated as 220 minus their age in beats per minute), exercising for 20 minutes, three days a week. Over time, they can gradually increase the intensity to reach 60 to 85% of their maximum heart rate, aiming for 30 minutes of exercise on five days per week. If fewer days are available for exercise, patients can opt for longer sessions, such as exercising for 50 minutes on three days per week, totaling approximately 150 minutes per week.

Monitoring exercise intensity using heart rate guidance requires owning a device that can track heart rate, and patients should be willing to utilize this technology. A practical way to gauge moderate intensity (40 to 60% of VO2 max) is to exercise at a level where one can comfortably converse but cannot maintain a full conversation.

However, these are general guidelines, and therapists will tailor exercise plans according to individual preferences and fitness levels. For example, some patients may start with leisurely biking for 25 minutes, three times a week, possibly with a partner on weekends. Using a step counter, patients can gradually increase their daily step count from 8000 to 10,000 steps, aiming for five days a week.

High-intensity interval training (HIIT) can be suitable for a variety of individuals, but it's particularly well-suited for certain groups. Typically, young, healthy, and asymptomatic individuals benefit most from HIIT. This form of exercise involves alternating between short bursts of intense activity and brief periods of low-intensity recovery. HIIT has been shown to induce similar improvements in cardiorespiratory fitness compared to traditional aerobic exercise, but in a shorter amount of time. However, it's essential to consider individual factors when determining the suitability of HIIT, as safety considerations may vary depending on factors such as age, overall health, and any existing medical conditions (35,36,37,38,39,40).

2.6.2. Resistance training

Resistance training, often referred to as strength training, is gaining recognition as a crucial component of physical activity for combating various chronic diseases, including cardiovascular disease, metabolic syndrome, and DM2. The benefits of physical activity are extensively documented, with evidence linking it to reduced risk of cardiovascular disease and mortality (41,42,43,44).

In recent years, strength training has garnered increased attention in biomedical literature due to its numerous health benefits, complementing aerobic exercise. While aerobic exercise is well-established for its cardiovascular benefits, strength training offers unique advantages for overall health and disease prevention.

By targeting muscle strength and endurance, resistance training contributes to improvements in metabolic health, including insulin sensitivity, glucose metabolism, and lipid profile. Additionally, it helps maintain muscle mass and bone density, reducing the risk of sarcopenia and osteoporosis.

Moreover, resistance training plays a crucial role in enhancing functional capacity and quality of life, particularly in older adults. It improves balance, stability, and mobility, reducing the risk of falls and injuries. Furthermore, building muscle strength can alleviate symptoms of chronic conditions such as arthritis and back pain, enhancing overall physical well-being.

As part of a comprehensive approach to physical activity, incorporating both aerobic exercise and resistance training offers synergistic benefits for health promotion and disease prevention. It provides a balanced framework for improving cardiovascular health, metabolic function, and musculoskeletal integrity, ultimately supporting long-term wellness and longevity.

Given that participants in this study are likely to have limited experience with resistance training, the prospect of joining a gym may seem daunting, especially if they have never been there before. To ease into this regimen, individuals can commence with bodyweight training under the guidance of a physiotherapist, gradually progressing to incorporating free weights.

For some, the initial apprehension may give way to a newfound appreciation for strength training, potentially leading them to consider joining a gym. Having a workout partner can further facilitate this transition and make the experience more enjoyable.

Importantly, participants will not be compelled to engage in resistance training if they do not express enthusiasm for it. Respecting their preferences and ensuring their comfort throughout the process is paramount to fostering adherence and promoting positive outcomes.

Bodyweight training offers an excellent starting point for exercise, but it does come with limitations. The primary method for progressive overload in bodyweight exercises is by increasing the volume, which can eventually lead to a shift towards more endurance-focused training rather than pure strength development. While bodyweight training is beneficial for beginners, its long-term effectiveness may be limited.

Alternatively, incorporating resistance bands can provide additional challenge and variety to bodyweight exercises. However, working with resistance bands can be somewhat challenging due to their unique properties and potential for improper use.

Strength training using machines or free weights offers distinct advantages over bodyweight training, albeit with associated time and financial investments, such as purchasing free weights or gym memberships.

A key emphasis is placed on targeting major muscle groups, including the core, upper body, and lower body. Compound exercises, which engage multiple joints and provide a more substantial stimulus per repetition, are particularly beneficial. Examples of such exercises include squats, deadlifts, chest press, shoulder press, and lateral pulldowns. Additionally, isolation exercises focusing on individual joints, such as bicep or triceps curls, can be incorporated based on the patient's preferences and goals.

When beginning resistance training, it's crucial to establish a solid foundation without getting bogged down in the minutiae. Progress can be achieved effectively through this approach.

For exercises involving free weights or machines, aiming for 8 to 12 repetitions at varying percentages of one's one-repetition maximum (1RM) is considered ideal. However, it's advisable to avoid testing the 1RM directly due to the risk of injury.

Instead, a practical method involves exercising until failure. This means reaching a point where the patient cannot perform another repetition safely. Optimal results are typically observed when pushing to complete at least 1 or 2 more repetitions until failure. Particularly at the outset of resistance training, it's prudent to avoid exercising to failure to minimize the risk of technique breakdown and injury.

A recommended regimen entails performing 2 exercises per body part for 3 sets, repeated twice a week on nonconsecutive days. Following this structure, a resistance training session typically lasts about 30 to 40 minutes. Rest periods between sets should range from 2 to 3 minutes, with longer breaks warranted if the patient does not feel fully recovered after a set.

Opting to join a gym for strength training is advantageous, provided time and cost considerations allow. Gyms offer a diverse range of equipment, including both machines and free weights, facilitating

progressive overload and varied exercise routines. Additionally, machines may be less intimidating for beginners due to their simpler mechanics, making them easier to master.

For novice gym-goers, it's beneficial to receive coaching during initial visits to ensure proper execution and range of motion for each exercise. This guidance helps establish good habits and minimizes the risk of injury.

There are three primary types of resistance training:

1. **Bodyweight Training:** This includes exercises such as planking, (assisted) push-ups, (assisted) pull-ups, squats, and reverse lunges. Bodyweight exercises leverage the individual's own body weight for resistance, making them accessible and effective for enhancing strength and endurance.

2. **Free Weight Training:** This category encompasses exercises like bench press, shoulder press, deadlifts, dumbbell rows, lunges, and squats. Free weights, such as dumbbells, kettlebells, and barbells, offer a versatile range of motion, enabling natural movement patterns. They provide a comprehensive stimulus for the musculoskeletal system, facilitating functional strength gains.

3. **Machine Training:** Machines like the leg press, hack squat, lateral pull-down, shoulder press, seated row, and Smith machine guide movements and provide stability. While machines may limit freedom of movement compared to free weights, they offer a safe and controlled environment for resistance training. Machines are effective for targeting specific muscle groups and accommodating individual needs and abilities.

Regardless of the type of resistance training equipment used, the principle of progressive overload remains crucial for continued adaptation and improvement. This involves gradually increasing the volume and/or resistance of the exercises over time to challenge the muscles and promote growth and strength gains.

The choice between bodyweight exercises, free weights, and machines depends on individual preferences, goals, and limitations. A well-rounded training program may incorporate a combination of all three types of equipment to maximize results and ensure balanced muscle development. Proper form, technique, and supervision are essential for safety and effectiveness in any type of resistance training regimen.

The primary goals of resistance training are effectiveness, safety, and adherence. A positive correlation exists between strength and muscle mass, underscoring the efficacy of resistance training in achieving desired outcomes. However, it's important to recognize that continual increases in strength throughout life may not be sustainable. As individuals age, the emphasis often shifts towards maintaining existing strength levels, though maintaining motivation at this stage can be challenging.

An individual's response to resistance training varies widely based on factors such as age, sex, and genetic predisposition. These factors influence anabolic potency, affecting muscle growth and strength gains. Understanding these variations allows for personalized training approaches tailored to individual needs and optimizing results.

Resistance training demands effort and carries a risk of injury, making proper warm-up and recovery essential. A thorough warm-up primes the body for exertion, while cooling down helps prevent post-exercise hypotension. Both warm-up and cool-down routines involve engaging in the same activities as the main exercise but at a reduced intensity. These practices support injury prevention and promote safe and effective workouts.

2.6.3. Non-exercise activity thermogenesis (NEAT)

NEAT, or Non-Exercise Activity Thermogenesis, refers to the energy expended for all activities except sleeping, eating, or sports-like exercise. It presents an opportunity for additional caloric expenditure throughout the day. In addition to structured exercise sessions, patients are encouraged to maximize their movement in daily life. This can include taking the stairs instead of the elevator, opting to walk instead of driving, or simply standing up and moving around periodically when seated. Even small increments of activity added to the daily routine can contribute to the overall goal of preventing type 2 diabetes (45,46,47).

2.6.4. Implementation of physical exercise

The GP and physiotherapist form the core of the physical exercise implementation process. They both play integral roles in facilitating aerobic exercise and promoting NEAT. When it comes to resistance training, the physiotherapist takes the lead, ensuring proper technique and execution. Collaboration between the patient, GP, and physiotherapist is essential in determining the type and duration of exercise. Shared decision-making allows for consideration of the patient's preferences, dislikes, and scheduling constraints.
It's important to note a common trend where patients tend to over-report their daily activity levels. To address this, there is a growing array of gadgets available that track steps and heart rate, providing more objective measures of physical activity.

The goal is to instill a change in lifestyle, teaching the patient to enjoy exercise so it becomes a habit. The more physical activity, the better we expect the results to be. As mentioned, dropout rates are a significant issue. In this study, we aim to take an individualized approach, discussing with each patient their preferences, dislikes, and goals. We intend to develop a flexible training program that can be adjusted as needed. It's recommended to start the training program gradually.

Following the initial assessment, decisions can be made regarding suitable sports and an initial program can be established.

The GP can provide a "prescription" during follow-up visits to establish weekly exercise goals for patients. This prescription typically includes: FITT

- Frequency: Ideally, exercise should be spread throughout the week for optimal health benefits and reduced risk of injury, aiming for at least 3 days a week. If achieving this frequency is challenging, 150 minutes over 2 days can provide similar health benefits but with a higher risk of injury. More frequent exercise is also beneficial for weight loss.

- Intensity: The intensity of exercise can vary, but generally, more intense activity for a shorter duration yields similar results. Intensity levels can be measured using VO2 max or perceived exertion, such as moderate activity where the patient can still speak in sentences versus higher intensity where speaking becomes difficult.

- Time: The duration of exercise depends on frequency and intensity, and there's flexibility in how it's structured. Sessions can be in blocks of 30 or 60 minutes or even shorter periods of 5 to 10 minutes spread throughout the day. Research suggests that shorter, more frequent bouts of activity are equally beneficial for health. However, highly intensive exercise, especially at older ages, may pose health risks, such as conduction disorders of the heart and musculoskeletal issues.

- Type of exercise: The choice of exercise is diverse, with the most important factor being the patient's willingness to engage in it consistently over the long term. Walking is a popular choice initially due to its simplicity and ease of measurement (e.g., 30 minutes equals approximately 4000 steps or 3.2 km). Recommended daily step counts typically range from 7000 to 10000 steps. Other options include biking, water aerobics, tennis, dancing, gardening, rowing, etc. Progression in activities is encouraged once a routine is established, which can be motivating for patients.

Table 2 presents a suggested consultation schedule with both the physiotherapist and GP over the course of one year. Following this schedule would result in an estimated cost of approximately 106 euros annually, excluding the non-refundable portion of medical expenses, if the GP does not factor it in.

Week:	1	2	3	4	6	8	12	16	20	24
Physiotherapist	XX[1]	XX[1]	X	X	X	X	X	X	X	X
GP				X		X		X		X[2]

Week:	28	32	36	40	44	48	52
Physiotherapist	X	X	X	X	X	X[3]	
GP		X		X			X[4]

Table 2: Proposed schedule for consultations with the physiotherapist and GP over the course of one year.

1: 2 consultations with physiotherapist in 1 week.

2: 6-month follow up consultation with GP

3: End of reimbursement for consultations with physiotherapist.

4: 12-month follow up consultation with GP

Consultations with the physiotherapist primarily focus on strength exercises and discussing the patient's progress with aerobic activities. Meanwhile, appointments with the GP are for general follow-up, addressing any issues, and conducting necessary tests like blood work. If needed, patients can always schedule an appointment with the GP to discuss their exercise program in further detail.

Once initiated, GPs and physiotherapists should have a plan in place to encourage ongoing participation and monitor the patient's health. The follow-up appointments serve as opportunities to assess progress, address any concerns or challenges the patient may face, and make any necessary adjustments to their exercise plan. By maintaining regular communication and monitoring, GPs and physiotherapists can provide ongoing support and guidance to help patients achieve their health and fitness goals effectively.

GPs should inquire about symptoms such as chest pain or pressure, significant shortness of breath, and palpitations during consultations. It's essential to proactively ask patients about these symptoms to ensure early detection and appropriate management.

Overtraining can occur due to excessive exercise, leading to symptomatic symptoms and reduced performance. Patients should be educated about the importance of recognizing signs of overtraining, such as persistent fatigue, decreased performance, and mood changes. Encouraging patients to prioritize rest after exercise, maintain adequate fluid intake, consume nutritious food, prioritize sleep and relaxation, engage in active rest, and seek support from their social circle can help prevent overtraining.

Moreover, patients should be educated about "red flags" indicating the need for medical attention, such as severe chest pain, shortness of breath, or palpitations during or after exercise. Being aware of these warning signs empowers patients to seek timely medical assistance when necessary, ensuring their safety and well-being during physical activity.

The benefits of exercise far outweigh the risks, with most injuries being preventable by paying attention to your body's signals and response to physical activity. Adjusting the intensity, duration, and frequency is advisable if you're not feeling well. It's best to avoid exercising when experiencing symptoms like fever, a productive cough, vomiting, diarrhea, or severe pain.

A thorough warm-up and cool-down routine can significantly reduce the risk of musculoskeletal injuries. A warm-up period of 5 to 10 minutes prepares the body for exercise, while a gradual cool-down helps lower heart rate and blood pressure. This gradual cooldown aids in venous return, reducing the risk of hypotension and the buildup of harmful catecholamines.

Some tips to enhance physical activity:

- Choose to park your car further away, take walks during lunch breaks, opt for biking over driving, and use stairs instead of elevators whenever possible.
- If your weekday schedule is too tight for exercise, aim for 75 minutes of physical activity on both Saturday and Sunday.
- Consider finding an exercise partner for added motivation and social interaction.
- Participate in group exercise classes or activities.
- Take your dog for regular walks as a form of exercise for both of you.
- Consider working with a coach or personal trainer for guidance and ongoing motivation.

While exercising at home can be convenient initially, it's common for enthusiasm to wane over time. Finding ways to stay motivated and engaged, such as varying your routine or seeking external support, can help maintain consistency in your physical activity regimen.

Individualized physical exercise programs are most productive and well-tolerated, as they cater to the unique needs and preferences of each patient. It's unnecessary to push patients into exercises they cannot do or do not enjoy. Significant improvements can still be achieved without adhering to a rigorous regimen.
Moreover, there's no emphasis on high intensity or strict training schedules; instead, examples are tailored to the individual. It's important to address any obstacles patients face in adhering to their exercise routines and provide support to overcome them. Communication about challenges and barriers to exercise is crucial for promoting long-term adherence and success (28).

2.7. Diet

Emerging evidence strongly suggests that adopting a healthy diet can play a crucial role in reducing the risk of progressing from prediabetes to DM2. Specifically, diets characterized by reduced portion sizes or rich in mono-unsaturated fats demonstrate the most promising outcomes in this regard. Conversely, diets with normal fat content, those combining various dietary components, or emphasizing increased consumption of fruits, vegetables, or dairy products, do not consistently yield significant results.

It's important to recognize that while dietary interventions can help reduce the risk of developing DM2 to some extent, their effectiveness seems to be less pronounced when compared to interventions focusing on physical activity. Additionally, there is a scarcity of studies demonstrating significant outcomes from dietary interventions specifically targeting individuals with prediabetes.

Given that a considerable portion of individuals with prediabetes and DM2 are overweight or obese, incorporating weight reduction as a secondary outcome in this protocol is undeniably justified, as it offers substantial health advantages. Achieving a weight reduction of at least 5% is deemed essential, and the maintenance of this reduction over the long term is imperative for optimal health outcomes (49,50,51,52,53).

In Belgium, there are no set prices for consultations with a dietitian. Instead, dietitians have the autonomy to determine their consultation fees. However, the Flemish professional association for dietitians offers recommended target prices. For instance, a 30-minute consultation for dietary and food guidelines was suggested to be around 20.60 euros in 2023. Initial consultations typically last about an hour. While some health insurance plans may partially reimburse the cost under specific circumstances, such as a diagnosis of DM2, individuals participating in this study often do not meet these conditions for reimbursement (54).

Guidance from a dietitian is crucial for individuals aiming to reduce their energy intake, as it can be a challenging endeavor with a high dropout rate.

The dietitian plays a vital role in ensuring adherence to the protocol's dietary guidelines while also ensuring a diverse range of nutrients is included in the diet, with a primary focus on calorie restriction.

Support from healthcare professionals is invaluable, but the encouragement of family and friends is equally crucial. Patients should feel comfortable discussing their emotions and cravings openly. Together, they can explore practical changes to make in the kitchen.

For the dietary recommendations in this protocol, we drew inspiration from various sources, including gezondheid.be, the IMAGE toolkit for the prevention of type 2 diabetes in Europe, NHS guidelines, Dutch guidelines for food intake in individuals with DM2, and several articles on dietary interventions for DM2 (49,50,51,52,53,55,56).

Individuals with prediabetes can generally consume a wide variety of foods, but it's important to limit certain food items. Emphasizing a diverse range of foods, including fruits, vegetables, and fiber-rich foods, is crucial. Additionally, it's advisable to minimize consumption of sugar, fat, and salt. Regular meal patterns, including breakfast, lunch, and dinner, are important for maintaining stable blood sugar levels. Rather than making drastic dietary changes all at once, gradual adjustments over time may be more sustainable. Planning meals ahead of time can also contribute to a greater sense of control over dietary choices.

Traditionally, individuals with prediabetes receive recommendations such as reducing sugar intake and adhering to specific dietary guidelines. However, current advice encourages making healthier choices more consistently and moderating portion sizes. This includes reducing consumption of red and processed meats, as well as processed carbohydrates like white bread.

Achieving sustainable dietary changes is key, and it's essential to set realistic goals tailored to each individual's dietary habits and desired outcomes, whether it's weight loss or cholesterol management. Support from healthcare professionals, as well as from family, friends, or fellow prediabetes patients, plays a crucial role in helping individuals adhere to their goals and maintain long-term success.

Focusing on a healthy diet doesn't mean sacrificing enjoyment in your meals. Simple adjustments and substitutions can make a big difference in choosing healthier options. Many favorite recipes can be adapted without significantly altering their taste or appeal. By incorporating easy hacks and swaps, you can continue to savor delicious meals while prioritizing your health.

It's important for patients to allow themselves occasional treats or indulgences. There will inevitably be days when calorie intake is higher, whether due to a bad day or special events, and it's essential to accept these occasions without guilt. One setback doesn't have to derail progress for an extended period. Instead of dwelling on occasional overconsumption, focus on getting back on track and maintaining overall consistency in the long term.

There is emphasizes on consuming more plant-based foods than animal-based ones. While there isn't a specific focus on carbohydrate restriction, it can be beneficial in maintaining a low-calorie diet.

Tracking your progress when managing weight can serve as a source of motivation, particularly if you're overweight. Additionally, meal planning can be instrumental in maintaining consistency and adherence to your dietary goals.

For breakfast, consider options like a bowl of whole-grain cereal with milk, two slices of whole-grain toast topped with olive oil-based spread, or natural unsweetened yogurt with fruit.

At lunchtime, you might enjoy a small pasta salad, a chicken or tuna salad sandwich, or a piece of salmon or tuna paired with salad and some fruit or natural unsweetened yogurt for dessert.

For dinner, you could try roast chicken with vegetables and potatoes, chicken tortillas with salad, or salmon served with vegetables and whole-grain noodles.

Some patients hold a misconception that fruit should be avoided when blood sugar levels are high. However, whole fruits are beneficial for everyone, including those with prediabetes. While fruits do contain natural sugars, they are in complex, unprocessed forms, making them a healthy choice.

The IMAGE guidelines offer comprehensive recommendations for maintaining a healthy body weight and preventing type 2 diabetes through dietary choices (55). These include:

- Consuming at least 500g of fruits and vegetables daily, equivalent to five portions.
- Opting for whole grains in cereal products.
- Limiting daily sugar intake to 50g or less.
- Prioritizing vegetable oils, soft margarines, or nuts as the primary fat sources, while restricting saturated fat consumption.
- Choosing low-fat milk and meats.
- Incorporating fish into the diet at least twice a week.
- Moderating alcohol intake to no more than two drinks per day for men and one drink per day for women, if consumed.

- Balancing calorie intake with physical activity levels.
- Ensuring total fat constitutes 25 to 35% of total calorie intake, with saturated or trans fats limited to less than 10%.
- Aim for a total fiber intake between 25 and 35 grams per day.
- Restricting daily salt intake to less than 6 grams.
- Adapting other dietary goals in proportion to individual needs, such as body weight, medications, age, and comorbidities.

The IMAGE guidelines provide a framework for healthy eating habits, but their implementation into daily food choices requires guidance from a dietician to ensure adherence and effectiveness for individuals with prediabetes.

Utilizing a food diary can foster awareness of dietary patterns, enabling patients to align them with the IMAGE guidelines. Assessing available resources and readiness to change dietary habits is crucial. The dietician should collaborate with the patient to establish realistic short and long-term goals, breaking them down into manageable steps.

Exploring available guidance and support options, including involving family, friends, or group counseling, can enhance the patient's journey. Encouraging the consumption of whole grains and moderate fats while limiting high-sugar and refined carbohydrate foods can mitigate the risk of progressing from prediabetes to type 2 diabetes. Additionally, incorporating herbs and spices can help reduce salt intake.

Recognizing the influence of culture, ethnicity, religion, and individual preferences on dietary choices is essential. Patients require assistance in navigating their unique pathways to lifestyle change, understanding that it's a gradual process with inevitable setbacks.

For overweight patients, gradual weight loss through substitution of high-saturated fat or processed carbohydrate foods with lower-energy options is recommended. Establishing a daily routine with a predefined meal plan aids in portion control and prevents overeating.

Encouraging variety in food choices fosters satiety and enjoyment, promoting adherence to a balanced diet. Patients should be empowered to read food labels confidently and explore new foods.

Self-monitoring, such as maintaining a food diary or using smartphone apps, is instrumental in sustaining healthy eating habits. Focus on incremental changes rather than crash dieting, as the latter may lead to unhealthy practices and psychological distress.

Addressing multiple lifestyle-related factors concurrently, including physical activity, is essential for successful weight reduction and diabetes management. The Dutch dietary guidelines should serve as part of a comprehensive approach that encompasses various lifestyle interventions (56).

3. Discussion

An urgent necessity arises for an efficacious prevention program targeting DM2, owing to its escalating prevalence coupled with significant mortality rates, morbidity burdens, and medical expenses.

Numerous clinical trials have underscored the advantages of early intervention among individuals with prediabetes. Engaging in regular physical exercise and adopting dietary modifications have demonstrated efficacy in reducing the risk of progression from prediabetes to DM2.

Lifestyle intervention programs often encounter significant dropout rates. However, leveraging the primary care setting for prediabetes screening and implementing personalized plans for physical activity and dietary changes could offer a promising solution. Despite ongoing uncertainties regarding optimal screening and intervention methods, translating these strategies into effective clinical practice requires realistic lifestyle interventions that are cost-effective and sustainable over the long term. The primary care environment emerges as an ideal setting to achieve these objectives.

Diverse diagnostic criteria for prediabetes pose challenges in consolidating various subcategories within an RCT. In this RCT, prediabetes is defined as fasting blood plasma glucose levels ranging from 100 to 125 mg/dL or HbA1c levels between 5.7% and 6.5%.

Screening for prediabetes in primary care settings not only identifies individuals at risk but also facilitates the early detection of DM2. The pertinent question arises: does this proactive approach lead to improved glycemic outcomes in individuals diagnosed with DM2, thereby offering clinical benefits?

Guidance plays a pivotal role in facilitating lifestyle changes. The aim of the RCT is to provide a seamless entry point for individuals to initiate physical exercise and adopt a modified diet. In this endeavor, the collaboration of key stakeholders including the GP, physiotherapist, and dietician is paramount in offering robust support to the patients.

If the RCT yields favorable outcomes in preventing DM2, long-term implications merit exploration. Does the intervention sustainably avert DM2 over the long term? Additionally, what is the role of weight loss in DM2 prevention? Are there benefits for cardiovascular morbidity and mortality? Furthermore, does the intervention influence overall morbidity and mortality rates?

In this RCT, the efficacy of intensive lifestyle interventions for prediabetes is being evaluated against standard care and recommendations. There is potential for future RCTs to explore the inclusion of metformin and compare its effectiveness alongside lifestyle interventions (57,58,59).

If the results of this RCT demonstrate positive outcomes, it could serve as a catalyst for implementing prediabetes screening and DM2 prevention as a primary healthcare initiative in Flanders, Belgium. This could involve a cost-effective intervention offering potential lifelong health benefits.

CONFLICT OF INTEREST

No conflicts of interest were present, no support or assistance from organizations external to K.U. Leuven were received.

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