Prebiotics, Mediterranean & Plant-based diet: Effect on Gut Microbiome Diversity Glycaemic Parameters and Metabolic Markers In Prediabetic/ Type 2 Diabetic Patients. Protocol For Systematic Review.

Nosipho Rosebud Dimba

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Abstract

Background: The prevalence of type-2 diabetes (T2D) has increased consistently and this type of diabetes is often preceded by a condition known as prediabetes (PD). The major contributor to the progression of PD to T2D is the chronic consumption of diets high in fat and carbohydrates. However, recent reports indicate that PD can be reversed through the use of different dietary interventions composed of low carbohydrate and low fat. This systematic review aims to evaluate the beneficial effects of three diets: prebiotics, Mediterranean, and plant-based diets on gut microbiota and glucose homeostasis in patients with PD/T2D.

Objective: Objectives: This review aims to provide a thorough synthesis of existing literature concerning the impact of prebiotics, Mediterranean, and plant-based dietary interventions on gut microbiota composition and glucose regulation in individuals diagnosed with prediabetes or type-2 diabetes. Methods: Methods: This review will be developed according to the 2020 PRISMA guidelines and checklist. The databases that will be used include PubMed, EBSCOhost, and Google Scholar. We will search for studies that assessed the effect of prebiotics, Mediterranean, and plant-based dietary intervention on gut composition and glycaemic indexes in prediabetic or type 2 diabetic patients. Studies will be screened by titles, abstracts, and keywords, followed by identifying the full-text articles. All studies that will pass the quality assessment will be included. Data extraction will be performed individually by three independent reviewers and discrepancies between them will be resolved by the fourth reviewer. To evaluate the risk of bias, the Downs and Black checklist will be used. If homogenous data is obtained then a meta-analysis will be conducted using a forest plot from the Review Manager software version 5.4 (RevMan). The strength of evidence will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE). Results: Results: This review will identify all the beneficial effects of prebiotics, Mediterranean, and plant-based dietary interventions on the intestinal flora and glucose homeostasis in prediabetic states and type 2 diabetes. The outcomes of this protocol will also guide future studies that can developed to further evaluate the effectiveness of these dietary interventions on other markers associated with the gut and immune function. Conclusions: Conclusions: The results of this review will assess the correlation between enhancing microbial diversity and glycemic management in individuals with prediabetes and type 2 diabetes. Furthermore, these dietary interventions are anticipated to improve glucose homeostasis in prediabetes and type 2 diabetes individuals. Clinical Trial: Systemic Review Registration Details: This systematic review has been registered at the International Prospective Registry of Systematic Reviews (CRD42023478352).

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Protocol

Title

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Abstract

Background: The prevalence of type-2 diabetes (T2D) has increased consistently and this type of diabetes is often preceded by a condition known as prediabetes (PD). The major contributor to the progression of PD to T2D is the chronic consumption of diets high in fat and carbohydrates. However, recent reports indicate that PD can be reversed through the use of different dietary interventions composed of low carbohydrate and low fat. This systematic review aims to evaluate the beneficial effects of three diets: prebiotics, Mediterranean, and plant-based diets on gut microbiota and glucose homeostasis in patients with PD/T2D.

Objectives: This review aims to thoroughly synthesize existing literature concerning the impact of

prebiotics, Mediterranean, and plant-based dietary interventions on gut microbiota composition, insulin sensitivity and glucose regulation in individuals diagnosed with prediabetes or type-2 diabetes.

Methods: This review will be developed according to the 2015 PRISMA guidelines and checklist. The databases that will be used include PubMed, EBSCOhost, and Web of Science, in addition Google Scholar will be used as a search engine. We will search for studies that assessed the effect of prebiotics, Mediterranean, and plant-based dietary intervention on gut composition, glycaemic indexes and HOMA-IR values in prediabetic or type 2 diabetic patients. Studies will be screened by titles, abstracts, and keywords, followed by identifying the full-text articles. All studies that will pass the quality assessment will be included. Data extraction will be performed individually by three independent reviewers and discrepancies between them will be resolved by the fourth reviewer. To evaluate the risk of bias, the Downs and Black checklist will be used. If homogenous data is obtained then a meta-analysis will be conducted using a forest plot from the Review Manager software version 5.4 (RevMan). The strength of evidence will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE).

Results: In this study, the pre-existing literature search in the electronic databases will be collected following the publication of this protocol.

Conclusions: This review will evaluate whether these dietary interventions included in this study could be effective in reversing prediabetes or preventing the development of type 2 diabetes. In addition, the obtained findings of this review will also guide future studies that can be developed to further evaluate the effectiveness of these dietary interventions on other markers associated with a leaky gut and immune function.

Systemic Review Registration Details: This systematic review has been registered at the International Prospective Registry of Systematic Reviews (CRD42023478352).

Keywords: Prebiotics; Mediterranean diet; plant-based diet; type-2 diabetes; prediabetes; gut microbiota; insulin sensitivity and glucose homeostasis.

Introduction

The changes in the gut microbiota composition also known as dysbiosis play a significant role in the dysregulation of intestinal integrity and the development of metabolic diseases such as type-2 diabetes (T2D) [1]. T2D is increasing in prevalence and is considered a global epidemic worldwide [2]. It is estimated that about 548 million people will be affected by 2045 [3]. T2D is often preceded by prediabetes, a condition of intermediate hyperglycaemia below the diagnostic threshold of T2D

[4]. The major contributor to the changes in gut microbiome diversity is the various types of diets consumed [5]. A study conducted in our laboratory showed that chronic consumption of a high-fat high carbohydrate diet is associated with dysregulation of the intestinal lining wall and is implicated in the development of prediabetes [6]. Other studies have reported that saturated fat, trans-fatty acid, refined sugars, and high-sweetened refined sugars also compromise the intestinal barrier, resulting in the translocation of toxins that elicit inflammatory responses, which contribute to the complications that are observed in type 2 diabetic individuals [7-9].

Approaches and strategies for managing and preventing metabolic diseases have arisen [10]. The approaches include dietary interventions, intense exercises, and pharmacotherapy such as metformin [11-12]. Dietary interventions have however become an area of interest recently as most studies have shown the beneficial properties of various types of diets such as Banting, ketogenic, and Atkins diets in reversing and managing prediabetes or T2D [13-15]. These diets involve the use of a low amount of carbohydrates and a high amount of unsaturated fats [15]. However, this review will mainly focus on prebiotics, Mediterranean and plant-based diets. Prebiotics are non-digestible food ingredients that are not metabolized or absorbed while passing through the upper gastrointestinal tract and are fermented by bacteria in the colon [16]. They have been reported to selectively enhance the growth activity of one or more potentially beneficial bacteria in the gut [17-18]. Mediterranean diets are composed of whole foods like fruits, vegetables, and whole grains, as well as healthy fats found in food such as olive oil and nuts [19-20]. This diet has been linked to better glucose control, reduced inflammation, and improved gut health due to its high fiber content in obesity and type 2 diabetic patients [21-23]. A plant-based diet predominantly consists of foods derived from plants such as fruits, vegetables, whole grains, nuts, seeds, and legumes, which can have several positive effects on the gut microbiome, glucose homeostasis, gastrointestinal disease, and liver disease [10], [23-24].

All these types of dietary interventions have been shown to contribute to a beneficial health status [10]. However, relatively few studies have investigated and reported the appropriate mechanisms by which these various types of diets effectively manage T2D or reverse prediabetes. Other studies have shown the effects of these diets on markers associated with prediabetes/ T2D, and gut microbiome composition, others did not. Therefore, this review aims to evaluate the effectiveness of prebiotics, Mediterranean, and plant-based dietary interventions on gut microbiota glucose homeostasis and insulin sensitivity in patients with prediabetes or type-2 diabetes.

Review Question

Are these dietary interventions (prebiotics, Mediterranean, and plant-based diets) effective in improving gut microbiota diversity and enhancing glucose homeostasis or insulin sensitivity in

individuals with type 2 diabetes or prediabetes?

Table 1: The PICO framework used to formulate the research question.

Population	Patients with prediabetes or type 2 diabetes
Intervention	Prebiotics, Mediterranean, and plant-based dietary intervention diets
Comparison	Placebo and control diets
Outcomes	1. Changes in the composition of the gut microbiome (*Firmicutes, Bacteriodetes,* and *Bifidobacteria*). 2. Changes in the concentration levels of glycaemic control indices such as fasting plasma glucose (FPG) and glycated haemoglobin (HbA1c) in the prediabetic state or T2D. 3. To evaluate changes in insulin sensitivity, using metrics such as HOMA-IR (Homeostasis Model Assessment of Insulin Resistance).

Objectives

➢ The first objective of this review is to determine the changes in gut microbiome composition of Firmicutes, Bacteriodetes, and Bifidobacteria in prediabetic or type 2 diabetic patients.

➢ The second objective is to investigate if there are changes in concentration levels of fasting plasma glucose and glycated hemoglobin (HbA1c) in prediabetic or type 2 diabetic patients.

➢ The third objective is to evaluate insulin sensitivity in prediabetic or type 2 diabetic patients.

Methods

This protocol was developed following the preferred reporting items for systemic review and meta-analysis (PRISMA) 2015 guidelines for reporting protocols (see Additional file 1 for the completed checklist) [25].

Eligibility Criteria of The Study

The inclusion criteria in this study were the following:

➢ Studies that reported prediabetic or type 2 diabetic patients will be considered eligible.

➢ Studies that included and compared either one of these dietary interventions (prebiotics, Mediterranean, and plant-based diet) with the placebo or control diets will be included.

➢ Studies that reported changes in the gut composition of *Firmicutes, Bacteriodetes,* and *Bifidobacteria* in prediabetic or type 2 diabetic patients will be considered eligible.

➢ Studies that reported changes in concentration levels of fasting plasma glucose and glycated

heamoglobin (HbA1c) and HOMA-IR in prediabetic or type 2 diabetic patients will be considered eligible.

➢ All categories of study designs will be included.

➢ Studies reported between the year 2000-2023 will be included.

The exclusion criteria were the following:

➢ We will exclude all animal studies, editorials, letters, and case studies.

➢ Studies with insufficient details on the methodology and findings will be excluded.

➢ Studies reported before the year 2000 will be excluded.

Information sources

The review will be based on the published data sources that include prebiotics, Mediterranean and plant-based diet effects on gut microbiome composition and glucose homeostasis between 2000-2023. The search strategy will be accomplished using a medical search heading (MeSH). A search of PubMed, EBSCOhost, Google Scholar and Web of Science will be used to search for published studies electronically. While searching through the databases for the eligible studies, we will also check the references to see if there are any more studies that we might have overlooked.

Search strategy

Using the 3 databases (PubMed, EBSCOhost, and Web of Science) and 1 search engine (Google Scholar), the keywords will include "prediabetes" OR "type 2 diabetes" "prebiotic diet" or "prebiotic supplements", "Mediterranean diet" OR "Mediterranean-style diet", "plant-based diet", "glucose regulation" OR "glucose homeostasis", "insulin sensitivity", "HOMA-IR", "prebiotics" AND "gut microbiome", "Mediterranean diet" AND "gut microbiome", "plant-based diet" AND "gut microbiome", "prebiotics" AND "glucose homeostasis", "Mediterranean diet" AND "glucose homeostasis", "plant-based diet" AND "glucose homeostasis".

Selection Process

The eligibility of the studies or literature search results will be conducted by three independent authors Nosipho Rosebud Dimba (NRD), Nhlakanipho Mzimela (NM), and Aubrey Mbulelo Sosibo (AMS) to prevent any discrepancies in terms of the eligibility of the studies. Cohen's Kappa coefficient will be used to measure the interrater reliability between the three independent authors.

The studies will be selected according to the title, and abstracts, followed by identifying the full-text articles. The literature that meets the eligibility criteria will then be selected. The duplicated results will also be excluded from all search results. The included studies will be subjected to data collection, critical appraisal, risk, and quality assessment. Should there be any disagreements between the three independent authors the fourth author Andile Khathi (AK) will screen these studies, and the agreement will be reached upon discussion.

Data Collection Process

NRD, NM, and AMS will extract the study characteristics information from each eligible study (title, author, year of publication, country, study design, sample size for each group, type of intervention, intervention period, placebo or control diet), and participant's characteristics including age, sex, weight, and whether they are normal or prediabetic or type 2 diabetic using a Microsoft Excel file to ensure that there is consistency between reviewers. In addition, bacterial composition (*Firmicutes, Bacteriodetes,* and *Bifidobacteria*), HOMA-IR values and glycaemic concentrations of FPG and HbA1c will be extracted. Cohen's Kappa coefficient will also be used to measure the interrater reliability between the three independent authors (NRD, NM, and AMS). The other author (AK) will check the quality of the extracted data should there be any disagreements arise an agreement will be reached through discussion. The article with the higher sample size will be chosen if the studies based on the same research population both published odds ratios.

Study Risk of Bias Assessment

The Downs and Black checklist will be used to measure the bias in each eligible study. The checklist is based on 4 domains: report of bias (10 items), external validity (3 items), internal validity (6 items), and selection bias (7 items). The scores will be rated as follows: excellent (25), good (20–24), moderate (14–19), poor (11–13) and very poor (<10). Three independent authors (NRD, NM, and AMS) will evaluate the quality of each study according to 4 domains. In case of disagreements between these authors, NRD, NM, and AMS, the fourth author (AK) will then be responsible for adjudication.

Data Synthesis Methods

If homogenous data is obtained, then a meta-analysis will be conducted using a forest plot from the Review Manager software version 5.4 (RevMan). The mean and standard deviation of the effect of each dietary intervention on gut microbiome composition (*Firmicutes, Bacteriodetes,* and *Bifidobacteria*) HOMA-IR value and glycaemic control of FPG and HbA1c, in both the prediabetic/ type 2 diabetic and control groups will be synthesized and reported in a forest plot. The statistical

heterogeneity in the selected studies will be evaluated using a RevMan 5.4 forest plot, I^2, and Chi^2 test. An I^2 value obtained lower than 25% will suggest low heterogeneity, whereas a value obtained higher than 75% will indicate high heterogeneity. However, a value of 50% will be regarded as moderate. The forest plot will also provide an odds ratio/ random effect and confidence interval where the solid lines will indicate the 95 % confidence interval. Each of the included studies will be denoted on the y-axis by a horizontal line with the primary author and year of the study displayed. Studies having an I^2 greater than 75% will be assessed for potential sources of heterogeneity using a sensitivity analysis, and subgrouping analysis to evaluate the cause of the variation between the studies. Furthermore, a significant overlap between the confidence intervals will suggest substantial homogeneity.

Reporting Bias Assessment

To determine if there is any common publication bias in the studies, we will statistically use the funnel plot, which will illustrate the effect size of individual studies against the accuracy of the estimate (sample size). Each study will be represented by a dot in the funnel plot chart and the symmetric funnel shape will indicate no publication while the asymmetric funnel shape will suggest a high risk of publication bias. To further test, Egger's linear regression test will be used to determine if the funnel plot asymmetry is statistically significant.

Certainty Assessment of Strength of Evidence

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system will be used to grade the quality of the evidence [26-27]. A tool for evaluating the quality of evidence, specifically for efficacy, is provided by GRADE.

Results

In this study, the pre-existing literature search in the electronic databases will be collected following the release of this protocol. The review will focus on selecting eligible studies that have reported changes in microbial diversity, HOMA-IR, fasting plasma glucose, and glycated hemoglobin levels in prediabetic or type 2 diabetic patients following the consumption of prebiotics, Mediterranean, or plant-based diet.

Discussion

Principal Findings

Type 2 diabetes (T2D) has been a significant global health burden for many years [2]. Various

strategies have been implemented to mitigate the progression of T2D, particularly by targeting prediabetes, an intermediate hyperglycemia state that precedes the onset of T2D [4]. This review aims to evaluate the effectiveness of prebiotic, Mediterranean and plant-based dietary interventions on gut microbiota, glucose homeostasis, and insulin sensitivity in patients with prediabetes or type 2 diabetes. The systematic review will accomplish this by synthesizing existing literature and conducting a comprehensive evaluation of the effectiveness of each dietary intervention. This analysis will provide insights into which diet can most effectively reverse prediabetes or delay the progression to T2D. Additionally, it will help determine the optimal duration of dietary intervention required to prevent the progression from prediabetes to T2D.

Limitations

Data from publications without a comparison group, such as studies without a comparison diet or placebo versus the dietary intervention group either plant-based, Mediterranean, or prebiotic diet, will not be included in this study.

Acknowledgments

Conflicts of interest

The authors report no conflicts of interest.

Abbreviations

T2D: type-2 diabetes; GRADE: Grading of Recommendations Assessment Development, and Evaluation; PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols; PRISMA: Preferred Reporting Items for Systematic review and Meta-Analysis; HbA1c: glycated heamoglobin; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; PROSPERO: International Prospective Register of Systematic Reviews; MeSH: Medical Subject Headings.

Ethics approval and consent to participate

Individual data will not be gathered; only data that has already been published will be analyzed. The authors state that no signed informed permission will be needed, hence the systematic review and meta-analysis will not need ethics approval.

Consent for publication

Not applicable.

Availability of data and materials

Because it is a protocol for systematic review, no more data is provided other than the attached supplementary file.

Funding

Author Contributions

NRD, NM, AMS, and AK helped with the conceptualization, designation, and reviewing of the eligible studies and the final draft of this protocol. Funders had no role in developing the protocol. All authors have read and agreed to the published version of the review.

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Supplementary Files

Multimedia Appendixes

Search strategy.
URL: http://asset.jmir.pub/assets/a752f85a465bb5f1dfc6f461783e6a0d.docx

CONSORT (or other) checklists

PRISMA-P 2015.
URL: http://asset.jmir.pub/assets/5946126463a7fcfa799a5d87d1124bb4.pdf