INPLASY

Effect of pre-, pro- and synbiotic consumption on glycemic control in prediabetes: a systematic review and meta-analysis protocol

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 February 2024 and was last updated on 16 February 2024.

INTRODUCTION

Review question / Objective The aim of this systematic review and meta-analysis is to determine the effect of dietary supplementation with pro-, pre- and synbiotics on the progression of prediabetes, by evaluation of glycemic control outcomes including FBG, HbA1c and 2h-OGTT. The gathered evidence will facilitate informed decision-making regarding the detection and interventions for prediabetes, leading to better health outcomes. The following question will be addressed: What is the effect of pro-, pre- and synbiotic consumption on the progression of diabetes?

Rationale Although previous studies have demonstrated the effect of these three dietary interventions on glycemic control in prediabetes, there is a lack of consistency in the outcomes. While some studies have reported improvements in glycemic control, others have found no beneficial effects [1,2]. Therefore, there is a need for more concrete evidence to establish a clearer understanding on the effectiveness of pro-, pre- and synbiotics in managing prediabetes and improving glycemic control.
Although probiotics and prebiotics are available in various preparation forms, oral formulations are the most preferred intervention for the maintenance of intestinal microflora. These formulations are often protected via microencapsulation or surface coating with polymers to survive the harsh acidic environment in the gastrointestinal tract. The high patient compliance, cost-effectiveness and ease of large-scale production further contribute to its benefits [3]. Hence, in our study, we focused on investigating the effect of oral supplementation.

Condition being studied Prediabetes, also referred to as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), is related to an increased risk of developing Type 2 Diabetes Mellitus (T2DM) and its associated complications. It is a state of intermediate hyperglycemia, where glucose levels are elevated above normal, but do

not meet the threshold for T2DM [4]. The diagnosis is based on laboratory measurements, including fasting blood glucose (FBG), glycated hemoglobin (HbA1c) and two-hour post load blood glucose via an oral glucose tolerance test (2h-OGTT). However, these diagnostic criteria tend to vary between different organizations such as the World Health Organization (WHO), National Institute for Health and Care Excellence (NICE) and American Diabetes Association (ADA) [5]. In our study, we adhered to ADA's diagnostic criteria to ensure consistency and comparability in our research findings.

METHODS

Search strategy A comprehensive search was performed using four electronic databases including PubMed, Cochrane, Scopus and Ovid from 2013 to 2023. The keywords included were prediabetes, impaired glucose tolerance, impaired fasting glucose, elevated HbA1c, prebiotics, probiotics and synbiotics. The following six search terms were formed by combining these keywords using Boolean operators ("AND", "OR").
1. Prediabetes OR impaired glucose tolerance OR increased HbA1C OR impaired fasting glucose
2. Prediabetes OR impaired glucose tolerance OR increased HbA1C OR impaired fasting glucose AND prebiotics
3. Prediabetes OR impaired glucose tolerance OR increased HbA1C OR impaired fasting glucose AND probiotics
4. Prediabetes OR impaired glucose tolerance OR increased HbA1C OR impaired fasting glucose AND synbiotics
5. Prediabetes OR impaired glucose tolerance OR increased HbA1C OR impaired fasting glucose AND prebiotics AND probiotics
6. Prediabetes OR impaired glucose tolerance OR increased HbA1C OR impaired fasting glucose AND prebiotics AND probiotics AND synbiotics
All identified records were uploaded onto Rayyan, which is a free web-application designed to aid the collaboration process between authors during the screening phases of a systematic review [6]. Duplicates that were automatically detected by Rayyan were manually screened for confirmation. All confirmed duplicates were deleted. Reference lists of included studies were also manually examined for eligible studies.

Participant or population Participants who have been diagnosed with prediabetes in accordance with the American Diabetes Association (ADA) guidelines were included. The ADA diagnostic criteria include an HbA1c of 5.7-6.4%, FBG of 100-125 mg/dl and a 2h-OGTT of 716 140-199 mg/dl [7]. Studies with T2DM patients and other diseases were excluded. No exclusions were based on ethnicity, gender or age.

Intervention Oral supplementation of prebiotics, probiotics or synbiotics as oral supplementation. Dietary preparations may be in the form of capsules, tablets, sachets, liquids etc.

Comparator Placebo drug or no intervention.

Study designs to be included Randomized controlled trials (RCTs).

Eligibility criteria Non-English publications were excluded in order to enhance the interpretability and synthesis of research materials. Additionally, included RCTs should have a duration of intervention of a minimum of eight weeks. This particular duration is specifically chosen to allow ample time for pro- and prebiotic strains to adapt and interact with the gut environment [8,9]. Given that many clinical effects take time to manifest, the longer treatment durations ensure a more accurate detection and assessment of the potential benefits of pro-, pre- and synbiotic supplementation on the host.

Information sources A comprehensive search was performed using four electronic databases including PubMed, Cochrane, Scopus and Ovid. Reference lists of included studies were also manually screened for relevant studies.

Main outcome(s) Glycemic control indicators measured as: 1) fasting blood glucose (FBG), 2) glycated hemoglobin (HbA1c) and 3) two-hour post load blood glucose via an oral glucose tolerance test (2h-OGTT). Adverse effects reported in studies were also considered.

Additional outcome(s) The following additional outcomes were incorporated to provide a more comprehensive understanding of the intervention effects.
1) The impact of single verses multi-strain probiotics on improving glycemic control: This outcome allows for evaluation of the comparative effectiveness of distinct compositions of probiotic interventions in enhancing glycemic control for the management of prediabetes.
2) Compliance to intervention observed across included studies: By assessing compliance rates, we can understand the practical viability of implementing pro-, pre- and synbiotic interventions within real-world scenarios.

Data management Titles and abstracts of all studies were screened by the primary author, Shenali Delgoda (SD) based on the relevant eligibility criteria mentioned above. Those that did not include any of the exclusion criteria were further assessed for eligibility on full text. Rayyan software classified the studies into three categories (maybe, include, exclude). The studies categorized by SD were independently assessed by the second reviewer, Dr. Brinell Annette Caszo (BAC), who was also the main supervisor of the project. Further discussions were held to resolve any discrepancies. All examined studies were recorded along with reasons for excluding studies. The four-phase PRISMA diagram was used as a guide for recording purposes [10].

A standardized data extraction form was designed on Microsoft Excel and used by SD to extract relevant information from all included studies. These extractions were verified by BAC. The following categories were used to guide the extraction process: 1) general information (first author's name, publication year and country); 2) study design and duration; 3) participants (number of participants in each group, age range); 4) intervention (type, dosage and preparation form of intervention, number of intervention groups); 5) any other interventions; 6) glycemic control outcomes measured; 7) results and 8) adverse effects.

Statistical analyses were performed using RevMan 5.4 (Review Manager), a statistical software commonly used for the preparation of Cochrane Reviews and academic purposes [11]. These analyses were performed by Dr Nur Aishah Che Roos (NCS).

Quality assessment / Risk of bias analysis The risk of bias was assessed for all included studies by using Version two of the Cochrane risk- of- bias tool for randomized trials (RoB 2) [12]. Each study was assessed based on five domains that cover all types of bias that may be introduced into the results. These include: 1) bias arising from the randomization process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome and 5) bias in selection of the reported result. The domain-level risk- of- bias judgements were provided as: 1) Low 2) Some concerns or 3) High. These judgements provided the basis for overall judgement of each study [13]. The risk of bias assessment was completed by SD and a second reviewing process was done along with BAC to ensure adequate reliability of final judgements of each study. Tests for funnel plot asymmetry to detect publication bias were not conducted as a minimum of ten studies should typically be included in the meta-analysis for a reliable assessment [14].

Strategy of data synthesis The statistical analyses for the meta-analysis were performed using RevMan 5.4 (Review Manager) [11]. The fixed effect model was chosen as the statistical model due to the limited number of trials identified following quality assessment, which amounted to only two studies. Continuous data were expressed as mean and standard deviation. Mean difference (MD) was used as the summary statistic along with 95% confidence intervals. Statistical significance was determined by a p-value of less than 0.05. Heterogeneity between studies was tested based on I^2 and Chi^2 statistics. I^2 values of less than 25% denoted low heterogeneity, between 25% and 50% indicated moderate heterogeneity and over 50% suggested high heterogeneity. In contrast, a Chi^2 p-value below 0.05 indicated statistically significant heterogeneity [15].

Subgroup analysis Although subgroup analyses were planned to further explore the effects of these interventions and potential sources of heterogeneity, they were not performed due to the limited number of identified trials.

Sensitivity analysis To assess the robustness of the meta-analysis results, the following sensitivity analyses were conducted for each glycemic control outcome of the identified studies: 1) Comparison of random-effects (RE) model with fixed-effect (FE) model: The FE model that was used in the main analysis assumed that one true effect size underlies all studies included in the meta-analysis. On the other hand, the RE model assumed that the true effect size varies across studies [16]. Hence, the comparison of results obtained from both models allowed for evaluation of the potential impact of these differing assumptions on the overall findings; 2) Comparison of per protocol (PP) analysis with intention-to-treat (ITT) analysis: The ITT analysis included all randomized participants, while the PP analysis only included data from participants who completed the study. Therefore, this sensitivity analysis aimed to examine the potential impact of participants' compliance to treatments on the observed effects [17].

Language restriction Only randomized controlled trials published in English were considered for inclusion.

Country(ies) involved Malaysia.

Keywords Prediabetes; Glycemic control; Impaired glucose tolerance; Impaired fasting glucose; Elevated HbA1c; Prebiotics; Probiotics; Synbiotics.

Dissemination plans A paper will be submitted to a leading journal in this field.

Contributions of each author

Author 1 - Shenali Annemarie Delgoda - The autor conducted the data search and screening of articles. The author conducted the first extraction of data. The author prepared the draft of the manuscript.

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