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Impact of High-Fiber Diet on Gut Microbiome and Insulin Sensitivity in Individuals with Prediabetes: A Research Protocol

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Abstract

Introduction: Approximately 537 million individuals globally are affected by type 2 diabetes (T2D), with projections of 780 million by 2045. T2D is a chronic condition characterized by insulin resistance or insufficient insulin production, leading to high blood sugar levels, because the body cannot use insulin effectively. The rise in the incidence and prevalence of prediabetes, where glucose levels are above normal range but below diabetes threshold, serves as a warning for T2D development. The interplay between the gut microbiome and host metabolic pathways has emerged as a critical area of research in understanding diabetes etiology. The gut microbiome's role in modulating immune responses, influencing metabolic health, and potential to ease the progression of diabetes via a high-fiber diet have garnered significant interest. This research protocol proposes an experimental design to investigate the effect of a high-fiber diet on gut microbiome composition and insulin sensitivity in individuals with prediabetes.

Methods: This randomized controlled trial will include 60 individuals with prediabetes, randomly assigned to either a high-fiber diet intervention group or a control group. Participants in the intervention group will follow a high-fiber diet for 12 weeks, while the control group will maintain their usual diet. Data collection will involve stool samples for gut microbiome analysis using 16S rRNA sequencing, dietary records, and blood samples for insulin sensitivity measures, including the oral glucose tolerance test (OGTT). Statistical analysis will compare pre- and post-intervention microbial composition and insulin sensitivity using paired t-tests.

Results: We hypothesize that a high-fiber diet will increase the abundance of beneficial bacteria such as Akkermansia muciniphila, Roseburia, Faecalibacterium prausnitzii, and Bifidobacterium, which are known to improve insulin sensitivity by producing short-chain fatty acids (SCFAs). Concurrently, we also expect a decrease in potentially harmful bacteria, including Enterobacteriaceae and Bacteroides fragilis, which are associated with metabolic inflammation and insulin resistance.

Conclusion: The results of this study will be analyzed to understand the relationship between dietary fiber intake and changes in gut microbiome and insulin sensitivity. The findings are expected to provide insights into the potential of dietary interventions for preventing and managing T2D.

Keywords: prediabetes; insulin resistance; type-2 diabetes; gut microbiome; high-fiber diet; blood glucose levels; T2D; diabetes; resistance; insulin; randomized control trial; digestive health

Introduction

Diabetes mellitus (DM) is a condition that centers on the metabolism of sugar, which is one of the body's primary biological fuels [1]. In people with diabetes, either the body does not synthesize enough insulin or is inefficient in using it properly, leading to elevated blood sugar levels. Therefore, DM is a chronic metabolic disorder that is characterized by consistent high blood glucose (blood sugar) [2]. Previous research studies have indicated that DM occurs primarily due to resistance to peripheral actions of insulin, impaired insulin secretion, or both [2]. According to the International Diabetes Federation, there are currently ~537 million people diagnosed with diabetes . It is estimated that by 2045, there will be 700 million people diagnosed worldwide [3]. T2DM is the most common form of DM accounting for 90% of all cases [1] . In T2DM, the body experiences insulin resistance, characterized by a reduced cellular responsiveness to insulin, impairing its ability to regulate glucose homeostasis [1]. Before progressing to T2DM, many individuals develop prediabetes, establishing this condition as the precursor to a diagnosis of DM [4]. Adults

with prediabetes have a blood glucose level above the normal range but below the threshold set for diabetes [5]. It is expected that patients with prediabetes have a glucose level between 110 mg/dL to 125 mg/dL [4]. Currently, the recent and emerging options available for DM management using drug development research and anti-diabetic agents have been promising [6]. However, it is important to note that metformin can sometimes lead to various side effects, including increased gastrointestinal intolerance, abdominal or stomach discomfort, decreased appetite etc. [6]. Moreover , examining the interplay of lifestyle nutritional factors and their impact on gut microbiota after following a low-glycemic, high-fibre diet revealed evidence of improved glycemic control through insulin signaling, and in some cases, remission of high blood glucose levels [6].

Insulin Resistance and Gut Microbiota

Two thousand years ago, Hippocrates famously stated, "All diseases begin in the gut," a sentiment that accurately reflects the link between immune system dysregulation and increased disease susceptibility [6]. The gut microbiome consists of a complex and distinct environment for microorganisms [6]. When there is a shift in the bacterial composition of the gut microbiota, known as dysbiosis, it predisposes individuals to inflammation [6]. Previous research shows that this inflammation is recognized as the initial stage of disrupted gut homeostasis in diabetes patients [6]. Various studies indicate that individuals with pre-diabetes and type 2 diabetes generally exhibit reduced gut microbiota richness and diversity compared to those with normal glucose tolerance [7]. Studies have demonstrated that modifying lifestyle factors, including diet and exercise, can significantly affect how gut microbiota influence blood glucose levels in individuals with prediabetes and type 2 diabetes [6]. Recent research has highlighted the potential impact of dietary fiber intake on the composition of human gut microbiota [7]. Research has demonstrated that dietary fiber intake plays an important role in shaping the gut microbiota composition, leading to the production of beneficial Short Chain Fatty Acids (SCFAs), such as butyrate and propionate, which are evidenced to enhance insulin sensitivity and glucose metabolism [8 ,9]. For instance, a high fiber diet increases the abundance of Akkermansia muciniphila, Prevotella, and Roseburia, bacteria that are linked to improved glycemic control [10]. Additionally, these bacterial shifts are accompanied by reduced inflammation, a key factor in metabolic diseases and insulin resistance [11]. On the other hand, studies have also demonstrated that diets low in fiber are associated with the overgrowth of inflammatory taxa like Enterobacteriaceae, which worsen insulin resistance and disrupt glucose homeostasis [12]. Furthermore, several studies have suggested that prediabetic individuals exhibit lower microbial diversity and increased dysbiosis, which can be mitigated by fiber-rich diets [13]. The interplay between fiber intake and gut microbiota offers a promising non-pharmacological strategy to delay or prevent the progression of T2D [14]. This research protocol aims to investigate whether high-fiber diet-based interventions can selectively be able to promote beneficial bacterial taxa, leading to long term improvements in insulin sensitivity and overall metabolic health. We hypothesize that the high-fibre diet will increase the abundance of beneficial bacteria, including Akkermansia muciniphila, Roseburia, Faecalibacterium prausnitzii, and Bifidobacterium, which are linked to improved insulin sensitivity through the production of short-chain fatty acids (SCFAs) such as butyrate and propionate. Conversely, we also expect a reduction in harmful taxa, including Enterobacteriaceae and Bacteroides fragilis, which are associated with inflammation and insulin resistance.

Methods

Study Design

This study is a randomized controlled trial designed to evaluate the impact of a high-fiber diet on gut microbiome composition and insulin sensitivity in individuals with prediabetes. The trial will be conducted over a 12-week period. Participants will be randomly assigned to either the intervention group, which will follow a high-fiber diet, or the control group, which will maintain their usual diet. Randomization will be stratified by gender to ensure balanced representation in each group.

Participants

Participants will be adults aged 18-60 years old, diagnosed with prediabetes, defined by fasting glucose levels of 100-125 mg/dL or HbA1c levels of 5.7-6.4% [16]. Inclusion criteria will require participants to be willing to adhere to the dietary intervention and provide stool and blood samples. Exclusion criteria will include the presence of any autoimmune diseases, gastrointestinal diseases (e.g., Crohn's disease, ulcerative colitis), or other chronic diseases that could impact the gut microbiome[7]. Additionally, individuals who have used antibiotics or probiotics in the three months prior to the study, pregnant or breastfeeding women, and those already diagnosed with diabetes (Type 1 or Type 2) will be excluded [15-17].

Participants will be recruited via advertisements in local clinics, community centers, and online platforms. Efforts will be made to ensure equal representation of males and females in each group [18]. Recruitment will aim for a total of 60 participants, with 30 assigned to the high-fibre diet group and 30 to the control group.

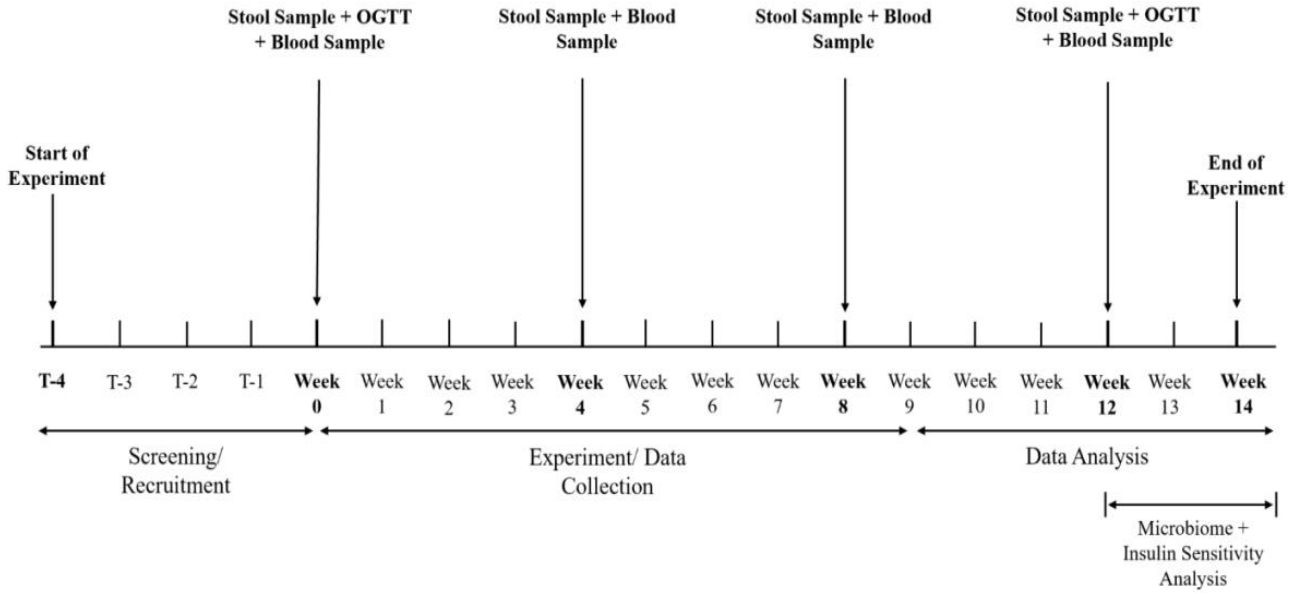

Figure 1. Study Timeline of Data Collection and Analysis. This figure illustrates the timeline of the randomized controlled trial, spanning over 14 weeks. Screening and recruitment begin in the first 4 weeks (T-4 to T-1). Participants begin the experiment at Week 0, where stool, blood samples and oral glucose tolerance tests (OGTT) are collected. Additional stool and blood samples are collected at Weeks 4 and 8. At the end of the intervention (Week 12), final stool, blood samples and OGTT measurements are taken. Data analysis begins at Week 12-14. Figure created with Powerpoint.

Intervention

The intervention group will follow a high-fibre diet for 12 weeks [19]. The diet will be designed to include at least 30 grams of dietary fibre per day, sourced from whole grains, fruits, vegetables, and legumes [19, 20]. Dietary guidelines and meal plans will be provided to participants to assist with rule adherence and consistency. The control group will be required to maintain their usual diet without any specific dietary modifications. Compliance will be monitored through regular check-ins and dietary records maintained by the participants [21].

Data Collection

Stool samples will be collected from participants at baseline (week 0), week 4, week 8, and week 12. Participants will be provided with stool collection kits and instructions for proper sample collection and storage. Samples will be stored at -80°C until analysis [22]. Participants will maintain detailed dietary records throughout the study period, recording daily food intake, which will be reviewed during bi-weekly check-ins. Blood samples will be collected at baseline (week 0), week 4, week 8, and week 12 to measure fasting glucose, insulin levels, and HbA1c [23]. An Oral Glucose Tolerance Test (OGTT) will be conducted at baseline and at the end of the 12-week period [24]. Participants will consume a glucose-rich drink, and blood glucose levels will be measured every 30 minutes for 4 hours.

Microbiome Analysis

Stool samples will be processed to extract DNA using the QIAamp DNA Stool Mini Kit (Qiagen) according to the manufacturer's instructions to ensure consistency and reliability [25]. The extracted DNA will then be used as a template for 16S rRNA gene amplification. 16S rRNA gene sequencing will be performed on the extracted DNA to identify and quantify bacterial taxa present in the gut microbiome [26]. 16S rRNA gene sequencing, known for its nine distinct hypervariable regions (V1–V9), is usually regarded as the preferred method for taxonomic classification using high-throughput sequencing techniques. Microbiome studies in this case often use sequences from multiple regions, but commonly V3 -V4, to improve the accuracy and specificity of bacterial identification [27]. Sequencing will be conducted using the Illumina MiSeq platform, focusing on the V3-V4 region of the 16S rRNA gene [27, 28].

The analysis will focus on major phyla, including Firmicutes and Bacteroidetes, which are crucial in metabolic processes [29]. Within these phyla, beneficial bacteria such as Bifidobacterium, Akkermansia muciniphila, Faecalibacterium prausnitzii, and Roseburia will be specifically analyzed [30-33]. Potentially harmful bacteria, including Enterobacteriaceae, Clostridium difficile, Bacteroides fragilis, and Prevotella, will also be examined [34-37].

The sequencing data will be processed to assess overall microbial diversity and the relative abundance of specific

bacterial taxa. Alpha diversity measures, such as the Shannon diversity index, will be calculated to assess the overall diversity within each sample [38]. The relative abundance of key beneficial and harmful bacteria will be quantified. Changes in the relative abundance of these bacteria between baseline and post-intervention will be analyzed using paired t-tests [39].

Insulin Sensitivity Analysis

Fasting blood samples will be collected at baseline (week 0), week 4, week 8, and week 12 to measure fasting glucose and insulin levels. Additionally, an oral glucose tolerance test (OGTT) will be conducted at baseline and at the end of the 12-week period. During the OGTT, participants will drink a glucose-rich beverage, and their blood glucose levels will be measured every 30 minutes for 4 hours to track changes in blood glucose levels over time [40]. These blood tests provide critical data for assessing insulin sensitivity and glucose metabolism, as this test shows how well the body processes glucose and responds with insulin [41]. The fasting blood samples, collected after an overnight fast, will measure baseline levels of glucose and insulin [42]. These measurements provide initial data on blood glucose and insulin levels without recent food intake. Two key metrics will be used to assess insulin sensitivity: the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and the Insulin Sensitivity Index (ISI) [43]. HOMA-IR is calculated using fasting glucose and insulin levels, with higher values indicating greater insulin resistance [44]. ISI is calculated using both fasting and OGTT data, with higher values indicating better insulin sensitivity [43]. Data analysis will involve paired t-tests to compare fasting glucose, insulin levels, HOMA-IR, and ISI before and after the intervention within each group [39].

Confounding Variables

Multivariate analysis will be performed to adjust and account for potential confounding variables such as age, sex and BMI. Multivariate analysis is a statistical technique used to understand the relationship between multiple variables simultaneously [45]. In this study, it will help to isolate the effect of the high-fiber diet on insulin sensitivity and gut microbiome composition by considering other variables that could potentially influence the results we obtain. Confounders are variables that can affect both the independent variable (dietary intervention) and the dependent variable (insulin sensitivity or gut microbiome composition) [46]. In this study, potential confounders include age, sex, and Body Mass Index (BMI) [47].

Stratification

Additionally, stratification based on baseline oral glucose tolerance test (OGTT) results will be done. Stratifying according to the 4-hour post-load glucose levels from the OGTT allows for a more accurate analysis as it is accounting for the already existing differences in glucose tolerance and insulin sensitivity among participants. This approach will also address concerns that factors such as age, sex, and BMI (confounders) alone can already significantly affect glucose tolerance and insulin sensitivity [47]. By stratifying participants based on their OGTT results, we can understand better how the high-fiber diet impacts individuals with different degrees of baseline glucose tolerances, which will provide a clearer picture of the diet's efficiency across different metabolic profiles of different people.

Results

Based on previous studies and the known benefits of dietary fiber, we anticipate that participants in the high-fiber diet group will show significant improvements in insulin sensitivity compared to the control group [48]. Specifically, we expect to observe a decrease in fasting glucose and insulin levels, as well as lower HOMA-IR values, indicating reduced insulin resistance [44]. Additionally, we anticipate an increase in the Insulin Sensitivity Index (ISI), reflecting enhanced insulin sensitivity [43]. In terms of gut microbiome composition, we expect to see an increase in overall microbial diversity (alpha diversity) in the high-fiber diet group [49]. Furthermore, we anticipate beneficial changes in the relative abundance of specific bacterial taxa. For instance, we predict an increase in beneficial bacteria such as Bifidobacterium, Akkermansia muciniphila, Faecalibacterium prausnitzii, and Roseburia [30-33]. Conversely, we expect a decrease in potentially harmful bacteria such as Enterobacteriaceae, Clostridium difficile, Bacteroides fragilis, and Prevotella [34-37]. These changes should correlate with improvements in insulin sensitivity, providing a certain link between dietary fiber intake, gut microbiome composition, and metabolic health [50].

Discussion

The anticipated results from this study will provide valuable insights into the relationship between dietary fiber, gut microbiome composition, and insulin sensitivity in individuals with prediabetes. By analyzing and interpreting these results, we can better understand the mechanisms through which dietary fiber exerts its beneficial effects on metabolic health.

Recent Studies have also demonstrated the potential of fecal microbiota transplantation (FMT) to improve insulin sensitivity by restoring gut microbial balance in individuals with metabolic disorders such as T2DM [53]. Given that our study aims to increase the abundance of beneficial bacterial taxa through a high-fibre diet, it is possible to stipulate that similar microbial shifts could in fact support the efficacy of FMT. For example, increased levels of Akkermansia muciniphila and Faecalibacterium prausnitzii, which are associated with better glucose regulation, are usually subject to being targeted by FMT protocols [54]. These findings suggest that dietary fiber interventions and FMT could in fact act as complementary strategies to

manage insulin resistance and prevent the progression of prediabetes to T2DM [55].

Implications

The potential impact of these findings is significant for both clinical practice and public health [50, 51]. If the high-fiber diet is shown to improve insulin sensitivity and beneficially alter gut microbiome composition, it could support the development of dietary interventions as a strategy for managing and preventing Type 2 diabetes [52]. This would provide a non-pharmacological approach to improving metabolic health, which could be particularly valuable for individuals with prediabetes. Furthermore, the study's results could contribute to a better understanding of the gut microbiome's role in metabolic diseases [53]. By identifying specific bacterial taxa that are influenced by dietary fiber and associated with improved insulin sensitivity, this research could pave the way for targeted microbiome-based therapies [54]. For example, probiotic or prebiotic supplements designed to increase beneficial bacteria could be developed as treatments for insulin resistance and Type 2 diabetes. The impact of such mitigation strategies to alleviate the progression of prediabetes into T2DM will prove to be incredibly profound [55].

Future Research Directions

Based on the findings of this study, future research could explore several avenues. Long-term studies could assess the sustainability of the benefits observed with a high-fiber diet and investigate whether these improvements translate into a reduced incidence of Type 2 diabetes over time in general. Additionally, research could also be done to examine the effects of different types of dietary fiber (via people's diet) on the gut microbiome and metabolic health, as well as potential effects with other dietary or lifestyle interventions. Regression analysis could also assess the relationship between changes in gut microbiome composition and changes in insulin sensitivity. Studies could also investigate the molecular mechanisms underlying the interactions between dietary fiber, gut bacteria, and host metabolism. This could include exploring the production of short-chain fatty acids (SCFAs) by gut bacteria and their impact on insulin sensitivity and inflammation [56-59].

Conclusion

The primary intent of this protocol is to investigate the effects of a high-fiber diet on gut microbiome composition and insulin sensitivity, in individuals with prediabetes. Additionally, it also consequently aims to provide evidence-based strategies to mitigate the progression of prediabetes into T2DM. By investigating these relationships, this research aims to provide evidence on how dietary fiber can influence metabolic health through targeted changes in the gut microbiome. This highlights diet as a crucial factor in managing and potentially preventing the progression into T2DM. Lastly, to conclude, this study aims to guide research one step closer to elucidating the complex relationship between dietary fiber, the gut microbiome, and insulin sensitivity. The anticipated findings have the potential to inform future dietary recommendations and interventions, aimed at improving metabolic outcomes. Ultimately, these insights may contribute to more effective, non-pharmacological strategies for the prevention and management of metabolic diseases, offering individuals with prediabetes actionable tools to take charge of and enhance their long-term health outcomes.

List of Abbreviations

16S rRNA: 16S ribosomal ribonucleic acid
BMI: body mass index
DNA: deoxyribonucleic acid
HOMA-IR: homeostatic model assessment for insulin resistance
ISI: insulin sensitivity index
mg/dL; milligrams per deciliter
OGTT; oral glucose tolerance test
PCR; polymerase chain reaction
RCT; randomized controlled t rial
RNA; ribonucleic acid
SCFAs: short-chain fatty acids
T2D: type 2 diabetes

Conflicts of Interest

The author(s) declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This research protocol did not require ethics approval and/or participant consent.

Authors' Contributions

MP: Contributed significantly to the conception, writing and design of the study, drafted and revised the manuscript critically, and gave final approval of the version to be published.
DJ: Contributed significantly to the conception, writing and design of the study, drafted and revised the manuscript critically, and gave final approval of the version to be published.
AS: Contributed significantly to the conception, writing and design of the study, drafted and revised the manuscript critically, and gave final approval of the version to be published.

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