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Gut Microbiota and the Development of Type 2 Diabetes

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Abstract

This paper explores the question: Can interventions focusing on healing the gut microbiome of a prediabetic patient prevent or delay the onset of type 2 diabetes? Diabetes is a major health problem that is becoming the biggest epidemic of the 21st century. Efforts to derail the progression of disrupted blood glucose metabolism are often futile leaving patients frustrated with a lifelong burden of disease management. Recent studies suggest that collectively the gut microbiome acts as an endocrine organ and that injury to this "organ" can lead to dysfunctional glucose regulation. A comprehensive literature review revealed that further studies are needed to explore alternative approaches to restoring normal glucose regulation. This proposed quantitative, experimental study aims to explore the effectiveness of a weekly program focusing on the establishment of a healthy gut microbiome to prevent the development of diabetes. The proposed sample will be 100 prediabetic adult patients (ages 25-65) who will be randomly divided into two groups: a treatment (Group A) and a control (Group B). All participants will provide a baseline fasting blood glucose, A1C and a fecal sample before the start of the study. Group A will attend an intensive educational program that consists of hour-long weekly meetings for 12 weeks. Group A will attend weekly discussions of evidence-based research on ways to promote a healthy gut microbiome. Activities that harm the gut thus promoting the growth of pathogenic bacteria will also be discussed and discouraged. Group B, the control group, will receive usual care which may or may not include recommendations from a physician about exercise, diet and weight loss. At the end of the study, we will compare the two groups' fasting blood glucose, A1C, and fecal microbiome composition.

Keywords: gut microbiota, gut microbiome, prediabetes, diabetes, glucose metabolism

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Gut Microbiota and the Development of Type 2 Diabetes

The Centers for Disease Control estimated in 2018 that 34.5% of the adult U.S. population has prediabetes and 10.5% of the U.S. population has diabetes (2019). The CDC cited a study by Gregg et al. in 2014 warning that two out of every five Americans are expected to develop type 2 diabetes in their lifetime. A primary nursing role is to decrease the prevalence of a disease such as type 2 diabetes by identifying the underlying cause and addressing it. In an attempt to identify the underlying cause of chronic diseases ranging from metabolic disease to gastrointestinal disorders to colorectal cancer, Hills et al. discuss how recent research findings implicate the gut microbiome as the major influencer in the development of these disorders (2019).

Humans have co-evolved with trillions of microbes, predominantly bacteria, living symbiotically on and within various sites of the human body. New discoveries are being made regarding the vital role the human microbiome plays in health and in disease. Microbiota is defined as the microorganisms, including bacteria, fungi, and viruses, present in a defined environment, such as a person's oral cavity, genital organs, respiratory tract, skin, and gastrointestinal system (Lloyd-Price et al., 2016). There are localized differences in the microbiota of each person and microbiota from the skin will be radically different from gut microbiota. It is estimated that there are roughly equal numbers of microbial cells inhabiting the human body as there are human cells (Sender et al., 2016). The human microbiome is defined as the collection of genomes, or DNA, from all the microorganisms in the environment (Kho et al., 2018). Of all the human microbiomes, the gut microbiome houses the most populous and diverse microbial communities. The gut microbiome, a topic of rapidly growing research, has been referred to as a separate "organ" or the "second human genome"

due to its large involvement in metabolic and immune activity (Ferranti et al., 2014). Advances in technology, such as next-generation DNA sequencing (e.g., 16s rRNA sequencing), have led to a surge in microbiome research as analysis has become faster and less costly, thus more available. These advances have allowed researchers to identify the microbiota present in the gut via stool sampling and to identify what physiological roles the microbiota plays. While a diverse microbiota is considered healthier, the ideal composition for a "healthy gut microbiota" has not yet been identified. However, a distinct microbial profile is becoming apparent for individuals with metabolic disorders and glucose dysfunction. For example, some researchers suggest that people with type 2 diabetes have a decreased number of bacteria that produce short-chain fatty acids (e.g., acetate, propionate, and butyrate) (Lv et al., 2018). Short-chain fatty acids are involved in mechanisms related to gut barrier function, glucose homeostasis, immunomodulation, appetite regulation, and obesity (Chambers et al., 2018). In summary, a closer look at the complex role of the gut microbiota is needed to understand the development of glucose intolerance and to prevent the onset of type 2 diabetes.

Literature Review

The objective for this literature review is to explore various studies and see if their findings can answer the following questions: What is the relationship between gut microbiota and glucose metabolism; and can certain practices either harm gut microbiota populations or promote a healthy gut microbiota to prevent the development of diabetes?

Search Strategy

The research literature was explored using multiple databases of the Dominican University of California library, such as UpToDate and CINAHL, as well as Google Scholar.

Various combinations of keywords were utilized in the search for research articles including the following: gut microbiota, gut microbiome, prediabetes, prediabetic, type 2 diabetes, glucose regulation, dysbiosis, artificial sweeteners, antibiotics, exercise, and fiber intake.

Six research articles were retrieved to create the literature review of this paper. These articles explore how various activities influence the health of our gut microbiota for better or for worse; either protecting us from developing diabetes or predisposing us to glucose metabolism dysfunction.

Although there is extensive research on the gut microbiome and how it affects different systems of our body, it was rather difficult finding primary quantitative research conducted on a large sample of human subjects related specifically to diabetes and the gut microbiota. The majority of research has been conducted on mice and the gut microbiota with a focus on inflammatory bowel diseases. Analysis of the gut microbiome can be expensive and tricky to manipulate due to its location and anaerobic microbiota. In fact, only in the last decade, as a result of the widespread use of polymerase chain reaction and DNA sequencing, 16S rDNA sequencing has allowed greater exploration of the role of the gut microbiome "including accurate identification of bacterial isolates and the discovery of novel bacteria" (Woo et al., 2008). Many studies included in this review utilized human fecal samples to explore the complex way that the gut microbiota interacts with the body's systems.

Road Map

The six articles discussed in this literature review are divided into three categories. The first section is called "The Connection Between Gut Microbiome Compositions and Glucose Metabolism." It contains two articles that compare the gut microbiome composition of individuals with normal blood glucose regulation with that of individuals with prediabetes or

diabetes type 2. The comparison shows that a diverse gut microbiota is positively correlated with normal glucose regulation. The second section is called "Activities that Result in Dysbiosis," and includes two research articles that explore practices that harm the gut microbiota, namely antibiotic use and nonnutritive sweetener consumption. These activities ultimately increase the risk of developing diabetes. The last section of the literature review is called "Activities that Promote Good Gut Health" and it discusses two articles that focus on exercise and fiber intake and their positive effects on gut microbiota. The objectives, methods, and findings of each article are discussed in detail, along with the study's strengths or limitations when appropriate. In addition, each article prompts a brief discussion of relative nursing implications making the research findings in these articles immensely valuable and practical. See Appendix A for a summary of the literature review.

The Connection Between Gut Microbiome Compositions and Glucose Metabolism

The article *Aberrant Intestinal Microbiota in Individuals with Prediabetes* by Allin et al. (2018) compared the gut microbiota of adults with prediabetes, obesity, insulin resistance, dyslipidemia, and low-grade inflammation with individuals with normal blood glucose regulation. The purpose of this study was to see if specific gut microbiota profiles are associated with prediabetes and a range of clinical biomarkers of poor metabolic health (Allin e al., 2018). Their inquiry was prompted by a former study called *Disentangling Type 2 Diabetes and Metformin Treatment Signatures in the Human Gut Microbiota* by Forslund et al. (2017). In the former study, associations between gut microbiota and type 2 diabetes were found, however, the accuracy of those associations were called into question by Allin et al. because individuals with diabetes 2 were taking metformin which actually alters gut microbiota. Therefore, Allin et al.'s newer study includes individuals not currently treated with glucose-lowering drugs.

This study compared the gut microbiota of 134 treatment-naïve Danish adults with prediabetes (n=268) with 134 Danish age- and sex-matched adults with normal blood glucose. Prediabetes is defined as a fasting plasma glucose of 6.1-7.0 mmol/l or HbA_{1c} of 6.0-6.5%. The design of this study is quantitative involving the analysis of fasting blood samples and the measurement of plasma high-sensitivity C-reactive, $HbA_{1c,}$ plasma glucose, triacylglycerol, and insulin levels. Fecal samples were collected by the participants at home and then they were frozen. The fecal microbiota composition was later profiled by 16S rRNA sequencing. This sequencing analysis "is a standard method in bacterial taxonomy and identification and is based on the detection of sequence differences (polymorphisms) in the hypervariable regions of the 16S rRNA gene which is present in all bacteria" (Kim et al., 2011).

The results of the analyses were that individuals with prediabetes had a depletion of several butyrate-producing bacteria compared to the individuals who had normal blood glucose metabolism. Specifically, Allin et al. found a decreased abundance of the genus *Clostridium* and the mucin-degrading bacterium *A. muciniphila* (2018). Butyrate is one of the three main short-chain fatty acids produced by the "friendly" bacteria in your gut. Multiple studies have found that butyrate has anti-inflammatory and anti-cancer properties; it can improve glucose metabolism and insulin sensitivity; and it can improve symptoms of ulcerative colitis and Crohn's disease (McNabney & Henagan, 2017).

There are important nursing implications of the findings that increased species diversity of the gut microbiota is associated with improved glucose regulation. These findings should guide discussions on the prevention and treatment of prediabetes. Reversing the depletion as well as preserving the populations of butyrate-producing bacteria in our gut could possibly delay the

onset of glucose metabolism dysfunction and other related chronic conditions, including metabolic syndrome.

The article *Human Gut Microbiota Changes Reveal the Progression of Glucose Intolerance* by Zhang et al. (2013) examined the relationship of gut microbiota with the development of type 2 diabetes. This quantitative, comparative study included 121 Chinese Han subjects that were divided into three distinct groups of varying glucose tolerance: Normal glucose tolerance (n=44), prediabetes (n=44), and newly diagnosed type 2 diabetes (n=13). Gut microbiota were analyzed using 16S rDNA-based sequencing. Disruptions in the normal balance of gut microbial populations were observed in the type 2 diabetes group. Metabolic parameters (insulin measurements, A1c, lipid profiles, BP, CRP, WHR, etc.) and microbiota diversity were compared and there was a significant association between the two. There was a higher abundance of butyrate-producing bacteria (e.g. *Akkermansia muciniphila*, and *Faecalibacterium prausnitzii*) in the normal glucose tolerance group than in the pre-diabetes group (Zhang et al., 2013). In the type 2 diabetic group, the abundance of Bacteroides at the genus level was half that of the normal glucose tolerance group and pre-diabetic group (Zhang et al., 2013). The study also found that *Verrucomicrobia* had a significantly lower abundance in both the pre-diabetic and type 2 diabetic groups (Zhang et al., 2013). Previous studies show that *Verrucomicrobia* may be a potential marker of type 2 diabetes (Barlow et al., 2015).

The nursing implication for this research is that gut microbiota is altered in different glucose intolerance status' and therefore plays a role in the pathogenesis of diabetes. Further studies are needed to explore this relationship so that we can prevent and treat glucose metabolic dysfunction.

Activities That Result in Dysbiosis

The article *Gut Microbial Diversity in Antibiotic-Naïve Children After Systemic Antibiotic Exposure: A Randomized Controlled Trial* by Doan et al. (2017) evaluated the effects of azithromycin on the gut microbiome diversity of children from an antibiotic-naïve community in Niger. This article was found on Iceberg using the keywords: microbial diversity and antibiotics. In this study, a population-based sample of 80 children (n=80), 1-60 months old, from Niger, was randomized to receive a single dose or oral azithromycin or placebo (Doan et al., 2017). The median age was 3 years old. After 5 days of treatment, 40 children were analyzed from the antibiotic group and 40 from the placebo group. The goal of this study was to compare the two groups' fecal samples that were collected immediately before the administration of the antibiotic and again 5 days after treatment. The samples were then profiled using 16S rRNA sequencing to identify bacteria thus determine the samples' composition and diversity. The design of this study was quantitative. The authors utilized a population-based sample randomized to receive the independent or the dependent variable. The results were statistically analyzed.

The outcome of the trial showed that "oral administration of azithromycin definitively decreases the diversity of the gut microbiome of children in an antibiotic-naive community" (Doan et al., 2017). The limitations of this study are the use of a pediatric population as the sample and the rural location in Niger. The results may not be generalizable to all ages or locations in the world. Furthermore, the second sample was collected after only 5 days showing that the antibiotic caused a short-term decrease in diversity but not necessarily a long-term change. A longitudinal study with a randomized control group of various ages and from various cities in the United States over a longer period of time would prove useful for this topic. Nevertheless, this study showed that even a single dose of antibiotics results in a reduction of

bacterial diversity. Antibiotic use may disrupt normal glucose regulation. The number of people diagnosed with diabetes continues to rise in the US. Therefore, healthcare providers need to thoroughly analyze the risks and benefits associated with antibiotic use before carelessly prescribing them to patients.

The article *Are Nonnutritive Sweeteners Obesogenic? Associations Between Diet, Faecal Microbiota, and Short-Chain Fatty Acids in Morbidly Obese* by Farup et al. (2019) explored changes in fecal microbiota and short-chain fatty acids of obese adults with a diet containing nonnutritive sweeteners. NNSs are also known as artificial sweeteners.

This study included 14 men and 75 women from Norway with morbid obesity (defined as BMI >40 or >35 kg/m^2 with obesity-related comorbidity) and with an average BMI of 41.8 (Farup et al., 2019). The ages of the participants ranged from 18-65 with a mean age of 44.6. All participants gave their medical history, had a physical exam, and had blood and fecal samples collected. Their diet was assessed with a validated food frequency questionnaire. Participants had an average intake of NNSs 7.5 units/day (SD 3.2; range 0–43). One unit of NNSs was equivalent to 100 mL beverage with NNSs or 2 tablets/teaspoons of NNSs (Farup et al., 2019). The fecal microbiota was assessed with a GA-map dysbiosis test. This advanced DNA testing targets variable regions (V3 to V7) of the bacterial 16S rRNA gene in order to identify bacteria present at different taxonomic levels (Farup et al., 2019). The short-chain fatty acids were assessed using gas chromatography and flame ionization detection (Farup et al., 2019). This is a quantitative, cross-sectional study of subjects who had been referred for evaluation for bariatric surgery in a hospital in Norway.

The findings of this study were that fecal butyric acid was positively associated with the intake of starch and negatively associated with the intake of nonnutritive sweeteners (partial

correlation=0.264 and partial correlation=-0.274 respectively) (Farup et al., 2019). NNSs were associated with changes in four out of 39 bacterial groups. Tests revealed reduced amounts of *Faecalibacterium prausnitzii,* a butyrate-producing bacteria and reduced amounts of *Bacteroides fragilis,* another bacterium that produces short-chain fatty acids. Farup et al. states that "lack of butyric acid has weight-inducing effects and metabolic consequences that are unfavourable for subjects with obesity" (2019). Tests also showed increased amounts of *Ruminococcus gnavus,* which multiple studies have associated as a prevalent gut microbe in Crohn's disease (Henke et al., 2019). There was also an increase in the *Streptococcus* species.

One strength of this study was that it took into account the following variables: gender, age, height, weight, BMI, coffee (cups/day), smoking (daily, previously, and never), previous and present diseases, and use of metformin and other drugs (yes/no). A limitation of this study was that the specific types of NNSs were not discussed. Also, the tests measured fecal amounts of short-chain fatty acids which could be construed as a poor estimate of short-chain fatty acids in the colon. On the other hand, perhaps measuring fecal SCFA was sufficient because quantities in feces depend on colonic production. Therefore, fecal measurements indirectly reflect intestinal quantities and activity.

The nursing implication of this study is that consumption of nonnutritive sweeteners should be discouraged, especially for individuals with prediabetes, type 2 diabetes, obesity or metabolic syndrome. NNS consumption for reducing caloric intake or weight loss counteracts the beneficial effects that butyric acid has on metabolism like reducing insulin resistance and improving dyslipidemia. Nonnutritive sweeteners should be avoided because they decrease beneficial gut microbiota populations and induce glucose intolerance.

Activities That Promote Good Gut Health

The article *Exercise and Associated Dietary Extremes Impact on Gut Microbial Diversity* by Clarke et al (2014) explored the positive impact that exercise and diet can have on gut microbiota. It was difficult to find studies about exercise and changes on microbiota that involved human participants, and not mice. Maybe it was difficult because there are many confounding variables when measuring results from exercise.

This study included 86 total subjects from Cork County in Ireland. Of the 63 subjects, forty (n=40) were male elite professional rugby players. The mean age was 29 ($\pm$ 4) years. The remaining 46 subjects were healthy male controls with a mean age of 29 ($\pm$6) years. The two groups of control were divided into a low BMI group $\leq$ 25 (n=23) and a high BMI group >28 (n=23). Participants were excluded if they had a BMI between 25 and 28, antibiotic treatment within the previous 2 months or were suffering from any acute or chronic cardiovascular, GI or immunological condition (Clarke et al., 2014). All participants were interviewed by a nutritionist and completed a detailed food frequency questionnaire that required diet recall from the past 4 weeks. Fecal and blood samples were collected and DNA was extracted from fresh stool samples which were stored on ice prior to use. The 40 athletes had to participate in a rigorous training camp and the physical activity levels of both control groups were assessed. The participants in the control groups were lean but considered sedentary. After four weeks, the fecal samples were examined using 16s rRNA sequencing. This was a quantitative, comparative study.

The results revealed that the athlete microbiota had a greater alpha diversity and a higher relative abundance of 40 different bacterial taxa compared to the microbiota of both sedentary controls (Clarke et al., 2014). Also, the alpha diversity of the two control groups did not differ significantly from each other. In other words, high or low BMI did not have an effect on

microbiota diversity. In terms of diet, the athlete group consumed "significantly higher quantities of calories, protein, fat, carbohydrates, sugar and saturated fat per day than either of the control groups and consumed significantly higher quantities of fibre, monounsaturated fat and polyunsaturated fat than the high BMI control group" (Clarke et al., 2014). In summary, the results of this study suggest that diet and exercise are contributors to diversity in the gut.

The nursing implication for this study is that exercise, coupled with healthy eating habits, can improve the diversity of the gut. Patients are frequently told that caloric energy spent should equal caloric consumption in a dry, mathematical type equation. The interaction of food, exercise and gut microbiota, which is considered a type of metabolic organ, is much more complex than a simple equation of counting calories in versus calories out. Teaching patients about the changes that occur at the microscopic level due to exercise and diet could guide interventions that focus more on microbiome health and less on strict calorie counting.

The article *Gut Bacteria Selectively Promoted by Dietary Fibers Alleviate Type 2 Diabetes* by Zhao et al. (2018) aimed to show that certain short-chain fatty acid-producing bacterial strains are promoted by dietary fibers which results in better hemoglobin A1c levels. This quantitative, randomized clinical study included specifically designed diets equal in energy, and fecal analysis using shotgun metagenomics to show that fiber increased the diversity and abundance of SCFA producers which in turn led to improved hemoglobin A1c levels (Zhao et al., 2018).

Patients with clinically diagnosed type 2 diabetes were randomized. The control group (U group; n = 16 patients) received the standard care according to 2013 Chinese Diabetes guidelines for T2DM, which includes patient education and diet recommendations (Zhao et al., 2018). The treatment group (W group; n = 27 patients) received a high-fiber diet composed of whole grains,

traditional Chinese medicinal foods, and prebiotics (also called the WTP diet) (Zhao et al., 2018) Both groups received an anti-diabetic prescription medication similar to metformin, called acarbose as the standardized medication. The daily energy and macronutrient intake were similar for both groups but the authors wanted the treatment group (W) to have a higher intake of dietary fibers to see if it would improve the HbA1c of the subjects. The subjects had their baseline hemoglobin A1c levels, fasting blood glucose levels, postprandial glucose levels, body weight and blood lipid profiles taken before the study (Pre; day 0) and after the treatment (Post; day 84). The clinical data showed that although both groups showed improved glycemic control, "the proportion of the participants who achieved adequate glycemic control (HbA1c < 7%) at the end of the intervention was also significantly higher in the W group (89% versus 50% in the U group)" (Zhao et al., 2018). The W group also showed a greater reduction in body weight and better blood lipid profiles than the U group. These findings indicate that increased availability of nondigestible, fermentable carbohydrates is "sufficient to induce clinically relevant metabolic improvements in patients with T2DM" (Zhao et al., 2018).

To determine causality between the gut microbiota and fiber-induced improvement of host glycemic control, two fecal samples were collected from the same participant; one from pre-intervention and one post-intervention. The gut microbiota from each of the fecal samples was then transplanted into germ-free mice (Zhao et al., 2018). Mice that received post-intervention microbiota from the W group had the lowest fasting and postprandial blood glucose levels among all mice which reflected the better metabolic outcomes in participants of the W group than in those of the U group (Zhao et al., 2018). The transferable effects of the treatments via microbial transplantation provided evidence that the gut microbiota can improve glucose regulation in patients with T2DM when gut microbiota is provided fiber to "eat."

The nursing implication for these findings is that nurses should encourage patients with dysfunctional glucose regulation to eat fiber. Feeding fiber to gut microbiota helps them flourish. When certain microbes ferment fiber they produce short-chain fatty acids that act as important metabolites for their human host. For example, short-chain fatty acids play a role in glucose regulation and lipid metabolism, and possibly reduce the risk of developing GI disorders like Crohn's, anti-inflammatory diseases, cancer, and cardiovascular disease (Tungland, 2018). Repopulating the gut with SCFA-producing bacteria may be the best way to treat various dysbiosis-related diseases, including diabetes, or at least an effective way to prevent the disease's progression.

Discussion

In summary, the aim of this literature review was to explore the connection between the gut microbiome and altered glucose metabolism. This review included six articles in total. Two articles identified the existence of a relationship between the gut microbiome and glucose metabolism dysfunction. Two articles illustrated that the gut microbiome can be negatively impacted by antibiotic use and artificial sweetener consumption. The last two articles illustrated that exercise and fiber consumption can promote healthy and diverse gut microbiota.

One strength of some of the studies was that they collected objective data and used advanced technology, such as 16s rRNA sequencing, for their analysis. A limitation was that a couple studies population samples were relatively small or from other parts of the world. Also, some of the findings may not be generalizable conclusions because of difficulty in controlling relevant confounding variables. Restricting patients to identical diets may be one way to control the confounding variables of diet assessment. Further studies on this topic could include bigger sample sizes and longitudinal studies. Nevertheless, the findings of this literature review are

definitely eye-opening and worthy of guiding practice in the prevention and treatment of glucose metabolism dysfunction.

Proposal for Further Study

It is clear that further studies are needed to explore how healthy gut microbiota promotion leads to better outcomes for people with prediabetes. In my literature review, I did not encounter quantitative research comparing a prediabetic group receiving conventional pharmacological treatment with a prediabetic group receiving educational intervention regarding practices that promote healthy gut flora. Traditional approaches to treat people with prediabetes are failing. According to Anthony Komaroff, MD, at Harvard Medical School, 25% of people with prediabetes will develop full-blown diabetes within 3-5 years and the percentage is significantly larger over the long term (2013). This prognosis could be due to a one-size-fits-all protocol treatment that focuses on symptoms of the disease instead of the cause. According to Medscape, people newly diagnosed with insulin deficiency or resistance are usually advised to reduce weight by 5-10%, exercise 30-60 minutes at least 5 times per week, eat or not eat certain foods, and take medication (2020). Many of the medications prescribed to patients with prediabetes are the same as those given to patients with type 2 diabetes. These medications treat the symptoms of dysbiosis such as elevated glucose levels, hyperlipidemia, and high blood pressure. These medications do not treat the cause of dysbiosis, so people are left with a lifelong list of prescriptions that carry with them side effects that often lead to nonadherence. Can patient education and further research on the relationship between gut microbiota health and chronic diseases like diabetes lead to better outcomes for patients with prediabetes?

Theoretical Framework

The nursing theory of Fay Abdellah serves as the framework for this study. According to the National Women's Hall of Fame website, Dr. Faye Abdellah was an educator, and the first nurse and woman to serve as Deputy Surgeon General (1981-1989) (2020). She helped transform the practice of nursing from "a disease-centered to a patient-centered approach," and raised the standards of nursing practice "by introducing scientific research into nursing and patient care" (National Women's Hall of Fame website, n.d.). The National Library of Medicine states that Dr. Abdellah advocated for nursing education to be based on science and research, for nurses to teach self-care to patients, and for an interdisciplinary approach to nursing care (2020).

Faye Abdellah's Twenty-One Nursing Problems Theory embodies the theoretical framework for this study. These twenty-one nursing problems are broken down into ten steps used to identify the patient's problems, and eleven skills used to develop a nursing care plan. The framework focuses on individualizing patient care, problem-solving, and patient-centered therapeutic plans. Skills of communication and education of patients and families are just two of her 11 skills listed (Abdellah, 1968). These are important aspects of this proposed study. For example, traditionally, the prediabetic patient is instructed to lose weight by avoiding sugar and excess calories. This explanation alone would result in patients reaching for foods that are low calorie or sugar-free, but that may also contain highly processed ingredients that wreak havoc on gut microbiota. The hypothesis of this study is that patient education will lead to a better understanding of the disease process which will ultimately guide patient behaviors and improve glucose metabolism.

Another step Faye Abdellah used to identify the patient's problem was "explore the patient and his or her family's reactions to the therapeutic plan and involve them in the plan"

(Abdellah, 1968). The success of a treatment plan depends on patient adherence. If the patient is actively involved in the formulation of the treatment plan, the patient will take more ownership of the implementation. Although diabetes causes common signs and symptoms in patients, a one-size-fits-all approach is not effective in treatment. The patient, and not the disease, will guide the details of a treatment plan in this study. Focusing on patient education and care plan individualization is paramount to this study and thus aligns well with Faye Abdellah's nursing theory.

Primary Research Aims

- This proposed quantitative, experimental study aims to compare fasting blood glucose and A1c, and microbial composition between two groups of prediabetic patients, one control group receiving usual care and an intervention group receiving weekly educational meetings and guidance on how to re-establish a healthy and diverse gut microbiome
- The hypothesis of this study is that the prediabetic group who participate in the educational program will have better markers of blood glucose control and an improved microbiota composition by the end of the study compared to the prediabetic group who only receive usual care

Ethical Considerations

The participants will be given a letter with the purpose of the study and what participation entails. Participants will be informed that they can drop out at any point in the study if they wish. Their participation is completely voluntary. The participants will not be compensated for their participation, but could hypothetically improve their health. The letter will state that there will not be any economic risk, psychological risk, nor physical risk as long as

moderate exercise is not contraindicated. The only physical discomfort will be from having blood samples collected three separate times. Participants' privacy and confidentiality will be honored throughout the process. Data collected will be used for research purposes only and stored in a password-protected computer to maintain strict confidentiality. The proposed study will be approved by Kaiser Permanente San Rafael's Internal Review Board.

Research Method

This proposed quantitative study will compare fasting blood glucose, A1C, and microbiota composition from two groups of prediabetic participants before the study begins, after the treatment, and 24 weeks after the beginning of the study. The population sample will include men and women from 25 to 65 years old who meet the criteria of prediabetic and who are patients at Kaiser San Rafael. The proposed sample size will consist of 100 prediabetic adults who will be randomly divided into two groups. The treatment group, Group A, will consist of 50 patients who will participate in an intensive educational program of hour-long weekly meetings for 12 consecutive weeks. The weekly discussions will cover evidenced-based research and literature on ways to promote a healthy gut microbiome as a means to obtain normal blood glucose regulation. Activities that harm the gut and diminish microbe diversity, such as taking antibiotics and consuming artificial sugar sweeteners, will also be discussed. Discussions will explain exactly how certain activities, like eating fiber and exercising, promote a healthy microbiome. The control, Group B, will consist of fifty patients who will not receive treatment in the form of an educational program. The only possible intervention Group B will receive are the standard verbal recommendations provided by their physicians. All participants will provide a baseline fasting blood glucose, HbA1C, and a fecal sample before the start of the study, after 12

weeks when the study concludes, and again at 24 weeks from the start of the study to test for long term effects.

Recruitment for this study will involve identifying Kaiser patients that meet inclusion criteria. Inclusion criteria include being prediabetic as defined as having a fasting blood glucose between 100 mg/dl and 126 mg/dl and a hemoglobin A1c from 5.7% to 6.4% (Dansinger, 2019). Exclusion criteria include antibiotic treatment within the past two months, current metformin or other antihyperglycemic therapy, or suffering from any severe cardiovascular, gastrointestinal or immunological condition. After identifying eligible patients, researchers will contact patients who will be given a brief description of the study, expected requirements for participation, and hypothesized outcomes. Patients will then be asked if they would like to volunteer. Patients will be informed that in the event they are randomly chosen for the control group, they will be able to attend an educational program at the end of the study if they chose. In this way, a service that is deemed beneficial is being offered to both groups but just not simultaneously. Participants will be reminded that even after providing informed consent, they can stop participating at any time.

For this quantitative, experimental study, a t-test will determine if there is a significant difference between the two groups' fasting blood glucose and HbA1c pre-treatment and post-treatment. 16s rRNA gene sequencing will be used to measure the microbial diversity and composition of the provided fecal samples from the two groups at the three different points in time. Gas chromatography and flame ionization detection will specifically measure the quantity of short-chain fatty acids, such as butyrate, in the stool samples as this is the byproduct of certain beneficial gut microbes. These beneficial species assist in gut homeostasis by their immunomodulatory functions as well as by maintaining metabolism such as blood glucose regulation (Nepelska et al., 2012).

Conclusion

After a thorough literature review of research, it is evident that there is a strong relationship between the health of the gut microbiome and human health. Gut dysbiosis and its role in the pathogenesis of disease needs to be further explored as it has been noted in patients with glucose metabolic dysfunction. More research is also needed on the beneficial role of the short-chain fatty acids produced by bacteria in the gut. Technological advances have made identification of gut microbial taxa possible, and the association between certain taxa and systemic inflammatory diseases is becoming evident. In the future, the presence of certain microbial populations or the absence of others might be used as biomarkers for diagnosing inflammatory diseases such as diabetes, ulcerative colitis, Crohn's disease, multiple sclerosis, rheumatoid arthritis, psoriasis and even cardiovascular disease (Barnes et al., 2016). To date, the majority of data analysis of microbial communities' role in disease has been collected from research on mice. The number of studies on human participants is growing at the same time as the prevalence of inflammatory diseases is growing, and scientists are desperately searching for their etiologies. The effectiveness of fecal microbiota transplantation in the treatment of Clostridium difficile infection has made manipulation of the gut microbiota even more attractive as a treatment option for diabetes and idiopathic conditions (Borody, 2011). In the future, fecal samples may be collected as routinely as blood samples to diagnose and treat inflammatory conditions.

This proposed research study with prediabetic patients will advance the nursing profession by exploring alternative methods to correct dysfunctional glucose metabolism. This proposed study uses Faye Abdellah's theory of nursing care by focusing on treatment that is patient-centered instead of disease-centered. The twelve-week educational program will allow

patients to understand the "why" behind specific recommendations which will lead to better treatment adherence and in turn better glucose regulation. Patients will understand that maintaining diverse and rich gut microbiota reduces inflammation and promotes healthy glucose metabolism. This study shifts the focus of nursing care from symptom management to patient education providing an opportunity for patients to take part in the prevention of their disease development. Patients will avoid a life sentence of pharmacological therapy, hospital visits, and potential complications such as amputations, end-stage kidney disease and dialysis treatment. In the future, more research is needed to explore the "neglected endocrine organ," known as our gut microbiota (Clarke et al., 2014). Let's listen to our gut.

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Zhao, L., Zhang, F., Ding, X., Wu, G., Lam, Y. Y., Wang, X., Fu, H., Xue, X., Lu, C., Ma, J., Yu, L., Xu, C., Ren, Z., Xu, Y., Xu, S., Shen, H., Zhu, X., Shi, Y., Shen, Q., . . . Zhang, C. (2018). Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science (New York, N.Y.), 359*(6380), 1151-1156. 10.1126/science.aao5774

Authors/Citation	**Purpose/Objective of Study**	**Sample - Population of interest, sample size**	**Study Design**	**Study Methods**	**Major Finding(s)**	**Strengths**	**Limitations**
1. Allin, K. H., Tremaroli, V., Caesar, R., Jensen, B. A. H., Damgaard, M. T. F., Bahl, M. I., … Pedersen, O. (2018). Aberrant intestinal microbiota in individuals with prediabetes. *Diabeto logia*, *61*(4), 810–820. doi: 10.1007/s00125-018-4550-1	• Compare gut microbiota of 134 adults with prediabetes, overweight, dyslipidemia and low-grade inflammation and 134 individuals with normal glucose regulation. • Determine whether specific gut microbiota profiles are associated with prediabetes and a range of clinical biomarkers of poor metabolic health.	n=268 134 Danish adults with prediabetes and 134 Danish adults with normal blood glucose regulation. Participants were same sex and roughly same age.	Quantitative, case-control study	• Analyzed the gut microbiome and differences in populations of certain bacteria of 268 Danish adults via fecal samples.	• *Individuals with prediabetes have aberrant intestinal microbiota characterized by a decreased abundance of the genus Clostridium and the mucin-degrading bacterium A. muciniphila.*	• *Quantitative data from population sample having specific inclusion criteria allowing for better isolation of factors to be compared.*	• Dietary habits only reliably compared between individuals with prediabetes and normal glucose regulation in a subset of the cohort.

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Zhang, X., Shen, D., Fang, Z., Jie, Z., Qiu, X., Zhang, C., Chen, Y., & Ji, L. (2013). Human Gut Microbiota Changes Reveal the Progression of Glucose Intolerance. *PloS One, 8*(8), e71108. 10.1371/journal.pone.0071108	•Explore the relationship of gut microbiota with the development of type 2 diabetes by analyzing metabolic parameters and microbiota diversity.	N=121 A total of 121 subjects from China were broken up into 3 groups based on their glucose intolerance status: normal glucose tolerance (NGT; n=44), prediabetes (Pre-DM; n=64), or newly diagnosed T2DM (n=13).	Quantitative, comparative observational study	•Gut microbiota characterizations were determined with 16S rDNA sequencing. •Clinical characteristics were also measured to assess the correlation between metabolic parameters and microbiota diversity using Kruskal-Wallis H tests. •Anthropometric and metabolic characteristics included body mass index, waist-hip ratio, fasting plasma glucose, plasma glucose 2 hrs after oral glucose challenge,	•Findings provide evidence of structural modulation of gut microbiota in the pathogenesis of diabetes. •A significant association between metabolic parameters and gut microbiota (T2DM-related gut dysbiosis) was found. •A total of 28 operational taxonomic units were found to be related to T2DM. •Butyrate-producing bacteria had a higher abundance in the NGT group than in	•Quantitative data allowed for objective analysis. •A large number of metabolic parameters were used. •A large number of bacteria ere analyzed. A total of 2.2 million sequence reads were generated from the 16S rDNA gene V3–V5 amplicons, with an average of 9474 (±3470 SD) reads per subject. •No subjects were taking antibiotics, hormones, or other drugs such as glucose- or lipid-lowering agents so they could not	•No dietary information was provided in the study. This may be a confounding factor because it has frequently been reported that the fat and fiber content of diets can affect gut microbiota composition.

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				triglyceride, fasting insulin concentration, 2-hr insulin concentration, insulin resistance index, and C-reactive protein values.	the pre-DM group. •*Verrucomicrobiae* may be a potential marker of T2DM-it had a significantly lower abundance in both the pre-DM and T2DM groups.	significantly change the gut microbiota composition.	
Doan, T., Arzika, A. M., Ray, K. J., Cotter, S. Y., Kim, J., Maliki, R., … Lietman, T. M. (2017). Gut Microbial Diversity in Antibiotic-Naive Children After Systemic Antibiotic Exposure: A Randomized Controlled Trial. *Clinical Infectious*	• Evaluate effects of azithromycin on the gut microbiome diversity.	n=80 Eighty antibiotic-naïve children 1-60 months from Niger.	Quantitative, randomized case control study	• 80 children received either oral azithromycin or placebo. Fecal samples were collected immediately before treatment and 5 days after treatment for 16S rRNA gene sequencing.	• Oral administration of azithromycin definitively decreases the diversity of the gut microbiome of children in an antibiotic-naive community.	• Similar age of participants. • No statistically significant differences in age, sex, breastfeeding, or solid food intake between the 2 study groups. • Quantitative data more reliable and objective.	• Population sample young children in rural community rural Niger so results may not be generalizable • Stool was sampled only after 5 days. Longer period may be necessary to provide insight into the resilience of the gut microbiome.

Authors/Citation	Purpose/Objective of Study	Sample - Population of interest, sample size	Study Design	Study Methods	Major Finding(s)	Strengths	Limitations
Diseases, *64*(9), 1147–1153. doi: 10.1093/cid/cix141							
Farup, P. G., Lydersen, S., & Valeur, J. (2019). Are Nonnutritive Sweeteners Obesogenic? Associations between Diet, Faecal Microbiota, and Short-Chain Fatty Acids in Morbidly Obese Subjects. *Journal of*	• Explore changes in fecal microbiota and short-chain fatty acids associated with the diet (nonnutritive sweeteners) and evaluate metabolic sequences. • Demonstrate for adults trying to lose weight, use of NNSs is suspect because	n=89 Study included 14 men and 75 women with a mean age of 44.6, BMI 41.8, and intake of NNS 7.5 units/day.	Quantitative, cross sectional study	• Fecal microbiota was assessed with GA-map dysbiosis test and SCFA with gas chromatography and flame ionization detection. • Participants diet was assessed with a validated food questionnaire.	• Nonnutritive sweeteners counteract the favorable effects of butyric acid which has anti-obesogenic effects, reduces insulin resistance and improves dyslipidemia. • Fecal butyric acid was positively associated with the	• Adjustment for multiple testing was performed for the main findings. • Analyses showed a showed a clear trend for an association between NNSs and butyric acid. • Quantitative data more reliable and objective.	• Study restricted to only participants with morbid obesity. • Measurement of SCFA in feces and not in proximal parts of colon, so more of an estimate of colonic SCFA. • Test could have examined more than the 39 bacterial groups included.

Authors/Citation	Purpose/Objective of Study	Sample - Population of interest, sample size	Study Design	Study Methods	Major Finding(s)	Strengths	Limitations
Obesity, *2019*, 1–8. doi: 10.1155/2019/4608315	they counteract the favorable effects of butyric acid.				intake of starch and negatively associated with intake of NNSs. • NNSs were associated with changes in four out of 30 bacterial groups.		Types of NNSs not included.
Clarke, S. F., Murphy, E. F., O'Sullivan, O., Lucey, A. J., Humphreys, M., Hogan, A., … Cotter, P. D. (2014). Exercise and associated dietary extremes impact on gut microbial diversity. *Gut*, *63*(12), 1913–1920. doi: 10.1136/gutjnl-2013-306541	• Explore the impact of exercise and diet on the gut microbiota. • Demonstrate that diet and exercise influence each component of the signaling network triad: the commensal microbiota, host immunity and metabolism.	n=63 • 40 young adult male athletes (professional rugby players) and 23 young, healthy adult males (the control) with similar BMI and age. • Participants from Cork in Ireland.	Quantitative, exploratory study	• Compositional analysis of the microbiota was explored by 16S rRNA amplicon sampling. • Each participant completed a detailed food frequency questionnaire.	• Athletes had a higher diversity of gut microorganisms, representing 22 distinct phyla, which positively correlated with protein consumption and creatine kinase.	• Two groups made up of healthy individuals with similar BMIs and of similar age. • Quantitative data more reliable and objective.	Athlete group on rugby team already physically fit, so presence of unknown confounder cannot be excluded.

Authors/Citation	**Purpose/Objective of Study**	**Sample - Population of interest, sample size**	**Study Design**	**Study Methods**	**Major Finding(s)**	**Strengths**	**Limitations**
Zhao, L., Zhang, F., Ding, X., Wu, G., Lam, Y. Y., Wang, X., Fu, H., Xue, X., Lu, C., Ma, J., Yu, L., Xu, C., Ren, Z., Xu, Y., Xu, S., Shen, H., Zhu, X., Shi, Y., Shen, Q., . . . Zhang, C. (2018). Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science (New York, N.Y.)*, *359*(6380), 1151-1156. 10.1126/science.aao5774	• To demonstrate that a select group of short chain fatty acid-producing strains is promoted by dietary fibers and that most other potential producers are either diminished or unchanged in patients with T2DM.	Patients from China with clinically diagnosed type 2 diabetes were divided into the control group (*n* = 16) or the treatment group (*n* = 27).	Quantitative, randomized clinical, open label, parallel group study	• Patients with T2DM were randomized to receive either the usual care (patient education and dietary recommendations based on the 2013 Chinese Diabetes Society guidelines for T2DM) as the control group (*n* = 16) or a high-fiber diet composed of whole grains, traditional Chinese medicinal foods, and prebiotics (the WTP diet) as the treatment group (*n* = 27 patients) in an open-label, parallel-group study.	• Increased availability of nondigestible but fermentable carbohydrates is sufficient to induce clinically relevant metabolic improvements in patients with T2DM. • When the fiber-promoted SCFA producers were present in greater diversity and abundance, participants had better improvement in hemoglobin A1c levels, partly via increased glucagon-like peptide-1 production.	• Quantitative data was gathered and analyzed using standard laboratory tests and the advanced technology of 16s rRNA gene sequencing. Many metabolic parameters were measured to reach findings.	•Sample size was small. •Confounding factors cannot be excluded.

Authors/Citation	Purpose/Objective of Study	Sample - Population of interest, sample size	Study Design	Study Methods	Major Finding(s)	Strengths	Limitations
				• After the specifically designed isoenergetic diets were administered, fecal samples were collected and analyzed using fecal shotgun metagenomics.			