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Effect of Probiotics on Honeymoon Period Duration and Glycemic Control of Type 1 Diabetes Mellitus: A Randomized Controlled Double Blind Clinical Trial Study Protocol

Nasrin Moazzen (MD)[1], Sepideh Bagheri (MD)[2*], Nosrat Ghaemi (MD)[3], Sara Nikpour (MD)[3] Mojtaba Lotfi (MD)[4], Hamid Ahanchian (MD)[1,5]

[1] Allergy Research Center, Mashhad University of Medical sciences, Mashhad, Iran
[2] Pediatric Department, Mashhad University of Medical Sciences, Mashhad, Iran
[3] Professor of Pediatric Endocrinology & Metabolism, Department of Pediatrics, School of Medicine, Akbar Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[4] Assistant Professor of Pediatric Endocrinology & Metabolism, School of Medicine, Akbar Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[5] Clinical Research Development Unit of Akbar Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Introduction: Type 1 diabetes is one of the most chronic childhood diseases. The therapeutic recommendation for this condition is complex and needs lifestyle changes. Recently, the role of gut microbiota has received attention as a possible mechanism in the pathogenesis and control of the disease.
Methods: A total of 130 children aged 6-18 years with newly diagnosed type 1 diabetes will participate in this trial. They are randomly assigned to the intervention and control group. The patients will receive a six-month course of probiotics or placebo in addition to their conventional treatment with insulin, and they are followed for at least one year. Participants are followed at 3-month intervals for one year. At each visit, anthropometrical data, glycemic control, and total dose of insulin required to keep the optimal glycemic control are evaluated and registered.
Discussion: There is evidence that alterations in gut microbiota is seen in children with diabetes. In this study, we aim to evaluate the effect of probiotic administration on the duration of the honeymoon period in pediatrics with type 1 diabetes and their glycemic control and insulin requirements.

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Introduction

Type 1 diabetes mellitus is among the most common chronic diseases of childhood in which the body is unable to produce insulin because of the autoimmune destruction of the pancreatic beta cells (1). The incidence of type 1 diabetes has increased worldwide during the past decades. There are no successful preventive or treatment strategies for type 1 diabetes because the exact mechanisms and pathophysiology are not well elucidated (1, 2). Genetic predisposition along with environmental factors are among the risk factors proposed for the development of type 1 diabetes in children (2). Recently, the role of gut microbiota in the pathology of type 1 diabetes has received attention (3, 4). Gut microbiota has an important influence on intestinal mucosal immune cells. The role of gut microbiota in the regulation of immunity and tolerance has been illustrated (5, 6).

Evidence shows that gut microbiota is different between children with type 1 diabetes and healthy children (7, 8).

***Corresponding author:** Sepide Bagheri,
Pediatric Department, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: bagheris@mums.ac.ir
Tel: 09155255451

Probiotics are live microorganisms that are considered to be beneficial to health. They help in the maintenance of the homeostasis of gut microbiota (9, 10). Probiotic administration in adults with type 1 diabetes has resulted in better glycemic control (11, 12). Herein, we describe a trial aiming to evaluate the effects of this supplement on the pediatric population with type 1 diabetes.

Objective and hypothesis

The purpose of this randomized controlled clinical trial is to study the effect of probiotics on glycemic control and the duration of the honeymoon period in newly diagnosed type 1 diabetic children.

The hypothesis is that probiotics may increase the duration of the honeymoon period or can induce better glycemic control due to their immunomodulatory effects on residual beta cells.

Materials and Method

Theoretical framework

Intestinal microbiota can have physiologic and pathologic effects on the immune system. This population has many known and waiting-to-be-known functions, including nutrition, protection, and trophic effects on GI epithelium and immune system. Nutritional effects are helping in food digestion and production of short-chain fatty acids, amino acids, and vitamins. Moreover, they promote carbohydrate breakdown and stabilize normal PH in the gut lumen. Furthermore, probiotics can have barrier effects against alien microbes (13, 14). They colonize in the gut lumen during the first weeks of life, produce anti-microbial substances (e.g., bacteriocins), adhere to gastrointestinal epithelium, compete with pathogenic microbiota, and impose a high genomic burden on the host. Gut microbiota overall has more than 100 times more genes than our genome (15).

Type 1 diabetes mellitus is an immune-mediated disease, and according to available evidence, patients in the preclinical and clinical stages of disease have altered intestinal microbiota. For example, in preclinical stages, the predominance of phylum bacteroidetes and, on the other hand, lack of butyrate-producing intestinal bacteria have been shown (16). Phylum firmicutes mainly produce butyrate in the gut lumen. These two types of phyla are most abundant among intestinal microbiota. While butyrate is a short-chain fatty acid and has many important immunomodulatory functions, the lack of microbial population that mainly produces it may be a clue for such immune dysregulation in type 1 diabetes mellitus (17, 18). Some butyrate functions promote regulatory T cells in the gut and enhance intestinal epithelial cells' ability in invading against pathogens (19, 20).

Therefore, while intestinal microbiota and the immune system can interact closely, probiotics and prebiotics must have important effects on human health. They promote mucin production, decrease intestinal permeability, activate macrophages, and enhance phagocytic capacity. In addition, they increase antibody production in the gut lumen, especially IgA. Production of cytokines and regulatory substances can maintain both immune system arms (14). Current evidence suggests prebiotics/probiotics as promising novel preventive and treatment strategies (21). Only one pilot study administered three months of multi-strain probiotics and found significant improvement in glycemic score and HbA1c (22). We aim to give symbiotics for six months and follow newly diagnosed children with type 1 diabetes for at least one year.

Study design and setting

This triple-blind randomized placebo-controlled clinical trial is carried out in the Endocrinology Department of Akbar Children's Medical Center. This hospital is a tertiary medical center located in Mashhad, the north-east of Iran. It is the biggest referral center of pediatric endocrinology and metabolism in the East of Iran and is affiliated with Mashhad University of Medical Sciences.

Participants and recruitment

At least, 130 children aged 6-18 years with newly diagnosed type 1 diabetes participate in the trial. Diagnosis of type 1 diabetes mellitus is made as defined by the International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria (1). Study recruitment will be from inpatients and outpatient Clinic of Akbar Hospital from March 2022 to March 2023. Patients who meet the inclusion criteria will enter the study.

Inclusion criteria

Newly diagnosed children with type 1 diabetes mellitus aged between 6-18 years old.

Exclusion criteria

Presence of comorbid conditions like significant cardiac, hepatic, or renal disease
- Presence of immunodeficiency
- Allergy to probiotics
- Patients not willing to participate in the study.

Randomization and blinding

The patients are randomly assigned to the intervention and control group. They are allocated in a 1:1 ratio to each group using a computerized research randomizer. The researchers are blinded to group assignments. All follow-up data are collected by two researchers who are blinded to group assignments. The researchers who generate the randomization sequence are not involved in the treatment or future evaluation of the participants.

Intervention

The intervention consists of the administration of probiotics or a placebo to newly diagnosed children with type 1 diabetes for a six-month period. The placebo is quite similar in taste and appearance to the active product. Products are manufactured in the form of capsules and are supplied free of charge by ZIST TAKHMIR company, Iran. This company has no role in the study concept, conduct, and the analysis and interpretation of data. Participants are followed at 3-month intervals for one year. At each visit, anthropometrical data, glycemic control, and total dose of insulin required to keep the optimal glycemic control are evaluated and registered.

Control group

The control group will receive a 3-month interval follow-up with standard medical care. The visits are quite similar to the intervention group.

Concomitant care

Patients will continue to receive their usual care and follow-up.

Patient and public involvement

After the completion of the study, the obtained findings will be presented as a research article, and patients will be informed of the results through an educational group on WhatsApp.

Measures

The main variables of the study are fasting c-peptide levels and HbA1c levels.

Secondary measures

Insulin requirements (Unit/kg/day)

Anthropometric parameters (weight, height, BMI)

Occurrence of concomitant autoimmune diseases (Celiac disease and Hashimoto thyroiditis)

Complications such as hypoglycemia or diabetic ketoacidosis during the study period.

Sample Size

The sample size was calculated according to sample size calculation formulas for studies that evaluate the effect of intervention. Due to the lack of similar trials in type 1 diabetes mellitus, and considering the researcher's assumption, which believes in 70% improvement in glycemic score with usual care and the minimum clinical effect size of 20% with this intervention, the study population was calculated to be 59 people. With an estimation of a 5% drop during intervention, 62 patients will be included in each group.

Statistical Analysis

Statistical analysis will be performed using the SPSS statistical package (version 22). Data will be presented using descriptive statistics, including means, standard deviation, and proportions. We will use the student's t-test for quantitative data and the Chi-square test for qualitative data. Kolmogorov-Smirnov test will be used to test the normality of the independent variables. For all parameters, a *P*-value less than 0.05 will be considered statistically significant.

Discussion

Type 1 diabetes mellitus is among the most common chronic diseases in the pediatric population (1). While this disease coincides with extensive changes in the lifestyle and diet of affected patients, gut microbiome changes are imaginable. A diabetic diet might influence the gut microbiota. However, there is not enough data regarding this variation. Another hypothesis might be the different gut microbiome in patients with type 1 diabetes mellitus, which may cause susceptibility to islet cell destruction (4, 23).

On the other hand, evaluating the probiotic immunomodulatory effect in this predominantly autoimmune disease is promising. Recently, a randomized, double-blind study evaluated the potential effect of a multi-strain probiotic in improving glycemic control. The results have shown a significant decrease in insulin requirement and better glycemic control (22).

In another study, among patients with type 2 diabetes mellitus, those who have consumed six weeks of fermented milk containing Lactobacillus acidophilus La-5 and Bifidobacterium animalis subsp lactis BB-12 have shown better glycemic control. In addition, a statistically significant decrease was seen in total and LDL- cholesterol in the probiotic group (23).

While this is the first clinical trial aiming to assess the impact of probiotics in the honeymoon period duration, we expect to demonstrate a

longer duration of the honeymoon phase.

Conflict of interest

None.

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