MAYO CLINIC

Gut Microbial Carbohydrate Metabolism Hinders Weight Loss in Overweight Adults Undergoing Lifestyle Intervention With a Volumetric Diet

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Abstract

The rising incidence of obesity requires the reevaluation of our current therapeutic strategies to optimize patient outcomes. The objective of this study was to determine whether compositional and functional characteristics of the gut microbiota in adults predict responses to a comprehensive lifestyle intervention program in overweight and obese adults. We recruited 26 participants from the Mayo Clinic Obesity Treatment Research Program between August 6, 2013, and September 12, 2013, to participate in a lifestyle intervention program for weight loss. Adults aged 18 to 65 years with a body mass index of 27 to 39.9 kg/m^2 and able to provide informed consent were included in the study. Fecal stool samples were obtained at baseline and after 3 months. Loss of at least 5% of baseline weight after 3 months was defined as *success*. Clinical characteristics and gut microbial composition and function were compared between those who achieved at least 5% and those who achieved less than 5% weight loss. After 3 months, 9 of 26 participants lost at least 5% of their weight. The mean weight loss was 7.89 kg (95% CI, 6.46-9.32 kg) in the success group and 1.51 kg (95% CI, 0.52-2.49 kg) in the less than 5% weight loss group. An increased abundance of *Phascolarctobacterium* was associated with success. In contrast, an increased abundance of *Dialister* and of genes encoding gut microbial carbohydrate-active enzymes was associated with failure to lose 5% body weight. A gut microbiota with increased capability for carbohydrate metabolism appears to be associated with decreased weight loss in overweight and obese patients undergoing a lifestyle intervention program.

 ■ Mayo Clin Proc. 2018;93(8):1104-1110

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Obesity is a chronic disease that is increasing in prevalence around the world and is now considered a global epidemic. Obesity, as measured by body mass index (BMI, calculated as the weight in kilograms divided by the height in meters squared) of 30 kg/m^2 or greater, has been consistently associated with increased all-cause mortality.[1]

A comprehensive lifestyle intervention is usually the first step for achieving weight loss. A weight loss of just 5% through a combination of dietary restrictions, physical exercise, and behavioral therapy is effective in achieving better glycemic control and preventing diabetes.[2,3] However, there is marked interindividual variability in the success of this approach that has often been attributed to patient adherence.[4]

The pathophysiology of obesity is complex, with contributions from host genes as well as environmental factors.[5] Recent evidence suggests that the human gut microbiome has a role in the pathophysiology of obesity by influencing host energy metabolism, adiposity,[6] neuroendocrine signaling, and insulin sensitivity.[7] Hence, the gut microbiome may be responsible in part for the interindividual differences in outcomes of obesity-directed interventions. In this study, we report potential microbial markers that predict responses to a comprehensive lifestyle intervention program for weight loss.

PATIENTS AND METHODS

Patient Selection

Patients were recruited between August 6, 2013, and September 12, 2013, from the Mayo Clinic Obesity Treatment Research Program. Adults aged 18 to 65 years with a BMI of 27 to 39.9 kg/m^2 and able to provide informed consent were included in the study. The exclusion criteria included health problems that prevented individuals from engaging in physical activity, previous operations for managing obesity (bariatric procedures and gastric bypass operation), concurrent participation in another weight loss program, and use of weight loss medications within the previous 30 days. Participants with any use of antibiotics within the previous 30 days were also excluded from the analysis. Other medications such as proton pump inhibitors, laxatives, statins, and analgesics were allowed. None of the included participants were taking probiotics.

Study Interventions

The Mayo Clinic Obesity Treatment Research Program is a 12-month comprehensive lifestyle intervention program. During the first 3 months, participants were followed through weekly 1-hour sessions, biweekly in the fourth month, and monthly thereafter until 12 months. To minimize the effect of participant nonadherence on the results, we selected the first 3 months as the time frame of our study. The nutritional intervention involved a volumetric approach[8] that included larger amounts of fruits, vegetables, and low energy density foods with lesser intake of foods with greater nutrient density. The goal was to reduce energy intake while achieving a high food intake volume.

The physical activity intervention involved recommendations to walk at least 10,000 steps per day or its equivalent. Physical activity was monitored using a pedometer with 7-day memory. Patients were instructed to wear the pedometer every day and review their step count data to assess progress toward the goal.

The behavioral intervention was given in weekly group sessions and included elements such as self-monitoring, managing expectations, goal setting, stimulus control, stress reduction, problem solving, social support, cognitive restructuring, and relapse prevention. The general outline of the sessions was based on the Look AHEAD protocol.[9]

Outcome Measures and Data Processing

Clinical, biochemical, and demographic information was collected from patients at baseline and after 3 months, including age, sex, race, weight, height, BMI, smoking status, hypertension, prediabetes, type 2 diabetes, fasting blood glucose, high-density lipoprotein levels, low-density lipoprotein levels, and triglyceride levels. The percent weight loss after 3 months was calculated on the basis of the participant's baseline body weight. A 5% or greater weight loss after 3 months was defined as *success*. Fecal stool samples were collected at baseline and after 3 months.

DNA isolation from stool samples was performed using the PowerSoil DNA Isolation Kit (Mo Bio Laboratories) after bead beating. The V4 variable region of bacterial 16S ribosomal ribonucleic acid (rRNA) was amplified from stool DNA and sequenced with the MiSeq platform (Illumina). Compositional and diversity data analysis was performed using the Quantitative Insights into Microbial Ecology (QIIME, version 1.9.1) pipeline.[10]

Predictive functional profiling from 16 rRNA was performed using the Phylogenetic Investigation of Communities by Reconstruction of Unobserved States pipeline.[11] Gene content was predicted against the following databases: the Kyoto Encyclopedia of Genes and Genomes database,[12] the Clusters of Orthologous Groups database,[13] and the Carbohydrate-Active Enzymes database.[14] The linear discriminant analysis (LDA) effect size (LEfSe) method[15] was developed to identify predictive compositional and functional biomarkers for weight loss. An α value of .05 and an LDA threshold of greater than 2.0 were used.

Statistical Analyses

Statistical analyses were performed using JMP Pro 12 software (SAS Institute) and the Quantitative Insights into Microbial Ecology pipeline. Two-sided Wilcoxon rank-sum tests were used to compare baseline differences in bacterial composition and α diversity, whereas permutational multivariate analysis of variance was used for β diversity. For interval changes in bacterial composition and diversity between baseline and after 3 months, 2-sided Wilcoxon signed-rank