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Impact of fecal microbiota transplantation with capsules on the prevention of metabolic syndrome among patients with obesity

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Abstract

Background: Fecal microbiota transplantation (FMT) has been studied for the treatment of metabolic syndrome with varying success. However, the possibility of utilizing FMT to prevent metabolic syndrome is to date unknown.

Methods: Secondary analysis of a double-blind, randomized, placebo-controlled pilot trial of FMT in obese metabolically healthy patients was conducted. Post-prandial glucose and insulin levels were measured.

Results: A total of 22 patients were enrolled, 11 in each arm. There were no baseline differences in the area under the curve (AUC) of glucose or insulin in the FMT group compared to placebo. There was a significant change in glucose AUC at week 12 compared to baseline, and in the insulin AUC at week 6 compared to baseline in the FMT group vs. placebo (change in glucose AUC (mg/dl x 60min): 579 vs 1978, p=0.03) (change in insulin AUC (μU/ml x 60min): 137 vs 2728, p=0.01).

Conclusions: These data suggest that FMT may have a potential role in preventing the development of metabolic syndrome in patients with obesity.

Keywords

Obesity; Diabetes; Metabolic syndrome; FMT

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Author contributions: JRA and BPC initiated the study concept and design acquisition of data, analysis and interpretation of data, and drafting of the manuscript. JH participated in data acquisition. ZK, AC, BHM, JRM, CCT participated in interpretation of data and critical revision of the manuscript.

JH, BHM, JRM, AC and **BPC** have no relevant conflicts to disclose.

Introduction:

Obesity continues to be a major health burden and public health concern, and is associated with chronic diseases such as diabetes mellitus and cardiovascular disease.[1] Given the lack of effective medical therapy for obesity and its consequences, fecal microbiota transplantation (FMT) has been studied for the treatment of metabolic syndrome with varying success.[2–4] However, the possibility of utilizing FMT to prevent metabolic syndrome is thus far unknown. Data are emerging suggesting that obese metabolically healthy patients may have metabolic alterations that confer potential future risk.[5] It is possible that preventative therapies initiated prior to metabolic derangement may be critical for obese patients. Clinical and microbial results from a pilot randomized-controlled trial evaluating FMT in obese metabolically healthy patients, utilizing a single lean donor stool, have previously been reported.[6] While FMT did not induce clinical weight loss in this pilot trial at an early timepoint, we did not assess the potential body weight-independent effects of FMT on blood glucose regulation. Herein, we report a secondary analysis of the impact of FMT on post-prandial glucose regulation.

Methods:

Secondary analysis was conducted of a single-center, double-blind, randomized, placebo-controlled pilot trial of FMT in obese metabolically healthy patients (body mass index [BMI], 35kg/m^2 or higher without diabetes, metabolic syndrome, or non-alcoholic fatty liver disease).[6] Participants were randomized 1:1 to receive treatment (an induction dose of 30 FMT capsules followed by two maintenance doses of 12 capsules at week 4 and week 8), or an identical placebo capsule. A single healthy lean donor (BMI, 17.5 kg/m^2) was used. Patients were assessed with a mixed meal tolerance test (MMT) at baseline prior to FMT, at week 6, and at week 12 post-FMT, with sampling at −15, 0, 15, 30, 45, and 60 min, in which glucose and insulin levels were measured. Insulin was measured by ELISA (Millipore, Burlington, MA, USA), and glucose was measured by colorimetric assay (ThermoFisher Scientific, Waltham, MA, USA). Data are presented as median (min, max) box plots. All statistical analyses were performed using GraphPad Prism 6. Data were analyzed by the Mann-Whitney test. Differences were considered significant at $p < 0.05$.

Results:

We enrolled 22 patients, 11 in each arm, primarily female (10 in each group). There were no significant baseline clinical differences between the FMT and placebo groups: baseline median BMI 40.8 (min 35, max 51.7) vs. 39.1 (min 36, max 49.1), p=0.73; age 44.5± 14.4 vs 43.3± 12.8, p=0.84. Two patients in the placebo group withdrew prior to week 12 and were excluded from the analysis. There were no statistically significant baseline differences in the area under the curve (AUC) of glucose or insulin in the FMT group compared to placebo (glucose AUC (mg/dl x 60min): 10389 vs. 10008, p=0.63; insulin AUC (μU/ml x 60min): 5668 vs 8008, p =0.07). Glucose and insulin excursions during the MMT remained stable in patients receiving FMT compared with placebo throughout the study. Overall, there was a significantly lower change in glucose AUC at week 12 compared to baseline in the FMT group compared to placebo (glucose AUC (mg/dl x 60min): 579 vs. 1978, p=0.03)

(Fig. 1A–B). A similar trend was observed when comparing the baseline to week 6 glucose AUC; however, this did not reach significance (−262 vs 862, p=0.17). Similarly, there was a significantly lower change in insulin AUC at week 6 compared to baseline in the FMT group compared to placebo (insulin AUC (μU/ml x 60min): 137 vs. 2728, p=0.02) (Fig. 1C–D). There were no significant weight changes observed in either group.

Conclusion:

To our knowledge, this is the first trial to assess the efficacy of FMT treatment in metabolically healthy patients with obesity. Studies have shown that metabolically healthy patients with obesity have altered metabolic profiling which may confer future cardiac risk, and that there is clearly a role for preventative therapies.[5] There has been variable response in insulin measurement post FMT for patients with metabolic syndrome. A recent study using FMT to treat metabolic syndrome among patients with obesity and insulin resistance did not report improvement in insulin sensitivity, as assessed by hyperinsulinemic euglycemic clamp.[4] In this trial, patients notably did not have evidence of baseline metabolic derangement. Patients in the FMT arm were found to have a decrease in the change in AUC of both glucose and insulin levels compared to baseline after FMT. Although there are limitations to this analysis, including the fact that a hyperinsulinemic euglycemic clamp measurement of insulin sensitivity was not performed as this was not the primary outcome, these preliminary data suggest that FMT may have the potential to serve a role in preventing the development of metabolic syndrome in patients with obesity. Further studies to assess this outcome are needed in view of the gravity of the obesity epidemic and the current lack of effective medical therapies.

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Conflicts of interest: JRA consults for and has research support from Finch Therapeutics Group. **ZK** is an employee/shareholder of Finch Therapeutics Group.

CCT: Apollo Endosurgery – Consultant/Research Support (Consulting fees/Institutional Research Grants), Aspire Bariatrics – Research Support (Institutional Research Grant), BlueFlame Healthcare Venture Fund – General Partner, Boston Scientific – Consultant (Consulting fees)/Research Support (Institutional Research Grant), Covidien/Medtronic – Consultant (Consulting Fees)

Fractyl – Consultant/Advisory Board Member (Consulting Fees), GI Dynamics – Consultant (Consulting Fees)/ Research Support (Institutional Research Grant), GI Windows – Ownership interest

Olympus/Spiration – Consultant (Consulting Fees)/Research Support (Equipment Loans), Spatz – Research Support (Institutional Research Grant), USGI Medical – Consultant (Consulting Fees)/Advisory Board Member (Consulting fees)/Research Support (Research Grant)

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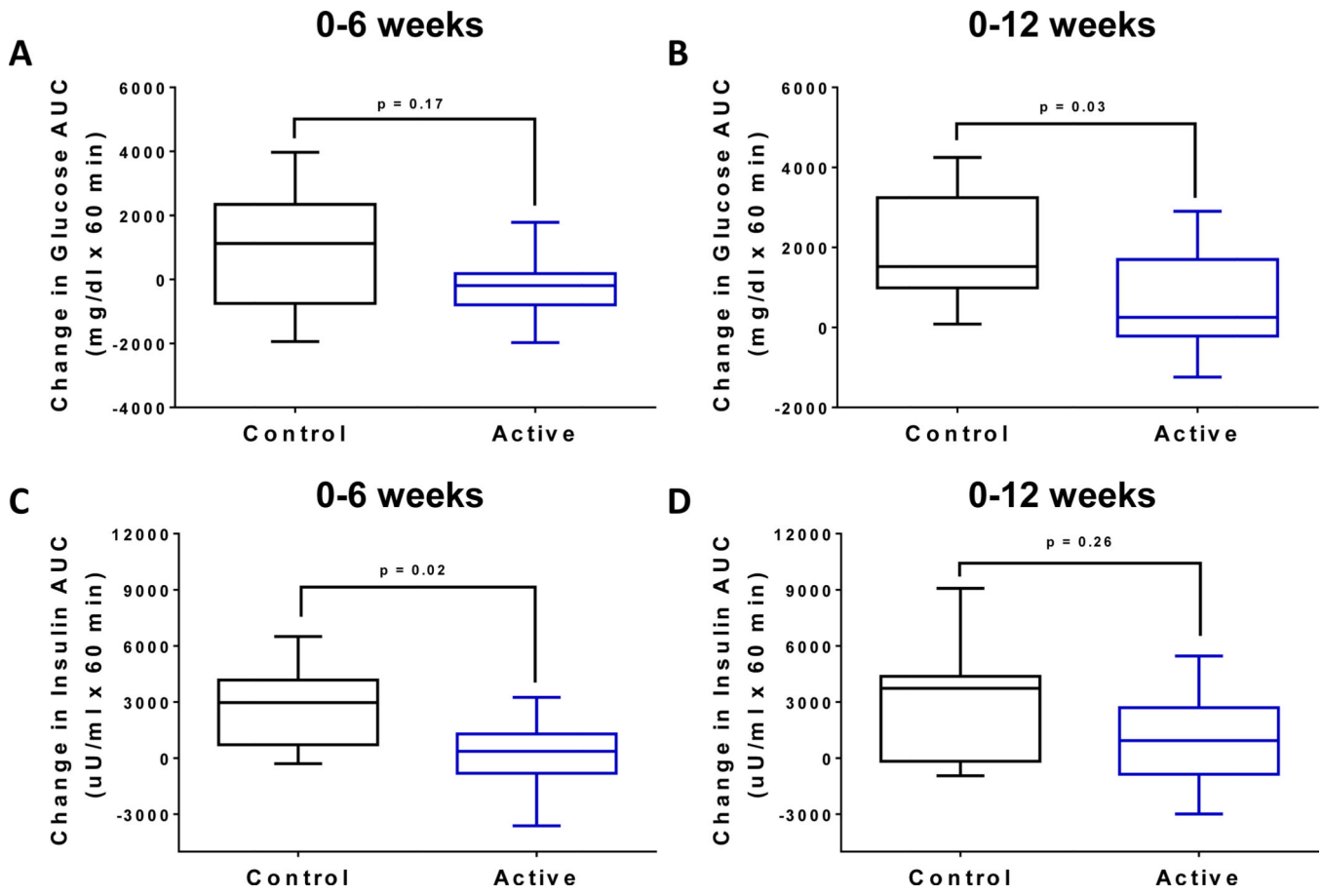

Fig. 1:

Impact of FMT on plasma glucose and insulin excursions during a mixed meal tolerance test. (A) Change in the AUC of plasma glucose levels at (A) week 6, and (B) week 12 relative to baseline in the active treatment arm compared to placebo. Change in the AUC of plasma insulin levels at (C) week 6, and (D) week 12 relative to baseline in the active treatment arm compared to placebo. Data are presented as median (min, max) box plots.