FEATURED NEW INVESTIGATOR

Significant differences in fecal microbiota are associated with various stages of glucose tolerance in African American male veterans

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The importance of gut microbiota in pathogenesis of diabetes remains unknown. This study investigated the relationship between microbiota and metabolic markers in African American men (AAM) with prediabetes and hypovitaminosis D. The study was ancillary to a randomized trial of vitamin D supplementation with weekly ergocalciferol (50,000 IU) conducted in AAM veterans over 12 months (D Intervention in Veterans Affairs). Glycemic groups (Gr) were characterized based on changes in oral glucose tolerance between baseline and exit. Subjects with stable normal glucose tolerance were assigned to Gr-1 and those with stable prediabetes (impaired glucose tolerance and impaired fasting glucose) to Gr-2. Microbiota composition was analyzed in stool collected at the exit (n = 115) and compared between Gr-1 and Gr-2, as well as between the lowest and highest quartiles of dietary intake of energy and fat, hemoglobin A1c, and serum 25-hydroxyvitamin D (25(OH)D) level. Differences between Gr-1 and Gr-2 included the Bacteroidetes/Firmicutes and Bacteroidales/Clostridia ratios and differences in genera such as Ruminococcus and Dialister. Changes in specific taxa associated with the lowest and highest quartiles of 25(OH)D (eg, *Ruminococcus*, *Roseburia*, *Blautia*, *Dorea*) were clearly distinct from those of dietary intake (eg, *Bacteroides*, *Bacteroides/Prevotella* ratio) or A1c (eg, *Faecalibacterium*, *Catenibacterium*, *Streptococcus*). These findings suggest a novel interaction between microbiota and vitamin D and a role for microbiota in early stages of diabetes development. Although results suggest that specific taxa are associated with glycemic stability over time, a causative relationship between microbiota makeup and dysglycemia is still to be demonstrated. (Translational Research 2015;166:401–411)

Abbreviations: T2DM = type 2 diabetes mellitus; A1C = glycosylated hemoglobin; 25(OH)D = serum 25-hydroxyvitamin D; AAM = African American men; NGT = normal glucose tolerance; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; RDA = Recommended Dietary Allowance; AI = Adequate Intake; OGTT = oral glucose tolerance test; SCFA = short-chain fatty acid

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AT A GLANCE COMMENTARY

Ciubotaru I, et al.

Background

Gut dysbiosis has been recognized as a potential player in diabetes pathogenesis. Although description of microbiota associated with diabetes has been reported, less is known about its makeup in prediabetes.

Translational Significance

We show that glycemic stability (stable normal glucose tolerance or stable prediabetes) is associated with specific microbiota makeup. There were significant correlations between glycemic control and the relative abundance of short-chain fatty acid producing genera *Ruminococcus*, *Faecalibacterium*, and *Dialister*. Higher abundance of these taxa was found in prediabetes and the highest glycosylated hemoglobin quartile, suggesting an adaptation for maintaining glycemia and preventing further worsening of the glycemic control.

BACKGROUND

The transition of normal glucose tolerance into type 2 diabetes mellitus (T2DM) includes contributions from genetic and environmental factors.[1] Intestinal microbiota existing in a state of symbiosis with the human host may be perturbed by environmental factors with unfavorable health consequences. Recently, the gut microbiota has become a focus of research as its manipulation could potentially help in managing various medical conditions including diabetes and obesity. Dysbiosis of the gut microbial community can trigger inflammation that plays substantial role in dysregulation of normal glucose tolerance into prediabetes and diabetes.[2-4] Prior studies have shown that in patients with T2DM, gut microbial composition has shown a number of significant alterations, including changes in the relative abundance of taxa within the dominant gut phyla Firmicutes and Bacteroidetes.[5] Prior studies also have demonstrated that the relative abundance of bacteria from the phylum Firmicutes and the class Clostridia has been significantly reduced in subjects with diabetes compared to those without diabetes.[5] Moreover, the ratio of Bacteroidetes to Firmicutes has been positively correlated with plasma glucose, whereas bacteria from the genera *Roseburia* and *Prevotella* were negatively and positively correlated with plasma glucose, respectively.[5] Bacteria from the genera *Roseburia*,[6,7] *Bifidobacterium*,[8] and *Akkermansia*[6,9,10] all have been implicated in glucose homeostasis and possibly in progression from normoglycemia to prediabetes and diabetes.[10] More broadly, obesity and diets high in calories and fat have been associated with significant differences in gut microbiota.[11-13] Obesogenic microbiota also seems to have increased energy harvesting capabilities.[14] In obese subjects, the ratio between phyla Firmicutes and Bacteroidetes has been inconsistently linked to body mass index (BMI) and dietary components.[13,15,16]

The wide range in relative abundance of these taxa in healthy humans,[17] the metabolic diversity contained by bacteria within each phylum, and functional redundancy present in microbial communities all increase the challenges in identifying diagnostic changes in the gut microbiome associated with T2DM. In addition, data from Han Chinese and European individuals have provided evidence for ethnicity and gender-related differences in the gut microbial makeup,[6,7] suggesting an uncertainty in generalizing findings, particularly to ethnic groups underrepresented in medical trials and research studies.[18,19]

Vitamin D deficiency may contribute to increased risk of diabetes and gut microbiota dysbiosis. In a prospective cohort study of 9,841 participants followed for up to 29 years, the risk of incident diabetes was 35% higher for the individuals from the lowest serum 25-hydroxyvitamin D (25[OH]D) level quartile relative to the highest quartile.[20] In mice, vitamin D deficiency at birth has resulted later in life in lower abundance of *Bacteroides* and *Prevotella*, increased expression of proinflammatory genes in the colonocytes, and higher serum lipopolysaccharide concentration.[21] Currently, there are no similar data on vitamin D and microbiota interaction in humans.

Here, we address T2DM and gut microbiota in an African American cohort. We examined the relationship of the gut microbiota with metabolic markers including dietary intake, glucose tolerance, and circulating vitamin D level to address the critical knowledge gap associated with gut microbial communities, vitamin D, and T2DM. The study focused on African American men (AAM), a major underserved population with poor dietary habits, relatively high burden of chronic disease and at risk for diabetes, and vitamin D deficiency.

DESIGN AND METHODS

This study was ancillary to "D vitamin Intervention in Veteran Administration" trial described elsewhere.[22] Briefly, this double-blind placebo-controlled randomized clinical trial tested the effect of 12-month high-dose vitamin D supplementation on oral glucose insulin sensitivity in AAM with dysglycemia and