Roles of Gut Microbes in the Development of Obesity

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With 425 million people in the world living with diabetes, chances are you have a family or friend who has this chronic disease. One of the primary risk factors for the development of type 2 diabetes is obesity. Changes in the gut microbiota have been implicated in the emergence of both obesity and type 2 diabetes in humans. This therefore begs the question: could changing the gut microbiota trigger, prevent or manage type 2 diabetes? And, if so, how?

Disruptions in the normal balance of gut microbial populations, termed dysbiosis, has been linked to a variety of gut-related diseases and conditions, including inflammatory bowel disease,[1] and nonalcoholic fatty liver disease,[1] as well as DM [2] and obesity.[3] The first studies linking gut microbes to weight gain were performed in mouse models, and showed that conventionally raised animals had 42% more total body fat than germ-free (GF) mice, even though the GF mice consumed 29% more chow.40 “Conventionalizing” the GF mice (by spreading cecal contents from conventionally raised donor son their fur and allowing them to lick it off) resulted in a 57% increase in total body fat content and a 61% increase in epididymal fat weight in the recipients,40 despite decreased chow consumption. Using cecal contents from genetically obese (ob/ob) mice resulted

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in an even greater increase in body fat. These data underscored that different gut microbial populations could have different effects on host weight gain and suggested the potential for the development of therapeutic strategies based on targeting (or augmenting) specific microbial populations. Subsequent studies focused on identifying gut microbial populations that were altered in obesity. Firmicutes and Bacteroidetes are the dominant gut phyla in both mice and humans, and while there are conflicting data, several studies have demonstrated an association between lower levels of Bacteroidetes (or lower Bacteroidetes to Firmicutes ratios) and obesity. Obese human subjects were shown to have lower levels of Bacteroidetes than lean subjects, which increased following weight loss on both low-fat and low-carb diets in a manner that correlated with percentage loss of body weight rather than changes in dietary calorie content over time. Dieting and Roux-en-Y gastric bypass (RYGB) have been shown to result in decreases in Firmicutes (genera Lactobacillus and Clostridium) and/or increases in Bacteroidetes (genera Bacteroides and Prevotella), as well as increases in Gamma proteobacteria (Escherichia) and Verrucomicrobia (Akkermansia) in human subjects. Taken together, these studies suggest that changes in specific gut microbial populations can directly affect host weight gain.

Roles of Gut Microbes in the Development of Diabetes Mellitus

In addition to the above-described potential roles of gut microbes in the development of obesity, alterations in gut microbial populations have been linked to changes in insulin sensitivity, altered glucose metabolism, and the development of the metabolic syndrome and T2DM. The first such study, performed by Larsen et al. in a Danish cohort, identified decreased overall microbial diversity in subjects with T2DM, decreases in Firmicutes (including Clostridia), and enrichment in Proteobacteria that correlated with plasma glucose on oral glucose tolerance test. Interestingly, they identified a negative correlation between Bacteroidetes to Firmicutes ratios and BMI but a positive correlation between Bacteroidetes to Firmicutes ratios and plasma glucose, which the authors suggested might indicate that obesity and DM are associated with different microbial populations. Subsequent meta genomic studies by Qin et al in a Chinese cohort and by Karls son et al in a cohort of 70-year old European women identified some comparable changes in gut microbes, as well as meta genomic markers that could accurately discriminate between subjects with T2DM and controls. Karlsson et al identified decreases in Clostridium species, similar to Larsen et al, as well as increases in Lactobacillus species, and demonstrated positive correlations between Clostridium species and fasting glucose and negative correlations for Lactobacillus species. Qin et al also observed decreases in butyrate-producing bacteria, such as Faecalibacterium prausnitzii, Roseburia intestinalis, Roseburia inulinivorans, and Eubacterium rectale and increases in bacterial genes related to oxidative stress in diabetic subjects. That there were also some differences in Meta genomics markers between the 2 populations is unsurprising given the disparity in age and ethnicity between the cohorts, further underscoring the influences of age, environment, and diet on the micro biome. A later study by the same Chinese group compared microbial populations in individuals with normal glucose tolerance, prediabetes, and T2DM and found increases in Betaproteobacteria in prediabetes and T2DM, consistent with results of Larsen et al, but they also found increases in Clostridium species in T2DM, in contrast to the findings of Larsen et al and Karlsson et al in European cohorts. Interestingly, the authors also found decreased numbers of F prausnitzii and Akkermansia muciniphila in T2DM subjects. The latter result was inconsistent with their earlier study, a discrepancy that the authors suggested might result from the use of different target genes to calculate abundances in the first (metagenomic) study vs the second (16S rDNA amplicon sequencing). The authors did note (1) that their finding of decreased Verrucomicrobia in prediabetes was consistent with the suggestion by Liou et al that Akkermansiamay have a substantial role in regulating host adiposity and weight loss, and (2) that their finding of decreased F prausnitzii was consistent with the negative correlation between F prausnitzii and insulin resistance identified by Furet et al in T2DM subjects who had undergone RYGB. Discrepancies notwithstanding, there do appear to be alterations in the gut micro biome in prediabetes and DM, although it remains to be determined whether these are the result of altered glucose metabolism and insulin resistance or contribute to their development. In addition to the difficulties created through the use of different technologies (noted by Zhang et al [11] and recently reviewed by Sankar et al [12], these studies were performed with stool/colonic samples. In the above-described study of duodenal samples from IBS subjects, Giamarellos-Bourboulis et al found that the microbial composition of human stool samples was highly dissimilar to the microbial composition of human duodenal samples. This illustrates that analyzing stool samples, while easily obtained, may have little or no relevance to changes in microbial populations that may be occurring in the metabolically relevant small intestines.

References


