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Methane-Producing Subjects Have a Significantly Higher Increase in Absolute Glucose Levels

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Abstract:
Important metabolic functions have been identified for gut microbes. Evidence from animal models suggests roles for gut microbes and gut-derived metabolic endotoxemia in fat accumulation, nonalcoholic steatohepatitis (NASH), and the development of type 2 diabetes mellitus. Moreover, modulation of gut microbial populations using non- absorbable antibiotics improves fasting and oral glucose tolerance in diet-induced obese and insulin-resistant mice

Keywords: Methanogens; hyperglycemia; diabetes mellitus; insulin resistance

Introduction

In last decade, important metabolic functions have been identified for gut microbes. Evidence from animal models suggests roles for gut microbes and gut-derived metabolic endotoxemia in fat accumulation, nonalcoholic steatohepatitis (NASH), and the development of type 2 diabetes mellitus [1-5]. Moreover, modulation of gut microbial populations using non- absorbable antibiotics improves fasting and oral glucose tolerance in diet-induced obese and insulin-resistant mice [6], and in mice fed a high-fat diet, antibiotic treatment ameliorates metabolic endotoxinemia and cecal lipopolysaccharide, which correlates with impaired glucose tolerance and body weight [2,7].

In humans, the intestinal tract is host to 1014 microbes from approximately 1000 species that include bacteria, archaea, and eukaryotes, which contribute to human health through roles in host metabolism and energy homeostasis, including breaking down non-digestible foods for absorption, energy harvest, and vitamin synthesis [8-10]. Methanogens are important constituents of the human gut microbiota. This distinct group grows primarily under anaerobic conditions [11], and produces methane (CH_4) as a byproduct of fermentation [12-14]. Methanogens are unique in that their metabolism increases in the presence of products from other bacteria [15], as they scavenge hydrogen and ammonia from other bacteria as substrates for the generation of methane [12-16].Once absorbed into the systemic circulation, methane is cleared via the lungs and can be quantitated by breath testing. The majority of methanogens colonizing the human gut are from the genus Methanobrevibacter; predominantly M. smithii [17-19]. While M. smithii is found in the isolated portion of the lower GI tract of 70% of with mental health disorders than non-obese children [6]. These facts unselected "normal" subjects, due to the threshold required for detection in the breath, only 15% of the population has methane on breath test (≥3ppm) [20,21], and we have previously shown that methane on breath test correlates with higher levels of M. smithii in stool [22].

In humans, breath methane has been associated with constipation: we found that subjects with IBS who have methaneon breath test were almost universally constipated [20], and subsequent studies showed methane to be predictive of constipation among functional bowel disease patients [23] as well as in IBS and non-IBS subjects [24]. In a meta-analysis of 1277 IBS patients, we found that methane was associated with constipation, with a pooled OR=3.51 (CI=2.00-6.16). Further, treatment with the non-absorbable antibiotics neomycin and rifaximin both eliminates methane and improves constipation, particularly in C-IBS subjects with successful eradication of methane on breath test (Pimentel et al., submitted), suggesting that methane itself is the cause of the constipation. Methanogenshave been shown to facilitate increased fermentation of dietary polysaccharides by other microbes, resulting in increased short-chain fatty acid (SCFA) production and enhanced availability of calories to the host. In two separate human studies, our group has now shown that the presence of both methane and hydrogen on breath test is associated with greater body mass index (BMI) [30,31] and percent body fat [31]. To further characterize the effects of methanogenic colonization on metabolic parameters, we examined whether elevated breath methane is associated with changes in glucose tolerance in humans.

Materials and methods

This study was approved by our institutional review board, and informed consent was obtained from all patients. Consecutive adult subjects undergoing lactulose breath testing at a tertiary care medical center were recruited. A total of 20 subjects were administered 10 gm oral lactulose load after a baseline breath sample. Lactulose is a polysaccharide that is not digested by humans, but can be utilized by enteric flora. Repeat breath samples were then obtained 15 minutes after lactulose ingestion,and levels of methane and hydrogen were analyzed using gas chromatography (Quintron

instrument company, Milwawkee, WI). A positive methane breath test was defined as a breath methane level ≥3 parts per million (ppm) as previously published[20,23]. Of these subjects, 15 non-methane and 5 methane positive subjects were consented to undergo an oral glucose tolerance test (OGTT). BMI was not a criterion for recruitment. All subjects underwent a standard 75 g OGTT with venous sampling for glucose and insulin levels at baseline and every 30 minutes for 3 hours post-ingestion. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to quantifyinsulin resistance and beta-cell function, according to the formula: glucose (mg/dL) x insulin (μU/mL) / 405. Mann Whitney U test was utilized for non-parametric data and student's t-test was used for normally distributed data. All tests were two-tailed and statistical significance was defined as $P < 0.05$.

Results

Study subjects

A total of 20 subjects were recruited for this study (15 nonmethane producing and 5 methane-producing). The average age of non-methane producing subjects was 37.7±12.1 years, vs. 48.8±10.0 years for methane subjects (P=0.17). The mean BMI in the non-methane group was 25.0±8.0 kg/m2, which was not statistically different from that in the methane group, 23.9±0.2 kg/m2 (P=0.53). Basal HOMA-IR levels were also comparable for the non-methane (2.21±1.52) and methane (1.32±0.72) groups (P=0.23), as were fasting blood glucose levels (80.26±8.1 mg/dL vs. 77.6±14.5 mg/dL, P=0.06) and fasting insulin levels (11.06±7.44 μU/ml vs. 7.16±3.85 μU/ml, P=0.28).

During the 180 minutes post-glucose load (i.e., post- OGTT), methane producers had a significantly higher serum glucose area-under-the-curve (AUC) (774.2±140.3 mg/dL) than nonmethane producers (585.5±128.3 mg/dL) (P=0.03In contrast, there was no significant difference in 180 minutes insulin AUC between methane producers (217.76±122.08 μU/mL) and non-methane producers (215.37±75.02 μU/mL) This resulted in a difference in glucose-toinsulin ratios post-OGTT between methane producers and non-methane producers.

We found that methane-producing subjects have a significantly higher increase in absolute glucose levels when undergoing an oral glucose challenge than their non-methane producing counterparts. This finding was independent of BMI. Further, there was no significant difference in the insulin resistance of methane-producing subjects (as measured by HOMAIR) as compared to non- methane producers. This suggests that subjects with intestinal methane production may have impaired glucose tolerance when challenged with a high carbohydrate load, and may a higher predisposition towards the development of hyperglycemia which appears to be independent of basal insulin resistance and BMI. Gut microbes contribute to human health through roles in host metabolism and energy homeostasis, including the break-down of otherwise non-digestible foods for absorption, energy harvest, and vitamin synthesis. The methanogenic archaea (methanogens) have been specifically linked to altered metabolism and weight gain in the host [11]. These anaerobic archaea utilize hydrogen and ammonia produced by other microbes as substrates for the generation of methane [12,13,15,]. The predominant methanogen in the human gut is Methanobrevibacter smithii [17-19], and there is increasing evidence for a specific role for M. smithii in the development of obesity. Using a germ free animal model, introduction of a single Bacteroides species (B. thetaiotaomicron) and M. smithii was found to result in greater weight gain than the introduction of B. thetaiotaomicron alone. The current hypothesis is that by scavenging hydrogen produced by syntrophic microbes for the production of methane (the "sink effect") [14],

M. smithii prevents excessive build-up of H2, allowing for increased polysaccharide fermentation by these syntrophs, resulting in increased short-chain fatty acid (SCFA) production and enhanced availability of calories to the host. Host absorption of SCFAs produced in this manner can provide up to 10% of daily caloric intake, depending on dietary content. In two human studies, our group has shown that the presence of both methane and hydrogen on breath test is associated with greater body mass index (BMI) and percent body fat, supporting the hypothesis that increased intestinal colonization with methanogens can contribute to increased caloric uptake and weight gain in the host. Another recent study suggested a role for differences in intestinal methane production in altered glycemic control in diabetic subjects, further supporting our finding of altered glucose levels in methane-producing individuals, and methane producers have also been shown to have higher fasting serum cholesterol concentrations when compared to age-, sex-, and BMI-matched non-methane producers. The alteration between systemic availability of acetate and propionate produced during carbohydrate fermentation by methanogenic archaea has been suggested to influence the blood lipid levels. Using an animal model and ex vivo studies, our group has also shown that methane may also directly affect intestinal transit and gut neuromuscular function, findings which have since been confirmed by an independent group. Slower gut motility could also result in increased time for nutrient absorption and energy harvest.

Recent reports in animal models have suggested possible contributing roles of enteric microbes in insulin resistance. Gut flora-derived metabolic endotoxemia via lipopolysaccharide production has been implicated in the development of type 2 diabetes mellitus [2,6]. Activation of the Toll-Like Receptor 4 (TLR4) cascade signaling system by enteric lipopolysaccharide ligands is believed to be one important mediator of insulin resistance [1]. Further, gut decontamination with norfloxacin and ampicillin enhanced insulin sensitivity in mice, independent of food intake and adiposity [7]. In another study, antibiotic treatment resulted in parallel amelioration of impaired glucose tolerance and reduction of body weight in mice [2]. The present study is the first description of an association between methane production and alterations in glucose metabolism in humans. However, our study has several limitations. Methane breath testing and OGTT were performed on separate days with a maximum difference of 7 days. However, it is unlikely to alter the findings as the presence and quantity of methanogens harbored by any given individual are remarkably constant over years [11]. It is also unclear at the present time whether this is simply an association or a cause-and-effect relationship. Moreover, due

to the small sample size in this study, further investigations are needed before firm conclusions can be drawn on the role of gut methanogens in development of hyperglycemia.

Given the potential significance of this finding, further large scale studies are warranted to confirm the association of gut methanogens and glycemic regulation, and to elucidate potential mechanisms.

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