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Probiotic Therapy to Attenuate Weight Gain and Trimethylamine N-oxide (TMAO) Generation: A Cautionary Tale

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Since the discovery of the contributory role of intestinal microbiota in the development of various chronic diseases, there have been valiant efforts by researchers to better define the potential role of probiotics as a potential therapy. The premise is relatively straightforward – the ability to modify the overall composition of intestinal microbiota may allow replacement of “bad” microbiota with “good” ones. What we have discovered over the years, however, is that the overall composition of the core microbiota is reasonably consistent, and it may be difficult to achieve significant shifts in microbial community structure with consumption of a probiotic. Indeed, recent reviews of existing randomized clinical studies of probiotics for the treatment of obesity and related metabolic disorders suggests that at present, there is inadequate evidence to support the clinical use of probiotics for the treatment of obesity as an indication[1].

But what of use of probiotics to selectively reduce generation of a specific, perhaps unwanted, gut microbial metabolite, rather than producing a significant shift in community composition? One attractive target for this line of investigation is trimethylamine *N*-oxide (TMAO). TMAO is an atherogenic metabolite that requires gut microbes for its generation through a metaorganismal pathway that begins with dietary consumption of trimethylamine (TMA) containing precursors such as choline, carnitine and phosphatidylcholine[2]. Western diets are rich in phosphatidylcholine (lecithin), the major dietary source of choline, and carnitine, an abundant nutrient in red meat. Recent studies employing microbial transplantation into germ-free recipients confirms a direct causal role for gut microbes in transmitting both overall TMAO production capacity and atherosclerosis susceptibility[3].

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DISCLOSURE

Dr. Tang has no relationships to disclose. Dr. Hazen is named as co-inventor on pending patents held by the Cleveland Clinic relating to cardiovascular diagnostics. Dr. Hazen reports having been paid as a consultant for the following companies: Cleveland Heart Lab, Esperion, Liposcience Inc., Merck & Co., Inc., P&G, and Pfizer Inc. Dr. Hazen reports receiving research funds from Abbott, Cleveland Heart Lab, Liposcience Inc., P&G, Pfizer Inc., Roche Diagnostics and Takeda. Dr. Hazen reports having the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics or therapeutics from the companies shown below: Cleveland Heart Lab., Siemens, Esperion, Frantz Biomarkers, LLC, and P&G.

Moreover, elevated TMAO levels have been shown to predict future risk of major adverse cardiovascular events[4], increased prevalence of cardiovascular diseases[2, 5], and to show a relationship with the number of diseased coronary vessels[2, 5]. Given the significant data demonstrating TMAO and the TMAO generation pathway is pro-atherogenic in multiple animal models of disease[2, 5], it has been suggested that the microbe-dependent production of TMA/TMAO is an excellent potential therapeutic target for both the prevention of cardiovascular disease risks, and attenuating the enhanced mortality and cardiovascular disease risks associated with a Western diet. Despite the many advances made recently in identifying gut microbes and their enzymes that participate in TMA and TMAO formation, little progress exists in how to therapeutically intervene and reduce TMAO formation.

In this issue, Boutagy and colleagues test whether the multi-strain probiotic, VSL#3, significantly impacts plasma levels of TMAO in subjects on a hypercaloric high fat diet[6]. The overall design involved a 2 week, eucaloric control diet run-in period, followed by randomization of subjects to either VSL#3 (900 billion live bacteria) or placebo (cornstarch) for a four week period, during which all subjects consume a high fat (55% fat), hypercaloric (+1,000 kcal/day) diet, and examine the impact of the probiotic on TMAO levels and other metabolic parameters. No differences in TMAO levels were observed in comparison of subjects in the probiotic vs control arms of the study. With the high-fat diet, the otherwise healthy subjects experienced an increase in systemic TMAO levels, whether the subjects were in the probiotic supplementation or the control group. Also, no significant differences in the microbiota composition with probiotic supplementation were observed, through the clinical study was relatively small and perhaps underpowered to see anything other than substantial reorganization of the community composition. Importantly, these neutral results were observed in setting of slight attenuation of weight gain and fat mass gain with treatment group albeit no differences in insulin sensitivity or *in vitro* skeletal muscle pyruvate and fat oxidation.[7] Thus, none of the expected signals attributed to the potential benefits of probiotics were observed despite carefully controlled dietary intake and probiotic supplementation efforts.

Perhaps the most important finding in this otherwise neutral intervention study is the direct link between a high-fat diet and a rise in systemic TMAO levels in humans. In fact, only systemic levels of the product (TMAO) but not the substrates (choline, betaine, L-carnitine) were increased following high-fat dietary intake, suggesting that TMAO formation has been induced by the high-fat diet. The authors note that there was an estimated increase in substrate delivery to the intestinal microbiota since the high fat diet increased both carnitine (45±3 mg/day) and total choline (176±13 mg/day) ingestion in subjects[6, 7]. While the high fat diet was apparently sufficient to enhance TMA and TMAO levels, no studies determined whether this was due to the enriched precursor nutrient load ingested, or whether there was also an accompanying induction of microbial metabolic capacity to catabolizing choline and carnitine into TMA, as has previously been observed in some studies. The finding that a high-fat diet can increase plasma levels of TMAO, while perhaps predictable, has not yet been reported, and thus this finding in the study by Boutagy and colleagues is of considerable interest. While it is interesting and newly noted that high-fat diet significantly increased TMAO, it is also important to highlight that baseline levels of TMAO in this otherwise healthy cohort were quite low (way below the first TMAO quartile in population-

based studies[4, 5]) – hence, these results may suggest further examination of the impact of a high-fat diet on subjects at higher risk (higher baseline TMAO levels) are also warranted. Regardless, it raises the possibility that the converse may be true – that switching from a hypercholoric high-fat diet to one that is eucaloric or hypocaloric, and low in fat, may effectively lower TMAO levels – a hypothesis that will require further testing.

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