

## REFLECTION

# Prebiotics, intestinal microorganisms and atherosclerosis

In Memory Emil Ginter, DSc, 1931–2017

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Recent advances in microbiology, microbial genetics and micro ecology greatly contributed to better understanding of diversity of the human microbiome. In contrast to the microbiota (microbes that actually inhabit a given ecosystem), microbiome is a collection of all genomes of microbes in an ecosystem (1). In humans the microbial ecosystem of the digestive tract consists of several trillion microbial cells.

Dysbiosis, an imbalance in the enormous diversity of intestinal microbes may adversely influence not only the gastrointestinal function but also contribute to disorders of other systems: respiratory, metabolic and cardiovascular.

Diversity of microbes identified by traditional culture- based technique is far smaller than that detected by molecular assays. Microbes exist in complex, interactive multispecies microbial communities. This applies also for every human habitat, a conglomerate of mammalian and multispecies microbial cells. Historically, over billion years of mammalian – microbial co evolution is the outcome of recent biological interdependency.

The intestinal microbiota contributes to the host immune response (2), to host cell proliferation, protection against pathogens, elimination of endogenous toxins, it contributes to metabolism of essential nutrients and to neuroendocrine regulation. The integrity of an adult human microbiome may depend on the in utero fetal environment (3), on the mode of delivery, the neonatal diet and timing of breast feeding . All these factors of postnatal microbial exposure predict future quality of the microbiome (4).

Proteins secreted by *Escherichia coli* were reported to have a potential to activate anorexigenic pathways in the brain, including those that mediate satiety (5). Gut microbiota has been shown to respond rapidly and reproducibly to dietary interventions. Predominantly meat-based food enriches the bile metabolizing microbiota, the prevalence of which may be associated with intestinal inflammation. Vegetable consumption enhances plant polysaccharide fermenting microorganisms.

There have been extensive speculations on possible cancer related role of specific diets (6). Certain microbes may enhance the efficacy of cancer immunotherapy (7).

Disorders of lipid metabolism contributing to atherosclerosis have been mechanically linked to dysregulation of lipoproteins

and cholesterol (8). It now appears that the gut microbiota is also prominently involved in the pathogenesis of atherosclerosis. This may be in line with observational studies on preventive potential of a mediterranean diet (9, 10).

Gut microbiota metabolism of dietary phosphatidylcholine and L-carnitine produces trimethylamine which undergoes oxidation to trimethylamine-N-oxide (TMAO). Elevated levels of TMAO appear to be a strong risk factor for atherosclerosis in humans and animals (11, 12). Experiments are under way to find if an analogue of choline dimethyl butanol may inhibit microbial trimethylamine production, lower plasma TMAO and prevent atherosclerosis (13).

Disease-related intestinal dysbiosis has been studied not only in observational association but also in sophisticated experiments employing RNA and DNA sequencing (14). Some epidemiological studies on intestinal microorganisms have been criticized regarding their design: intra individual variability, poorly controlled changes in lifestyle and heterogeneity among the cases and controls. Similar criticism has accompanied the variability of success in large observational studies testing efficacy of probiotics (live microorganisms that may provide health benefits when administered in adequate amounts) and prebiotics (nutrition substrates promoting growth of microbes that offer health benefits) (15).

Even with variable scientific evidence, prebiotics for prevention and probiotics for therapeutic intervention are welcome components of healthy life style.

Intestinal microbiosis is affected not only by the diet but also by numerous other exogenous influences. Modern world intensifies the impact of medications, xenobiotics and invasive medical procedures. Antibiotics drastically influence symbiosis of intestinal microbiota. Treatment with antibiotics in early life may increase the risk of overweight in later childhood (16).

Clinically very important is a specific dysbiosis, the overgrowth of *Clostridium difficile* after aggressive exposure to antibiotics. Strong proof that healthy gut microbiota is essential for stable micro environment is the success of transplantation of fecal microbiota from healthy donors to patients with complicated cases of *C. difficile* enteritis (17).

Increasing numbers of patients are subjected to aggressive surgical procedures on the digestive tract. Epidemics of obesity is exposing patients to bariatric surgery, in order to alleviate metabolic abnormalities that do not respond to conservative measures (18). Gastric and small bowel interventions drastically alter nor-

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mal digestive anatomy, disturbing physiological motility, digestive juice production, humoral coordination and altering neuro-endocrine regulations.

Interference in physiological intestinal microbiota, in order to remedy previous lack of self discipline, dietary excesses (overeating, obesity, metabolic syndrome) is a stiff penalty for disregarding preventive maintenance of normal intestinal microorganisms.

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