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PERSPECTIVES

Gut microorganisms and cardiovascular disease: carnitine is the answer

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Abstract: This short paper summarizes the current understanding regarding carnitine and gut bacteria which will provide new clues to uncover the background of multifactorial diseases such as cardiovascular disorders (CVD). Carnitine is a quaternary ammonium compound biosynthesized from phosphatidylcholine and the amino acids lysine and methionine *(Fig. 3, Ref. 12)*. Text in PDF *www.elis.sk.*
Key words: cardiovascular disease, carnitine, choline, gut bacteria, multifactorial diseases, atherogenesis.

This short paper summarizes the current understanding regarding carnitine and gut bacteria which will provide new clues to uncover the background of multifactorial diseases such as cardiovascular disorders (CVD) (1). Carnitine is a quaternary ammonium compound biosynthesized from phosphatidylcholine and the amino acids lysine and methionine. It is required for the transport of fatty acids from the cytosol into the mitochondria for the generation of energy. It is widely available as a nutritional supplement. Although L-carnitine has been marketed as a weight-loss supplement, there is no scientific evidence to show that it contributes to weight loss. Even without solid evidence, carnitine is being used by athletes, fashion models and general public to control body weight. Past clinical trials indicated that L-carnitine and propionyl-L-carnitine can be used along with conventional treatment for coronary insufficiency to reduce medication needs and improve the ability of those with angina to exercise without chest pain (2).

Recent reports documented that carnitine in the presence of gut microorganisms (microbiota) undergoes molecular transformation to trimethylamine (TMA). This is further metabolized in the liver to proatherogenic trimethylamine-N-oxide (TMAO) (Fig. 1). Metabolic activities of intestinal microrganisms have been likened to a "forgotten" organ. Metabolism of carnitine, choline and phosphatidylcholine by the intestinal microbiota produces TMA which is further metabolized into a proatherogenic TMAO (3).

Human gastrointestinal tract, mostly the large bowel contains more than 1,000 grams, about 100 trillion microorganisms, a number ten times greater than the total number of human cells in the body. Dietary components have a substantial influence upon the intestinal microorganisms that are integrally linked to the human host genome. Changes in the gut microorganisms affect the human phenotype and may contribute to the development of obesity, metabolic syndrome and type 2 diabetes (4–6). Some types of normal gut bacteria (e.g. Acinetobacter spp.) and liver cells convert dietary carnitine to TMAO. The generation of TMAO depends on flavin-containing monooxidase compounds, which are potent factors oxidizing the TMA to TMAO (7). TMAO potentially promotes atherogenesis by stimulating the production of foam cells from macrophages. TMAO alters cholesterol metabolism in the intestine, liver and arterial wall. In the presence of TMAO, there is an increased deposition and decreased removal of cholesterol from peripheral cells such as those in the artery wall (Fig. 2). In mice with an intact intestinal microbiota, dietary supplementation with TMAO or either carnitine or choline reduced *in vivo* reverse cholesterol transport (8). Since in the presence of TMAO there is an increased deposition and decreased removal of cholesterol from the artery wall, it is presumed that TMAO impairs metabolism of discoidal high-density lipoproteins (HDL) (Fig. 3). The role of electrostatic interactions in the kinetic stability of HDL was found (9).

There is novel information indicating biochemical pathways that associate gut microbiota also with human CVD. Three me-

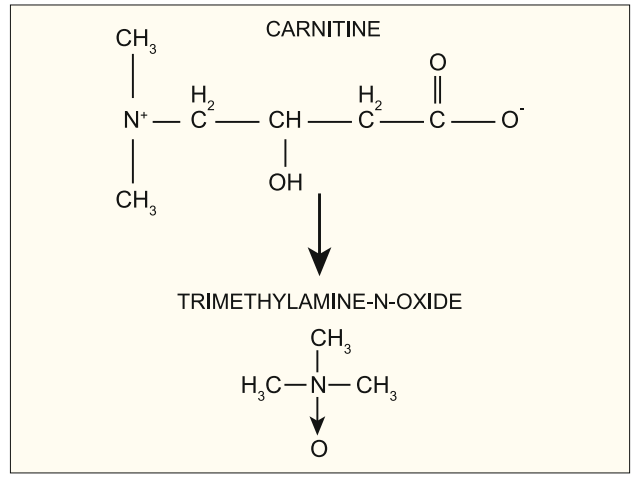

Fig. 1. Transformation of carnitine to trimethylamine-N-oxide.

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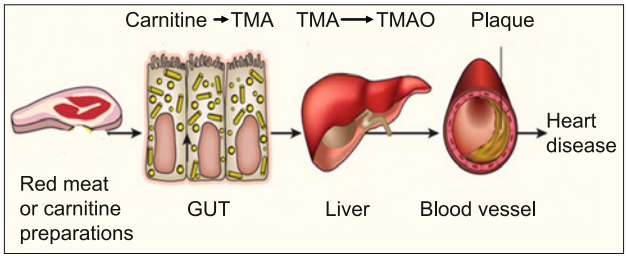

Fig. 2. Negative effect of carnitine on blood vessels. According to Rak and Rader (8).
PC – phosphatidylcholine, C – carnitine; TMA – trimethylamine, TMAO – trimethylamine-N-oxide.

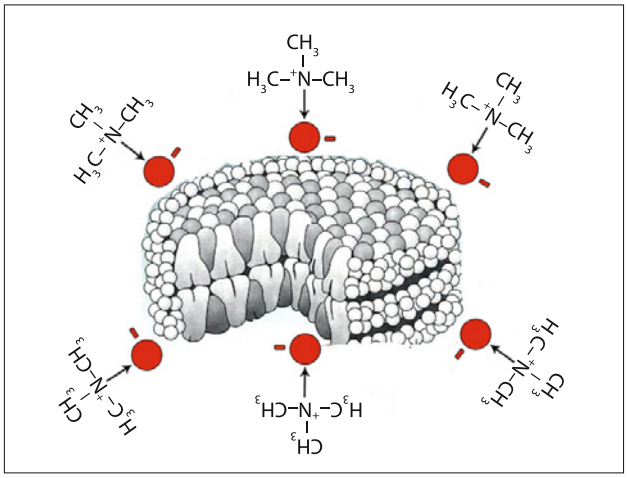

Fig. 3. Hypothetical attack of trimethylamine-N-oxide on discoidal HDL particle.

tabolites of the dietary lipid phosphatidylcholine, namely choline, trimethylamine N-oxide (TMAO), and betaine, were identified and then shown to predict the risk of CVD in an independent large clinical cohort (10). Plasma L-carnitine levels in subjects undergoing cardiac evaluation (n = 2,595) predicted increased risks for both prevalent CVD and incident major adverse cardiac events (myocardial infarction, stroke or death), but only among subjects with concurrently high TMAO levels. Plasma levels of palmitoyl-carnitine were associated with serious adverse events (i.e., all-cause mortality and heart transplantation) (11). Most recently, Tang et al. (12) examined the relationship between fasting plasma levels of TMAO and incident major adverse cardiovascular events (death, myocardial infarction, or stroke) during 3 years of follow-up in 4,007 patients. Increased plasma levels of TMAO were associated with an increased risk of a major adverse cardiovascular event. In spite of these new scientific discoveries more evidence is needed for human medicine.

Carnitine is available without a prescription as a nutritional supplement; supplemental doses usually range from 500 to 2,000 mg/ day. In comparison, a serving of 100 grams of red meat contains approximately 80 mg of carnitine. It has been speculated that some unexpected sudden deaths of young athletes, body builders and fashion models may be related to prolonged excessive intake of products containing carnitine. Experimental data so far available indicate that body supplementation with carnitine is not protective in stress and it does not enhance utilization of fatty acids in overweight individuals. Even under the condition of extreme metabolic requirements, carnitine concentration is not rate limiting for the transport of fatty acids. Importantly, the body pool of carnitine is very large and when there is adequate supply of lysine and methionine its body synthesis is so efficient that any exogenous supplementation with carnitine is unnecessary. For all these reasons carnitine is not considered a medication and it is not approved for therapy. Sustained interest about carnitine is demonstrated by repeated publications in this journal (13, 14).

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