

Is L-Carnitine the Link between Red Meat and Heart Disease?

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A recent article in *Nature Medicine* (2013) suggests that the nutrient L-carnitine, found in red meat and nutritional supplements, promotes atherosclerosis as a result of enteric bacteria in the gut forming a toxin called trimethylamine (TMA), which is further metabolized to trimethylamine-*N*-oxide (TMAO) [1]. Two other articles by many of the same authors similarly argue that gut bacteria transform dietary choline and phosphatidylcholine to yield TMA with negative cardiovascular consequences [2,3]. Furthermore, omnivorous human subjects produce more TMAO than do vegans or vegetarians; this difference is possibly related to the higher dietary L-carnitine intake of the non-vegetarians. We argue that the conclusions from these studies relating TMO/TMAO to dietary L-carnitine, whether from food or dietary supplements, are misleading and, in fact, L-carnitine is cardioprotective.

L-Carnitine and Human Studies

Cardiac metabolism needs L-carnitine for normal functioning. In fact, as much as 95% of the L-carnitine stores are in the heart and skeletal muscles. The adult heart normally derives 50–70% of its ATP from fatty acid β -oxidation, which requires L-carnitine to be able to metabolize fatty acids for fuel [4].

The benefits of L-carnitine are well established. Of the more than 2,000 entries on PubMed under the search terms, “carnitine” and “heart,” none appear to be linked to direct evidence of harm. Just the opposite — studies typically show positive and protective effects for the heart. For example, a randomized, double-blind, placebo-controlled trial, using L-carnitine in patients with suspected acute myocardial infarction, found that total cardiac events in the carnitine-supplemented group (2 grams/day for 28 days) were 15.6% versus 26.0% with placebo ($p \leq 0.05$) [5]. Similarly, 2 grams/day of oral L-carnitine improved the three-year survival rate of patients with heart failure caused by dilated cardiomyopathy [6]. In another study, investigators randomly provided 4 g/day of L-carnitine to 81 patients for 12 months, in addition to the usual pharmacological treatment [7]. After 12 months, compared to controls, improvements were observed in heart rate ($p < 0.005$), systolic arterial pressure ($p < 0.005$) and diastolic arterial pressure (NS); there were decreases in angina attacks ($p < 0.005$), in rhythm disorders (NS) and in clinical signs of impaired myocardial contractility (NS). Mortality was significantly different between the two groups in favor of the L-carnitine patients (1.2% vs. 12.5%; $p < 0.005$).

A meta-analysis of L-carnitine and cardiovascular disease (CVD) found analogous results [8]. Compared with placebo or control, increased dietary L-carnitine is associated with a 27% reduction in all-cause mortality, a 65% reduction in ventricular arrhythmias, and a 40% reduction in angina symptoms in patients experiencing acute myocardial infarction. Thus, based on the totality of the clinical evidence, as much as 4 grams L-carnitine per day administered up to 12 months not only improved cardiac function, but also increased life expectancy. It is, therefore, difficult to understand how others have linked dietary L-carnitine to worsening CVD outcomes [1].

TMA/TMAO under Normal Diets

Fears of possible negative health consequences from ingested

L-carnitine due to its role as a precursor to TMA are not new. Researchers for several decades have been exploring possible relationships between TMA and various pathological conditions, including CVD and cancer. Individuals with normal kidney function have no difficulty in excreting TMA/TMAO [9]. The rapid clearance of these compounds under normal circumstances suggests that dietary intake of L-carnitine-containing food is not sufficient to produce toxic levels of TMA/TMAO. Also, it is likely that the association between CVD and elevated blood concentrations of L-carnitine and related compounds such as choline are indicative of dysfunction(s) elsewhere and not causal.

Substrates potentially used by gastrointestinal bacterial flora for TMA production include not just L-carnitine sources, such as red meat and supplements, but also betaine, choline, creatinine, phosphatidylcholine and lecithin. Significant sources of these substrates are found in eggs, liver, and many commonly consumed vegetables. According to the USDA Database for the Choline Content of Common Foods and the USDA National Nutrient Database for Standard Reference, high choline-containing foods include (per 100 g): beef liver (430 mg), eggs (250 mg), spinach (24.8 mg), cooked broccoli (40.1 mg), Brussels sprouts (40.6 mg), and tomato paste (38.5 mg). No clinical evidence exists linking the TMA/TMAO generated by ordinary diets to health risks. In one trial, TMA/TMAO levels in the urine were insignificantly small after consumption of 45 different foods from a varied diet including meat, fruit, vegetables, cereal and dairy products [10].

In humans, blood levels of TMA/TMAO are directly associated with weekly fish consumption [11]. A serving of red meat results in the release of 77 μ mol TMA/TMAO over 8 hours, whereas a 7-ounce portion of halibut can lead to the excretion of more than 100 hundred times that amount (8,230 μ mol). Fish consumption typically leads to the release of 3,000–5,000 μ mol of TMA/TMAO into the blood for elimination, mostly via the kidneys. Non-fish eaters have a 10-fold lower excretion of TMA/TMAO, compared to those who consume a lot of fish [10]. Regardless of fish consumption and/or the consumption of food contaminated with TMA/TMAO due to poor handling, humans do not produce much of these compounds [12]. More sophisticated analytical techniques can now measure previously unquantifiable levels of blood TMA confirming that fish, and not red meat, is the primary dietary source for TMA/TMAO. More importantly, no study has shown a benefit of consuming beef over fish for cardiovascular health. The increased risk of CVD from elevated TMA/TMAO levels was deduced primarily from animal data [1]. Others have pointed out that the TMA

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thesis may not hold up even in an atherogenic-prone mouse model selected to demonstrate various aspects of the same argument [1,13].

Koeth et al. aver that elevated blood levels of choline and L-carnitine, and not just elevated levels of TMA/TMAO, are associated proportionately with increased CVD risk [1]. They state that there is a causal relationship between consuming foods rich in these compounds and CVD risk [2,3]. We disagree with this. First, the elevated blood levels of choline sometimes seen in patients with artery plaque instability are produced as a result of the instability itself and unrelated to diet [14]. Second, similarly disturbed L-carnitine regulation arguably is a result of cardiovascular dysfunction and not due to dietary intake [15].

A Role for Probiotics

Koeth et al. determined that gut bacteria caused the production and release of TMAO in humans [1,16]. Using radio-labeled carnitine, non-vegetarian subjects consumed a serving of steak and 250 mg of L-carnitine (the amount found in 1.5 pounds red meat). After 24 hours, blood levels of TMAO rose to 1.8 parts per million. Vegetarian subjects who followed the same protocol produced significantly less TMAO ($p < 0.05$). When both groups of subjects were pre-treated with antibiotics, no TMAO was detected. These trials demonstrated that gut bacteria form TMAO and are associated with the habitual consumption of meat.

An interesting continuation of the experiment illustrated the impact of habitual food choices [1]. Three weeks after antibiotic administration to kill gut bacteria, the same dietary challenge (steak and L-carnitine) was implemented. Gut bacteria of the omnivore group produced TMAO levels 7 times higher than found previously, indicating the potential of meat and carnitine in the diet to affect the repopulation of the gut by bacteria after antibiotic treatment. Therefore, frequent antibiotic use may lead to alteration in the normal microbiome resulting in chronically high outputs of TMAO in omnivores and, possibly, increased risk of CVD. More work is needed to confirm this hypothesis.

It is significant that the differences between blood TMAO concentration in omnivores and vegetarians were small. Seventy-five percent of omnivores had TMAO excretion levels that were in the same range as 90% of the vegetarians, meaning that 25 percent of the omnivores and 10 percent of the vegetarians exhibited elevated TMAO levels [1]. This would suggest that meat *per se* does not cause the blood elevation of TMAO, but rather specific gut bacteria do. Subjects with high gastrointestinal counts of *Prevotella* and low *Bacteroides* had three times higher blood TMAO levels compared to those with low *Prevotella* and high *Bacteroides* microflora [1]. Such findings indicate that there may be a role for supplemental probiotics to correct these imbalances. In addition, it is likely that the high producers of TMAO also consumed a diet low in fermentable fibers, which are known to favorably modulate gut bacteria. However, dietary histories were not obtained to confirm this hypothesis [1].

Conclusions

1. Neither dietary L-carnitine found in red meat nor choline and phosphatidylcholine found in liver, eggs and broccoli under normal circumstances contribute to a significant elevation of blood TMAO.
2. Fish appears to be the primary source of TMAO in the diet.
3. Gut bacteria can contribute to the formation of TMAO; this seems to reflect not only routine meat consumption, but also possibly antibiotic use and a low dietary fiber intake.

4. A healthful diet is key to reducing CVD risk and to promoting the reduced formation and proper disposal of TMA/TMAO. Consume seafood at least twice weekly and limit intake of saturated fats from meats and eggs. Include plenty of fruit, vegetables and whole grains in the diet to provide soluble fiber while limiting the intake of sugars and refined carbohydrates. Healthy fats like olive oil and those from nuts also promote heart health. Drink adequate fluids, especially water, to support kidney function inasmuch as the kidneys clear TMAO from the body.

Conflict of Interest

Drs. Clouatre and Bell are consultants to Jarrow Formulas, which sells L-carnitine as a dietary supplement.

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