Media Generates Misleading Report about Carnitine

On **April 13, 2013**, a meta-analysis performed by the **Mayo Clinic** studied **3,600** patients and found huge cardiac benefits in those who supplemented with **L-carnitine**. This study represented the largest, most powerful scientific review of carnitine's cardiovascular benefits to date.

This same study found carnitine supplementation was associated with a ***27% reduction*** in all-cause mortality**,** a ***65% reduction*** in ventricular arrhythmias**,** and a ***40% reduction*** in angina symptoms in patients who had experienced a heart attack. This media overlooked this favorable report.

A new study asserted that carnitine found in **red meat** would react with certain gut bacteria in certain individuals to promote a compound (TMAO) that would then cause heart disease.

These findings we based on an evaluation of less than **10** people. They were obscure, theoretical and preliminary. Yet the media ignored hundreds of studies showing significant cardiovascular benefits to carnitine, choosing instead to use this study in isolation to bash anything that contained carnitine.

I work as a Medical advisor to the Life Extension® foundation and Bill Faloon Dr. Seidman and teams of scientists have thoroughly analyzed the report used by the media to attack carnitine, reviewed the published literature on carnitine and heart disease, and conducted a survey of our members using carnitine. It may not surprise you to learn that our findings contradict the mainstream's propagandized carnitine attack.

Preliminary Study Questions Carnitine's Role in Cardiovascular Disease, Generates Misleading Media Headlines

A recent investigational study published by Koeth et al. in the journal *Nature Medicine*[1] examined levels of a compound called trimethylamine-N-oxide (TMAO) in relationship to microbial metabolism of carnitine in the gut. The researchers cite very recent, limited research suggesting TMAO may be a risk factor for cardiovascular disease. They then provocatively propose that carnitine consumption may increase cardiovascular risk in some individuals due to increasing TMAO levels following microbial metabolism of the compound.

The authors report the intestinal bacterial flora of people who consume **red meat**, a source of dietary carnitine, was conducive to TMAO production in the presence of carnitine, whereas ***vegetarians*** produced little to no TMAO under the same circumstances. They concluded that alterations in the intestinal microbiota associated with meat consumption may promote the formation of TMAO from dietary carnitine, and therefore suggested that the carnitine content of red meat may be one of the reasons it is linked to heart disease.

Following publication of this study, mainstream media outlets propagated misleading headlines blaming carnitine for heart disease without explaining that these findings were very preliminary and that red meat consumption was required for the observed effect. We are all aware of the potential health threats associated with red meat consumption, such as exposure to ***saturated fats*** and ***advanced glycation end products.***[3]

These deceptive media headlines have generated concern that supplemental forms of L-carnitine may be detrimental to heart health. This notion flies in the face of numerous published, peer-reviewed studies showing L-carnitine ***promotes*** cardiovascular health in a variety of ways. The media's effort to generate headlines has undermined decades of scientific research on the heart-health benefits of carnitine. At Body Language Vitamin Co and Visalus Sciences we use the best form called Acetyl-L-Carnitine, which is a very different molecule from "straight" carnitine.

New Mayo Clinic Meta-Analyses: Carnitine Improves Outcomes in Heart Attack Patients

Ironically, days after publication of the Koethe et al. carnitine article, a new **meta-analysis** of the research on **carnitine and heart health** was published by researchers from **Mayo Clinic.** This large systematic review provides strong evidence for carnitine's benefits in heart health. This article examined 13

controlled trials that enrolled, collectively, 3629 participants, representing the largest, most powerful scientific review of carnitine's cardiovascular benefits to date.

The authors the Mayo Clinic study found carnitine supplementation was ***associated with a 27% reduction in all-cause mortality,*** a ***65% reduction in ventricular arrhythmias,*** and a ***40% reduction in angina symptoms in patients who had experienced a heart attack.*** These effects were thought to occur through multiple mechanisms, including improved energy metabolism in the mitochondria, decreased ischemia, and enhanced left ventricle function.

The authors describe carnitine (***remember that Acetyl-L-Carnitine is a much better compound and better supports brain, muscle, nerve and mitochondrial function***). as an inexpensive therapy with an ***"excellent safety profile"*** which could potentially be used in patients with angina or who are at risk for angina after suffering from a heart attack. Based on the results of this meta-analysis, the authors suggest L-carnitine as a potential future therapy for heart attack and secondary coronary prevention and treatment, including angina. The scientists state ***"Further study with large randomized controlled trials of this inexpensive and safe therapy in the modern era is warranted."*** Unfortunately they also note: ***"However, a large trial may never be performed because L-carnitine is an over-the counter supplement available to the public, which decreases the potential revenue compared with a synthesized [pharmaceutical] product."***

Carnitine's benefits are well established. The next several paragraphs describe some of the key health benefits associated with carnitine.

Carnitine Reduces Death Rates

The heart muscle uses fat as its primary energy source. Carnitine is a fat-transporting compound that is absolutely essential for normal heart function.[4] Over time, the decline of carnitine plays a role in the weakening of the heart's muscles.[5]

People with heart muscle damage due to heart attacks or heart failure have especially low carnitine levels.[6-8] Fortunately, carnitine supplementation has proven to be remarkably effective in fighting and even reversing the heart-weakening effects of that drop in carnitine levels.[5]

In one study, 160 male and female heart attack survivors between 39 and 86 years old received either **4 grams/day** of L-carnitine or a placebo for 12 months.[9] The patients taking L-carnitine experienced significantly favorable decreases in heart

rate and blood pressure; they also had improved blood lipid profiles. Most importantly, those supplementing with carnitine had a dramatically reduced **death rate** compared to those not taking carnitine. ***Patients taking carnitine had a death rate of just 1.2% in the entire year, while 12.5% of control patients died, with the majority of deaths attributed to repeat heart attacks***.[9]

L-carnitine supplementation also prevents the progression of heart muscle damage in people with congestive heart failure and improves exercise tolerance in people who develop chest pain (angina) with exertion.[6] In one study, ***55% of patients experienced improvement in their standard heart failure classification***.[6]

People with angina, an early sign of impaired blood flow (ischemia) to the heart muscle, benefited from carnitine supplements. A natural carnitine derivative (propionyl-L-carnitine), at a dose of 500 mg 3 times daily***, increased the average time patients could exercise without EKG signs of ischemia by an impressive 450%***.[16] That result indicated improved blood flow to heart muscle cells following ischemia, an effect amply demonstrated in animal studies.[10,11]

Carnitine also increases concentrations of nitric oxide, which helps endothelial cells relax and increase blood flow, an effect that can help lower blood pressure.[12-14] Three weeks of supplementation with **2 grams** of L-carnitine improved blood flow by 17% during the critical after-meal period in a group of people fed a high-fat meal; placebo patients had a 12% decrease in blood flow.[15] And a daily 6-gram intravenous dose of propionyl-L-carnitine for one week improved walking distance in people with peripheral arterial disease by 28%.[16]

Carnitine Fights Diabesity

As ***obesity*** rates skyrocket, more and more Americans are developing **type II diabetes** as a result, producing a syndrome called "diabesity."[17,18]

Since carnitine helps the mitochondria utilize energy, it plays a critical role in reducing the occurrence and impact of diabesity.[19] Recent studies show that in addition to helping the mitochondria burn fat as energy, carnitine is also vital for removing waste products from mitochondria.[20,21] This is important, because we now recognize that the buildup of mitochondrial waste products is one of the most important contributors to insulin resistance, which further promotes high blood sugar and obesity.[22]

Obesity and aging contribute to low carnitine levels, which compromises mitochondrial performance and increases insulin resistance, promoting further obesity and carnitine reduction. Restoring carnitine levels to their youthful values is an effective way to break this deadly cycle.[20]

Human volunteers who took L-carnitine **3 grams/day** for 10 days had favorable changes in body composition.[23] ***Supplemented patients used their fat for energy, burning it 22% faster than control patients, without any increase in muscle protein breakdown***. Another study, ***using 2 grams/day for 6 months, demonstrated a loss of total fat mass of 4 pounds, with a gain in lean muscle mass of 8.4*** **pounds**.[24]

Animal studies confirm and extend these findings, showing that propionyl-L-carnitine decreases body weight gain, food intake, and fat composition, while improving insulin resistance.[19]

Carnitine also has multiple favorable effects on blood sugar and insulin resistance, the hallmarks of type II diabetes.[21] Animals fed a high fat diet develop the same symptoms and signs that humans do: obesity, insulin resistance, abnormal lipid profiles, and liver damage, which are known as ***metabolic syndrome***. Just 4 weeks of treatment with L-carnitine reversed all of those abnormal parameters.[17,25-27]

Similar effects have been found in diabetic humans. **Two grams of L-carnitine** twice daily for 10 days ***improved insulin sensitivity and reduced insulin levels***.[28] L-carnitine supplementation of **2 grams/day** caused a significant reduction in plasma free fatty acids, which contribute to insulin resistance.[29] **Three grams/day** were shown to ***reduce simulated after-meal blood sugar spikes from 157 mg/dL to 132 mg/dL (oral glucose tolerance test***).[30] A significant number of studies document the deadly impact of elevated ***after-meal*** glucose levels.

Carnitine Protects Against Heart Disease

Research suggests that a specific form of carnitine, called acetyl-L-carnitine (ALC), plays an important role in protecting the function and health of endothelial cells.[31-33] Studies also indicate that ALC may act as a nutritional corrective agent, relieving clinical symptoms of cardiovascular conditions such as peripheral arterial disease, angina, coronary artery disease, cardiomyopathy, intermittent claudication, ischemic heart disease, atherosclerosis, and congestive heart failure.[34-41] ALC appears to be more potent than L-carnitine in improving vascular function.[42]

ALC passes across the mitochondrial membrane to supply L-carnitine directly to the mitochondria, the energy-producing organelles of all cells. This is important because heart muscle cells and endothelial cells burn fatty acids rather than glucose for 70% of their energy. By contrast, most cells generate 70% of their energy from glucose and only 30% from fatty acids.[43]

Carnitine deficiency has been associated with congestive heart failure.50 ALC supplementation has been reported to increase exercise capacity, optimize energy production, and reduce ventricular size in patients with congestive heart failure.[37]

The myocardium, the muscular substance of the heart, comprises cells called cardiomyocytes. A study of cardiomyocytes found that ALC helped to correct an imbalance between the production and utilization of adenosine triphosphate (ATP), the energy currency used throughout the body. This suggests that ALC may improve cardiac performance by improving energy metabolism and optimizing ATP levels.[44]

An animal study suggests ALC may help to prevent or decrease the severity of atherosclerosis. In rabbits fed a high-cholesterol diet, which normally induces endothelial dysfunction and subsequent atherosclerosis, supplementation with ALC resulted in reduced plaque thickness, markedly lower triglyceride levels, and reduced proliferation of foam cells, thereby preventing the progression of atherosclerosis.[40]

PLC (propionyl l carnitine) has been shown to have a protective role against vascular cell inflammation that other carnitines do not. When rodents were exposed to irritating chemicals, PLC protected their vascular cells from this source of damage, but L-carnitine and acetyl-L-carnitine did not, leading the study authors to support "a specific protective role of PLC in the vascular component of the inflammatory process."[32]

PLC improves endothelial function by increasing nitric oxide production in animals with normal blood pressure and in animal models of hypertension. The increased nitric oxide production induced by PLC is related to its antioxidant properties; PLC reduces reactive oxygen species and increases nitric oxide production in the endothelium in the presence of superoxide dismutase (SOD) and catalase.[45]

Oxygen-deprived endothelial cells produce large amounts of free radicals. Laboratory findings suggest that PLC protects these cells during periods of oxygen

deprivation. When blood flow is restored, PLC also allows the cells to regain their lost energy charge much faster.[33]

An animal study indicates that PLC prevents abnormal heart muscle function associated with diabetes. The researchers found that PLC significantly increased both fatty acid and glucose utilization while restoring cardiac muscle function. These findings suggest PLC prevents diminished cardiac function associated with diabetes, possibly by promoting a favorable shift in glucose and fatty acid metabolism.[46]

The totality of these numerous studies contradicts the report that carnitine in red meat diets increases atherosclerosis risk.

Summary Examination of the Media-Hyped Carnitine Article Exposes Several Problems

Despite the media attention given to the study published in *Nature Medicine* by Koeth et al., caution must be used when applying the results to cardiovascular risk. Life Extension® has carefully examined this study and identified the following factors with this study that are summarized below.

1) **Limited research on TMAO and associated effects on human health prevents causal interpretation at this time**. A search of the peer-reviewed literature using terms "TMAO" and "atherosclerosis" yields *only* 3 results, with the first suggestion of a potential association in 2011.[47] Correlation is not causation, and in fact, TMAO is found in relatively large quantities in fish, a food that is linked to a markedly reduced risk of cardiovascular events. In contrast, components of red meat such as saturated fat raise LDL cholesterol, and a search of the peer-reviewed literature using the terms "LDL", "cholesterol", and "atherosclerosis" returns over 10,500 results.

2) **Only 10 human subjects were examined in carnitine supplementation substudy.** The researchers used only 10 subjects in their small substudy of carnitine supplementation and TMAO levels. This is a very small data set with which to make such sweeping conclusions. Since so few humans were directly examined in this context, the validity and applicability of the scientists' findings are questionable at best.

3) **Published, peer-reviewed research demonstrates L-carnitine prevents the progression of atherosclerotic lesions.** The study by Koeth et al. focused upon the metabolic conversion of L-carnitine to TMAO by gut bacteria, and the differences in the gut microbiome between red meat eaters and vegetarians. In fact, many studies show that L-carnitine has a variety of beneficial effects upon cardiovascular function, including prevention of the progression of atherosclerotic lesions. For example, one study reported that in the context of hypercholesterolemia, L-carnitine supplementation *"completely prevented the progression of atherosclerotic lesions induced by hypercholesterolaemia in both aorta and coronaries."*[48] In another study, supplementation with propionyl-L-carnitine (PLC), a derivative of carnitine used as a drug in Europe for treatment of atherosclerosis, *"induced a marked lowering of plasma triglycerides, very low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL) triglycerides…"* while plasma cholesterol was slightly and transiently reduced. In addition, PLC treatment *"…exhibited a reduction of plaque thickness and extent…and a reduction of the number of both proliferating macrophage- and smooth muscle cell-derived foam cells."*[40] Foam cells are precursors to atherosclerotic lesions.

4) **Published, peer-reviewed evidence shows L-carnitine effectively treats peripheral artery disease caused by atherosclerosis.** Intermittent claudication (IC) is a painful, atherosclerotic syndrome that is known to be caused by peripheral artery disease.[49] A 2013 systematic review of 40 articles on IC found that L-carnitine demonstrates a benefit in functional performance with carnitine supplementation. The authors suggest routine supplementation with carnitine *"may therefore be a useful adjunct therapy for management of intermittent claudication."*[50]

5) **Heavy red meat consumption is a known, well-validated risk factor for atherosclerosis in contrast to plant-based diets.** In the study by Koeth et al., L-carnitine alone did not raise TMAO levels – the increases in TMAO were observed when L-carnitine was exposed to the bacterial gut microbiome of red meat eaters in comparison with vegetarians' gut microbiome. Extrapolation of these preliminary test results involving the gut microbiome in heavy red meat eaters is not representative of health conscious individuals who typically limit red meat consumption given the known adverse health effects associated with a diet rich in red meat.

5) **Heart-healthy salmon is associated with high TMAO levels.** Consistency of association is critical in order to draw conclusions from study data across the published literature**.** The fact that heart-healthy fish consumption is associated with an increase in TMAO levels is challenging to reconcile with the idea that TMAO necessarily causes atherosclerosis. For example, Lloyd et al[51] reported that consumption of salmon, a food known for cardiovascular health benefits, led to an increase in TMAO levels in human test subjects. In another study, it was also observed that TMAO levels increased in individuals consuming large amounts of seafood products.[52]

6) **Carnitine decreases LDL and VLDL cholesterol, *established risk factors* for cardiovascular disease.** *Unlike TMAO,* LDL and VLDL cholesterol blood levels are widely recognized risk factors for cardiovascular disease. Carnitine supplementation has been shown to reduce both LDL and VLDL cholesterol levels.[2]

7) **The gut microbiome of red meat eaters is different from vegetarians.** In this study vegans had almost no increase in TMAO levels. It was suggested that this was due to a different gut microbiota that develops in vegetarians compared to omnivores. Health conscious people have long known of the potential adverse effects of diets rich in red meat given the multiple cardiovascular risks associated with ingestion of red meat.

8) **Probiotic supplementation may modulate gut microbiota and suppress formation of TMAO.** Not all gut bacteria strongly generate TMAO. On the contrary, certain strains of commensal bacteria have been shown to manipulate the gut microbiome in a manner favorable to human health. Specifically, members of the *Lactobacilli* species were inversely associated with TMAO in the human subjects examined by Koeth, et al. Also, *Lactobacilli spp.* have been shown to increase the ratio of genus *Bacteroidetes* to genus *Firmicutes* in the human intestine following oral administration; this is important because many species of the *Firmicutes* genus were shown to produce TMAO by Koeth et al (though the associations were not consistent across all species of *Firmicutes* tested).[53] In addition, Koeth et al showed that antibiotics, by suppressing intestinal bacterial colonization, virtually abolished TMAO formation. While antibiotic prophylaxis is not an ideal method for reducing TMAO formation since it also eliminates beneficial intestinal bacteria, evidence suggests that certain members of the probiotic species *Bifidobacterium* and *Lactobacilli*

may generate antibiotic-like metabolic byproducts called short-chain fatty acids that modify the intestinal microbiota in a favorable way.[54]

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