EDITORIAL

ROLE OF CARNITINE IN MYOCARDIAL ENERGY METABOLISM AND ATHEROSCLEROSIS: A DOUBLE EDGED SWORD?

L Carnitine is a trimethyl amino quaternary ammonium compound synthesized in thehuman body (1.2 micro mol/kg of body weight) from amino acid lysine with the help of methionine as well as ferrous and ascorbic acid. This synthesis occurs primarily in the liver and to some extent in kidneys.[1] The major exogenous source of L Carnitine is red meat, especially beef, which contains large amount of L Carnitine (95 mg/kg of beef). Approximately 2.4 million tons of red meat is yearly consumed in Pakistan including 1.4 million tons of beef and veal (58.3%). India, which is largely a vegetarian population, consumes large amount of red meat other than beef. In the USA, in 2010, 53million tons of red meat was consumed including 12 million tons of beef & veal (22.6% of total red meat consumption). The world consumption of red meat in the year 2010 was estimated at 159million tons including 56 million tons of beef and veal (35%).

Physiological Role of L Carnitine

L Carnitine plays an essential role in the provision of energy for myocardialcontraction and other metabolic functions. The myocardium as well as skeletal muscles acquire energy for contraction and other metabolic functions though the Kreb's citric acid cycle in the matrix of the mitochondria from long chain (>12 carbon atoms)free fatty acids (FFA).[1] The matrix of the mitochondria is a space enclosed by the inner and outer mitochondrial membranes. The product of catabolism of the long chain free fatty acids (FFA) need L-Carnitine to be transported through the cytosol across the inner mitochondrial membrane in order to become available for beta oxidation so that it can join the Kreb's citric acid cycle to produce ATP. Beta oxidation is the process of free fatty acids catabolism to produce acetyl coenzyme A(ACCA). "Carnitine Shuttle" (the process of transportation of long chain FFA and its product Acetyl coenzyme A by L Carnitine), is thus essential to make available Acetyl CoA to Kreb's citric acid cycle for production of ATP (Energy). The ATP yield for every cycle is 14. Keeping in viewthe physiological role of L Carnitine as an essential nutrient in red meat, a definite intake is certainly needed.[1]

Therapeutic Effects

During myocardial ischemia of 30 minutes, myocardial Carnitine levels decrease by about 50% thus causing a significant reduction of ACCA and Beta-oxidation with resultant deprivation of ATP production & acute reduction in myocardial contraction of the affected segments. Failure of transport of FFA leads to accumulation of these highly arrhythmogenic molecules (fatty esters) in the cytosol leading to decreased threshold for ventricular arrhythmias.[2,3]

Given the important role of L Carnitine, several studies have been performed to evaluate the role of L Carnitine supplementation in acute myocardial infarction (MI).[2,3] A recently published meta-analysis of 13 studies comprising 3629 patients with MI showed a significant reduction in Mortality [27%; number needed to treat (NNT) 38)] and occurrence of ventricular arrhythmias (40%;NNT 4) with the use of L Carnitine (compared to placebo) at a mean follow up of two months. No difference was found in the incidence of heart failure or reinfarction. This study although labeled as secondary prevention study is infact establishesthe therapeutic effect of L Carnitine in patients with acute ischemic myocardial injury. The dosage, route of administration, duration of therapy and the exact time of start of therapy are all in the gray zone and no clear answer is available at this time.[2,3]

L Carnitine and atherosclerosis

Gut flora forms part of microbiom of human body, 99% of gut bacteria are anaerobes but aerobic bacteria predominate in the cecum.[4-6] The total mass of the microbiom is estimated to be more than 10 times of human body cells and 100 times of the human genome. Wu et al found that long term dietary intake habits strongly correlate with gut flora types.[6] The Bacteriodes entero types are highly associated with dietary content of animal proteins (25%) Amino acid& saturated fat intake (38%). The Prevotella entero types in contrast predominate when dietary carbohydrates, simple sugars intake is high (69%) fat (16.1) proteins (8.1%). Diet rich in L Carnitine and choline (red meat & egg yolk) are converted by gut entero type (Acino Bacter & Bacteriodes) into trimethyl amine (TMR) which after absorption is converted to trimethylamine-N-oxide (TMAO) in the liver.

The relationship of TMAO blood levels with cardiovascular adverse events (CVE) has been studied in multiple studies. In on such study, comprising 4007 patients with at least one vessel CAD, followed for 3 years.[5] Participants who had CVE had significantly higher prevalence of baseline risk factors including diabetes, hypertension, dyslipidemia and smoking compared to those without CVE. More importantly, participants who had experienced CVE

had higher levels of TMAO (lowest quartile vs. high quartile Hazard Ratio 2.54, 95% C.I, 1.96-3.28 (P<.001). After adjustment for traditional risk factors and other base line covariates, elevated TMAO levels remained a significant predictor of major adverse CVE. Furthermore, higher blood levels of L Carnitine are associated withadverse CVE & atherosclerosis, only when TMAO levels are also elevated.[5]

The mechanism of TMAO enhancement of atherosclerosis has been worked out on its effect on inhibition of reverse cholesterol transport (RCT) and enhancement of macrophageuptake of LDL cholesterol by increasing CD 36 and SRA cell surface scavenger receptorexpression, both of these being proatherogenic, thusfacilitating foam cell formation and plaque increment.[5]

Reconciling the role of L Carnitine

The above basic facts substantiated by clinical studies, although very preliminary in nature, present aninitial fragmented set of inconclusive evidence to consider the measurement of TMAO in lowrisk individuals with CAD as well as high risk persons for considering primary or secondaryprevention. The atherogenic effects of TMAO are well documented, however further studies are needed to clarify if adverse coronary events will be reduced by decreasing levels of TMAO either by dietary intervention or specific inhibitors. The role of TMAO as a risk factor in an otherwise low risk population will have to be tested in population studies. In persons with otherwise low risk profile but high TMAO levels, dietarymodification (red meat & egg yolk avoidance) should be considered. As the role of antibiotics on gut bacteria and thus TMAO blood levels is only for a short duration of time, dietary intervention is certainly needed for long term effects.Lowering of TMAOand its clinical benefits will certainly need further studies.

The long term use of L Carnitine supplementation for secondary prevention at this time cannot be recommended. However, short term use to prevent arrhythmias as wellas early mortality will need to be considered when proper dosage, time of start of therapy &duration of therapy is ascertained in a large well designed clinical trial.

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