Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 808–814

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

VIEWPOINT

Carnitine therapy for the treatment of metabolic syndrome and cardiovascular disease: Evidence and controversies

A.M. Johri [a,*], D.K. Heyland [b], M.-F. Hétu [a], B. Crawford [a], J.D. Spence [c]

[a] Department of Medicine, Division of Cardiology, Cardiovascular Imaging Network at Queen's University, Kingston, ON, Canada
[b] Department of Medicine, Division of Community Health and Epidemiology, and Clinical Evaluation Research Unit at Queen's University, Kingston, ON, Canada
[c] Robarts Research Institute and University of Western Ontario, London, ON, Canada

Received 19 December 2013; received in revised form 19 March 2014; accepted 25 March 2014
Available online 3 April 2014

KEYWORDS
Metabolic syndrome;
Diabetes;
Atherosclerosis;
Cardiovascular disease;
Coronary artery disease;
Plaque;
L-Carnitine

Abstract As the incidence of metabolic syndrome increases, there is also a growing interest in finding safe and inexpensive treatments to help lower associated risk factors. L-carntine, a natural dietary supplement with the potential to ameliorate atherosclerosis, has been the subject of recent investigation and controversy. A majority of studies have shown benefit of L-C supplementation in the metabolic syndrome or cardiovascular risk factors. However, recent work has suggested that dietary L-C may accelerate atherosclerosis via gut microbiota metabolites, complicating the role of L-C supplementation in health.

Introduction

Central obesity and insulin resistance are the main contributors to the metabolic syndrome (MetS); a clustering of cardiovascular risk factors including diabetes, hypertension, elevated triglycerides, increased low-density lipoprotein (LDL) cholesterol, and increased waist circumference, associated with progressive atherosclerotic disease [1,2]. This syndrome is now considered the driving force of the new cardiovascular disease (CVD) epidemic worldwide. [3] The underlying mechanisms are unknown and specific pharmacologic agents are not yet available, with current therapies targeted to the individual components of the syndrome [4]. Given the continued growth of this condition, the development of novel therapies capable of reducing associated CVD risk is of considerable importance [5]. L-carnitine (L-C) is a dietary amino acid derivative that participates in energy metabolism and has been investigated for its potential ability to ameliorate components of MetS and CVD.

In this narrative review, we summarize the studies that have shown benefit or harm associated with L-C supplementation, in both animals and humans, in relation to MetS, CVD, and atherosclerosis. We also briefly address the pharmacology of L-C and its use in nutritional deficiency and athletic performance enhancement.

Pharmacology

L-C is a natural constituent of human cells [6] and participates in fatty acid metabolism [7]. L-C is synthesized from lysine and methionine in addition to being available from dietary sources such as meat, poultry, and dairy sources. In the body, carnitine exists as the biologically active L-

* Corresponding author. Queen's University, Department of Medicine, 76 Stuart Street, FAPC 3, Kingston, ON, Canada K7L 2V7.
E-mail address: amerschedule@gmail.com (A.M. Johri).

0939-4753/$ - see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.numecd.2014.03.007

List of abbreviations

ALC	acetyl-L-carnitine
AMI	myocardial infarction
BP	blood pressure
CAD	coronary artery disease
CIMT	carotid intima–media thickness
CPTI and CPTII	carnitine palmitoyltransferase I and II
CRAT	carnitine acetyltransferase
CVD	cardiovascular disease
FMOs	flavin monooxygenases
HDL	high-density lipoprotein
IDL	intermediate density lipoprotein
L-C	L-carnitine
LDL	low-density lipoprotein
MetS	metabolic syndrome
PAD	peripheral artery disease
PDH	pyruvate dehydrogenase
PLC	propionyl-L-carnitine
RCT	randomized clinical trial
SMC	smooth muscle cell
TMA	trimethylamine
TMAO	trimethylamine-N-oxide
VAs	ventricular arrhythmias
VLDL	very low density lipoprotein.

carnitine and the inactive stereoisomer D-carnitine [8]. The internal carnitine pool consists of free carnitines (L-C, about 80%) or acylcarnitines, which are short chain (acetyl) to long chain (palmitoyl) molecules [9]. L-Carnitine plays an important role in lipid metabolism by acting as an obligatory cofactor for oxidation of fatty acids and facilitating the transport of long-chain fatty acids (LCFAs) across the mitochondrial membrane (Fig. 1) [7]. The short ester forms, acetyl-L-carnitine (ALC) and propionyl-L-carnitine (PLC), also have therapeutic benefits. ALC stimulates glucose oxidation [10] through the enzyme carnitine acetyltransferase (CRAT) [11], which in turn regulates mitochondrial and intracellular carbon trafficking; promoting "metabolic flexibility" [12]. PLC is highly specific to skeletal and cardiac muscle [13] and plays an important role in the metabolism of carbohydrates and lipids; enhancing ATP efflux [14]. Carnitine palmitoyltransferase I and II (CPTI and CPTII) catalyse the reversible formation of L-C esters of LCFAs [15]. Defects in the corresponding genes lead to CTP enzyme deficiencies and are associated with mitochondrial LCFA oxidation disorders [16] and statin myopathy [17].

Carnitine supplements are available as L-C, PLC, and ALC, but L-C is believed to have a greater maximum plasma concentration and longer half-life than ALC and PLC [18,19]. No significant toxicity up to 2000 mg/day of L-C has been reported in humans [20–24]. Some patients complain of a fishy odour, likely due to the production of trimethylamine by intestinal bacteria as discussed below.

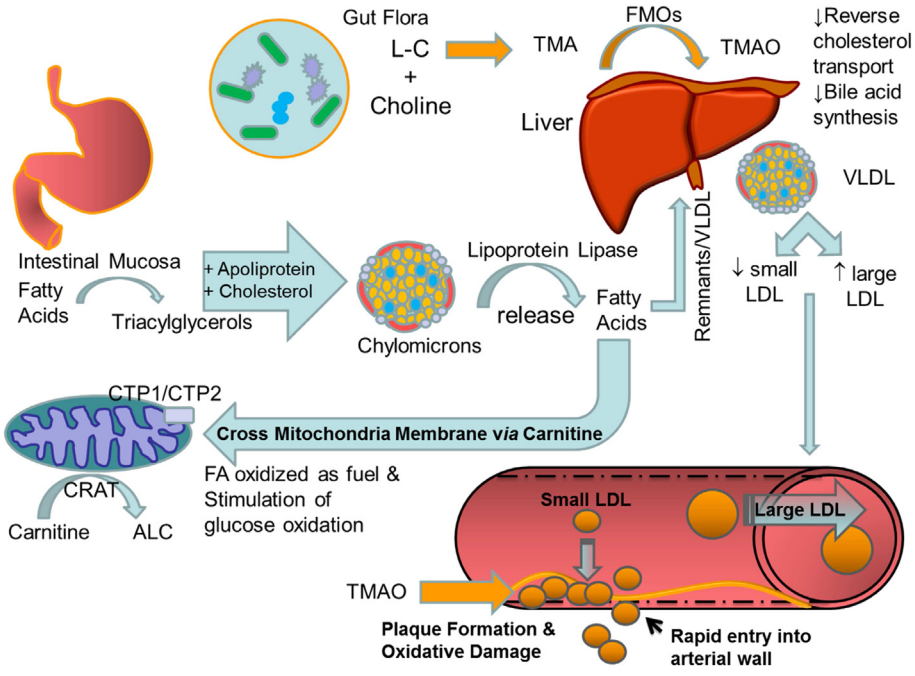

Figure 1 The transportation of LCFAs by L-C may reduce the level of fatty acid inflow for small LDL, increasing the proportion of less atherogenic large LDL, and potentially reducing plaque formation [65]. In contradiction, L-C may combine with choline and increase the release of plasma TMAO, accelerating atherosclerosis [81]. In diabetics/metabolic syndrome, carnitine may improve insulin resistance by stimulating glucose oxidation through the enzyme CRAT. Abbreviations: CPT – carnitine palmitoyltransferase; CRAT – carnitine acetyltransferase; FA – fatty acids; LDL – low-density lipoprotein; VLDL – very low density lipoprotein; TMAO – trimethylamine-N-oxide, TMA – trimethylamine; FMOs – flavin monooxygenases; (+) – combined.