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Newer Aspects of Carnitine Metabolism in Uremia

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New knowledge on the physiologic role of L-carnitine and on the rationale of its use in patients on maintenance hemodialysis is provided. In particular, carnitine normalizes plasma and muscle carnitine levels and modifies both enzymatic pattern of muscle and morphology of single fibers, improving exercise tolerance. In addition, carnitine reduces erythropoietin requirements, the number of hypotensive episodes, improves ejection fraction, and decreases hospitalization.
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Carnitine (3-hydroxy-4-N-trimethylaminobutyric acid) is a highly polar compound that is distributed widely in nature. Carnitine is present in living organisms as free carnitine and as acylcarnitines (carnitine esters) formed during cell metabolic processes involving a family of membrane-bound carnitine acyltransferases localized in mitochondria, peroxisomes, endoplasmic reticulum, and nucleus.[1] Carnitine acyltransferases (carnitine palmitoyltransferases, carnitine acetyltransferases) are important regulatory targets for fatty acid metabolism and coenzyme-A (CoA) release, and are present in tissue-specific isoforms with different kinetic properties.[2] Carnitine/acylcarnitine translocase is another crucial actor in carnitine homeostasis. Carnitine/acylcarnitine translocase exchanges mitochondrial carnitine for cytoplasmic acylcarnitines, and permits the flux of carnitine and short-chain acylcarnitines from and into the mitochondria.[3]

Carnitine and its esters enter the cell through plasma membrane carnitine transporters named *OCTN1* (low-affinity, sodium-independent carnitine transporter) and *OCTN2* (high-affinity, sodium-dependent carnitine transporter).[4] Carnitine, acylcarnitines, carnitine-dependent enzymes, and carnitine transporters constitute the carnitine system. The carnitine system has the main function to fulfill 2 cell requirements: the control of both CoA concentration and acyl moiety concentrations. This physiologic activity is at the basis[5,6] of the regulation at various stages of intermediary metabolism (Table 1).

Carnitine Deficiency

Carnitine is available from the diet, with the major sources being red meats and dairy products and is synthesized endogenously from methylated lysine residues released during protein degradation. The initial steps of synthesis are in muscle with the final step in liver, kidney, and brain. Carnitine is filtered readily by the glomerulus and 90% of free carnitine is reabsorbed in the proximal tubule, with the majority of acylcarnitine being excreted.[7]

Primary and secondary carnitine deficiencies occur when this homeostasis is perturbed. Consequences of carnitine deficiency represent a heterogeneous group of diseases with widely varying clinical symptoms, further complicated by the fact that the carnitine requirement depends on several other factors such as age, diet, metabolic conditions, and tissue dependence on fatty acid oxidation.[8] Because of the different causes of carnitine deficiencies, they are classified as primary and secondary[9,10] carnitine deficiencies (Table 2).

Carnitine Homeostasis in Uremic Patients

In healthy patients, plasma and tissue carnitine levels are maintained by saturable absorption from the gastrointestinal tract (12 μm/kg/d), endogenous synthesis (1-2 μm/kg/d), and carrier-mediated renal tubular reabsorption (renal clearance, 1-3 mL/min). Therefore, in a 24-hour period, healthy human beings who consume a normal diet excrete between

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Table 1 The Role of Carnitine Metabolism

Mitochondrial β-oxidation of medium-chain and long-chain fatty acids
Peroxisomal oxidation of very long chain fatty acids
Modulation of the mitochondrial acetyl CoA/free CoA ratio
Transfer of acetyl and other short-chain acyl groups from peroxisomes to mitochondria
Provision of acyl moieties for the endoplasmic reticulum synthesis of triacylglycerol
Phospholipid deacylation and reacylation to remodel erythrocyte membranes
Removal from the mitochondria of potentially toxic byproducts of fatty acid metabolism and eventual excretion in the urine
Synthesis and elongation of polynsaturated fatty acids
Stimulation of pyruvate and branched-chain amino acid oxidative metabolism
Production of ketone bodies

100 and 300 micromoles (μm) of total carnitine. The preferential reuptake of carnitine by the kidney is the cause of higher urinary excretion of acyl compounds. This homeostasis results in plasma carnitine concentrations of 40 to 90 μm/L, strictly equilibrated with tissue carnitine content.[11]

Therefore, the kidneys are important to help maintain normal levels of free carnitine, remove the excess short-chain acyl groups arising from fatty acid oxidation, and, consequently, maintain an appropriate acylCoA/CoA balance in the mitochondria that is necessary for normal cellular metabolism. Given the role of the kidney in carnitine synthesis and conservation, it is not surprising that alterations in the homeostasis of carnitine occur in uremic patients. In uremic patients the glomerular filtration rate is reduced, a lower amount of carnitine is reabsorbed and excreted, and the mechanism of acylcarnitine elimination is less effective as during normal kidney function.[12] Increased plasma levels of acylcarnitines have been attributed to this defect, and a direct correlation between the progression of the uremic state with increased plasma acylcarnitine and free carnitine levels has been found.[13]

Hemodialysis lacks the kidney homeostatic control mechanisms involved in the conservation of carnitine, nevertheless, it has been observed that weekly carnitine loss through hemodialysis is similar to weekly loss through a healthy kidney. Studies concluded that this means that in hemodialysis (HD) patients, carnitine input through diet and endogenous synthesis is lower than in healthy patients. A clear and progressive decrease of plasma and skeletal muscle carnitine concentration closer in magnitude to those observed in some patients with primary carnitine deficiency has been reported.[11,14-16] Consideration must be given to the possible reasons for this decrease including reduced dietary intake, impaired biosynthesis, impaired transport from the site of biosynthesis to plasma, and more efficient loss through dialytic membranes. Other factors must be considered to disrupt carnitine homeostasis in HD patients (Table 3).

Table 2 Primary and Secondary Carnitine Deficiency

Primary deficiency
OCTN2 defects
Secondary deficiency
Fatty acid oxidation defects
Carnitine system enzyme defects
Defects in the mitochondrial respiratory chain
Drug interactions
Dietary deficiency
Poor intestinal absorption (chronic malabsorption, cystic fibrosis, acute or chronic diarrhea illnesses)
Decreased renal reabsorption (hemodialysis, Fanconi syndrome)

Table 3 Factors Affecting Carnitine Homeostasis

Drugs used by HD patients
Cefasoludine, emetin, and cortisol have been shown to interfere with OCTN2 activity in in vitro studies [17]
Statins have been shown to reduce tissue carnitine levels and to increase tissue CPT activities in experimental studies[18]
Inflammation
Reduced myocardial and red blood cell CPT activity [19,20] has been found, inflammation and sepsis reduced CPT activity[21]
Poor nutritional status
Leptin resistance and insulin resistance, characterizing the poor nutritional status of the HD patient, affect CPT activity[22] and CACT activity,[23] as shown in obese patients

Abbreviation: CPT, carnitine palmitoyltransferase.

All of the earlier-described considerations lead to much information about carnitine status in healthy patients, uremic patients, and hemodialyzed patients,[12,19] which are outlined in Table 4. Of paramount importance are the data on renal clearance, on palmitoyltransferase concentration in skeletal muscle and in blood cells.

Carnitine status has been correlated strongly with many parameters in HD patients by several investigators. Positive correlations were found with dialytic age, Karnofsky scale, hematocrit level, peak exercise performance, and fiber diameter. Negative correlations were found for plasma-free carnitine with dialytic age, ejection fraction, intradialytic hypotension, and erythrocyte fragility (Table 5).

Clinical Indications for L-Carnitine in HD Patients

Dialysis-related carnitine disorder is the definition recognized by the National Kidney Foundation to identify the syndrome biochemically associated with (1) significant reduction of tissue carnitine content, (2) low plasma-free carnitine concentrations, (3) increased ratio of acylcarnitine to free carnitine; and clinically with (1) anemia hyporesponsive to erythropoietin therapy; (2) intradialytic hypotension, (3) cardiomyopathy, and (4) skeletal muscle dysfunction mani-

Table 4 Plasma and Muscle Carnitine Status in Healthy Patients, CKD Patients, and Hemodialyzed Patients

	Healthy	CKD	Hemodialyzed
Carnitine plasma concentration (m/L)	40–90	84–117	Pre-HD: 19.5 Post-HD: 5
Plasma acylcarnitine/free carnitine ratio (AC/FC)	≤0.4		>0.4
Carnitine renal clearance (mL/min)	1–3		130
Carnitine skeletal muscle concentration (m/g NCP)	19.3–27.7		9.88–12.9
Red blood cell CPT activity (nmol/min/mg protein)	0.42 ± 0.14		0.32 ± 0.17
Skeletal muscle CPT activity (nmol/min/mg protein)	1.80 ± 0.51		0.57 ± 0.28

Table 5 Positive and Negative Correlations Between Plasma Carnitine Concentrations and Functional Parameters

Positive correlations		
Plasma acylcarnitine/free carnitine ratio	versus	Months on dialysis[14-16,24]
Plasma-free carnitine levels	versus	Karnofsky functional activity scale[25] Hematocrit level[26]
Muscle total carnitine levels	versus	Peak exercise performance[27]
Plasma and muscle free carnitine levels	versus	Skeletal muscle type 1 fiber diameter[14,28]
Negative correlations		
Plasma-free carnitine levels	versus	Months on dialysis[24] Cardiothoracic index[29] Ejection fraction[30] Intradialytic hypothension[25] Erythrocyte fragility[31]
Plasma total carnitine levels	versus	Weekly maintenance recombinant human erythropoietin (RHuEPO) dose[32]
Muscle total carnitine levels	versus	Years on dialysis[27]

Table 6 Clinical Indictaions for L-Carnitine Administration in Patients on Maintenance HD

Clinical Symptoms	Rationale
Anemia	
Administration of LC is recommended for HD patients who	Reduction of EPO requirement [34]
Are unable to maintain a target hemoglobin level of [Hgb]/[Hct] (11–12 g/dL/33–36%) with use of EPO-based products	Increased hematocrit level and reduced rigidity index [35]
Require [EPO] doses >300 U/kg/wk intravenously or >200 U/kg/wk subcutaneously (or an equivalent dose of other EPO-based products), de spite adequate iron stores (transferrin saturation >20%, ferritin >100 ng/mL)	
Intradialytic hypotension	
Administration of LC is recommended for HD patients who, without clinically identifiable causes, repeatedly experience symptomatic hypotension that requires a therapeutic intervention	Reduced number of hypotensive episodes[36]
Cardiomyopathy	
Administration of LC is recommended for dialysis patients who have New York Heart Association functional class III-IV or American College of Cardiology/American Heart Association stage C-D heart failure symptoms, or symptomatic cardiomyopathy with documented impaired ejection fraction, and who have not responded adequately to standard medical therapy	Improved ejection fraction [30,37] Decreased hospitalization
Muscle weakness	
The administration of LC is recommended for selected patients with symptoms such as muscle weakness and fatigability that affect their quality of life. LC should be reserved for those patients in whom other causes have been excluded and who have been unresponsive to standard therapies	Normalization of plasma and muscle carnitine levels and modification of both the enzymatic pattern of muscle and the morphology of single fibers [14,28] Improvement of exercise tolerance[27]

Abbreviations: LC, L-carnitine; EPO, erythropoietin

fested as generalized fatigability.[33] The panel of experts, from the National Kidney Foundation, reviewed the scientific literature and developed the following clinical indications for L-carnitine administration in HD patients (Table 6).

The limited experience with the oral route of administration for L-carnitine and the bias related to it (ie, trimethylamaine production after oral administration) precludes making a recommendation for oral therapy.

The recommended dose of intravenous L-carnitine is 20 mg/kg total body weight, administered after the end of the dialysis procedure. Data from recent studies have shown that although this dosage level will lead to a supraphysiologic concentration of plasma-free carnitine, there are very few associated side effects. High plasma concentrations are advantageous to force the movement of carnitine into the target tissues in a reasonable period of time, yet, even at these doses, it may take weeks to months to replenish muscle stores of carnitine.[33]

Very recently a new aspect of carnitine activity in HD patients was reported by Savica et al,[38] who showed the capacity of L-carnitine treatment in suppressing serum C-reactive protein levels and in increasing nutritional status.

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