REVIEW

History of L-Carnitine: Implications for Renal Disease

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L-Carnitine (LC) plays an essential metabolic role that consists in transferring the long chain fatty acids (LCFAs) through the mithocondrial barrier, thus allowing their energy-yielding oxidation. Other functions of LC are protection of membrane structures, stabilizing a physiologic coenzyme-A (CoA)-sulfate hydrate/acetyl-CoA ratio, and reduction of lactate production. On the other hand, numerous observations have stressed the carnitine ability of influencing, in several ways, the control mechanisms of the vital cell cycle. Much evidence suggests that apoptosis activated by palmitate or stearate addition to cultured cells is correlated with de novo ceramide synthesis. Investigations in vitro strongly support that LC is able to inhibit the death planned, most likely by preventing sphingomyelin breakdown and consequent ceramide synthesis; this effect seems to be specific for acidic sphingomyelinase. The reduction of ceramide generation and the increase in the serum levels of insulin-like growth factor (IGF)-1, could represent 2 important mechanisms underlying the observed antiapoptotic effects of acetyl-LC. Primary carnitine deficiency is an uncommon inherited disorder, related to functional anomalies in a specific organic cation/carnitine transporter (hOCTN2). These conditions have been classified as either systemic or myopathic. Secondary forms also are recognized. These are present in patients with renal tubular disorders, in which excretion of carnitine may be excessive, and in patients on hemodialysis. A lack of carnitine in hemodialysis patients is caused by insufficient carnitine synthesis and particularly by the loss through dialytic membranes, leading, in some patients, to carnitine depletion with a relative increase in esterified forms. Many studies have shown that LC supplementation leads to improvements in several complications seen in uremic patients, including cardiac complications, impaired exercise and functional capacities, muscle symptoms, increased symptomatic intradialytic hypotension, and erythropoietin-resistant anemia, normalizing the reduced carnitine palmitoyl transferase activity in red cells.

A betaine derivative of β-hydroxybutyrate, L-carnitine (LC), was identified as a nitrogenous constituent of muscles in 1905.[1] After its identification as a growth factor for worm larvae (*Tenebrio molitor*, a parasitic bug of flour, Fig. 1) by Frankael et al,[2] the biologic role of LC was disregarded until the late 1950s, when in the laboratories of Fritz and Bremer[3] its essential metabolic function in mammals was established; it consisted in transferring the long chain fatty acids (LCFA) through the mitochondrial barrier, allowing their energy-yielding oxidation.

The fundamental role of LC in the biologic activities, which emerges from the fact that it is found in virtually all cells of higher animals and even in some micro-organisms and plants, is so important that it well deserves the name vitamin B_t, suggested by some authors.[4–7] Fatty acids constitute the lipid qualifying components, the energetic function of which is expressed just through the oxidative processes and, fundamentally, mitochondrial fatty acid β-oxidation; indeed, their elevated caloric coefficient provides about 40% of the calories of the whole demand of the human organism.[8]

Triglycerides represent almost the totality of the quickly usable fatty acids and may be consid-

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Figure 1. *T. molitor*, a parasitic bug of flour.

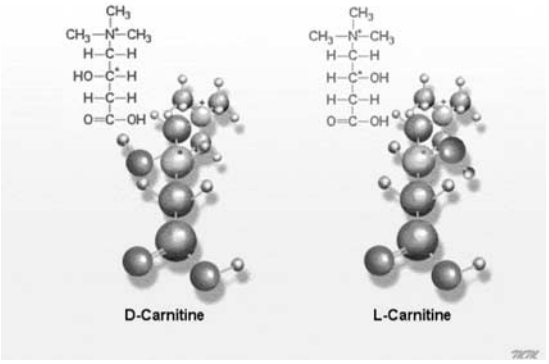

Figure 3. Carnitine enantiomers (isomeric spatially opposite compounds), called the D- and L- forms.

ered the main energetic source from which many tissues, particularly the skeletal and the cardiac muscle, draw for their activity.[9] Because the most abundant portion of triglycerides is deposited in the adipose tissue, it provides, after hydrolysis, the oxydable fatty acids to other tissues, through the hematic circle; therefore, the process starts from the lipolysis of the triglycerides, under the control of regulation systems that adjust the speed and entity of reaction to the energetic demand.[10]

Physiologic and Pharmacologic Actions

The structural formula of carnitine (β-hydroxy-γ-trimethylammonium butyrate) is shown in Figure 2. The carnitine molecule possesses an asymmetric carbon atom (ie, that binds four different groups, which can occupy reciprocally various positions), and then it can originate L and D enantiomers (isomeric pair of spatially opposite compounds; Fig. 3). As other biomolecules of chilarity, only the isomer L is active biologically, because it can interact with biologic substrata.[11]

The administration of LC to normal individuals has no appreciable effects, and oral doses of up to 15 g per day are usually well tolerated; only local adverse events could be observed, mainly constituted by gastrointestinal disturbances, as nausea, vomiting, diarrhea, and abdominal pain.[12,13] By contrast, whereas low doses of D-carnitine are lacking in action, the administration

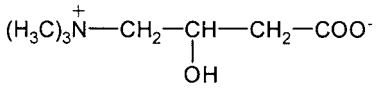

Figure 2. Structural formula of carnitine.

of raceme (D- and L-forms of carnitine; DLC) can produce a syndrome that resembles myasthenia gravis, presumably because of the inhibitory effects of the D isomer on the transport and function of LC.[14–16] In agreement with the most recent criteria of enantioselective pharmacology, only carnitine L-derivatives are useful in clinical applications.[17]

The shuttle activity of LC in the transport of LCFAs is possible because of the presence of oxidryl group (-OH), that can be contrarily esterified by various acyl radicals, and this function is very important because coenzyma-A (Co-A) fatty acid esters are formed and activated almost exclusively in the cytosol and on the surface of the mitochondrial outer membrane, but are not able to cross the membranes.[8] Hence, the oxidation of fatty acids requires the formation of acylcarnitines and their translocation into mitochondria, where the CoA esters are reformed and metabolized.

The intracellular homeostasis is controlled by different membrane transporters. Organic cation transporter function primarily consists of the elimination of cationic drugs, endogenous amines, and other xenobiotics in tissues such as the kidney, intestine, and liver. Among these molecules, LC is an endogenous amine that is an essential cofactor for mitochondrial β-oxidation. Recently, a new family of transporters, named organic cation transporters (OCT), has been described. The recent knowledge of OCT and the focus on carnitine transport, more particularly by the organic cationic transporter 2 (OCTN2), has been presented in a recent short review.[18]

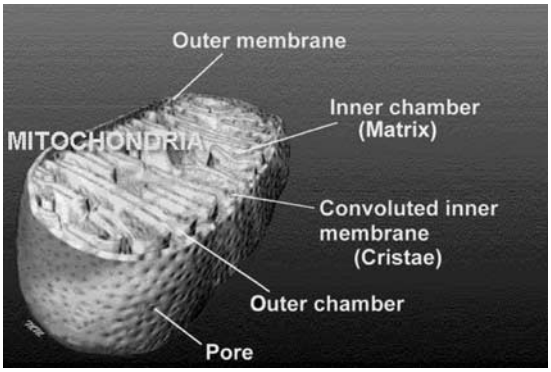

Figure 4. Mitochondria is surrounded by double highly specialized lipoprotein membranes that limit 2 separate compartments, the inner and the outer chambers.

Mitochondria and Carnitine

The recently described hydrogen hypothesis invokes metabolic symbiosis as the driving force for a symbiotic association between an anaerobic, strictly hydrogen-dependent organism (the host) and a eubacterium (the symbiont) that is able to respire, but which generates molecular hydrogen as an end-product of anaerobic metabolism.[19] The resulting protoeukaryotic cell, hypothesized by Wood[20] in nineteenth century, would have acquired the essential of eukaryotic energy metabolism, evolving aerobic respiration. Because of the high presence of enzyme systems and specific functions developed resulting in the adenosine triphosphate (ATP) synthesis, the mitochondria must be considered the real, energetic power center of the eukaryote cell.

Mitochondria are surrounded by double, highly specialized lipoprotein membranes, that delimit 2 separate compartments of crucial importance for its activity. The inner layer is subdivided into folds, called cristae, giving the mitochondria their characteristic striped appearance (Fig. 4). The material confined by the cristae (inner chamber) is termed matrix. A number of enzymes, concerned with oxidative metabolism, and the mitochondrial genome are located in the matrix. The intermembranal space, limited by the outer membrane, is called the outer chamber. A high–molecular-weight protein (porine) is distributed largely in the external layer, thus forming transport channels for molecules with a molecular weight up to 5 kD.[21,22]

The enzymes and coenzymes concerned with oxidative phosphorylation, that is, with the link between oxidative processes and the formation of high-energy phosphate bonds of ATP, are located on the inner membrane and form part of its structure. The amount of folding is a reflection of the rate of oxidative phosphorylation of which the mitochondrion is capable. The composition of mitochondrial membranes differs from that of the plasma membrane in that the protein content is about 75% (compared with about 50% for the plasma membrane). Much of the protein is in globules of 5 to 10 nm in diameter, many of which take up the whole thickness of the membrane; about 19% to 20% of the area of the membrane is composed of such protein globules. The enzyme systems concerned with the oxidative phosphorylation are attached as knobs of about 9 nm diameter to the inner surface of the cristae. The lipid of mitochondrial membranes is characterized by a high content of cardiolipin (a phosphatidic acid), in which about 80% of the fatty acid residues consist of linoleic acid.[23-26]

Little is known about the permeability of the mitochondrial membranes, but, presumably, they are freely permeable to a wide range of substrates and products of mitochondrial enzymes. However, the outer membrane is impermeable to some key intermediate compounds of mitochondrial metabolism, acetyl-CoA and other CoA-coniugates that have formed in the mitochondria.

As the fatty acid β-oxidation occurs primarily in the mitochondrial matrix, long-chain acylcarnitines generated outside of the mitochondrial inner membrane must transverse that membrane. In the matrix, the conversion of acylcarnitine to acyl-CoA will generate intramitochondrial carnitine.[10]

CoA fatty acid esters are formed almost exclusively in the cytosol and on the surface of the mitochondrial outer membrane, but are not able to cross the membranes to reach the matrix of the mithocondria. Therefore, they would remain imprisoned and would not be metabolized into the organelles.

Thus, some mechanisms must exist for fatty acid mitochondrial transport. Many observations substantiate the view that a system exists in mitochondria for the transport of carnitine and its esters and that the matrix has a pool of carnitine compounds that has access to that carnitine acyltransferase.[6,27,28]

Ramsay and Tubbs, using ox-heart mitochondria loaded with ^{14}C-carnitine, showed that in-

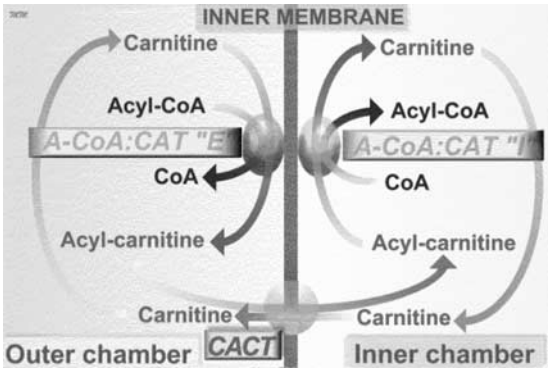

Figure 5. The mitochondrial CACT and CAT (named A-CoA, CAT) distinguished as external and internal) limit the pool of compartmentalized CoA.

cubation with extramitochondrial carnitine or acetylcarnitine increased the efflux of radioactivity without changing the mitochohdrial carnitine content. The mitochondrial carnitine-acylcarnitine translocase (CACT, Fig. 5) subsequently has been well characterized. The translocase is temperature-dependent, not energy-dependent. The carnitine–carnitine and LC-acetyl–LC exchanges involved a mole-to-mole exchange, and the reaction did not require energy. Rapid acetylation of intramitocondrial free LC occurred when acetyl-CoA was generated intramitochondrially but not with exogenous acetyl-CoA. The carnitine acylcarnitine translocase activity is unlikely to be shared by one of the carnitine acyltransferases.[29–31]

In fact, the acylation state of the mobile carnitine pool is linked to that of the limited and compartmentalized CoA pools by the action of carnitine acyltransferase family and the mitochondrial membrane transporter, CACT. There are 3 groups of transferases distinguished primarily by their substrate specificities. The trivial names for each of the groups have been in common usage but, as pointed out by Biebe,[10] the substrate specificity differs depending on the source of the carnitine acyltransferase.[32,33]

Carnitine acetyltransferase (CAT; also named A-CoA; Fig. 6) activity has been shown in mitochondria, peroxisomes, and microsomes, and the enzyme has been purified from many sources. The submitochondrial localization in mitochondria is on the inner membrane facing the matrix. The enzymes isolated from mammalian sources show a broad substrate activity that is higher with propionyl-CoA, whereas the activity with acetyl-CoA and butyryl-CoA is somewhat lower.[34–39]

Carnitine octanoyltransferase (COT), which facilitates the transport of shortened fatty acyl-CoAs from peroxisomes to mitochondria, is found in microsomes and peroxisomes associated with specific proteins that have been purified. In mitochondria, the COT activity is expressed in the intestinal mucosa of suckling rats, associated with mitochondrial CAT and carnitine palmitoyltransferase (CPT); the existence of a separate enzyme has not been shown. This acyltransferase showed maximal activity with decanoyl-CoA and myristoyl-CoA as substrates in both of them intact peroxisomes and mitochondria. In microsomes, the velocity is 10 times faster with decanoyl-CoA as a substrate, compared with palmitoyl-CoA. These very interesting observations raise questions concerning the regulation of the synthesis of acylcarnitines in both organelles.[40–43]

CPTs are key enzymes in the regulation of

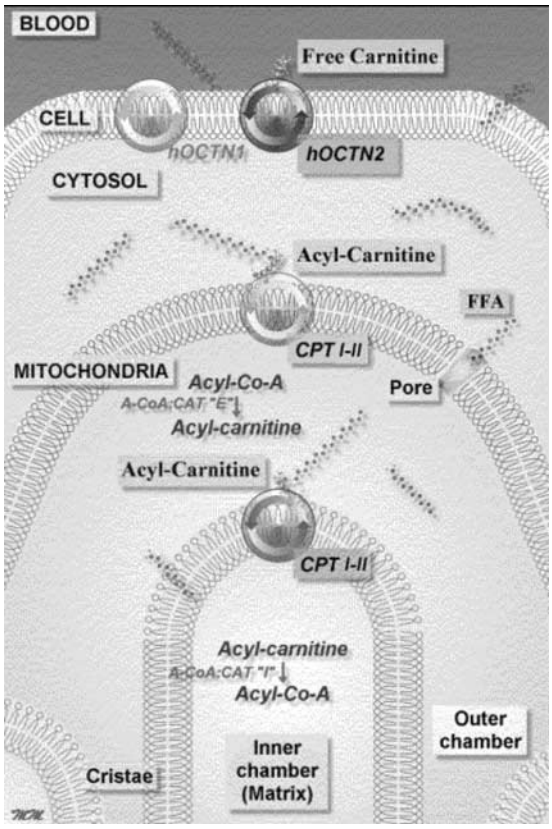

Figure 6. The whole transport system of carnitine and its esters from blood as far as the mitochondrial matrix.

intracellular long-chain fatty acyl-CoA transport from the cytosol to the mitochondrial matrix for β-oxidation, and they have been described as an exclusively mitochondrial enzyme. CPT deficiency results in a decrease rate of fatty acid β-oxidation with decreased energy production. Miyazawa et al[36] showed that CAT, COT, and CPT were immunologically different.

Two immunologically distinct CPTs have been identified: CPTs I and II. These enzymes showed broad substrate specificity with maximal activity with myristoyl-CoA and palmitoyl-CoA or with decanoyl-CoA as substrate. Because of such a complex mechanism, LCFAs can be transferred across the mitochondrial convoluted inner membrane, where β-oxidation occurs.[8] The bond formation both with LC and CoA requires the same quantity of energy (reactions thermodinamically equivalent) and, therefore, either prevalence depends on the reacting relative concentration. On the other hand, the expression of the whole transferring system also is regulated through mechanisms of gene regulation in adaptation to the availability of oxydable fatty acids: carnitine deficiency or one of the lacking enzymatic chain components, preventing the fatty acid transport, provokes their accumulation in the cytoplasm, where they are converted into triglycerides. Therefore, the congenital carnitine deficiency is responsible for the myocite fatty infiltration, proper to the muscular steatosis.[44]

The main function of mitochondria is the energy-yielding oxidation of pyruvic acid, fatty acids, and certain amino acids. The liver produces ketone bodies by oxidizing free fatty acids in acetyl-CoA, which is then converted into acetoacetate and β-hydroxybutyrate. The initial step in fatty acid oxidation is the transport of the fatty acid into the mitochondria. This involves the interconversion of CoA and LC esters of fatty acids by the acylcarnitine transferase pool. The activity of this enzyme is inhibited by intramitochondrial malonyl CoA, which is one of the products of fatty acid synthesis.

These substances first are metabolized to acetyl or other groups, which are oxidized, coenzymes being reduced and carbon dioxide liberated. The coenzymes are reoxidized, oxygen being consumed and water being formed. The energy made available from these oxidations is used in the formation of ATP from adenosine diphosphate and inorganic phosphate. In these aerobic processes, about 60 steps can be observed, compared with the 11 steps of the anaerobic process of glycolysis, but ATP is formed 5 times more abundantly per mole of glucose metabolized (ie, 30 moles per mole versus 6 in glycolysis).

The kidney plays an important role in the homeostasis of LC by its ability to reabsorb carnitine almost completely from the glomerular filtrate. The uptake process was effected from hOCTN2, a physiologically important Na(+)-dependent high-affinity carnitine transporter in humans.[45] The process was saturable, with a M_m constant of 14 ± 1 μmol/L. The Na^+:carnitine stoichiometry ratio was 1:1. The same process also was found to be responsible for the uptake of acetylcarnitine and propionylcarnitine, (2 acyl esters of carnitine with potentials for therapeutic use in humans), but not for the uptake of long-chain carnitine esters, which, therefore, may be eliminated.[46] This action appears particularly useful in the cases of congenital lack of one of the systems of acyl-CoA dehydrogenase, whereas in nephropathic patients the structural and functional alteration, not allowing the carnitine reabsorption, can induce serious carnitine deficiency.[47]

Cells contain a network of transport systems for LC that work together to maintain carnitine's concentration at its sites of action. The properties of these systems determine many of the characteristics of in vivo carnitine homeostasis and the fate of exogenous LC. The efflux and influx kinetics will determine the steady-state tissue LC content at a given plasma concentration and the kidney adaption to LC intake by reducing the efficiency of LC reabsorption. These parameters also contribute to the tissue individual turnover characteristics. Both kidney and liver have significant net carnitine efflux systems, and these compartments have turnover times 1 order of magnitude lower than the heart or skeletal muscle. The slow turnover of muscle carnitine and the effectiveness of renal reabsorption result in a slow whole-body turnover.

From the whole processes in which carnitine participates, it results that, on one hand, it sustains the energetic output through the increase of free CoA share and oxidable fatty acids in mitochondria and, on the other hand, it develops its scavenger role, handling their removal and protecting cells from possible injurious effects.[48] In addition to its role as a carrier of activated acyl groups, LC

functions as a buffer for acetyl groups that may be present in excess in different tissues during ketosis and hypoxic muscular activity. Other functions of LC concern the protection of membrane structures, stabilizing a physiologic CoA-SH/acetyl-CoA ratio and reduction of lactate production. Animal-derived feed is rich in LC, whereas plants usually contain very little or no carnitine.

It has been hypothesized that, because of its ability to enhance the rate of oxidative phosphorylation, to promote the excretion of certain organic acids, and to remove toxic metabolites during ischemia, carnitine therapy may be useful in the treatment of various cardiac diseases.[49] Also, similar to how often it happens in physical exercise, it favorably influences the fatty acid use in striated muscles and heart, and this is translated in an antihyperlipaemic action on the very low density lipoproteins (VLDL) and a chylimocron clarifying activity[50]; moreover, a higher and more rapid normolipidemic effect was obtained after using L-carnitine associated with simvastatin in regard to the separated substances.[51]

Human Requirements: Absorption, Activity, and Excretion

The need for carnitine in adults is satisfied by dietary sources and by synthesis, primarily in the liver and kidney. The primary sources of dietary compound are meat and dairy products. Dietary LC is absorbed quickly and almost completely from the small intestine, largely by active (mainly hOCTN2) and passive transport mechanisms. As active transport is saturable, a decrease in fractional carnitine absorption was observed when the oral dose of carnitine was increased. D-carnitine also is transported and can inhibit the uptake of LC. Slow movements of the drug across gastrointestinal membranes appear as flip-flop disposition kinetics after oral dosing (the half-life of the drug after oral administration ranges from 3 to 4 hours). Based on a comparison of urinary recovery data (total carnitine excretion after baseline subtraction) between humans and animals, one would expect a similar value (10% to 30%) in humans.[52,53] However, low-birthweight and preterm infants are at greatest risk for carnitine deficiency. These infants are subjected to high-fat intakes to encourage growth and may benefit from exogenous carnitine.[13,54]

Skeletal muscles constitute the main reservoir of carnitine in the body and have a carnitine concentration at least 200 times higher than blood plasma. Uptake of carnitine by skeletal muscles takes place through an active transport mechanism that transports LC into muscles probably in the form of an exchange process with γ-butyrobetain. In young animals, including foals, the capacity for biosynthesis of carnitine is not yet fully developed and apparently cannot meet the requirements of sucking animals. Therefore, sucking animals depend on an extra supply of carnitine, which usually is provided with milk. In resting skeletal muscles, about 90% of the total carnitine content is present as free carnitine with the remaining part being available as carnitine esters. With increasing exercise intensity, an increasningly greater proportion of free carnitine (up to 80%) is converted into carnitine esters, mainly into acetylcarnitine. This shift from free- to acety-LC readily is reversed within about 30 minutes after ending the exercise. It appears that acute exercise does not have a marked effect on the content of total carnitine in skeletal muscle, whereas training seems to elevate its total concentration in the middle gluteal muscle of 3- to 6-year-old horses and to reduce variation of its concentration compared with age-matched untrained horses.[47] LC is virtually not degraded in the body, and most of it is excreted in urines as acylcarnitines; because renal tubules usually reabsorb more than 90% of unesterified compound, renal excretion of carnitine is comparatively lower under normal conditions.[52]

Carnitine Biosynthesis

In animals, carnitine is synthesized almost exclusively in the liver; kidney; and, secondarily, in the brain (in which it is a specific reserve for the cerebral tissue). It is synthesized from lysine residues in various proteins, beginning with formation of 6-*N*-trimethyllysine by a sequence of reactions involving S-adenosylmethionine. Also required for its synthesis are sufficient amounts of ascorbic acid, niacin, pyridoxine, iron, and folate.[55,56]

Although carnitine deficiency can be induced by administration of a diet that is restricted to cereal grains and other vegetable sources of protein, formal nutritional requirements have not been established. Mammals meet their carnitine needs through diet and biosynthesis, and endog-

enous synthetic pathways are presumed to be sufficient to provide adequate amounts of carnitine to meet the needs of the body; however, circulating carnitine levels of strict vegetarian adults and children, and particularly infants, fed with carnitine-free formulas are significantly lower than normal.[54]

Carnitine Deficiency

Carnitine deficiency was recognized as a cause of human myopathy in 1973. Since then, several patients with progressive muscular weakness and wasting; accumulation of lipid droplets in type I muscle fibers; and low carnitine in skeletal muscle but not in plasma, liver, or heart have been described.[57,58]

Primary carnitine deficiency is most clearly observed in a group of uncommon inherited disorders. Lipid metabolism is severely affected, resulting in storage of fat in muscle and functional abnormalities of cardiac and skeletal muscle. These conditions have been classified as either systemic or myopathic. Systemic deficiency is a potentially lethal, autosomal recessive disorder characterized by cardiomyopathy, myopathy, recurrent episodes of hypoketotic hypoglycemia, hyperammonemia, and failure to thrive. It is manifested by low concentrations of carnitine in plasma, muscle, and liver. Symptoms are variable, but include muscle weakness, cardiomyopathy, abnormal hepatic function, impaired ketogenesis, and hypoglycemia during fasting. This form of carnitine deficiency is caused by a defect in the active cellular uptake of carnitine, and the gene encoding the high-affinity carnitine transporter OCTN2 recently has been shown to be altered in patients suffering from this disorder.[59]

Myopathic disease is characterized primarily by muscle weakness. Fatty infiltration of muscle fibers is observed at biopsy, and the concentration of carnitine is low; however, plasma concentrations of carnitine are normal (20 to 70 mmol/L). Several severe congenital cardiomyopathies are known to be associated with deficiencies in long-chain fatty acid transport and oxidation. It is known from studies in rats that chemical inhibition of both CPT1 isoforms results in hypertrophy of the cardiomyocytes, leading to an increase in heart weight of up to 25%.[60] Defective transport of carnitine into muscle cells coupled with faulty renal reabsorption may underlie many cases of primary carnitine deficiency.[61]

Carnitine deficiency, either primary or drug-induced, causes critical symptoms, and it is thought to even involve alteration of active transport of carnitine across the plasma membrane of tissues. The importance of the sodium-dependent carnitine cotransporter, OCTN2, comes from various recently reported mutations in the gene that give rise to the primary systemic carnitine deficiency (SCD). SCD is an autosomal recessive disorder of fatty acid oxidation characterized by skeletal myopathy, progressive cardiomyopathy, hypoglycemia, and hyperammonemia. Most of OCTN2 mutations identified in humans with SCD result in loss of carnitine transport function. The characteristics of the juvenile visceral steatosis (JVS) mouse, an animal model of SCD showing similar symptoms as humans having this genetic disorder, also are described. Although various OCTN carnitine transporters have been identified and functionally characterized, their membrane localization and regulation are still unknown and must be investigated.[62]

Patients with inborn errors of metabolism associated with increased circulating concentrations of organic acids also may become deficient in carnitine. This consequence is not surprising in view of the role of carnitine in promoting the excretion of organic acids.

Secondary forms of deficit can be correlated with severe nutritional inadequacies: vegetables are lacking in carnitine, as are cereal grains, and also may be relatively deficient in lysine and methionine, its amino acid precursors. For this reason, a rigidly vegetarian diet can be the cause of deficit conditions that will appear of greater gravity if quantitatively poor in some protein components (ie, legumes).[49] Occasionally, patients receiving total parenteral nutrition with solutions lacking in carnitine also may show biochemical and symptomatic evidence of carnitine deficiency that is reversed by supplementation. In the premature or in low-bodyweight newborn, an elevated risk of lack exists, for the increase in the lipid metabolism is necessary for growth, and a diet supplementation often is imposed.[63] Other secondary forms of carnitine deficiency also are recognized. They include patients with renal tubular disorders, in which excretion of carnitine may be excessive, and patients on hemodialysis (Fig. 7).

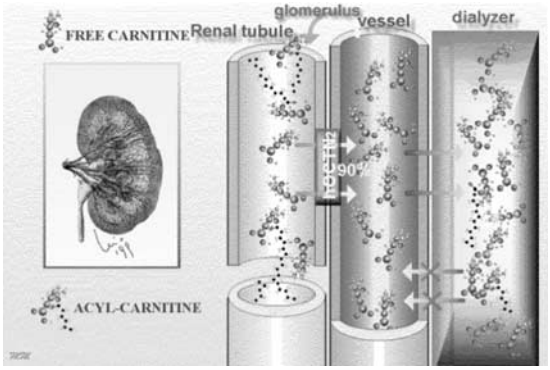

Figure 7. The kidney plays an important role in the homeostasis of LC in its ability to reabsorb it almost completely from the glomerular filtrate. Hemodialysis may promote excessive losses because of dialyzer does not allow the carnitine reabsorption.

Role of Carnitine Metabolism in Uremia

The disturbance and progressive metabolic dysfunction of the carnitine system attributable to the uremic state is not likely to worsen during dialysis treatment. Hemodialysis involves carnitine as one of the solutes capable of crossing the dialyzer membrane through osmosis, which, because of the increase in the age of the patients on dialysis, impairs the metabolic system. Indeed, older patients on dialysis present changes in the serum concentration of carnitine during dialysis treatment that are correlated with a decrease in carnitine contents, thus leading to a dysfunction of carnitine metabolism and a decreased tolerance of tissues to osmotic stress.

In the absence of dialysis therapy, the uremic patient presents greater serum concentrations of free and total carnitine, reaching values between 84 and 117 μmol/L. Long- and short-chain acylcarnitines show an increase that is directly correlated with serum creatinine and, therefore, with the progression of the uremic state. Carnitine muscular concentrations greater than those observed in the healthy subject and alterations in the lipidic metabolism are included in these situations.[64]

Dialysis therapy in uremic patients determines a decrease in both free carnitine and plasmatic acylcarnitines after only 6 months of dialysis treatment. Such concentrations are lower after only 1 dialysis treatment. After 6 months of treatment with carnitine given through intravenous injection at the end of the dialysis session, plasma concentrations of free carnitine and acylcarnitines are undoubtedly greater than the concentrations observed in healthy subjects.

Concentrations above normal can be observed immediately after the dialysis session. Therefore, during dialysis treatment, there is a loss of carnitine, but we can observe that whereas in the normal subject the acyl/free carnitine ratio is 1:5, in the dialysis patient it is 1:3 both before and after dialysis treatment. In addition to such values, we can observe in the normal subject a loss of carnitine of about 500 mg with an acyl/free carnitine ratio of 1:1 and in the dialytic patient a lower loss of carnitine of about 180 mg with an acyl/free carnitine ratio of 1:2 on a weekly basis.[65]

The special contribution of the kidney to the carnitine systemic balance is more evident when we observe subjects on a vegetarian diet characterized by very low carnitine content, which is present, on the other hand, in great abundance in an omnivorous diet (ie, a diet that includes meat). It is worth noticing that almost the same loss of carnitine can be observed in both vegetarians and uremic patients compared with carnitine dietary contents, which are undoubtedly greater in the dialysis patient. Vegetarians show a normal acyl/free carnitine ratio compared with low-carnitine diets. Quantitative and qualitative alterations in the carnitine present in urines also are noteworthy: Lacto-ovovegetarians eliminate about 180 mg of carnitine with an acyl/free carnitine ratio of 5:1, whereas vegetarians eliminate about 100 mg of carnitine with an acyl/free carnitine ratio of 34:1.[66]

It is evident that the exclusion of the kidney leads to an alteration in the acyl/free carnitine ratio, but the exclusion of the kidney does not explain the loss of carnitine, including problems concerning its synthesis, transport, and enzymes.[67] As far as the synthesis is concerned, the absence of the kidney makes the liver the main source of endogenous carnitine. The hypothesis that the liver synthesis may be inhibited or reduced has not been investigated yet. It is well known that the plasmatic concentration of ϵ-*N*-trimetyl-lisyne, as a precursor in the carnitine synthesis, is considerably greater than in the normal subject, who does not show noteworthy levels.[67]

The transportation of carnitine leads to different impairments. The increase in ϵ-*N*-trimetyl-lisyne inhibits, in a competitive way, the high-

affinity carnitine carrier, Na+-dependent OCTN2, being itself transported. In addition, even worsening its function, the same carrier is inhibited by some drugs, ie, cefsoludine, emetin, and cortisone, which are used in the therapy of the dialytic patient.[68] The metabolic effects of decreased transportation of carnitine are exemplified by gene-deleted animal models codified for OCTN2, in which hypertriglyceride levels can be observed.[69] As far as the carnitine-dependent enzymes are concerned, it has been observed that the palmitoil-transferase carnitine activity is reduced in the skeletal muscle and in the red cells of the dialysis patient.[70,71]

It is well known that patients on hemodialysis have low plasmatic carnitine concentrations, although they have a diet with a normal carnitine intake and a loss during dialysis lower than the loss of normal subjects through urinary excretion. Patients on hemodialysis treated for more than 12 months with LC intravenously have normal plasmatic values of carnitine at the end of dialysis session. Carnitine washout for 4 months induces a mild reduction of plasmatic values. The reintroduction of LC for 4 months, in the dialysate, does not increase plasmatic values.[72] The importance of such variations in plasmatic carnitine values is correlated with changes in the composition of skeletal muscle fibers. Those changes are characterized by a predominant type I fiber (oxidative) composition after a LC supplementation intravenously, whereas a predominant type II fiber (glycolytic) composition after carnitine interruption and after carnitine supplementation in dialysate is observed. For this reason, it has been concluded that, in the skeletal muscles of dialysis patients untreated with LC, the morphologic pattern of fiber types reflects a glycolytic anaerobic metabolism. A change in carnitine supplementation route, through its introduction in the dialysate to prevent the osmotic loss during the dialysis session, does not improve the ability of skeletal muscle to determine a normal intake of carnitine. Indeed, the skeletal muscle needs intravenous route administration to induce an oxidative functional phenotype.

LC Supplementation in Uremic Patients

Therapeutic effects of LC in hemodialysis patients have been evaluated in several studies.

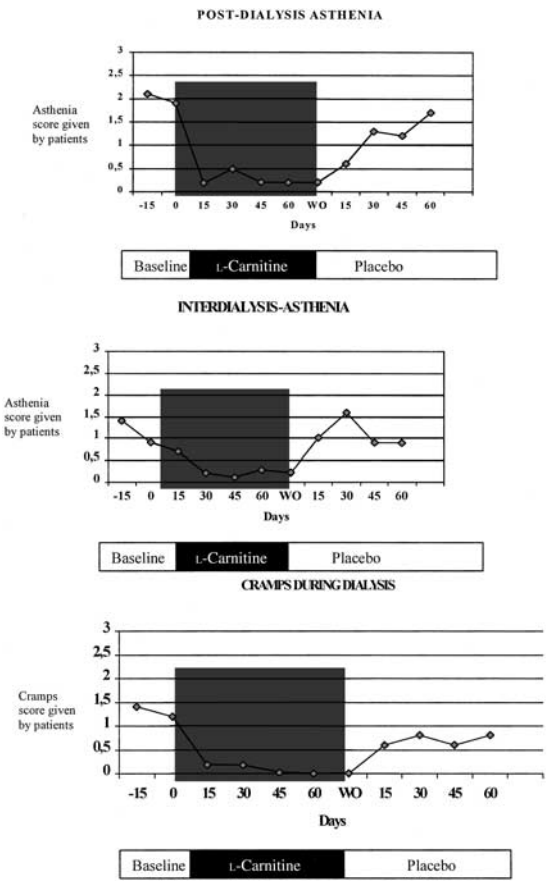

Figure 8. Asthenia and cramps in hemodialysis patients. Treatment: oral carnitine (2 g/d), placebo. (Reproduced with permission by the *American Journal of Clinical Nutrition.* © Am J Clin Nutr. American Society for Clinical Nutrition.[74])

These studies mainly show that carnitine supplementation in hemodialysis patients may improve hematologic status by increasing hematocrit or allowing a reduction of epoietin dosage; moreover, it may improve tolerance to exercise by increasing the aerobic capacity and decreasing cramp appearance and lipid abnormalities through a reduction in cholesterol and triglyceride levels.[73–84]

Exercise capacities are severely limited in hemodialysis patients. Carnitine insufficiency may contribute to impaired exercise and functional capacities in uremic patients. Our group showed a reduction of asthenia and cramps after LC treatment that was correlated with increased levels of the metabolite in blood and muscle (Fig. 8).[74]

Brass et al[75] studied the effects of exercise capacity in patients with end-stage renal disease after carnitine supplementation. In this random-

ized, placebo-controlled study, patients were assigned to receive carnitine (20 mg/kg) and placebo intravenously for 24 weeks. They showed that patients treated with carnitine showed statistically significant smaller deterioration in $V_{O_{2max}}$ ($P = .009$), and improvement of fatigue domain ($P = .03$) with the kidney disease questionnaire (KDQ).

Another study[76] evaluated the concentration of carnitine and glycogen in the skeletal muscle of patients in hemodialysis, starting from the assumption that plasmatic carnitine concentrations do not reflect the carnitine tissue content. Comparing the skeletal muscle of normal subjects, they observed 1. similar levels of total carnitine with reduced levels of free carnitine; 2. skeletal muscle of total and free-carnitine significantly reduced; 3. negative correlation between total and free skeletal muscle carnitine and increased age on dialysis; 4. no correlation between plasmatic and skeletal muscle carnitine concentration; and 5. glycogen concentration significantly higher, probably because of the changes in type of muscle fibers observed in uremic patient, lower physical activity, or both.

Matsumoto et al[77] studied the effects after 6 months of treatment with LC (15 mg/kg intravenously at the end of each dialysis session) on lipid metabolism, free radicals, and red cell count. They showed that LC treatment induced a significant reduction in plasmatic levels of total and high-density lipoprotein (HDL) cholesterol ($P < .05$); significant increase in plasmatic antioxidant ability ($P < .001$), associated with a reduction of malonyl-aldeide ($P < .001$) plasmatic concentrations; a significant reduction of intra–red cell glutation concentrations ($P < .001$); and reduced erythropoietin consumption.

Lipid abnormalities are very common in hemodialysis patients. In some studies, supplementation with carnitine showed a normalization of fatty acid profiles. Moreover, a recent meta-analysis failed to show the positive effects of carnitine supplementation on lipid abnormalities.[78] From 1978 to 1999, they analyzed data from 481 patients in 21 trials in which LC was used and examined changes in serum triglycerides and cholesterol fractions. In their conclusion, LC was not recommended for treating dyslipidemia of hemodialysis patients. Another important factor correlated with carnitine deficiency in hemodialysis patients is anemia. Many studies found that patients with lower carnitine levels required higher erythropoietin dosages and carnitine deficiency may be responsible of erythropoietin resistance.[79-82]

The effects after 3 months of treatment with LC (500 mg/d oral) on anemia were evaluated in hemodialysis patients resistant to erythropoietin treatment. The results showed an increase in hematocrit levels ($P = .003$) and total ability of iron binding ($P = .05$) together with a significant reduction of ferritin serum levels ($P = .005$).[79]

De los Reyes et al[71] studied the intra–red cell carnitine and acylcarnitine variations and CPT activity in uremic patients versus normal subjects. They found the following alterations: higher concentration of free carnitine, lower proportion of long-chain acyl-CoA versus free CoA, reduced activity of CPT and glycerophospholipid acyltransferase, and a higher long-chain acyl/free carnitine ratio. They concluded that LC treatment induced a positive effect on these parameters through an improvement of acylation and reacylation processes of red cell membrane.

A defect in sodium transport system has been shown in uremic patients, which was improved by LC supplementation. The average value of sodium efflux of dialysis patients (through the Na+/K+ oubain-sensitive pump), is significantly reduced whereas sodium content is higher and there are no differences in sodium passive permeability.[80]

Matsumura et al[81] also showed that the serum free and total carnitine levels, but not acyl-carnitine, correlate with erythrocyte osmotic fragility evaluated as a point of maximal emolysis, starting emolysis, and average of final emolysis. Moreover, both types of carnitine correlate with erythropoietin dosage. Indeed, low serum levels of free carnitine worsened the condition of erythrocyte osmotic fragility and negatively influenced the therapeutic efficacy of erythropoietin on anemia.

Nikolaos et al[82] showed that 3-month treatments with LC (30 m/kg for dialysis session) significantly reduces the red blood cell deformability ($P = .004$) and significantly increases Ht ($P = < .001$). Echocardiographic measurements of cardiac activity have been performed on dialysis patients to study the effects of chronic oral supplementation of LC; the results showed a statistically significant improvement of systolic and diastolic function of left ventricula.[83] Sakurabayashi et al[84] performed a myocardial

scintigraphy with β-methyliodophenyl pentadecaonic acid, which showed improved cardiac activity connected with reduced time of washout of β-methyliodophenyl pentadecaonic acid ($P < .05$). Recently, carnitine supplementation has been approved by the United States Food and Drug Administration not only for treatment, but also for the prevention of carnitine depletion in dialysis patients.

In conclusion, available studies on carnitine supplementation suggest the use of this molecule in dialysis, especially for those patients with cardiac complications, impaired exercise and functional capacities and caused a lack of energy affecting quality of life and increased episodes of hypotension. Moreover, in some patients, the improved stability of erythrocyte membranes may decrease erythropoietin requirements, thus leading to a reduction of dialytic costs.

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