The Role of L-Carnitine in Kidney Disease

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Kidney disease is associated with a wide variety of metabolic abnormalities that accompany the uremic state and the state of dialysis dependence. These include altered L-carnitine homeostasis, mitochondrial dysfunctions, and abnormalities in fatty acid metabolism. L-carnitine is essential for fatty acid metabolism and proper mitochondrial function. L-carnitine deficiency is also seen in acute kidney injury (AKI) resulting from trauma and/or ischemia, drugs such as cisplatin, and from infections such as covid.

acute kidney disease L-carnitine Kidney disease

1. Pathophysiology of Kidney Disease and Relationship between Carnitine Metabolism and Kidney Function

1.1. Metabolic Alterations in Kidney Disease and Potential Protective Role of L-Carnitine

Chronic kidney disease is associated not only with a wide variety of metabolic abnormalities that accompany the uremic state but also with specific changes related to the dialysis procedure. These include altered L-carnitine homeostasis, mitochondrial dysfunction, and abnormalities in fatty acid metabolism. Carnitine deficiency is common in kidney disease and dialysis. L-carnitine has been shown to be an effective adjunctive treatment for anemia, intradialytic hypotension, hyperlipidemia, and muscle weakness.

L-carnitine is an amino acid derivative naturally produced by the body and obtained from the diet, especially from red meat. Its primary function in cells is to transport long-chain fatty acids across the inner mitochondrial membrane for β-oxidation and generation of ATP energy [1][2]. L-carnitine also plays a role in transporting potentially toxic acyl molecules out of the cells and in balancing the coenzyme A (CoA) ratio within mitochondria, acting as an indirect antioxidant. Therefore, it protects cellular membranes and prevents fatty acid accumulation. L-carnitine also controls the levels of β-oxidation and the acetyl CoA/CoA ratio, which are involved in modulating ketogenesis and glucogenesis.

Kidneys are the main organs responsible for the regulation of body fluids. They balance the volume, pH, and osmolality of the extracellular fluid and regulate the amount of sodium and water excreted. The kidneys are also specifically involved in regulating L-carnitine levels by controlling the excretion and reabsorption of L-carnitine as well as the endogenous synthesis of L-carnitine. The carnitine pool results from the combination of intestinal absorption, endogenous synthesis, and high tubular reabsorption [3].

The majority of L-carnitine (90–99%) filtered in the kidney is reabsorbed in the distal parts of the nephron until saturation is reached. The renal threshold for L-carnitine excretion is around 50 µmol/L. The kidneys are very efficient in maintaining normal levels of plasma L-carnitine by modulating urinary L-carnitine excretion depending on the intake from the diet [4].

At the onset of kidney disease, the glomerular filtration rate is reduced, and due to tubular dysfunction, a lower proportion of L-carnitine is reabsorbed, and the mechanism of acylcarnitine elimination is less efficient than with normal kidney function [5][6]. Initially, carnitine levels are higher, but as kidney disease progresses, more acylcarnitine is formed in the body, especially in the muscles and kidneys, while its excretion is reduced. This results in an increase in acylcarnitine in the cells and in the blood, which can lead to cellular toxicity by altering cellular and mitochondrial functions [7]. A buildup of acylcarnitine, usually due to defective β-oxidation, can increase the level of unmetabolized long-chain fatty acids (LCFA) within the mitochondria, which exert a detrimental effect on cellular membranes and proteins possibly due to a detergent-like action on the membranes [8].

As more acylcarnitine is formed, L-carnitine is decreased resulting in a free carnitine level <40 µmol/L or an acylcarnitine/free carnitine ratio of more than 0.4 in the blood, which is a sign of L-carnitine deficiency. Numerous studies investigating these changes have established that a deteriorating renal function is associated with decreased carnitine clearance and impairment of normal excretion of acylcarnitine [9][10].

L-carnitine depletion in the body may lead to frequent complications, such as anemia hyporesponsive to erythropoietin, intradialytic hypotension, muscle weakness, and cardiac arrhythmias. L-carnitine treatment has been shown to be beneficial in these dialysis-related complications [4][5][11].

1.2. Role of the Mitochondria in Kidney Disease

Mitochondrial dysfunction has been implicated in the pathogenesis of many diseases including kidney disease. Altered mitochondrial function leads to a reduction of ATP, an increase in ROS, and an increase in acylcarnitine, which can damage cells leading to a negative impact on kidney function in acute and chronic kidney disease states [12][13][14][15][16][17].

In AKI and diabetic nephropathy, β-oxidation in the mitochondria is decreased and the formation of lipid droplets inside the cell is increased, resulting in diminished ATP production [18][19][20][21].

Mitochondrial dysfunction also plays a key role in the pathogenesis of diabetic nephropathy, which occurs in 40% of patients with diabetes. A recent study showed that in diabetic nephropathy there is downregulation of the antioxidant superoxide dismutase 2 (SOD2), whose function is to prevent the excess buildup of mitochondrial reactive oxygen species (mtROS) [22]. The increase in reactive oxygen species (ROS) can damage mitochondrial membranes and proteins, compromising mitochondrial function [23][24][25][26][27].

2. L-Carnitine in Acute Kidney Injury

AKI in adults and children is associated with conditions such as sepsis, multi-organ failure, nephrotoxins, congenital heart disease, malignancies, primary kidney disease, hypotension shock, hypoxemia, and renal ischemia. These probably contribute to the increased mortality in AKI. Several authors found that L-carnitine treatment can mitigate the negative effects of acute kidney injury in both children and adults.

In children receiving continuous kidney replacement therapy (CKRT) for AKI, intravenous L-carnitine, added to total parenteral nutrition (TPN) at a dose of 20 mg/kg/day, improved myocardial strain [28]. Another study showed that L-carnitine treatment of 50 mg/kg/d L-carnitine per day added to antibiotic regimens decreased renal scarring in children with acute pyelonephritis [29].

In adults undergoing prolonged kidney replacement therapy for AKI the plasma carnitine levels can diminish, causing metabolic disturbances and potential neurological symptoms. A recent study in patients receiving long-term tube feeding and continuous renal replacement therapy (CRRT) for more than 1 week suggested that L-carnitine supplementation at a dosage of 0.5 to 1 g/day may be beneficial in reducing neurological symptoms [30].

In patients undergoing percutaneous coronary intervention (PCI), oral L-carnitine 1 g 3 times a day, 24 h before the procedure and 2 g after PCI lowered plasma neutrophil gelatinase-associated lipocalin (NGAL) concentration, a marker for kidney damage following contrast medium administration [31].

3. Conclusion

L-carnitine may be an adjuvant therapy in dialysis patients. The administration of L-carnitine to patients suffering kidney disease may have protective effects possibly by the amelioration of the balance in metabolism such as restoring the acetyl CoA pool, and also by its effects on decreasing ROS levels in part due to the improvement in mitochondrial function.

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