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A Review: Role of Levocarnitine in Various Disease

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ABSTRACT

This article enlightens the role of levocarnitine and its use in various diseases. The objective is to study the metabolic role of levocarnitine and its mechanism and use of levocarnitine in the treatment of various conditions. The levocarnitine is a naturally occurring substance that produces energy in the cell. It transports long-chain fatty acids into the mitochondrial membrane for beta-oxidation and subsequent energy production in skeletal muscle and myocardium. Carnitine deficiency prevents the body from using certain fats for energy and causes various dysfunctions. Carnitine supplementation has a beneficial effect on metabolic syndrome, cardiovascular disease, sarcopenia, fatigue, septic shock, kidney disease, renal anemia.

INTRODUCTION:

Levocarnitine is a naturally occurring substance in which the cells of mammals produce energy. Levocarnitine is synthesized in the human body from lysine and methionine.[1] Levocarnitine processes the transport of long-chain fatty acids into the membrane of mitochondria for beta-oxidation and production of energy in the myocardium and skeletal muscle. Carnitine deficiency prevents certain fats usage in the body for energy and causes dysfunction such as cardiomyopathy, encephalopathy, cardiomegaly, sarcopenia, septic shock, hypoglycemia, confusion, and vomiting. Levocarnitine is obtained from dietary sources such as meat and dairy products. The dietary sources and levocarnitine supplementation are majorly used to treat carnitine deficiency.[2] Levocarnitine supplementation provides a beneficial effect on inflammation, oxidative stress, fatigue, and sarcopenia in the elderly and Chronic diseases such as liver cirrhosis, cancer, chronic hepatitis, type II diabetes mellitus, chronic kidney disease, chronic heart failure, and human immunodeficiency virus infection. Levocarnitine also improves the quality of life and nutritional status.[3] Levocarnitine provides antioxidant properties and anti-inflammatory and increases insulin sensitivity, protein nutrition, and membrane stability. Levocarnitine is maintained within a relatively narrow normal range which is obtained by gastrointestinal absorption from dietary sources, extensive renal tubular reabsorption, endogenous biosynthesis, carrier-mediated transport between tissue and plasma.[4] The dosing forms and strength of levocarnitine for adults and pediatrics are tablets (330 mg, 500 mg), capsule (250 mg), oral solution (1g/10 ml), and injectable solution (200 mg/ml). The mechanism of action of levocarnitine is it facilitates the transportation of long-chain fatty acid from the cytosol to the mitochondria and it provides substrates for oxidation and helps in the subsequent cellular energy production.[5]

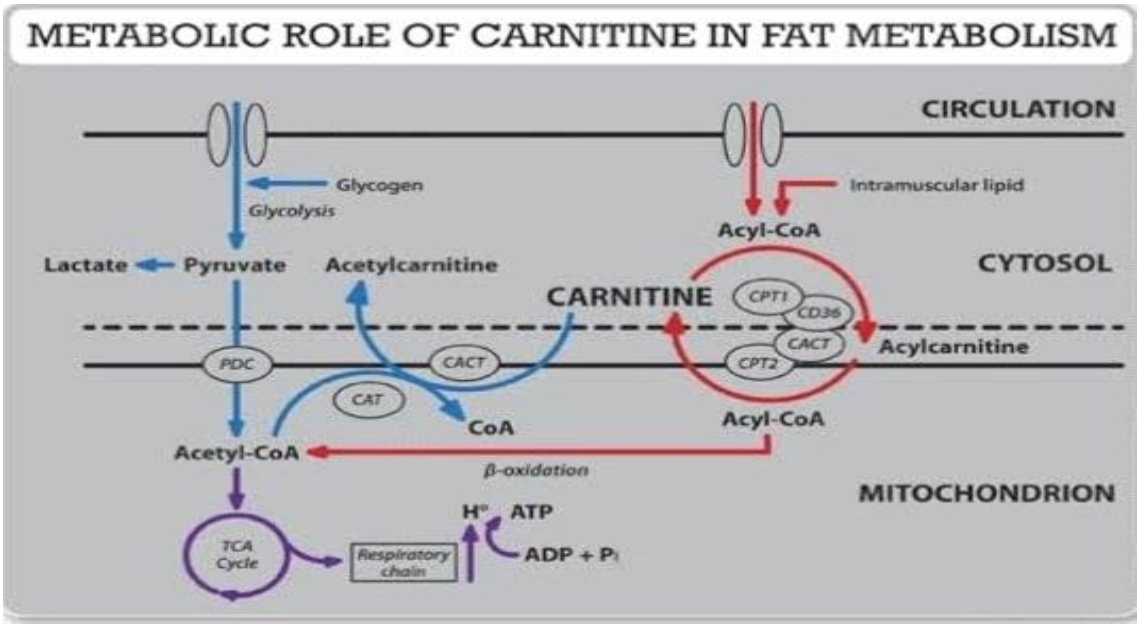

Figure 1: Carnitine facilitates the transports of long-chain fatty acids into mitochondria from the cytosol for beta-oxidation.

LEVOCARNITINE THERAPY FOR METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE:

Insulin resistance and central obesity are the main precursors for metabolic syndrome and cardiovascular risk factors such as hypertension, diabetes, atherosclerotic disease, elevated triglycerides, and increased low-density lipoprotein cholesterol. [6,7] Metabolic syndrome is now considered the major problem of the new cardiovascular disease all over the world.[8] Due to this condition, the development of novel therapies is of considerable importance in reducing cardiovascular disease risk. Levocarnitine is an amino acid derivative that helps in energy metabolism and improves metabolic syndrome and cardiovascular disease.[9] The carnitine deficiency exists in primary carnitine deficiency and secondary carnitine deficiency together with metabolic pathways.[10] The primary carnitine deficiency is due to a genetic disorder and it leads to decreased carnitine accumulation in the heart and skeletal muscle.[11] The secondary carnitine deficiency is due to metabolic disorders, liver or kidney disease, or certain drug interactions.[12] Levocarnitine supplementation has been recommended in the treatment of cardiovascular disease and acute myocardial infarction.[13] Levocarnitine improves myocardial ischemia through stimulation of glucose oxidation.[14] Levocarnitine acts as an obligatory cofactor for fatty acids oxidation and facilitating the transport of long-chain fatty acids across the mitochondrial membrane.[15] The short ester forms such as acetyl-levocarnitine and propionyl-levocarnitine have a therapeutic benefit.[16] The acetyl-

levocarnitine promotes glucose oxidation through the carnitine acetyltransferase enzyme and it regulates mitochondria and promotes metabolic flexibility. The propionyl-levocarnitine helps in the metabolism of carbohydrates and lipids and enhances adenosine-triphosphate efflux and is highly specific to skeletal and cardiac muscle. Carnitine palmitoyltransferase I and II catalyze the reversible formation of levocarnitine esters of long-chain fatty acids. Oral levocarnitine supplementation improves factors associated with metabolic syndrome and cardiovascular diseases such as arterial hypertension, impaired glucose tolerance, insulin resistance, and cholesterol level.[17]

DiNicolantonio, *et al,* conducted a meta-analysis study in 2013 with 13 controlled trials to assess the effects and outcomes of levocarnitine. The levocarnitine promotes a beneficial effect in angina, ventricular arrhythmia, and acute myocardial infarction, and reduction in mortality.[18]

LEVOCARNITINE AND ITS DERIVATIVES IN THE MANAGEMENT OF TYPE II DIABETES MELLITUS:

Type II diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia and it is associated with several complications such as neuropathy, nephropathy, retinopathy, and hyperlipidemia. The dysregulation of fatty acid metabolism and lipid accumulation leads to the development of insulin resistance and type II diabetes mellitus. The levocarnitine plays a major role in lipid accumulation and beta-oxidation of long-chain fatty acids and it also has antioxidant properties. Carnitine has a crucial role in fatty acid metabolism, and it acts as a potential adjuvant in the treatment of type II diabetes mellitus. Several studies suggest that levocarnitine plays a central role in oxidative stress in the pathogenesis of the disease.[19,20] The levocarnitine supplementation acts as a significant tool in the management of type II diabetes mellitus. Several human and animal studies show that levocarnitine supplementation has a significant effect on whole-body glucose utilization and it improves several lipid parameters as well as oxidative stress markers whereas low levels of levocarnitine are associated with various diabetic complications. Furthermore, a clinical trial proves that administration of carnitine derivatives such as acetyl-levocarnitine and propionyl-levocarnitine improves neurophysiological parameters and it reduces pain, and also reduces vascular-related symptoms in diabetic patients. Hence levocarnitine acts as a promising adjuvant in the treatment of diabetes mellitus and its complications.[21]

G Mingrone, *et al,* conducted a study in 1999 to evaluate the effects of levocarnitine on insulin-mediated glucose uptake and oxidation in type II diabetes mellitus patients and compared it with healthy individuals. It shows that administration of levocarnitine improves insulin sensitivity, glucose storage, and glucose oxidation.[22]

LEVOCARNITINE IN THE MANAGEMENT OF DILATED CARDIOMYOPATHY:

Dilated cardiomyopathy manifest as a chronic systolic heart failure which leads to arrhythmias and sudden death. During heart failure, cardiac muscle cells lead to ischemia and hypoxia, and beta-oxidation of fatty acids is suppressed. Levocarnitine improves the quality of life and prevents the progression of myocardial remodeling and thereby reducing the mortality and hospitalization rate due to heart failure.[23] Studies have shown that levocarnitine supplementation is beneficial in improving the energy metabolism in cardiac muscle cells and protects the myocardium. Levocarnitine increases the level of adenosine triphosphate through its anti-oxidation effect and helps to maintain mitochondrial membrane potential and it inhibits myocardial apoptosis through the mitochondrial pathway. The levocarnitine supplementation reduces myocardial damage, reduces the accumulation of toxic lipid metabolites, increases prostacyclin production, and thereby improves cardiac function and reduces heart failure in patients with cardiac fibrosis.[24] The supplementing levocarnitine for the conventional treatment for chronic heart failure can significantly improve cardiac function, reduce myocardial injury markers and reduce clinical adverse events without significant adverse reactions.[25,26] After supplementing conventional treatment with levocarnitine oral solution, the ejection fraction and fractional shortening were significantly improved and the left atrium and left ventricle diameters were significantly reduced. It shows that levocarnitine may enhance the therapeutic effect in dilated cardiomyopathy.[27]

Yuwen Wang, *et al,* a study was conducted in 2018 with twenty-nine children with dilated cardiomyopathy. They were divided into two groups such as control groups and experimental groups according to simple randomization. The patients in the experimental groups received additional treatment with oral levocarnitine solution. The cardiac function was significantly improved in the experimental group compared with the control group.[27]

LEVOCARNITINE IN THE MANAGEMENT OF SEPTIC SHOCK:

Sepsis leads to metabolic dysfunction. The levocarnitine decreases metabolic dysfunction by increasing fatty acid shuttling and enhancing glucose and lactate oxidation. In septic shock

patients, levocarnitine plays a major role to reduce cumulative organ failure. Sepsis is the leading cause of death and the mortality rate approach to be 40% at 28 days when a shock is present [28,29] The metabolic abnormalities in sepsis are hyperlactatemia, hyperglycemia, ketosis, and increased free fatty acids. The levocarnitine reduces metabolic effects of sepsis by enhancing fatty acid entry into the mitochondria and clearing their toxic effects from the cytosol and sequencing intramitochondrial acetate and on the pyruvate dehydrogenase complex, it leads to a decrease in the inhibitory effect of acetyl coenzyme A. Therefore, levocarnitine is used for the management of septic shock. [30,31]

Alan E. Jones, *et al,* A double-blinded, parallel-group randomized clinical trial was conducted in 2018. They randomized 250 patients with septic shock and moderate organ dysfunction for the treatment of levocarnitine. The levocarnitine administration shows a beneficial effect in the management of septic shock.[32]

LEVOCARNITINE IN THE MANAGEMENT OF SARCOPENIA:

Sarcopenia is due to the loss of skeletal muscle strength and mass. Sarcopenia is common in patients with liver cirrhosis.[33] The levocarnitine supplementation has a positive effect on sarcopenia in the elderly. A Sarcopenia develops due to either reduction in protein synthesis and an increase in proteolysis or even both. The mechanism of sarcopenia in liver cirrhosis patients is dependent on several factors and can include hyperammonemia, low levels of branched-chain amino acids, low testosterone, low growth hormone, and high levels of inflammatory cytokines. The hyperammonemia in skeletal muscle causes transcriptional upregulation of myostatin and increases autophagy. The levocarnitine is proven to have a protective effect against hepatic encephalopathy and it is also proven to be an ammonia-lowering therapy and improves skeletal function. And it shows that administration of levocarnitine significantly reduced serum ammonium levels. Therefore, levocarnitine supplementation significantly decreases ammonia levels and a significant increase in muscle mass. The administration of levocarnitine seems to suppress the progression of sarcopenia and in the improvement of hyperammonemia in patients and used in the management of sarcopenia.[34]

Akira Hiramatsu, *et al,* A retrospective study was conducted in 2019, they evaluated 52 patients with liver cirrhosis and treated them with levocarnitine for more than 3 months between February 2013 and June 2017. It shows the relative changes in skeletal muscle index

in each patient. The administration of levocarnitine leads to a significant and gradual reduction in serum ammonia levels and improves muscle mass and strength.[34]

LEVOCARNITINE IN THE MANAGEMENT OF CHRONIC HEART FAILURE:

Chronic heart failure is a complex clinical syndrome that is characterized by decreased contraction of the myocardium, hemodynamic abnormality, and activation of the neuroendocrine.[35] The growing evidence shows that a high concentration of levocarnitine provides beneficial effects in various diseases such as congestive heart failure, peripheral vascular diseases, coronary artery disease, type II diabetes mellitus, dyslipidemia, and hypertension.[36] The levocarnitine acts as a safe and effective adjuvant therapy by increasing high energy phosphate for systolic and diastolic function and shows a synergistic effect with other drugs. The levocarnitine treatment acts as a good tolerance and it is effective for chronic heart failure in improving cardiac functions and clinical symptoms and thereby decreasing serum levels of B-type natriuretic peptide and Non-active prohormone B-type natriuretic peptide.[37]

Xialong song, *et al,* conducted a randomized controlled trial in 2017 with 1625 chronic heart failure patients. Levocarnitine shows an overall improvement in efficacy, left ventricular ejection fraction, stroke volume, cardiac output and resulted in a significant decrease in serum levels of B-type natriuretic peptide and non-active prohormone B-type natriuretic peptide, left ventricular end-systolic volume in chronic heart failure patients.[37]

LEVOCARNITINE SUPPLEMENTATION FOR THE TREATMENT OF END-STAGE KIDNEY DISEASE:

End-stage kidney disease patients usually suffer from levocarnitine deficiency. It is due to the loss of levocarnitine through dialysis. The exogenous supplementation of levocarnitine can be given for dialysis-related carnitine deficiency.[38] The National Kidney Foundation in 2003 developed a practice recommendation for use of levocarnitine in dialysis-related carnitine disorders, erythropoietin-resistant anemia, intradialytic hypotension, cardiomyopathy, and fatigability.[39] The US Food and Drug Administration in 1999 approved the use of levocarnitine in hemodialysis. The US Centers for Medicare and Medicaid services in 2004 and 2012 approved national reimbursement for the intravenous and oral administration of levocarnitine for end-stage kidney disease patients.[39,40] A potent risk marker for cardiovascular mortality and of all-cause in hemodialysis patients is serum C-reactive protein.

Levocarnitine significantly decreased serum low-density lipoprotein and C-reactive protein. It shows that levocarnitine suppresses chronic inflammation through a reactive reduction of serum C-reactive in hemodialysis patients. The levocarnitine acts as a potent anti-inflammatory effect and it inhibits inflammation-induced hepcidin overexpression and helps to maintain the iron homeostasis. The levocarnitine significantly increases hemoglobin and decreases the required erythropoietin dose.[41]

Yizhi Chen, *et al*, a systematic review and meta-analysis of randomized controlled trials was performed in 2014 to evaluate the effects of levocarnitine. It includes 49 randomized controlled trials enrolling 1734 participants. It shows that levocarnitine significantly decreases serum low-density lipoprotein and C-reactive protein for a patient with end-stage kidney disease.[41]

Hurot JM, *et al*, a meta-analysis published in 2002, summarized the effect of levocarnitine in maintenance hemodialysis patients. It includes 18 randomized controlled trials enrolling 482 patients. The levocarnitine treatment significantly increases hemoglobin and decreases the required erythropoietin dose and improved resistance to erythropoietin when patients are commonly given erythropoietin.[42]

LEVOCARNITINE IN THE MANAGEMENT OF HYPERAMMONEMIA:

Ammonia is a toxic gas that is generated as a byproduct of protein digestion and bacterial metabolism. Hyperammonemia is an uncommon condition in which there is an elevation of ammonia levels in the blood with varied physiological etiologies.[43] The primary function of the liver is the elimination of ammonia. When the liver cannot eliminate ammonia more effectively from the body, the elimination of ammonia depends on the brain, kidney, and muscle. The brain does not have an effective urea cycle and when there is an increase in the entry of ammonia to the brain it may lead to neurological disorders and there should be an immediate decrease in ammonia levels to prevent neurological damage.[44] Levocarnitine administration lowers blood ammonia and helps to improve mental status. A carnitine deficiency is associated with the accumulation of excess acyl-CoA esters and disrupts intermediary metabolism. Hyperammonemia is due to the result of acute liver failure or chronic liver disease but can occur with no hepatic injury. The patients with acute hyperammonemia may present with encephalopathy that ranges from mild mental status, deterioration to coma, brainstem herniation, cerebral edema, and even death. The levocarnitine is also an effective treatment for certain cases of hyperammonemia-induced

encephalopathy with unknown etiology. The levocarnitine therapy is therefore cost-effective in lowering blood ammonia levels.[45]

Chukwuma Anyanwu, *et al*, a case report study was conducted in 2018. It examines the clinical and economic impact of a pharmacist in managing acute hyperammonemia of unknown etiology in a 62-years old Hispanic man who had been diagnosed with metastatic medullary thyroid cancer and associated with hypercalcemia. After the failure of several other treatments the patients were treated with levocarnitine, levocarnitine therapy helps to control the high level of ammonia levels and decline mental status deterioration to baseline. This case concludes that levocarnitine may be an effective treatment for certain cases of hyperammonemia-induced encephalopathy with unknown etiology.[45]

LEVOCARNITINE IN THE MANAGEMENT OF FATIGUE IN HYPOTHYROIDISM:

Hypothyroidism is one of the most common abnormalities of the endocrine. The deficiency of thyroid hormone in hypothyroidism significantly decreases the biosynthesis of carnitine which contributes to fatigue.[46] Levocarnitine transports the long-chain fatty acids into mitochondria in which adenosine-triphosphate is synthesized in mitochondria. The thyroid hormone is also involved in the oxidation of fatty acid and transfer of free fatty acids into the mitochondria and the free fatty acid is converted into acyl-CoA derivatives inside cells and then transported into the inner mitochondrial membrane for the oxidation process.[47] When there is a lack of levocarnitine, the transport of long-chain fatty acids into the mitochondria gets interrupted and the formation of adenosine-triphosphate is less which leads to deprivation of energy resulting in fatigue. The reports show that there is 53% of patients with chronic illnesses such as hypothyroidism, diabetes mellitus or malignancy suffer from levocarnitine deficiency which might be predisposed to chronic fatigue state. [47,48] It shows that fatigue symptoms in hypothyroid patients are related to levocarnitine deficiency. When a hypothyroid patient is treated with levocarnitine, it promotes carnitine synthesis and accelerates mitochondrial fatty acid oxidation by utilizing carnitine. Levocarnitine administration shows significant effects on fatigue symptoms in hypothyroid patients receiving thyroid hormone replacement.[49]

Farjana Akhter, *et al*, a randomized controlled trial was conducted in 2020 the hypothyroid patients receiving levothyroxine have been suffering from fatigue symptoms. Patients were divided into two Groups A and B.Group A was control group n=35 and group B was

experimental group n=36. Patients of Group A were treated with Levocarnitine only and Group B patients received Levocarnitine 2g/day along with Levothyroxine therapy for 8 weeks. The fatigue score was assessed by fatigue severity scale, physical fatigue, and mental fatigue scores. The data were collected at the beginning and after 8 weeks of intervention regarding fatigue status, serum thyroid-stimulating hormone, and free thyroxine. The result shows that the administration of levocarnitine along with levothyroxine in hypothyroid patients significantly reduces physical and mental fatigue.[49]

LEVOCARNITINE IN THE MANAGEMENT OF CANCER-RELATED FATIGUE:

Cancer deficiency is the metabolic disturbances that may contribute to fatigue in a cancer patient. Administration of exogenous Levocarnitine helps to reduce fatigue symptoms. A micronutrient deficiency leads to nutritional and metabolic disorders that may cause fatigue.[50] Carnitine is a micronutrient involved in the production of energy in the cell and it is commonly deficient in chronically ill patients suffering from cancer.[51] The deficiency of carnitine may predispose to chronic fatigue by damaging the utilization of long-chain fatty acid substrate into the cell in which it is metabolized to release energy. Cancer patients are at risk for carnitine deficiency due to decreased oral intake and increased renal losses.[52] The levocarnitine treatment helps to improve cancer-related fatigue and may lead to other positive outcomes.[53]

Ricardo A. Cruciani, *et al*, phase I/II open-label trial was conducted in 2016 used to assess the safety and tolerability of exogenous levocarnitine. Adult patients with advanced cancer had carnitine deficiency with moderate to severe fatigue and a Karnofsky Performance Status score was entered by groups of at least three into a standard maximum tolerated dose design. Each successive group received a higher dose of levocarnitine with 250, 750, 1250, 1750, 2250, 3000 mg/day respectively, administered for 7 days in two daily doses. Twenty-seven patients participated with 17 males and 10 females and 21 completed the study. Among them, 17 of these patients had increased carnitine levels at the end of the supplementation period. The highest dose achieved was for the patient is 3000 mg/day and no patient experienced adverse reactions and no toxicities were noted. These findings result that levocarnitine may be safely administered at doses up to 3000 mg/day to the patient with cancer-related fatigue.[54]

LEVOCARNITINE USE ON RENAL ANEMIA AND OXIDATIVE STRESS:

Renal anemia is one of the common complications in patients with chronic renal failure during the end stage where the glomerular filtration rate is used by over 50%.[55] Some patients with renal anemia who undergo hemodialysis treatment because of iron deficiency, chronic infection, and malnutrition respond poorly or not at all to erythropoietin, and hence supplementing with iron saccharate is regarded to be an adjuvant therapy.[56] Levocarnitine is an amino acid that is extensively distributed in the tissues of the body and transports long-chain fatty acids into the body and is used for the treatment of chronic renal failure with associated complications in patients who undergo long-term hemodialysis and develop with secondary carnitine deficiency. Levocarnitine deficiency may affect metabolism, damages the normal red blood cells, and shorten the life of the red blood cells.[57] Levocarnitine significantly relieves malnutrition and antioxidation and allows the erythropoietin dose to be lowered and hence reduces the economic stress on patients. The Erythropoiesis-Stimulating Agents include adverse reactions such as the increased risk of cardiovascular events and death. Carnitine also helps with the maintenance of red blood cells, promotes the synthesis of albumins, increases hematocrit, and improves the stability of the erythrocyte membrane.[58] The carnitine supplementation in hemodialysis patients results in the formation of red blood cells, improve their function, and thus decreasing the need for erythropoiesis-stimulating agents. Levocarnitine injection helps to improve the response to erythropoiesis-stimulating agents in patients undergoing hemodialysis by maintain the hemoglobin levels and decreasing the required dose of erythropoiesis-stimulating agents. Levocarnitine when combined with iron saccharides gave a positive therapeutic effect on renal anemia in patients undergoing hemodialysis. This therapy significantly improves renal anemia and improves the patient quality of life and reduces oxidative stress.[59]

Hong-Xia Cui, *et al,* A study was conducted in 2016, a total of 156 patients with renal anemia were divided randomly into control groups (78 cases) and test groups (78 cases). The Patients in the control group were treated with erythropoietin, iron saccharides, and other conventional symptomatic treatment, whereas patients in the test groups were treated with levocarnitine additionally. The anemia indices, oxidative stress indices, response rate, and erythropoietin dose were compared. The levocarnitine helps to relieve oxidative stress reactions effectively. Therefore, a combination of levocarnitine and iron saccharides had a significant positive effect on renal anemia.[59]

CONCLUSION:

The administration of levocarnitine supplementation may be significantly effective for certain cases of metabolic syndrome and cardiovascular disease, type II diabetes mellitus, dilated cardiomyopathy, septic shock, sarcopenia in patients with liver cirrhosis, chronic heart failure, end-stage kidney disease requiring maintenance hemodialysis, hyperammonemia in a cancer patient, fatigue on the hypothyroid patient, cancer-related fatigue, renal anemia and oxidative stress in patients undergoing hemodialysis.

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