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REVIEW ARTICLE

Understanding Causes, Symptoms, and Treatment Options of Carnitine Deficiency

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Abstract: Carnitine is a water-soluble quaternary amine involved in fatty acid oxidation. Defects in carnitine homeostasis can result in carnitine deficiency, a condition characterized by low carnitine levels and systemic metabolic abnormalities. Carnitine deficiency can occur due to primary defects in carnitine transport or secondary to underlying diseases that increase carnitine demand or impair synthesis. A lack of carnitine transporters or synthesis enzymes can limit carnitine uptake and recycling, depleting body stores. Insufficient carnitine impairs mitochondrial fatty acid breakdown, causing accumulation of toxic intermediates like acylcarnitines and ammonia. This can induce symptoms including fatigue, muscle weakness, hypoglycemia, and cardiomyopathy. At-risk populations include individuals on long-chain fat-restricted diets or parenteral nutrition, and those with inborn errors of metabolism. While carnitine supplements may benefit some patient groups, further research is needed to fully evaluate efficacy, optimal dosing, and long-term safety.

Keywords: Carnitine; Fatty acid oxidation; Carnitine deficiency; Acylcarnitine; Cardiomyopathy; Parenteral nutrition.

1. Introduction

As a naturally occurring hydrophilic amino acid derivative, carnitine is made in the kidneys and liver and comes from eating meat and dairy products. The body naturally produces energy from fats by using a chemical called carnitine. It is necessary for the long-chain fatty acids to be transferred into the mitochondria for beta-oxidation. As a result of its ability to bind and aid in the removal of acyl residues, carnitine increases the ratio of free to acylated CoA and decreases the amount of acyl residues conjugated with Coenzyme A (CoA)[1,2].

Beta-hydroxy-gamma-trimethylammonium butyrate, or carnitine, is a necessary water-soluble compound that is made of amino acids. The main source of carnitine for non-vegetarians is food, which makes up nearly three-fourths of the body's total storage[3]. Red meat, poultry, and dairy products are the primary dietary sources of carnitine. Of the carnitine found in food, 54% to 87% is bioavailable. Liver and kidneys can synthesise lysine and methionine, which together make up one-fourth of the carnitine pool. The plasma carnitine level of vegetarians is comparatively lower than that of non-vegetarians. More than 90% of carnitine is created internally in severe vegetarians [4]. While excess carnitine is quickly eliminated in the urine, an effective renal reabsorption mechanism keeps the plasma carnitine level within the normal range even in the face of variations in dietary carnitine consumption. Typically, the renal tubules reabsorb between 90% and 99% of the filtered carnitine.[5,6]

Less than 1% of the body's stocks of carnitine are turnover rates (300–500 micromol/day); the remaining 98% are intracellular stores. Clinically meaningful effects of decreased carnitine levels may not occur until they fall below 10–20% of normal. A primary or secondary carnitine deficit is possible. An important physiological function of carnitine is found in the metabolism of fats and intermediate metabolic pathways. The pathophysiology section goes into detail about how carnitine helps move long-chain fatty acids from the cytoplasm to the mitochondrial matrix, where they are broken down for beta-oxidation. This process is facilitated by the carnitine shuttle [7].

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Body stocks of carnitine are mostly contained within cells; plasma makes up only around 0.5% of the total. Since the Krebs cycle and fatty acid oxidation are the two ways that exercising muscles produce energy, skeletal muscle contains more than 95% of the body's total carnitine. The remaining carnitine is stored in the kidneys, liver, and heart [8-10].

2. History of carnitine deficiency

Various racial groups exhibit differing rates of primary carnitine insufficiency (PCI), with variations in the occurrence of PCI across countries. For instance, in the United States, the incidence, as per neonatal screening data, is approximately 1 in 142,000, whereas in Japan, it affects about 1 in 40,000 individuals. The Faroe Islands, located in the North Atlantic, report the highest known incidence at 1 in 300. [9] However, some individuals with PCI may go undiagnosed due to lack of symptoms. Therefore, accurately determining the overall prevalence of PCI characteristics proves challenging. Since PCI is inherited in an autosomal recessive manner, it is expected to be distributed equally among genders. Nonetheless, many mothers are diagnosed with PCI shortly after childbirth due to newborn screening indicating low carnitine levels in their babies. Moreover, females may display clinical symptoms more frequently, especially during pregnancy-related stress. To address the associated risks of mortality and morbidity, several US states have included primary carnitine insufficiency in expanded newborn screening programs, which employ tandem mass spectrometry to detect PCI in infants. A decrease in free carnitine (C0) serves as a detectable marker, with maternal PCI possibly contributing to low carnitine levels in newborns. [10]

3. Types of carnitine deficiency

There are 3 types of carnitine deficiency which are discussed in the Table 1.

Table 1. Types of carnitine deficiency

Type	Definition	Causes	Symptoms
Primary carnitine deficiency	This is an uncommon disease brought on by a faulty gene. The gene disrupts a molecule that penetrates cells and transports blood carnitine. Sometimes the illness only causes low amounts of carnitine in the muscles [11].	An atypical gene is the cause of this uncommon illness. A molecule that transports carnitine from the blood into cells is impacted by the gene.	Symptoms of primary carnitine insufficiency usually appear in the first few years of life in children. But occasionally, symptoms could manifest as adults. While they can vary, muscle weakness is a common symptom.
Secondary carnitine deficiency	The ailment in question is increasingly prevalent. Carnitine entry into cells is not an issue in this instance. The issue lies in the blood's insufficient amount of carnitine. Numerous medical conditions may be the cause of it.	Excess Loss, Hereditary Disorders, Increased Requirements: greater demands for fat oxidation result in greater carnitine requirements during critical illnesses (e.g., sepsis, extensive burns), or following major gastrointestinal surgery [12].	Muscle Necrosis, Myoglobinuria (excess myoglobin in urine), Lipid-Storage Myopathy, Hypoglycemia, Fatty Liver.
Carnitine Palmitoyltransferase (CPT) Deficiency	Muscle weakness is one of the signs of an extremely uncommon disorder called carnitine palmitoyltransferase (CPT) insufficiency. One of two enzymes, CPT1 or CPT2, is malfunctioning, which is why it happens. Chemical reactions can be aided by the presence of enzymes in the body.	One of the two enzymes, CPT1 or CPT2, can malfunction in CPT deficiency, an extremely uncommon disorder. Fatty acids can enter cells more easily to produce energy thanks to these enzymes.[13]	This illness is typified by muscle weakness and other associated symptoms. Enzymes known as CPT are essential for delivering fatty acids into cells for use as fuel.

4. Pathophysiology

Under normal physiological settings, fatty acids are the primary source of energy while fasting. The liver, heart, and skeletal muscles produce energy from fatty acids through beta-oxidation. Long-chain fatty acid (LCFA) beta-oxidation takes place entirely in the mitochondrial matrix. The mitochondrial membrane is impermeable to LCFAs and requires the carnitine shuttle[14]. LCFAs are converted to long-chain fatty acyl-CoAs in the cytoplasm before being transported across the mitochondrial membrane. This reaction is facilitated by long-chain fatty acyl-CoA synthetase. The enzyme carnitine palmitoyltransferase-1 (CPT-I) converts LCFA-CoAs to acylcarnitine in the presence of carnitine after they diffuse through the outer mitochondrial membrane[15]. In normal conditions, acylcarnitine synthesis reduces the proportion of acyl residues associated with coenzyme A (CoA) and increases the ratio of free CoA to acyl-CoAs. Acylcarnitine is transported across the inner mitochondrial membrane by the carnitine-acylcarnitine translocase (CACT) using the carnitine shuttle. Carnitine palmitoyltransferase-2 (CPT-II) converts acylcarnitine back to LCFA-CoAs and free carnitine in the mitochondria [16].

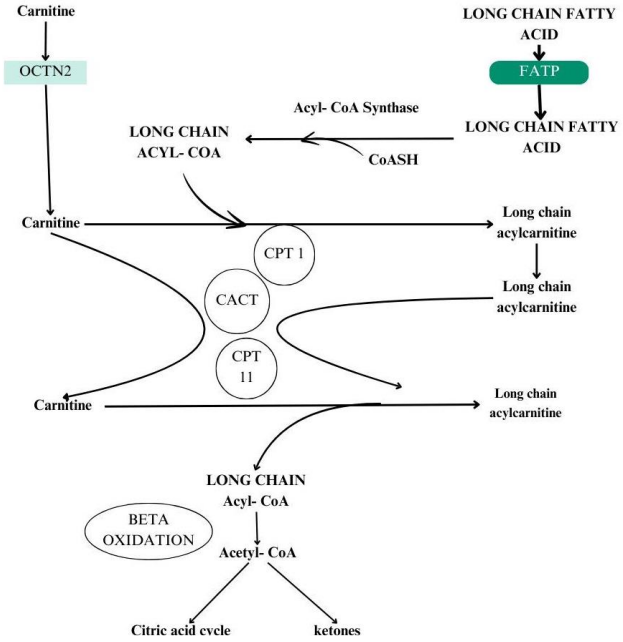

Figure 1. Pathophysiology of Carnitine deficiency

5. Causes

5.1. Primary carnitine deficiency

One classic initial presentation is hypoketotic hypoglycemic encephalopathy, accompanied by hepatomegaly, elevated liver transaminases, and hyperammonemia. Cardiomyopathy is the other classic presentation [17]

5.2. Muscle carnitine deficiency

Carnitine deficiency limited to the muscle is observed in myopathic carnitine deficiency with severe reduction in muscle carnitine levels. The basic biochemical defect has not been identified [18]

5.3. Secondary carnitine deficiency

Secondary carnitine deficiency, which manifests with a decrease of carnitine levels in plasma or tissues, may be associated with genetically determined metabolic conditions, acquired medical conditions, or iatrogenic states. [19]

6. Risk factors

The risk factors of carnitine deficiency are:

- Liver disease.

- Kidney disease, especially with dialysis.
- Digestive disease that causes poor absorption.
- Malnutrition.
- Mitochondrial disease.
- Certain metabolic disorders.
- Certain medicines, such as valproate.[20]

7. Symptoms and manifestations

Muscle weakening or decreased tone, commonly accompanied by floppiness, is a prominent symptom associated with primary carnitine insufficiency. Fatigue and intolerance are also frequently reported, reflecting the systemic impact of the condition. Additionally, delayed motor development and movement may be observed, indicating neurological involvement [21].

Unexpected death can tragically occur as the initial clinical manifestation in asymptomatic individuals with primary carnitine deficit. This is a sobering reality, particularly as patients with secondary carnitine insufficiency may also face sudden death due to ventricular fibrillation or tachycardia [22].

Heart failure is a significant complication of primary carnitine insufficiency, characterized by progressive cardiomyopathy that typically emerges later in life. Conventional treatments like diuretics and inotropes offer limited efficacy in managing heart function. Without timely diagnosis and initiation of carnitine supplementation, progressive heart failure can lead to mortality. In cases of secondary carnitine deficiency resulting from beta-oxidation abnormalities such as LCHAD and VLCAD deficiency, heart failure may present as a primary symptom.

Hypoglycemic hypoketotic encephalopathy is a serious complication observed in younger infants with primary carnitine insufficiency. These infants often present with acute encephalopathy during episodes of hypoketotic hypoglycemia, triggered by fasting periods combined with viral infections. Such episodes are associated with CNS dysfunction and developmental delay. Without prompt carnitine replacement therapy, these encephalopathic episodes may recur [23].

Contrary to previous beliefs that primary carnitine insufficiency predominantly manifests in infancy or early childhood, expanding newborn screening programs have identified a significant proportion of asymptomatic individuals who remain undiagnosed until adulthood. These findings underscore the importance of vigilance in diagnosing the condition, especially considering that affected individuals may only exhibit mild or subtle symptoms. For instance, syncope history worsening during pregnancy, a period characterized by physiological reduction in plasma carnitine levels, has been observed in some women with primary carnitine insufficiency [24]

8. Diagnosis

A diagnosis of carnitine insufficiency may be made by a geneticist or neurologist, with newborns often identified through routine screening procedures. Initial diagnostic steps involve a thorough health history and physical examination, which may include neurological assessment. Various tests are then conducted [25]:

8.1. Blood Examinations

These tests measure carnitine levels in the blood and assess markers like creatine kinase for muscle damage and enzymes indicating liver function.

8.2. Urine Examination

This test checks for ketones, a protein indicative of certain metabolic issues.

8.3. Genetic Examination

Confirmation of primary carnitine deficiency can be achieved through genetic testing. Molecular genetic testing is essential for diagnosing carnitine deficiency secondary to systemic primary carnitine deficiency (CDSP), particularly identifying mutations in the SLC22A5 gene. Newborn screening helps identify infants with CDSP who have low carnitine levels

8.4. Cardiac Examinations

Echocardiography helps assess cardiac involvement.

8.5. Mass Spectrometry

Mass spectrometry is utilized in newborns to detect carnitine palmitoyltransferase deficiency. Prenatal diagnosis can also be performed using amniotic villous cells.

8.6. Adult Diagnosis

Acylcarnitine levels in serum, urine, and tissues assist in diagnosing carnitine insufficiency in adults.

8.7. Skin Biopsy

A skin biopsy may reveal decreased carnitine transport in fibroblasts, confirming the diagnosis of primary carnitine insufficiency.

9. Treatment

Supplementation with L-carnitine serves as the primary treatment, available in tablet form. Regular intake increases blood and intracellular carnitine levels. Oral intake of L-carnitine at 25 mg/kg every 6 hours is prescribed for various causes of carnitine insufficiency. Patients are advised to avoid fasting and intense activity and to consume uncooked cornstarch before bed to prevent morning hypoglycemia. Certain patients may require supplementation with essential fatty acids and medium-chain triglycerides. A low-fat, high-carbohydrate diet is recommended for those with fatty acid oxidation disorders. Lifelong L-carnitine therapy is typically necessary for primary carnitine insufficiency, while the duration may be limited for secondary forms. Regular monitoring of carnitine levels via blood tests is essential. [26] Patients with liver and cardiac complications may require additional therapeutic interventions. Avoiding triggers that exacerbate symptoms, such as skipping meals, exposure to cold, or intense physical activity, is crucial. Several drugs are employed in the management of carnitine deficiency, including Levocarnitine, Dextrose, Riboflavin, Betaine, Hydroxocobalamin, Ubidecarenone, and Biotin. These medications may be prescribed based on individual patient needs and specific clinical presentations. [27]

10. Conclusion

In summary, the detrimental effects of carnitine deficiency on various aspects of overall health, particularly fatty acid utilization and energy metabolism, underscore the significance of timely diagnosis and effective management strategies. Dietary modifications and supplementation play pivotal roles in symptom alleviation and mitigating potential complications associated with this condition. Close monitoring and collaboration with healthcare professionals are imperative to optimize outcomes and uphold general well-being. Carnitine insufficiency highlights the importance of comprehending metabolic disorders and their impact on physiological functions. Timely intervention and ongoing support are essential for effective disease management and enhancement of quality of life for affected individuals. Continued research into novel diagnostic modalities and therapeutic interventions holds promise for advancing the treatment of carnitine deficiency and associated health concerns. Through collective efforts, we can strive towards improved clinical outcomes and better management of this condition, ultimately fostering advancements in the field of metabolic medicine

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