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Disorders of carnitine biosynthesis and transport

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ABSTRACT

Carnitine is a hydrophilic quaternary amine that plays a number of essential roles in metabolism with the main function being the transport of long-chain fatty acids from the cytosol to the mitochondrial matrix for β-oxidation. Carnitine can be endogenously synthesized. However, only a small fraction of carnitine is obtained endogenously while the majority is obtained from diet, mainly animal products. Carnitine is not metabolized and is excreted in urine. Carnitine homeostasis is regulated by efficient renal reabsorption that maintains carnitine levels within the normal range despite variabilities in dietary intake. Diseases occurring due to primary defects in carnitine metabolism and homeostasis are comprised in two groups: disorders of carnitine biosynthesis and carnitine transport defect. While the hallmark of carnitine transport defect is profound carnitine depletion, disorders of carnitine biosynthesis do not cause carnitine deficiency due to the fact that both carnitine obtained from diet and efficient renal carnitine reabsorption can maintain normal carnitine levels with the absence of endogenously synthesized carnitine. Carnitine transport defect phenotype encompasses a broad clinical spectrum including metabolic decompensation in infancy, cardiomyopathy in childhood, fatigability in adulthood, or absence of symptoms. The phenotypes associated with the carnitine transport defect result from the unavailability of enough carnitine to perform its functions particularly in fatty acid β-oxidation. Carnitine biosynthetic defects have been recently described and the phenotypic consequences of these defects are still emerging. Although these defects do not result in carnitine deficiency, they still could be associated with pathological phenotypes due to excess or deficiency of intermediate metabolites in the carnitine biosynthetic pathway and potential carnitine deficiency in early stages of life when brain and other organs develop. In addition to these two groups of primary carnitine defects, several metabolic diseases and medical conditions can result in excessive carnitine loss leading to a secondary carnitine deficiency.

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1. Introduction

Carnitine is an amino acid derivative whose name was derived from the Latin word "carnis" that means meat or flesh because it was first isolated in meat extract in 1905 [1,2]. Carnitine is obtained from both diet and endogenous biosynthesis and is not metabolized but is excreted as free carnitine in urine. It is an essential metabolite with a number of

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indispensable roles in intermediary metabolism with the main function being the transport of long-chain fatty acids from the cytosol to the mitochondrial matrix, where β-oxidation takes place.

Defects in carnitine metabolism were first linked to human disease in 1975 when an 11-year old boy was reported to have recurrent episodes of hepatic and cerebral dysfunction, muscle wasting and weakness, in addition to marked carnitine deficiency in skeletal muscle, plasma, and liver. This condition was named "syndrome of systemic carnitine deficiency" [3]. Several years after that initial report, a 3.5 year old boy with cardiomyopathy and muscle weakness was reported to have low carnitine in muscle and plasma. When he was treated with carnitine, his urinary carnitine dramatically increased and he was found to have increased renal clearance of carnitine. These results suggested at that time that a defect in renal transport of carnitine was a likely cause of the child's disorder [4]. In 1988 it was suggested that individuals with systemic carnitine deficiency had a defect in the carnitine transport across the plasma membrane because the carnitine concentration in fibroblasts from affected individuals was found to be very low when they were incubated in carnitine rich media. These results suggested an inability to maintain a concentration gradient of intracellular carnitine over the plasma due to a defect in a carnitine transport [5,6]. Ten years later, in 1998 the gene responsible for systemic carnitine deficiency was mapped to chromosome 5q31.1-q32 through linkage analysis [7]. In 1999, the gene encoding the carnitine transporter OCTN2 (organic cation transporter 2) was cloned. The transporter was analyzed and found to have the ability to transport carnitine in a sodium-dependent manner. Sequencing the gene encoding OCTN2, *SLC22A5*, identified mutations in patients with systemic carnitine deficiency providing the first evidence that loss of OCTN2 function causes systemic carnitine deficiency. These mutations were also shown to decrease the levels of mature OCTN2 mRNA and result in a nonfunctional transporter, confirming that the defective function in OCTN2 was responsible for primary carnitine deficiency [8,9].

Defects in carnitine biosynthesis were not described until recently. In 2011, while performing array CGH (comparative genomic hybridization) on individuals with autism spectrum disorders, a hemizygous deletion in *TMLHE* was found in a male child with autism [10]. The *TMLHE* gene is located on chromosome X and encodes the enzyme catalyzing the first step in carnitine biosynthesis. Subsequently, other mutations in the *TMLHE* gene identified in children with autism raised the possibility of a relation between carnitine biosynthetic pathway defects and autism spectrum disorders [11–13]. More recently, a homozygous deletion that contains *BBOX1* gene encoding the last enzyme in carnitine biosynthesis was first reported in a child with growth failure and speech delay [14]. The phenotypic consequences of these recently described carnitine biosynthetic pathway defects are still emerging.

In this review article we summarize carnitine function and metabolism. Then we discuss the defects in carnitine biosynthesis and transport.

2. Carnitine function, biosynthesis, and homeostasis

Carnitine (3-hydroxy-4-N-trimethylaminobutyrate) is a hydrophilic quaternary amine which is an essential metabolite with a number of indispensable roles in intermediary metabolism. The main function of carnitine is the transport of long-chain fatty acids from the cytosol to the mitochondrial matrix, where β-oxidation takes place. Carnitine is also involved in the transfer of the products of peroxisomal β-oxidation, including acetyl-CoA, to the mitochondria for oxidation via the Krebs cycle. Other functions include modulation of the acyl-CoA/CoA ratio, storage of energy as acetyl-carnitine, and modulating the toxic effects of poorly metabolized acyl groups by binding and excreting them as carnitine esters in urine [15–19].

Carnitine is present in most, if not all, animal species, and in several micro-organisms and plants. Animal tissues contain relatively high amounts of carnitine, varying between 0.2 and 6 μmol/g, with the highest concentrations present in heart and skeletal muscle [16].

Carnitine is obtained from both diet and endogenous biosynthesis and is not metabolized but is excreted as free carnitine in urine [20]. The main sources of dietary carnitine are animal products including red meat, chicken, fish, and dairy products. Carnitine is synthesized ultimately from the amino acids lysine and methionine. Lysine provides the carbon backbone of carnitine and the N-methyl groups originate from methionine. Lysine residues of certain proteins, such as calmodulin, myosin, actin, cytochrome c, and histones, undergo post-translational N-methylation. This reaction is catalyzed by methyltransferases using S-adenosylmethionine as a methyl donor and resulting in 6-N-trimethyllysine (TML) residues. Lysosomal hydrolysis of the TML-containing proteins results in the release of TML, which is the first metabolite of carnitine biosynthesis. TML is hydroxylated by TML dioxygenase (TMLD) to yield 3-hydroxy-6-N-trimethyllysine (HTML). Subsequently, HTML aldolase (HTMLA) cleaves HTML to 4-N-trimethylaminobutyraldehyde (TMABA) and glycine. Dehydrogenation of TMABA by TMABA dehydrogenase (TMABADH) results in the formation of 4-N-trimethylaminobutyrate (butyrobetaine). In the last step, butyrobetaine is hydroxylated by γ-butyrobetaine dioxygenase (BBD) to yield carnitine (3-hydroxy-4-N-trimethylaminobutyrate) (Fig. 1) [16].

The first three enzymes of carnitine synthesis TMLD, HTMLA, and TMABADH are widely distributed, however, BBD is only present in liver, kidney and brain. Therefore many tissues can synthesize butyrobetaine from TML, whereas, carnitine is synthesized in kidney, liver, and brain. BBD activity is highest in kidney and lowest in brain. In contrast to BBD enzymatic activity in kidney which is not age-dependent, the BBD activity in liver in infants is about 10% of the adult levels [21,22].

The endogenous carnitine biosynthesis is estimated to be 1.2 μmol/kg/day, whereas regular diet provides 2–12 μmol/kg/day carnitine. Therefore, in individuals consuming a regular diet about 75% of carnitine (~300 μmol daily) comes from diet and only 25% of it (~100 μmol daily) comes from endogenous synthesis. Since carnitine is present primarily in animal products, strict vegetarians (vegans) and lacto-ovo-vegetarians obtain very little carnitine from diet (<0.1 μmol/kg/day). Therefore, vegetarians obtain more than 90% of their carnitine through biosynthesis (Fig. 2) [23,24].

The carnitine pool consists of non-esterified carnitine (free carnitine) and many acylcarnitine esters, the later representing the carnitine pool bounded to different fatty acids. About 99.5% of body carnitine is intracellular (~50,000 μmol), while circulating plasma carnitine accounts for only 0.5% of total body carnitine (~200 μmol). Total plasma carnitine concentration is 30–70 μmol/L, whereas, the carnitine concentration within tissues such as muscle and liver is 25–50 times higher than plasma levels (2000–3000 μmol/L). Carnitine is not metabolized but is excreted as free carnitine in urine. Daily urinary carnitine excretion equals the sum of dietary absorption and endogenous synthesis (~400 μmol daily) (Fig. 2) [23,24].

Carnitine homeostasis is maintained by absorption from the diet, a modest rate of synthesis, and an efficient renal reabsorption. At normal circulating carnitine concentrations, renal carnitine reabsorption is highly efficient (90–99% of filtered load), but displays saturation kinetics with a renal threshold for carnitine excretion being ~50 μmol/L which is equal to the normal plasma carnitine concentration. Thus, when circulating carnitine concentration increases, efficiency of reabsorption decreases and clearance increases, resulting in rapid decline of circulating carnitine concentration to baseline. On the other hand, when dietary carnitine intake is reduced, efficiency of renal reabsorption increases and clearance decreases, resulting in maintaining the circulating carnitine concentration within the normal range. Therefore, as the dietary carnitine intake varies, urinary carnitine excretion varies to maintain the plasma carnitine level within the normal range [25].

The main factor regulating carnitine body pools is OCTN2 which is a high affinity plasma-membrane sodium-dependent carnitine

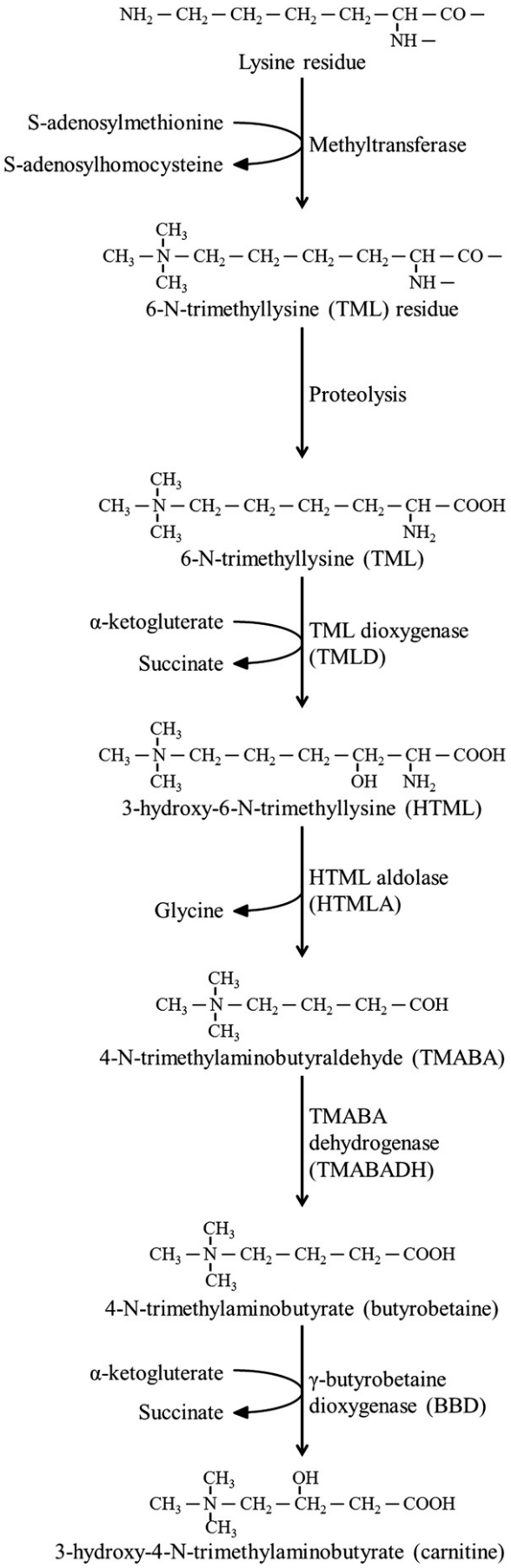

Fig. 1. Carnitine biosynthetic pathway.

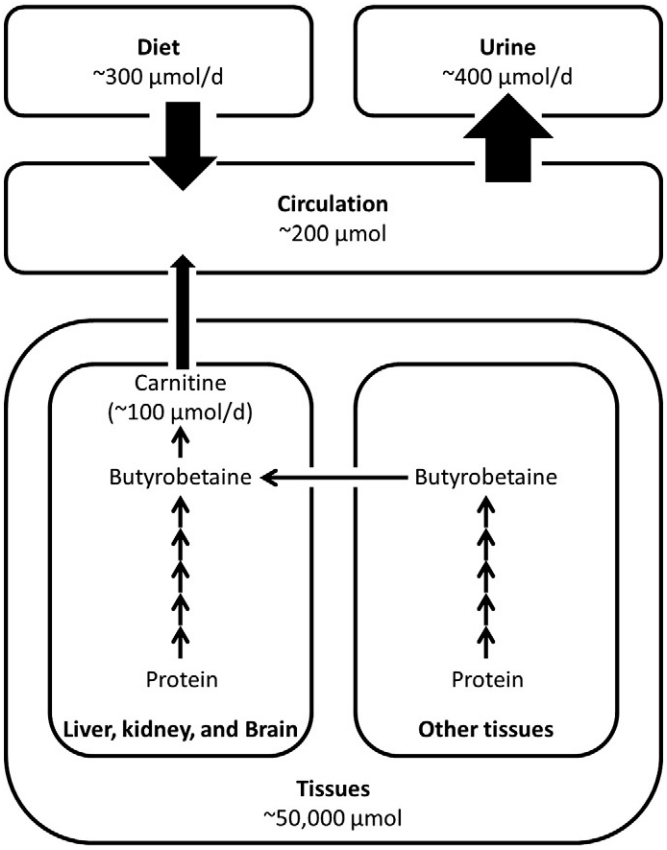

Fig. 2. Carnitine sources and distribution.

transporter. OCTN2 contains 12 transmembrane segments that transfer carnitine across cell membranes. OCTN2 expression is not limited to polarized cells of intestine, kidney, placenta, and mammary gland but has been found in many other tissues such as liver, heart, testis, skeletal muscle, and brain, guaranteeing carnitine absorption and distribution within the entire body. OCTN2 in the apical membrane of renal tubular epithelial cells is responsible for the concentrative reabsorption of carnitine after glomerular filtration in the kidney to maintain a constant plasma carnitine level. Whereas, OCTN2 in other tissues pumps carnitine inside the cells to maintain high intracellular carnitine gradient compared to the plasma carnitine level. OCTN2 has well-defined substrate specificity for carnitine and its derivatives whose transport is coupled to sodium. Additionally, OCTN1, which is strongly expressed in renal epithelium and at a lower level in various tissues, also transports carnitine, but has a lower affinity than OCTN2 [26–28].

3. Disorders of carnitine metabolism and homeostasis

Diseases occurring due to primary defects in carnitine metabolism and homeostasis are comprised of two groups: disorders of carnitine biosynthesis and carnitine transport defect. While the main feature of carnitine transport defect is profound intracellular and plasma carnitine depletion, disorders of carnitine biosynthesis do not cause carnitine deficiency due to the fact that both carnitine obtained from the diet and efficient renal carnitine reabsorption can maintain normal carnitine levels with the absence of endogenously synthesized carnitine which normally contributes to a small fraction of the total pool of carnitine [16]. In addition to these two groups of primary carnitine defects, several metabolic diseases, medical conditions, and drugs can result in excessive carnitine loss leading to a secondary carnitine deficiency.

3.1. Disorders of carnitine biosynthesis

Carnitine biosynthesis defects due to TMLD and BBD deficiencies have been recently described. As endogenous carnitine biosynthesis provides only a small amount of carnitine compared to dietary intake, carnitine biosynthesis defects do not cause carnitine deficiency in individuals consuming a regular diet.

TMLD deficiency was the first enzyme deficiency in carnitine biosynthesis to be described. TMLD which is localized in mitochondria and mediates the first step of carnitine biosynthesis, is encoded by the *TMLHE* gene which maps to the long arm of chromosome X [10,11]. While performing array CGH on individuals with autism spectrum disorders, a hemizygous exon 2 deletion in *TMLHE* was found in a male child raising the question of whether there is a relationship between carnitine biosynthesis defects and autism spectrum disorders [10]. Subsequent screening of autism cohorts identified additional *TMLHE* gene mutations including a duplication of exon 1, a frame shift deletion, and missense and nonsense point mutations in children with autism spectrum disorders [12,13]. The *TMLHE* exon 2 deletion was also found to be relatively common in healthy males with an estimated frequency of 1:350 males. Such data suggested that TMLD deficiency may not have clinical consequences in the vast majority of cases; however, it is a risk factor for autism spectrum disorders associated with low penetrance (2–4%) [11]. Children with TMLD deficiency and autism spectrum disorders were described to be non-dysmorphic, and with intellectual disability in some of them. This deficiency exhibits a biochemical profile consistent with the TMLD enzyme defect. TMLD activity in cultured lymphoblastoid cell lines is undetectable or severely reduced. Plasma and urine TML levels are increased typically about three folds that of the controls. However, one child with TMLD deficiency was reported with normal TML in plasma but elevated level in urine. Plasma TMLH is typically undetectable whereas plasma butyrobetaine is either undetectable or reduced. However, one affected individual was reported to have normal butyrobetaine level. Although these biomarkers can be individually normal on rare occasions, the (HTML+ butyrobetaine)/TML and the TML/butyrobetaine ratios have showed their utility in detecting the biochemical abnormalities with the former being very low and the later very high in individuals with TMLD deficiency. Plasma carnitine levels are within the normal range [11–13]. The etiology of autism in TMLD deficiency is not fully understood. Toxic accumulation of TML or deficiency of HTML, TMABA, and butyrobetaine can play roles. Alternatively, the inability of endogenous carnitine biosynthesis may result in brain carnitine deficiency that may have detrimental effects on brain development during early stages of life [11,12]. More recently, a 4-year old male with TMLD deficiency was reported to show improvement of regression symptoms and gaining of milestones after the initiation of carnitine supplementation suggesting that early carnitine supplementation may be useful in treating and potentially preventing regression episodes in children with carnitine biosynthesis defects [13]. Interestingly, this child was reported to have low plasma carnitine levels despite consuming red meat, chicken, and fish regularly which cannot be explained solely by the TMLD deficiency. The low carnitine level in this child could be from other unrecognized causes of secondary carnitine deficiency or inadequate dietary carnitine intake during the period before measuring the carnitine level.

BBD deficiency was reported once in a girl with microcephaly, speech delay, growth retardation, and minor facial anomalies. She was found to have a homozygous microdeletion in 11p14.2 that contains *BBOX1* gene encoding BBD and *FIBIN* gene encoding fibin which is a signal transduction protein. Plasma carnitine levels were within normal range. With a single case report, it is difficult to correlate the phenotype with the loss of function of any of these genes [14].

The phenotypic consequences of these recently described carnitine biosynthetic pathway defects are still emerging. Although these defects do not result in carnitine deficiency, they could still be associated with pathological phenotypes. Potential disease mechanisms may include excess or deficiency of intermediate metabolites in the carnitine biosynthetic pathway and carnitine deficiency in early stages of life when brain and other organs develop.

3.2. Carnitine transport defect

In contrast to carnitine biosynthesis defects which do not result in carnitine deficiency, defects in carnitine transport result in severe intracellular and plasma carnitine depletion. Therefore, the phenotypes associated with carnitine transport defect result from the unavailability of carnitine to perform its functions particularly in fatty acid β-oxidation.

Carnitine transport defect is caused by recessive mutations in the *SLC22A5* gene which is located on chromosome 5q23.3 and encodes OCTN2. When OCTN2 is not working properly, this can result in improper transfer of carnitine across the cell membrane resulting in both urinary carnitine wasting leading to low plasma carnitine levels, and decreased intracellular carnitine accumulation. During periods of fasting, fatty acids are the predominant source of energy production. As the main function of carnitine is to transfer long-chain fatty acids from the cytoplasm into the mitochondria for β-oxidation, carnitine deficiency will result in defective fatty acid oxidation. When fat cannot be utilized glucose is consumed without regeneration via gluconeogenesis resulting in hypoglycemia. In addition, fat released from adipose tissue accumulate in the liver, skeletal muscle, and heart resulting in hepatic steatosis and myopathy [29].

The clinical manifestations of carnitine transport defect can vary widely with respect to age of onset, organ involvement, and severity of symptoms. The phenotypes associated with the carnitine transport defect encompass a broad clinical spectrum including metabolic decompensation in infancy, cardiomyopathy in childhood, fatigability in adulthood, or absence of symptoms.

Approximately half of the affected individuals presented during the childhood have an infantile metabolic (hepatic) presentation which usually present before the age of 2 years with episodes of metabolic decompensation triggered by fasting or common illnesses such as upper respiratory tract infection or gastroenteritis. These episodes are characterized clinically by poor feeding, irritability, lethargy, and hepatomegaly. Laboratory evaluations usually reveal hypoketotic hypoglycemia, hyperammonemia, and elevated liver transaminases. If affected children are not treated with intravenous dextrose infusion during episodes of metabolic decompensation, they may develop coma and die. The remaining half have a childhood myopathic (cardiac) presentation that typically present between age 2 and 4 years with dilated cardiomyopathy, hypotonia, muscle weakness, and elevated CK (creatinine kinase). Cardiomyopathy in children with carnitine transport defect can be progressive and may result in death before a diagnosis is established or treatment initiated. Older children with the infantile presentation may also develop myopathic manifestations including elevated CK, cardiomyopathy, and skeletal muscle weakness [29–32].

Less frequently, carnitine transport defect can be diagnosed in adulthood. Adults with carnitine transport defect can be asymptomatic, have mild symptoms including decreased stamina or easy fatigability, or have cardiac manifestations including dilated cardiomyopathy and arrhythmias [33–36]. Some women with carnitine transport defect have been diagnosed after newborn screening identified low carnitine levels in their infants [34–37]. Carnitine is transferred from the placenta to the fetus during the prenatal period. Therefore, shortly after birth, carnitine levels in newborns reflect those of their mothers [38]. About half of those women diagnosed to have carnitine transport defect after abnormal newborn screen in their infants complained of fatigability, whereas the other half were asymptomatic. Affected women can also have decreased stamina or worsening of cardiac arrhythmia during pregnancy, suggesting that carnitine transport defect may manifest or exacerbate during pregnancy [34–37]. This can be explained by the fact that pregnancy is a metabolically challenging state because energy consumption significantly increases. In addition, during pregnancy plasma carnitine

levels are physiologically lower than those of non-pregnant controls [39].

Other, less common and atypical manifestations that can occur in individuals with carnitine transport defect include anemia, proximal muscle weakness and developmental delay, respiratory distress, and arrhythmias and electrocardiographic (ECG) abnormalities including long QT syndrome [40–44].

Measurement of plasma carnitine levels of individuals with carnitine transport defect shows extremely reduced plasma free carnitine levels (<5 μmol/L, normal 20–50 μmol/L) [29]. Urine carnitine excretion in individuals with carnitine transport defect who are on carnitine supplementation is typically very high. The diagnosis of carnitine transport defect may first be suspected when low plasma carnitine concentration is identified via newborn screening using tandem mass spectrometry (i.e. low levels of free carnitine (C0)) [45]. Further confirmation of the diagnosis, however, relies on molecular genetic testing of the *SLC22A5* gene. Sequence analysis can detect at least one mutation in approximately 70% of affected individuals. Large deletions and duplications of the *SLC22A5* gene have been reported rarely in individuals with carnitine transport defect [36]. If molecular testing fails to confirm the diagnosis, a skin biopsy may be considered to assess carnitine transport in cultured fibroblasts. Carnitine transport in skin fibroblast from individuals with carnitine transporter defect is typically reduced below 10% of control rates [29].

The metabolic and myopathic manifestations of carnitine transport defect can be prevented by maintaining normal plasma carnitine levels. Primary treatment involves supplementation of oral carnitine at a dose of 100–400 mg/kg/day divided into three doses. The exact dose of carnitine supplementation should be adjusted accordingly based on the individual's plasma carnitine level. While carnitine supplementation has relatively few side effects, high doses may result in increased gastrointestinal motility, diarrhea, intestinal discomfort, and/or the production of trimethylamine, which can result in a fishy odor. Decreasing the carnitine dose may reduce this potential side-effect. If that does not improve the odor, then a course of oral metronidazole at a dose of 10 mg/kg/day for 7–10 days may be indicated [29–32].

Treatment with oral carnitine at these pharmacological doses can raise plasma carnitine level nearly to normal, but only increases muscle carnitine concentration to 5–10% of normal. This poor response in increasing muscle carnitine level is due to the inability of the defective OCTN2 to transport carnitine into muscle cells and having carnitine uptake by muscle limited to passive diffusion from plasma and through the low affinity transporters. Since restoring muscle carnitine to 5–10% of normal levels in patients with carnitine transport defect is sufficient to prevent complications, the tissue level at which carnitine becomes limiting for muscle function is believed to be less than 5% of values seen in unaffected individuals [19,20,28].

Maintaining plasma carnitine levels will also reduce the risk of hypoglycemic episodes. Other ways to prevent hypoglycemic episodes in individuals with carnitine transport defect would include frequent feeding and avoiding fasting. If an individual with carnitine transport defect is hospitalized for hypoglycemia, or needs to fast because of a medical or surgical procedure, treatment with intravenous dextrose is recommended [29–32].

Treatment with carnitine supplementation should be initiated as soon as possible before irreversible organ damage occurs. Metabolic decompensation and skeletal and cardiac muscle functions improve after carnitine supplementation. The long term prognosis is favorable as long as individuals remain on carnitine supplementation [29–32].

3.3. Secondary carnitine deficiency

Carnitine depletion caused by carnitine transport defect is called primary carnitine deficiency. Carnitine deficiency resulted from other causes is called secondary carnitine deficiency. In primary carnitine deficiency, carnitine levels are typically very low (free carnitine <5 μmol/L), treatment requires high carnitine doses, improvement in carnitine level takes a long time, and normal carnitine levels may not even be achieved. In contrast, secondary carnitine deficiency is usually associated with higher carnitine levels, and small doses of carnitine can normalize the carnitine levels in a relatively short period of time [31,32].

As carnitine biosynthesis constitutes only 25% of carnitine pool, defects in carnitine biosynthesis do not result in carnitine deficiency in individuals with normal renal absorptive function and regular diet. On the other hand, decreased dietary intake in vegetarians does not result in carnitine deficiency due to endogenous carnitine synthesis and the effective renal carnitine absorption [25,29,46]. However, restricted carnitine intake can result in carnitine deficiency in infants. Carnitine deficiency was reported in infants fed early preparations of soy formulas that were deficient in carnitine and in neonates receiving carnitine-free total parenteral nutrition (TPN) [47,48]. This can be due to combined effect of the immaturity of liver enzymes, in particular the BBD, resulting in limited endogenous carnitine synthesis and immaturity of renal tubular absorption resulting in deceased ability of kidneys to preserve carnitine.

Several groups of inherited metabolic disorders can cause secondary carnitine deficiency, including, organic acidemias and fatty acid oxidation defects such as very long chain acyl-CoA dehydrogenase (VLCAD), medium chain acyl-CoA dehydrogense (MCAD), long-chain hydroxyacyl-CoA dehydrogenase (LCHAD), carnitine palmitoyltransferase II (CPT II), and carnitine-acylcarnitine translocase (CACT) deficiencies. These metabolic disorders are associated with accumulation of acylcarnitines which can also be transported by OCTN2. Therefore, the acylcarnitine accumulation results in the inhibition of carnitine transport by OCTN2 which results in reduced renal carnitine threshold leading to increased loss of carnitine in urine [20,28].

Some pharmacological therapies, such as cyclosporine, pivampicillin, and valproate can bind carnitine forming compounds that are excreted in urine resulting in carnitine depletion. Other medications can inhibit OCTN2 leading to secondary carnitine deficiency. These medications include anticancer drugs (etoposide, actinomycin D and vinblastine), omeprazole, β-lactam antibiotics (cephaloridine, cefepime, and cefluprenam), and quinolone antibiotic (levofloxacin and grepafloxacin). Hemodialysis and renal Fanconi tubular dysfunction can also result in carnitine deficiency due to excessive loss of carnitine. Premature neonates may have low plasma carnitine concentrations due to a lack of carnitine placental transfer in the third trimester and decreased tissue stores, immature renal tubular function leading to increased renal carnitine elimination, and immature BBD activity resulting in decreased carnitine biosynthesis [20,24,32,49–51].

4. Conclusions

Carnitine is an amino acid derivative that is essential for transporting long-chain fatty acids to the mitochondrial matrix for β-oxidation. A small fraction of carnitine is obtained from endogenous biosynthesis while the majority is obtained from diet, mainly animal products. Carnitine homeostasis is maintained by the dietary carnitine absorption, carnitine biosynthesis, and renal reabsorption that maintain carnitine level within the normal range despite variabilities in dietary intake. Primary defects in carnitine metabolism and homeostasis include disorders of carnitine biosynthesis and carnitine transport defect. In carnitine transport defect profound carnitine depletion occurs resulting in an unavailability of carnitine to perform its functions particularly in fatty acid β-oxidation. Whereas, the recently described carnitine biosynthesis disorders do not cause carnitine deficiency and the phenotypic consequences of these defects are still emerging. In addition to these two groups of primary carnitine defects, several conditions can result in excessive carnitine loss leading to a secondary carnitine deficiency.

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