

Carnitine Therapy for Fatty Acid Oxidation Defects

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Carnitine is a natural substance important to the transport of fat into the mitochondria where it is "burnt" for energy. Carnitine is also important in removing the biochemical "ashes" remaining after the fat is metabolized to energy. It does this by binding to the biochemical ashes and carries them out of the mitochondria and then out of the body as carnitine bound "ashes" (acylcarnitine derivatives) dissolved in the urine. Carnitine is eaten in the diet in red meats and dairy products, including breast milk, and is also made in the body from breaking down muscle protein and converting it to carnitine.

As with all natural substances, deficiency can occur. **Carnitine deficiency is nearly always secondary to other problems and may often be due to more than one factor.** In infants and small children with small muscle masses, carnitine deficiency can develop easily due to poor muscle protein supplies for synthesis. These small children are very dependent on dietary carnitine for their supply. If the diet is inadequate from generalized malnutrition, or due to a special formula not supplemented with carnitine or Total Parenteral Nutrition (TPN) that is unsupplemented, deficiency can develop within weeks. Children and adults with gastrointestinal malabsorption, such as those with cystic fibrosis or chronic diarrhea, can develop deficiency. Increased loss of carnitine from the blood or urine can occur with hemo - or peritoneal dialysis as it is a small chemical and comes out in the dialysis fluids. Carnitine deficiency is also seen in children with kidney disorders affecting the reabsorption of needed chemicals from the filtered urine, renal Fanconi syndrome. **In children with genetic metabolic disorders affecting fat oxidation, carnitine deficiency occurs due to a massive excretion of carnitine in the urine bound to the unburnt "ashes" of fat metabolism.** These unburnt fats attached to carnitine can be detected in the urine of these patients in high levels and this is the **basis of the acylcarnitine derivative testing being used for newborn screening using the tandem MS-MS method.**

Carnitine deficiency is associated with many symptoms.

Since the deficiency is nearly always secondary to another disease process, the symptoms are often those of the primary disease plus additional problems that can be reversed with carnitine replacement therapy. Deficiency of carnitine results in **decreased energy** available to muscle and **muscle weakness** and low muscle tone. Growth of muscle, and thus weight gain, also requires energy and the child with carnitine deficiency usually has **failure to thrive**. Carnitine deficiency can affect the cardiac muscle and result in poor cardiac contractions (**cardiomyopathy**). Energy is important to brain function and abnormalities of brain function can be seen including **convulsions, lethargy, irritability, and even coma**. These children are very **susceptible to infections** and with the frequent infections they often show signs of deterioration of mental and physical status. Liver function may worsen and **liver failure** may occur. In children with genetic metabolic diseases, **carnitine deficiency can be life threatening due to the inability to excrete the unburnt "ashes" left over from incomplete fuel burning. These accumulating ashes are toxic and poison the individual**. Without carnitine to take these toxins out, the individual may die or suffer irreversible damage.

Carnitine is available as a medication and is approved by the FDA for treating secondary deficiency due to metabolic diseases. **In the USA, only one company, Sigma-tau Pharmaceuticals, Inc., sells pharmaceutical grade L-carnitine (Carnitor®) that is available through prescription. Oral L-carnitine** is available as a liquid with 100 milligrams of carnitine in each milliliter and as a **tablet** with 330 milligrams of carnitine per tablet. **Intravenous L-carnitine** is also available in vials each containing 1 gram in 5 milliliters of solution. **Oral carnitine is poorly absorbed and only about ¼ of what is swallowed is taken into the body**. The rest is excreted in the stool. This can result in diarrhea, stomach upsets and in about 5% of people, a very fishy odor caused by certain bacteria in the bowel of some people converting carnitine to trimethylamines. **Intravenous carnitine is fully available for body use** as it bypasses the bowel absorption problems and for this reason **is the preferred route of administration in**

children in life threatening crisis. Doses of carnitine used are variable and range from 50 to 600 milligrams/kg/day with oral carnitine and 25 to 300 milligrams/Kg/day with IV carnitine. Higher doses are usually used in children and adults with serious metabolic disorders during times of metabolic stress and decompensations.

Complications of long term or short-term carnitine treatment reported have been few and not serious. The **body odor** due to trimethylamines can be **treated by taking a low dose of an antibacterial substance such as metronidazole** to kill off the bacteria making the trimethylamines. The **gastrointestinal upset and diarrhea** is often short lived and usually **improves if the dose is lowered or given with food or more frequently.** With IV carnitine, the medication may burn if infused too quickly and may cause reversible pain and irritation if it gets under the skin (interstitial).

Treatment of fatty acid oxidation defects with L-carnitine has been shown to be safe and, especially during the times of metabolic stress, life saving. Theoretical concerns regarding cardiac arrhythmias in children with long chain fat metabolism defects have never been substantiated and no ill effects have been reported in this group of patients. Many children with long chain defects have been shown to reverse serious complications such as cardiomyopathy on carnitine therapy. **In general, carnitine therapy has markedly improved the health and life style of children with fatty acid oxidation defects.**

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[*Please note that not ALL children/adults with an FOD are treated with carnitine supplementation. EACH child/adult should be medically evaluated (i.e. is there a documented carnitine deficiency, is there low muscle tone, are seizure meds being taken that can deplete carnitine, etc) to determine if this treatment is appropriate for their specific disorder and medical situation. Please also note that even if the blood plasma carnitine levels are normal, one can still be deficient in the muscles. DLG]