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### **Carnitine and the ketogenic diet**

I have been asked to make a few comments on carnitine for the Matthews Friends website, as this is a very topical (and controversial!) subject. I will start with a background to carnitine, and then discuss why it might be important on the ketogenic diet, how we can best assess carnitine status, and supplementation.

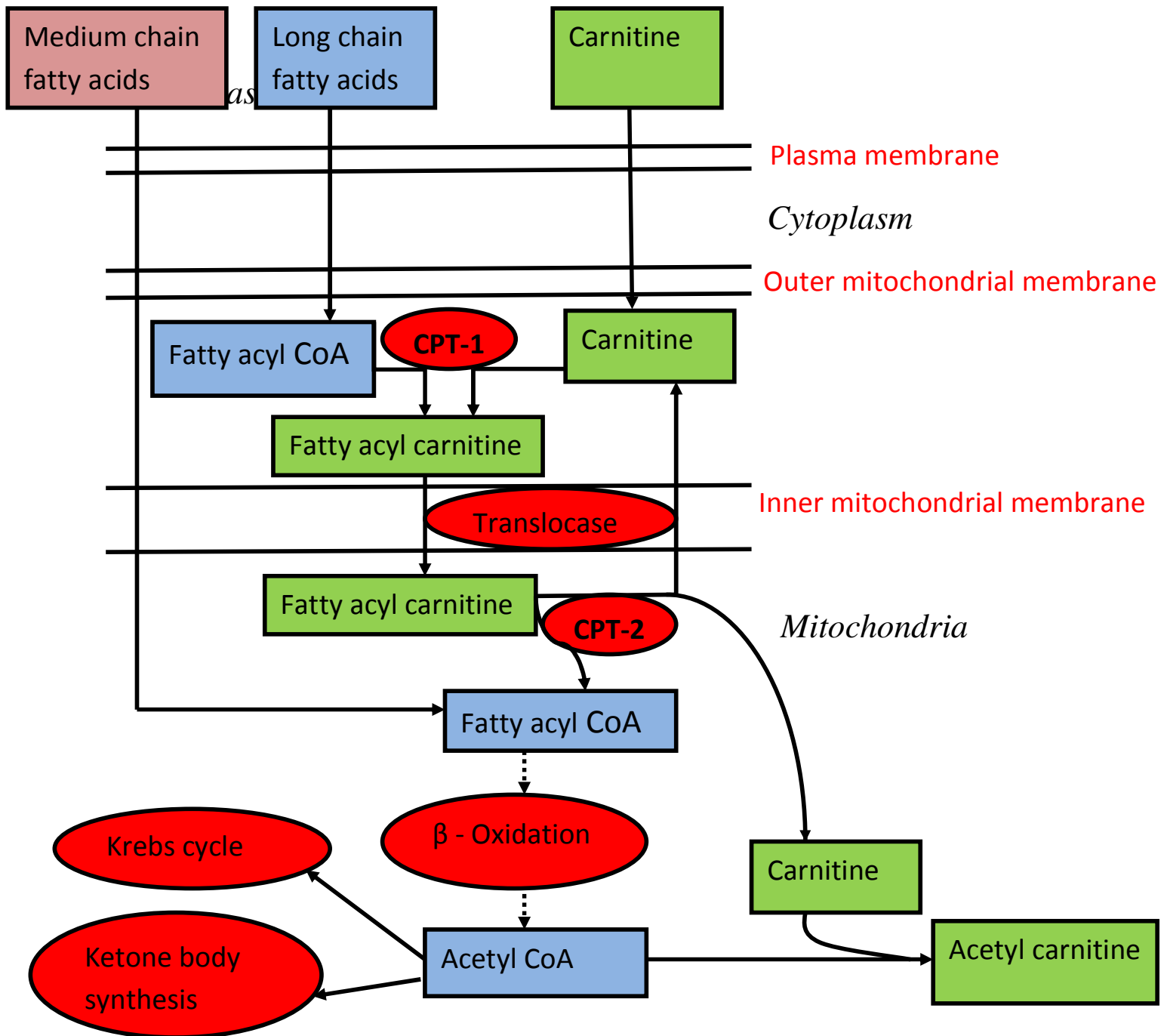
#### 1. Background

Carnitine is a small water soluble compound. It is absorbed well from food, with the main dietary sources being animal based, such as milk, meat and eggs. It can also be synthesised in the body, formed from two amino acids, lysine and methionine. Over 90% of body stores are in muscle. The term L-carnitine is sometimes used; this is the only biologically active form of carnitine.

Carnitine has an essential role in fat metabolism; long chain fatty acids have to combine with carnitine to form acylcarnitines (esters) in order to be transported into the cell mitochondria for oxidation. This process by which carnitine facilitates the transfer of long chain fat into the mitochondria is often referred to as the carnitine shuttle, as once carnitine has done its job of transporting the fatty acid esters across the inner mitochondrial membrane, it is shuttled back across this membrane for the process to be repeated. Once inside the mitochondria, oxidation of fatty acids occurs in stages, with two carbons removed at each stage to form acetyl coA; this either enters the Krebs cycle, or is used to synthesise ketone bodies. An important point, which will be explained in more detail later, is that all the intermediates of this oxidation process can combine with carnitine in the mitochondria, forming acylcarnitines. Acetyl coA also combines with carnitine within the mitochondria to form acetyl carnitine; this then leaves the mitochondria with ketone bodies.

The metabolism of medium chain fatty acids is different, they have a direct passage into the cell mitochondria for oxidation, and so have no need for the carnitine shuttle.

The figure below illustrates some of these processes (CPT-1, translocase and CPT-2 are enzymes involved in the carnitine shuttle)



## 2. Carnitine and the ketogenic diet

The reason why carnitine is thought to be important on the ketogenic diet is because of the high fat intake. As explained above, more fat means more fatty acids, which need to be transported into the mitochondria for oxidation, which means more carnitine is needed and therefore an increased risk of depletion of body carnitine stores. This risk may be magnified because the dietary restrictions could theoretically mean reduced dietary intake of carnitine as well. Increased carnitine requirements however do refer specifically to the long chain fat, or classical, ketogenic diet. As already mentioned, medium chain fat does not require carnitine for its oxidation process. An additional risk in some individuals with epilepsy is that long term use of the medication sodium valproate also can lead to carnitine deficiency. If carnitine is deficient, it will be difficult to achieve adequate ketosis on the ketogenic diet, due to impaired ketone body synthesis, as illustrated in the figure above; energy levels may also be impaired.

There have been limited studies examining whether carnitine deficiency does occur on the ketogenic diet. Berry Kravis et al, in 2001, reported a study which looked at plasma total carnitine levels in 46 patients (age range 1-24 years) who were on the classical ketogenic diet; this included 38 who were followed from diet initiation, and an additional eight already on the diet at the time of the study. Of the 38 patients monitored from diet initiation, three were started on carnitine supplementation at baseline due to low levels, and five others needed supplementation later in diet treatment (3 after 1 month, 2 after 6 months). One of the additional eight patients already on the diet needed carnitine supplementation due to low levels after 1 year. So, out of all the ketogenic diet patients who were not started on carnitine when starting the diet, 6 (18%) went on to have low total carnitine levels and need supplementation later. None of them showed any clinical signs of carnitine deficiency, and did not show any worsening of seizure control with low carnitine levels. The average total carnitine in patients who were never carnitine supplemented was lower after one and six months on the diet than at baseline, but this then increased again by 12 and 24 months. The conclusions from this study were that although total carnitine does decrease over the first few months of ketogenic diet treatment, and in some patients, dip into the deficiency range, it then normalises after the first months, with no evidence of a continued decline in levels.

One other study, reported in 2005 by Coppola et al, measured plasma free carnitine levels in 164 epilepsy patients (age 1mo-26 years), of which 11 were on the classical ketogenic diet. None of these 11 diet patients developed abnormal levels of free carnitine.

Despite these results, it is clear from discussions over the Matthews Friends forum that many parents or carers are finding that carnitine supplementation does show benefits for children on the ketogenic diet, irrespective of plasma levels. However there are differing views among paediatric neurologists around the UK with regard to carnitine; although some are happy to prescribe it on a trial

basis as an additional tool for dietary fine-tuning, even if levels are normal, others would look for either biochemical or clinical deficiency before starting treatment. As carnitine can be bought over the counter in some health shops, many parents or carers have gone ahead with supplementing their ketogenic diet child anyway, although should have hopefully informed their medical team of this decision.

### 3. Assessing carnitine status and supplementation

The two studies discussed above used total and free carnitine. Total carnitine includes the free carnitine levels, and the sum of all the acylcarnitines, that is, the sum of all carnitine-fatty acid esters, including the intermediates of the fat oxidation process that have combined with carnitine, and acetyl carnitine. In a state of ketosis, even  $\beta$ -hydroxybutyrate will combine with carnitine to form  $\beta$ -hydroxybutyryl carnitine – these will all be included in the acylcarnitine fraction. Another measure of carnitine status that has been suggested is the ratio of plasma acylcarnitine to free carnitine. A consensus statement paper by DeVivo et al, in 1998, on carnitine supplementation in childhood epilepsy, suggested that a free carnitine level of less than  $20\mu\text{mol/litre}$  or an acyl:free carnitine ratio greater than 0.4 (after 1 week post term) indicated a deficiency. However, these were arbitrary values, and different centres around the UK may use slightly different, age-dependent cut-offs for deficiency. We do not know what measures accurately determine status as plasma levels are not a true reflection of total body stores, most of these being in muscle. However, although free carnitine does give some useful indication of status in patients on the ketogenic diet, the acyl:free ratio does not. Because of the increase in fat metabolism and ketosis that occur while on the diet, as discussed above, levels of acylcarnitines, including acetyl carnitine, will be greatly increased, and this will result in an elevated ratio. This is a normal consequence of being on the ketogenic diet, and is likely to reflect the level of ketosis, rather than an indication of carnitine status. Indeed, further supplementation with carnitine will have no effect on reducing the ratio, and may even cause it to increase due to increased formation of acetyl carnitine. It has been suggested that the ratio may normalise slightly with time on the ketogenic diet, due to adaptations to the ketotic state.

When assessing carnitine status, it is also important to note that if there is a carnitine deficiency then oxidation of fatty acids in the mitochondria and ketone production will be impaired; a drop in ketone levels would be expected.

If carnitine supplementation is used, what is the suggested dose? The DeVivo et al consensus paper of 1998 recommended supplementing patients with biochemical deficiency at  $100\text{mg per kg body weight per day}$ , in three or four divided doses, up to maximum of  $2\text{g/day}$ . The patients in the Berry-Kravis paper were given  $50\text{mg per kg body weight per day}$  of carnitine if deficient. There

may be poor absorption, diarrhoea and in some cases even a worsening of seizures, if these high doses are started without a gradual build-up. A low starting level of 10mg/kg has been suggested for the ketogenic diet, to be increased as needed, although these doses should always be discussed with a medical team, as individual requirements may differ.

#### 4. Conclusion

Although I have hopefully been able to provide some more information about carnitine and the ketogenic diet, I am aware that I have still not answered the question of should we be using it. Obviously if there is a deficiency, then the answer is yes. The international consensus group recommendations on optimal clinical management of the ketogenic diet by Kossoff et al, published in 2008, recommend only supplementing carnitine if levels are low or children show deficiency symptoms. However, some people will want to try carnitine as an option for their child, even if not showing low levels, as there are many anecdotal reports on its benefit. If this is the case, I would recommend the following – always discuss this with your medical team and seek their advice before commencing supplementation, start slowly and build up a dose, monitor plasma carnitine status where possible, and, just as when doing any dietary fine-tuning, only make one change at once. That is, if starting carnitine, make sure you do not change any other aspects of the diet or medications at the same time, so you can fully assess any benefits of carnitine for at least a week or two before trying something else. In view of the controversy that surrounds the use of carnitine with the ketogenic diet, it is clear we as a scientific community need to do more work on this subject, and I am sure, in due course, there will be more publications which will guide us further.

#### Useful references

1. Berry-Kravis et al (2001). Carnitine levels and the ketogenic diet. *Epilepsia* 42 (11), 1445-51.
2. Coppola et al (2006). Plasma free carnitine in epilepsy children, adolescents and young adults treated with old and new antiepileptic drugs with or without ketogenic diet. *Brain & Development* 28 (6), 358-65.
3. DeVivio et al (1998). L-carnitine supplementation in childhood epilepsy: current perspectives. *Epilepsia* 39, 1216-1225.
4. Kossoff et al (2008). Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group. *Epilepsia*. Feb 2009; 50(2):304-17. Epub 2008 Sep 23.