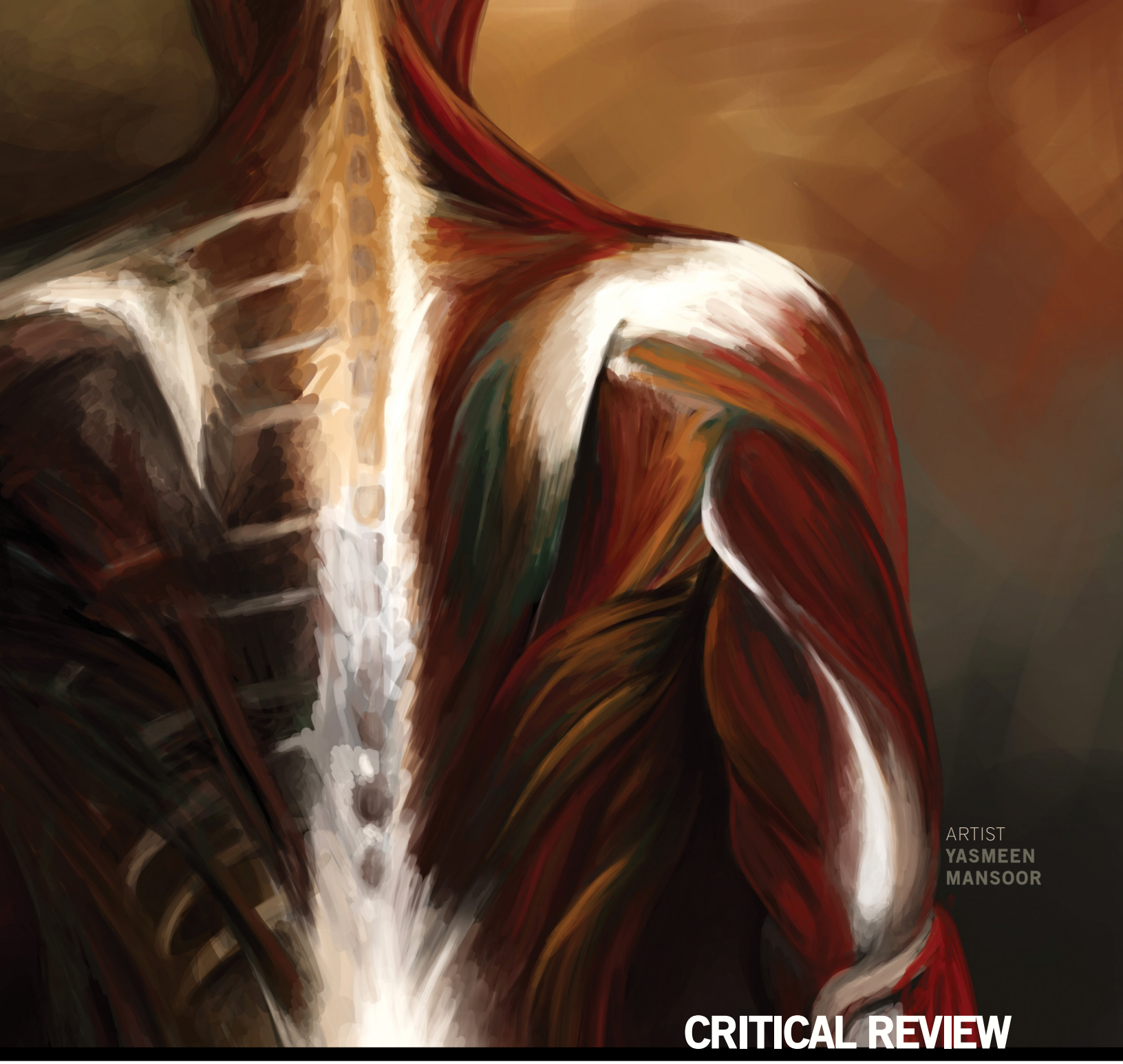

CRITICAL REVIEW

L-Carnitine Supplementation

A POTENTIAL TREATMENT FOR CANCER CACHEXIA

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ABSTRACT

Cachexia is a paraneoplastic syndrome that exhibits rampant muscle wasting, unintentional weight loss, fatigue, weakness, and overall loss of appetite, none of which can be abated by an increase in caloric intake. Metabolic derailment by cachexia is so severe in cancer patients that it can shorten lifetime expectancy and lead to death before the course of treatment is finished. Etiology may involve proinflammatory cytokines, but the abnormal loss of muscle, protein, and fat suggests an underlying metabolic dysfunction that contributes to cachexia. Previous research has shown reduction of L-carnitine in cachectic patients and chemotherapy-induced damage to the L-carnitine transport system that may further exacerbate symptoms. As such, a possible avenue of treatment for cachexia-induced fat loss may involve L-carnitine supplementation to restore metabolic homeostasis through various mechanisms such as lowering levels of proinflammatory cytokines and restoring L-carnitine palmitoyl-transferase activity. While the precise mechanism of L-carnitine-mediated amelioration has not been determined, research findings support the notion of L-carnitine as an alleviator of several cachectic symptoms that have previously been unmanageable in a clinical setting.

If you were to walk down your local supermarket's health and fitness aisle, you would quickly find yourself lost in the vast array of commercially available workout supplements. Stacked bottles of pills and powders with eye-catching claims such as "enhance your workout" or "burn more fat" can be quite overwhelming to a novice in the field of fitness supplements. Today, supplements have become a popular option for augmenting one's workout regime, as they can offer an increasingly wider range of functions and applications for consumers with varying lifestyles and needs. Looking for a supplement to enhance muscle mass? Try whey protein shakes to stimulate muscle protein synthesis.[1] Want to increase the number of repetitions during high intensity training? Consider using creatine supplements.[2] Need an affordable supplement for endurance training? Simple chocolate milk has been shown to provide benefits as a post-workout recovery aid.[3] Indeed, advancements in research have provided greater insight into the benefits and optimal uses of various supplements.

In addition to their benefits in fitness training, workout supplements are now being considered as treatments for various metabolic disorders. One such condition is cancer cachexia (CC), a syndrome of progressive muscle atrophy and weight loss that is often observed in patients with malignant tumours. Levo-carnitine (L-carnitine), an amino acid derivative involved in fat and muscle metabolism, is a commonly-used supplement currently being considered as a potential therapeutic agent for treating CC. Studies on this molecule have shown it to have promising benefits for cancer patients.

L-CARNITINE IN FATTY ACID METABOLISM

L-carnitine is a popular workout supplement which prevents exhaustion by assisting with the conversion of fat into useful energy during exercise.[4] It is a naturally synthesized metabolite found in the human body, and is necessary for fatty acid metabolism. In eukaryotic cells, the mitochondria plays the role of energy production by metabolising dietary carbohydrates, fats, and proteins into useful energy for the body. In general, energy-rich nutrients must be transported past the mitochondrial double membrane into the inner matrix core, which is composed of a complex "soup" of protein machinery which serves to break down nutrients. The outer and inner mitochondrial membranes act as a gated checkpoint to regulate molecules entering or leaving the mitochondria. Since the mitochondrial membranes have a relatively low permeability to fatty acids, these molecules are unable to passively enter the mitochondrial matrix core.[5] Instead, L-carnitine is required as a molecular "chauffeur" to allow passage of fatty acids through the inner mitochondrial membrane to initiate fat catabolism.

CANCER CACHEXIA (CC)
A PARANEOPLASTIC SYNDROME THAT IS CHARACTERIZED AS SKELETAL MUSCLE AND ADIPOSE TISSUE ATROPHY, WEIGHT LOSS, FATIGUE, NEGATIVE ENERGY AND PROTEIN BALANCE, AND REDUCED TOLERANCE TO ANTICANCER THERAPY.[7,8,9]

Fat catabolism begins with the physical linkage of the long-chain acyl groups of fatty acids and L-carnitine in the cytosol through transesterification, carried out by the integral mitochondrial membrane protein L-carnitine palmitoyltransferase I (CPT I). The fatty acids linked to L-carnitine can then be transported through the outer and inner mitochondrial membranes (Figure 1). Once inside the mitochondria, the complex

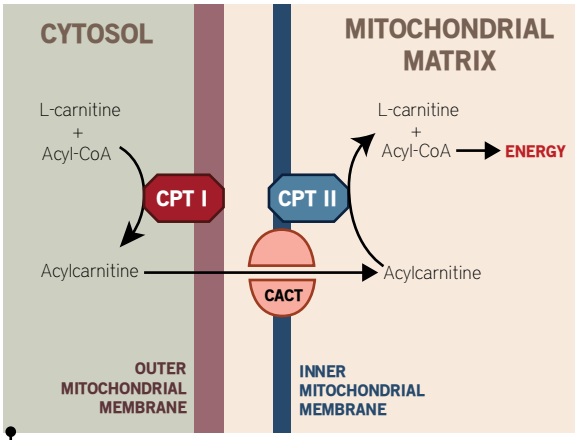
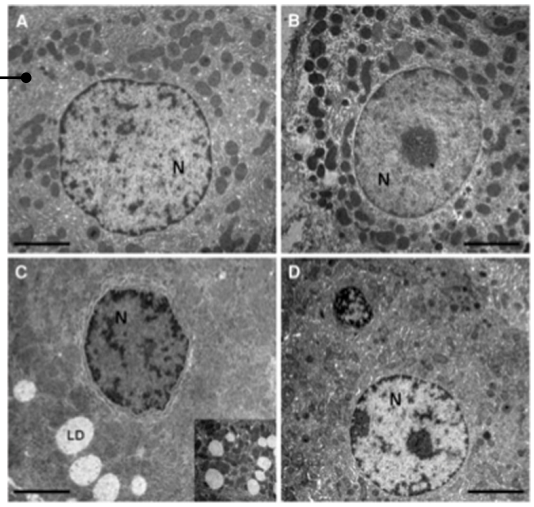


FIGURE 1: The carnitine transport system: L-carnitine is linked to long-chain acyl groups of fatty acids by CPT I, forming acylcarnitine. Acylcarnitine is transported passively through the outer mitochondrial membrane and through carnitine–acylcarnitine translocase (CACT) on the inner mitochondrial membrane. CPT II then cleaves acylcarnitine into acyl-coA and L-carnitine. L-carnitine is recycled back into the cytosol (not shown), while Acyl-CoA undergoes β-oxidation in the mitochondrial matrix in order to produce useful energy.[6]

FIGURE 2: Effects of L-carnitine supplementation on hepatocyte morphology in experimental cancer cachexia. Ultrastructural aspect of hepatocytes from control (a) control, (b) control supplemented with L-carnitine, (c) tumour-bearing supplemented, (d) tumour-bearing supplemented with L-carnitine rats. Note the presence of lipid droplets in the cytoplasm of tumour-bearing rats. LD lipid droplets, N nucleus. Bars 1 μm. Adapted from: Silvério, R., Laviano, A., Fanelli, F. R., and Seelaender, M. (2012) Amino acids, 42, 1783-1792



is cleaved by CPT II to produce L-carnitine, which will be recycled for additional fatty acid transport, and Acyl-CoA, which will be further catabolized to produce useful energy.[6] By regulating the entry of fatty acids into the mitochondrial matrix, L-carnitine serves as the rate-determining factor which dictates how much fat can be catabolized at a given time. By increasing the amount of L-carnitine in the body, fat can be metabolised at a higher rate, thus providing more energy for the body during periods of exercise. This also has the benefit of enhancing weight loss during exercise by metabolising more fat.

APPLICATION TO CANCER CACHEXIA

The uses of L-carnitine are not solely limited to weight loss and perturbing the onset of exhaustion during exercise. The concept of upregulating the L-carnitine-CPT transport system can also be used therapeutically in the newly classified disease of cancer cachexia (CC). CC is a paraneoplastic syndrome that is characterized by skeletal muscle and adipose tissue atrophy, weight loss, fatigue, negative energy and protein balance, and reduced tolerance to anticancer therapy. This condition is often what leads to an unhealthy, gaunt complexion in cancer patients.[7,8,9] Approximately two-thirds of late-stage cancer patients prematurely die due to CC, making it an imposing health risk for cancer patients.[8,10,11] CC is thought to result from a combination of altered intermediary metabolic processes and inflammatory responses in patients with cancer. These changes result in a significant degree of catabolism in affected individuals, to the extent that increases in caloric intake do not abate weight loss.[7,8] Simple nutrition supplementation plans are not sufficient to counteract the severe weight loss and tissue degeneration observed in these patients. In clinical practice, CC is often not recognized or managed appropriately,[12,13] in part due to a lack of sophistication in characterizing and diagnosing this syndrome.[8] It is only recently that diagnostic criterion for different stages of CC were more clearly defined.[9]

As the aetiology of CC is multifactorial, its underlying mechanism has yet to be completely elucidated. However, L-carnitine supplementation has recently been shown to buffer the symptoms of CC, making it a promising treatment for combating this deadly syndrome. Current research exploring the molecular-level modulation of CC through L-carnitine supplementation has demonstrated two unique modes of action: manipulation of proinflammatory cytokine levels and restoration of L-carnitine palmitoyl-transferase (CPT) activity.[14,15,16]

EFFECTS ON PROINFLAMMATORY CYTOKINES

Both host-derived and tumour-secreted proinflammatory cytokines interleukin 1 (IL-1) and interleukin 6 (IL-6) are known contributors of inflammation. Excess levels of these signalling molecules are associated with muscle wasting and impaired lipid metabolism, which are characteristics of severe CC. Thus, by reducing inflammation through decreasing proinflammatory cytokine levels, it may be possible to mitigate the severity of cachexia and impede muscle wasting. A study conducted by Winter et. al (1995) examined the effects of L-carnitine supplementation on cytokine levels, and the possible amelioration of cachexia symptoms in sarcoma-induced rats. Daily administration of L-carnitine was associated with significant reductions in tumour necrosis factor α (TNF-α) (54.6%) and IL-1 (37.4%) levels, compared to saline-injected tumourous rats.[17] These depressed cytokine responses are a promising sign for treating inflammation-based weight loss in CC patients.

RESTORATION OF L-CARNITINE PALMITOYL-TRANSFERASE ACTIVITY

The fundamental role of L-carnitine in the CPT transport system is to shuttle fatty acids into mitochondria, thereby rendering L-carnitine as a key regulator of fatty catabolism.[18] The decrease in CPT I and CPT II activity, coupled with other CC symptoms such as hypertriglyceremia and low lipoprotein lipase activity, would

therefore increase the risk of fatty liver disease tremendously.[18,19] When this was investigated by Silvério et al. (2011), they found large lipid droplets in the liver hepatocyte cells of carcinosarcoma rats (Fig. 2C).[20] Indeed, decreased activity of CPT I was observed in tumour-bearing rats, while no significant difference was observed in CPT II activity or mRNA levels of CPT I and II. When these rats were given injections of L-carnitine, their CPT I activity was partially restored and elicited 1.4 times the activity in untreated rats. However, increase in activity could not be attributed to mere increase of L-carnitine availability, since tumour-bearing rats in fact had greater liver incorporation of L-carnitine, suggesting that L-carnitine may have a role in mediating anti-inflammatory properties as well.[20] Although several studies on the effects of L-carnitine have indicated improvement in lipid metabolism and decrease in cytokine levels,[17,21] more clinical trials are needed to improve other symptoms observed in CC, such as fatigue and the oxidative profile in cachectic patients.[9]

EICOSAPENTANOIC ACID SUPPLEMENTS

Alternate treatments for CC have focused on mechanisms separate from targeting the CPT transport system and cytokine signalling. A promising treatment that targets the rampant proteolysis observed in cachexia is eicosapentanoic acid (EPA), an omega-3 fatty acid that is the only supplement currently known to interfere with proteolysis in cachexia.[21,22] There have been reports of small-scale human trials in which decreased levels of cytokines, improvement of weight and functional status, and increased appetite were observed in cachectic patients treated with EPA.[23,24] However, trials investigating anti-cachectic effects of EPA are contradictory and the largely successful trials observed in animal models have not been conducted in humans to the same extent.[25] Interestingly, the combination of EPA treatment with physical exercise have been shown to effectively ameliorate the symptoms of CC.[26] It seems the future of CC treatments may be a cocktail of different chemical and physical therapeutic agents to simultaneously tackle this deadly disease.

CONCLUSION

In summary, muscle and fat atrophy caused by CC can be drastic and may impede the effectiveness of cancer treatment. In experimental models of CC in rats, L-carnitine supplementation has been found to lower levels of TNF-α and IL-1, which would otherwise increase inflammation-based muscle wasting and fat loss. L-carnitine supplementation has also been shown to partially rescue the CPT transport system for shuttling fatty acids into the mitochondria in liver hepatocytes, thus lowering the risk of hypertriglyceridemia-related diseases such as fatty liver disease. Elevated proinflammatory cytokine levels exist in cachectic cancer patients and are caused directly by the tumour, indirectly by an innate bodily response to the tumour, or an entirely separate cause elicited from chemotherapy. Current research supports the ability of L-carnitine supplementation to decrease these levels. Maintaining normal cytokine levels helps to resume a balance between catabolic and anabolic processes. It is likely that future therapeutic applications of L-carnitine for treating CC symptoms will be incorporated into cocktail treatments. Indeed, L-carnitine supplementation is a promising therapeutic tool with applications that can extend beyond the gym and be delivered as a lifesaving product in a hospital setting. ■

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