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L-Carnitine

GUEST EDITOR
David L. Coulter

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Original Article

Carnitine in Human Immunodeficiency Virus Type 1 Infection/Acquired Immune Deficiency Syndrome

Mark Mintz, MD

ABSTRACT

There is an increasing body of evidence that subgroups of patients infected with human immunodeficiency virus type 1 possess carnitine deficiency. Secondary carnitine deficiencies in these individuals may result from nutritional deficiencies, gastrointestinal disturbances, renal losses, or shifts in metabolic pathways. However, tissue depletion precipitated by drug toxicities, particularly zidovudine, is a major etiology and concern. Carnitine deficiency may impact on energy and lipid metabolism, causing mitochondrial and immune dysfunction. There are convincing laboratory data showing the in vitro ameliorative effects of L-carnitine supplementation on zidovudine-induced myopathies and lymphocyte function. Studies measuring the impact of L-carnitine supplementation on clinical characteristics are ongoing. (*J Child Neurol* 1995;10(Suppl):2S40–2S44).

Human immunodeficiency virus type 1 (HIV-1) can lead to severe and multisystem abnormalities. Both adults and children with acquired immune deficiency syndrome (AIDS) eventually suffer from systemic immunodeficiency, but many patients also manifest multiorgan failure, including central and peripheral nervous system disease, cardiac dysfunction, and a "wasting" syndrome.[1] The pathogenic mechanisms for many of these syndromes have not been fully elucidated. Although the predominant hypotheses focus on direct virulence of HIV-1, opportunistic infections, or secondary cytotoxic processes instigated by immune dysregulation, many of the HIV-1–associated syndromes may possess a metabolic or nutritional component.[1-7] Further aspects of drug toxicity and nutritional deficiency may precipitate, enhance, or exacerbate underlying pathogenic metabolic mechanisms.

There is evidence that patients with HIV-1 infection have an alteration of lipid and fatty acid metabolism, possibly resulting from cytokine dysregulation.[2,4,8-13] This may contribute to impaired immune function, either by altering the membranes of HIV-1–infected cells to a syncytial-forming type or through up-regulation of cytokines, and it can be hypothesized that a secondary L-carnitine deficiency could further exacerbate such a compromised situation.[13] Thus, it has been a valid pursuit to search for evidence of secondary L-carnitine deficiency and differentiate the adverse effects of HIV-1 from the other secondary complications of nutritional embarrassment, immune dysregulation, opportunistic infections, and drug toxicities. Unfortunately, there is only a small body of data concerning the effect of in vivo L-carnitine supplementation on laboratory variables and little accompanying clinical correlation.[13,14]

L-CARNITINE DEFICIENCY IN HIV/AIDS

HIV-1–infected patients, both adults and children, can have impaired nutritional profiles secondary to HIV-1–associated gastrointestinal complications, particularly resulting from malabsorption syndromes, opportunistic infections, reduction of nutritional intake, or complications of drug therapies.[7,15] Micronutrient deficiencies in HIV-infected individuals are common, and it can be expected that there may exist concomitant L-carnitine deficiency.[16,17] However, in the HIV-1–infected population, there have been very few studies directed at determining the extent of L-carnitine deficiency, either primary or secondary. DeSimone et al investigated 29 adult patients with AIDS, adequate nutrition, and no evidence of myopathy or cardiac dysfunction.[17] They found that

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From the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School at Camden, Division of Pediatric Neurology, Cooper Hospital/ University Medical Center, Camden, NJ.

Address correspondence to Dr Mark Mintz, Division of Pediatric Neurology, Cooper Hospital/University Medical School, UMDNJ–Robert Wood Johnson Medical School at Camden, 3 Cooper Plaza, Camden, NJ 08103.

72% of the patients had reduced plasma total and free L-carnitine levels compared to controls. However, all patients were receiving the nucleoside analogue zidovudine (see below), although the separate effects of zidovudine, opportunistic infections, and other drugs were not distinguishable in their study. Interestingly, 14% of the patients had levels of total L-carnitine higher than controls. Similarly, in a series of 30 adult patients, Bogden et al found 37% of patients with levels of total plasma L-carnitine above the upper limit of the normal laboratory range.[18] However, many of these patients self-supplemented their diet with vitamin preparations, and the extent of supplemented L-carnitine was not clear. In the study of Tomaka et al, no L-carnitine deficiency was noted in screening HIV-1–positive patients from a private practice, outpatient setting for various vitamins and minerals; however, there was no correlation reported to zidovudine or other nucleoside status.[16] In very preliminary findings, we have found deficiencies of free and total L-carnitine in 25% of children with HIV-1 infection who have received zidovudine for longer than 6 months (Mintz, unpublished data, 1994).

Studies of L-carnitine serum levels that have appeared in the literature must be scrutinized according to whether there is a differentiation of total versus free; short-, medium-, and long-chain acylcarnitine; or if the carnitine is tissue associated, because there may be a difference between cellular and serum levels.[13,14,19–21] It is important to determine whether individuals are self-administering carnitine supplementations, which would obviously render results inaccurate. Further, in addition to potential "risk" factors of carnitine deficiency, such as poor nutritional intake, cachexia, cardiac disease, or muscle weakness, the concomitant use of various drugs, particularly zidovudine or pyrimethamine/sulfadiazine, appears to enhance the finding of L-carnitine deficiency.[17,22]

CARNITINE AND IMMUNE FUNCTION

It has been suggested that L-carnitine may play a role in immunomodulation, particularly if impaired lipid metabolism exists.[23–25] It was known since the early years of the HIV-1 epidemic that lymphoid cells from HIV-1–infected individuals are poorly responsive to mitogenic stimuli in vitro and in vivo. In a series of 21 AIDS patients, DeSimone et al have observed that the percent of peripheral blood mononuclear cells in the S and G_2-M phases that are hyporesponsive (< 20%) to phytohemagglutinin mitogenic stimulation can be significantly augmented if the culture is pretreated with L-carnitine in doses of 100 to 200 μg/mL.[26] In patients who possessed normoresponsive peripheral blood mononuclear cells (> 20% of cells in the S and G_2-M phases), L-carnitine did not enhance proliferative responses. Additionally, no correlations with these proliferative lymphocyte findings and in vivo serum carnitine levels could be detected.

The same investigational group assessed 20 adult male patients with advanced AIDS and normal serum levels of total, free, and short-chain carnitine, low CD4 counts (22×10^6 to 109×10^6/L), receiving zidovudine (600 mg/day) and pyrimethamine/sulfadiazine, but no supplemental nutritional support, and without signs of muscle or cardiac disease.[13] They found significantly lower concentrations of total L-carnitine in the HIV-1–infected patients' peripheral blood mononuclear cells compared with controls.[13] When these patients' diets were supplemented with high-dose (6 g/day) oral L-carnitine for 2 weeks, there was a significant trend toward restoration of peripheral blood mononuclear cell L-carnitine concentrations, accompanied by an increase in serum levels. When peripheral blood mononuclear cells were isolated from patients who were exposed to high-dose L-carnitine, there was an enhancement of in vitro mitogenic responses to phytohemagglutinin stimulation, again measured as a function of the percent of lymphocytes entering the S and G_2-M phases. However, there was no change in CD4 counts before and after treatment, and thus, it can be inferred that L-carnitine supplementation for 2 weeks did not cause an expansion of the CD4 lymphocyte pool despite the peripheral blood mononuclear cell mitogenic enhancement. On the other hand, enhancement of proliferative lymphocytic responses raises the concern of increased HIV-1 replication, but markers of HIV-1 replication, such as p24 antigen, did not rise in the L-carnitine–treated group. Of interest was the significant reduction of triglycerides in L-carnitine–treated patients—an important marker of immune activation and possibly cytokine production.[4,27–29] Although there was no clinical correlation in this study, there were a number of participants who reported subjective improvements in "energy levels," "well-being," and weight gain. These results were similar to those in an earlier study showing that adult AIDS patients receiving high-dose L-carnitine supplementation for 2 weeks showed statistically significant reductions in triglyceride levels and β_2-microglobulin (a potential marker for AIDS and AIDS dementia complex), and a trend in the lowering of tumor necrosis factor levels (a potential causative factor in HIV-1–associated central nervous system disease), as well as enhancement of in vitro lymphocyte proliferation responses, but no significant effect on CD4 counts.[1,2,14,30–32] Effects of L-carnitine administration for periods longer than 2 weeks are presently being investigated by this group and others.

CARNITINE AND HIV-1–ASSOCIATED NEUROMUSCULAR DISEASE

Patients with HIV-1 infection can experience a multitude of peripheral nervous system complications, resulting from HIV-1 infection, secondary opportunistic infections, or toxicities of various drugs, particularly the nucleoside analogues.[33–35] Painful neuropathies and debilitating myopathies have been extensively delineated.[33] Additionally, there is an extensive literature on the effects of mitochondrial abnormalities inducing myopathic processes (reviewed elsewhere in this supplement), which proffers

the hypothesis of mitochondrial and carnitine involvement in HIV-1–associated or drug-induced myopathies in patients with AIDS.[36–40]

Dalakas and colleagues have reported extensive studies concerning the effects of zidovudine on muscle.[35–38,41,42] In well-nourished HIV-1–infected patients with varying degrees of myopathic signs and symptoms (fatigue, myalgia, weakness, and increased serum creatinine phosphokinase) who received zidovudine at standard dosages for more than 9 months and did not have major systemic AIDS complications, muscle specimens revealed extensive depletion of mitochondrial DNA, as well as carnitine deficiency, with associated lipid storage; many of these patients manifested clinical and laboratory symptomatology of a zidovudine-induced myopathy.[35,37,38] The severity of histologic pathology in the muscle ("zidovudine fibers," which are muscle fibers displaying ragged red–like features, red-rimmed or empty cracks, granular degeneration, and rods, which are histologic markers of muscle mitochondria proliferation or destruction) correlated with the extent of carnitine depletion and lipid accumulation.[38] Interestingly, six of the 21 patients in this study had normal histologic and muscle carnitine findings, but complained subjectively of fatigue and myalgia.[38] Furthermore, the cumulative dose and duration of therapy of zidovudine did not correlate with the severity of muscle fiber abnormalities or carnitine levels. Weakness did not correlate with the histologic or biochemical abnormalities.

Many hypotheses can be considered, but zidovudine-induced myopathy may result from impairment of the cytochrome system and inefficient oxidative phosphorylation, which may in turn lead to a deficiency of muscle carnitine.[43] Alternatively, the uptake of L-carnitine may be reduced if the mitochondria are dysfunctional, or free carnitine may be esterified and exported out of the mitochondria if dysfunctional mitochondria cause a shift toward the glycolytic pathway.[38] The end result of whatever mechanism is at play likely is a substantial reduction of available energy resources in muscle fibers, which is expressed clinically as myopathic symptoms.[38]

The role of carnitine in zidovudine myopathy is further supported by the observations of in vitro myotube cultures supplemented with L-carnitine. Supplementation of myotube cultures reversed many of the destructive effects of zidovudine including a preservation of the structure and volume of mitochondria and prevention of lipid droplet accumulation.[41,42] These findings are provocative and lend additional support for the study of L-carnitine in HIV-1–infected individuals receiving zidovudine, both in the asymptomatic stages and particularly if they are experiencing myopathic symptoms, but as yet there exist no in vivo data on the protective or preventive effects on myopathy. Ongoing clinical trials will soon shed some light on the clinical use of L-carnitine in HIV-1–infected patients for the prevention or treatment of zidovudine-induced myopathies. Results may somewhat extrapolate to other nucleoside analogues.[44]

CARNITINE AND THE CENTRAL NERVOUS SYSTEM

An HIV-1–associated neurologic syndrome has been well defined in adults and children, termed AIDS dementia complex and HIV-1–associated progressive encephalopathy, respectively. The exact neuropathogenic mechanisms have not been fully elucidated, but there has been speculation surrounding direct neurovirulence of HIV-1; secondary cytotoxic mediators produced from macrophages, arachidonic acid metabolites, and activated neural elements; and dysregulation of calcium channels.[1,2,31,32,45–47] Possibly, unrecognized metabolic mechanisms are contributing.[3,5,6]

Cytokines, particularly tumor necrosis factor and arachidonic acid metabolites, likely play an important role in the development of AIDS dementia complex/progressive encephalopathy, as well as in the up-regulation of HIV-1 replication.[2,32,46,48] In addition to antiretroviral therapies, specific ways in which cytokine activity may be reduced may provide important future adjunctive therapies in the treatment or prevention of AIDS dementia complex/progressive encephalopathy.[1] There has been some anecdotal evidence of anti-inflammatory therapy being beneficial in progressive encephalopathy, but other recent studies investigating tumor necrosis factor inhibitors have been disappointing.[49,50] In studies of inflammation, there is evidence that carnitine may modulate cytokine production.[13,14,25] This suggests a potential pathogenic or therapeutic role of L-carnitine in AIDS dementia complex/progressive encephalopathy. However, there is no direct evidence to date correlating plasma or tissue L-carnitine status with AIDS dementia complex/progressive encephalopathy, and as well there are no data concerning L-carnitine supplementation affecting AIDS dementia complex/progressive encephalopathy.

DISCUSSION

There is a growing body of evidence that HIV-1–infected individuals, particularly those receiving the nucleoside analogue zidovudine, may possess a carnitine deficiency syndrome. Such a deficiency can be measured in serum, peripheral blood mononuclear cells, or muscle tissue. Many mechanisms producing carnitine deficiency may be involved, but the effect of zidovudine on mitochondrial function appears to be a predominant mechanism. Alternatively, HIV-1–infected patients are prone to nutritional deficiencies, through an inadequate diet, malabsorption, chronic diarrhea, or opportunistic infections, which may create a secondary carnitine deficiency. Renal disease or a shift toward glycolytic pathways may add excessive urinary excretion as an additional mechanism of carnitine loss. Patients who supplement their diet with vitamins may be receiving exogenous L-carnitine, obscuring the true extent of carnitine deficiency. Likewise, the overwhelming use of nucleoside analogues in AIDS patients makes it very difficult to distinguish the natural history of carnitine deficiency from the effects of drug toxicity. Additionally, studies in the literature require more consis-

tency in measuring L-carnitine in the free, short- or long-chain, or acetyl forms, and in various tissues or peripheral blood mononuclear cells.

When L-carnitine deficiency has been identified in peripheral blood mononuclear cells or muscle tissue in patients receiving zidovudine, the in vitro supplementation of culture media with L-carnitine has effected a reversal of the identifiable carnitine deficiency; immune enhancement as measured by lymphocyte mitogenic responses to phytohemagglutinin; and amelioration of abnormal muscle histology and biochemical findings. However, sufficient data concerning beneficial effects on clinical features has been lacking, although there is a suggestion of subjective improvement in some studies.

Carnitine deficiency in HIV-infected patients places them at risk for alterations in fatty acid oxidation and potential mitochondrial dysfunction. Laboratory findings suggesting that carnitine supplementation may be beneficial in energy utilization provide hypothetical evidence that carnitine supplementation may assist in avoiding or reversing the antimitochondrial effects of zidovudine or other nucleoside analogues. Clinical trials of L-carnitine supplementation involving clinical correlation with laboratory findings in HIV-1–infected patients receiving zidovudine, particularly those with myopathic symptoms, are ongoing, but no data are presently forthcoming. However, many difficulties in measuring outcomes—amelioration of clinical or laboratory myopathic symptomatology, enhancement of immune function, effects on the central nervous system—will be encountered and may require large cohorts to reach statistical significance. Additionally, the lack of patients with AIDS who are zidovudine or nucleoside naive are presently rare, and garnering appropriate control groups may present additional difficulties. Nevertheless, with the data reported to date and the low toxicity profile of L-carnitine, the pursuit of further clinical investigations of the effects of L-carnitine supplementation in HIV-1–infected individuals is warranted. In addition to addressing issues of efficacy, studies may assist in providing guidelines for dosing and the timing of commencing L-carnitine therapy. Only a small number of laboratories and investigators have reported data concerning L-carnitine and HIV-1 infection or AIDS, and reproducible findings in additional centers would be desirable.

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