

ARTICLE

Lipid Replacement/Antioxidant Therapy as an Adjunct Supplement to Reduce the Adverse Effects of Cancer Therapy and Restore Mitochondrial Function*

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The most common complaints of cancer patients undergoing chemo- or radiotherapy are fatigue, nausea, vomiting, malaise, diarrhea and headaches. These adverse effects are thought to be due to damage of normal tissues during the course of therapy. In addition, recent evidence indicates that fatigue is related to reduced mitochondrial function through loss of efficiency in the electron transport chain caused by membrane oxidation, and this occurs during aging, in fatiguing illnesses and in cancer patients during cytotoxic therapy. Lipid Replacement Therapy administered as a nutritional supplement with antioxidants can prevent oxidative membrane damage to normal tissues, restore mitochondrial and other cellular membrane functions and reduce the adverse effects of cancer therapy. Recent

clinical trials using patients with chronic fatigue have shown the benefit of Lipid Replacement Therapy plus antioxidants in restoring mitochondrial electron transport function and reducing moderate to severe chronic fatigue by protecting mitochondrial and other cellular membranes from oxidative and other damage. In cancer patients a placebo-controlled, cross-over clinical trial using Lipid Replacement Therapy plus antioxidants demonstrated that the adverse effects of chemotherapy can be reduced in 57-70% of patients. Dietary use of unoxidized membrane lipids plus antioxidants is recommended for patients undergoing cancer therapy to improve quality of life but should not be taken at the same time of day as the therapy. (Pathology Oncology Research Vol 11, No 3, 139-144)

Key words: lipids, antioxidants, cancer therapy, dietary supplement, fatigue, mitochondria

Introduction

Cancer patients undergoing cytotoxic therapy frequently complain of adverse effects due to their therapy. Fatigue is usually the most common complaint, but other complaints include pain, nausea, vomiting, malaise, diarrhea, headaches, rashes, infections and other problems.¹⁻² Over 75% of cancer patients reported fatigue associated with cancer therapy, whereas only 32% of treating physicians recognized this problem.² Both physicians and patients complained more often of fatigue than of pain, and most patients believed that fatigue associated with cancer therapy was untreatable.²

Fatigue can vary in degree from mild to severe during cancer therapy. In many studies fatigue was reported as the most troublesome and disabling side effect during cancer therapy,³⁻⁶ and it is often a significant reason why patients discontinue treatment.⁷ Although fatigue is often the most commonly reported adverse symptom during cancer therapy, there has been little progress in controlling and reducing fatigue in cancer patients.⁸ Therefore, reducing fatigue associated with cancer therapy is an important goal, and this brief review will concentrate on new nutritional methods to reduce fatigue and improve the quality of life of cancer patients.

Fatigue and oxidative damage to mitochondrial membranes

Intractable or chronic fatigue lasting more than 6 months, not reversed by sleep, is the most common complaint of patients seeking medical care.^{9,10} It occurs naturally during aging, and is also an important secondary condition in many clinical diagnoses.⁹⁻¹¹ The phenomenon of

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fatigue has been defined as a multidimensional sensation, and recently attempts have been made to determine the extent of fatigue and its possible causes.¹¹⁻¹³ Most patients understand fatigue as a loss of energy and inability to perform even simple tasks without exertion. Many medical conditions are associated with fatigue, including respiratory, coronary, musculoskeletal, and bowel conditions as well as infections and cancer.¹⁰⁻¹⁴

Fatigue is related to reductions in the efficiency of cellular energy systems found primarily in mitochondria. Damage to mitochondrial components, mainly by oxidation, can impair their ability to produce high-energy molecules such as ATP and NADH. This occurs naturally with aging and during chronic illnesses, where the production of Reactive Oxygen Species (ROS) can cause oxidative stress and cellular damage, resulting in oxidation of lipids, proteins and DNA.^{16,17} When oxidized, these molecules are structurally and sometimes functionally changed. Important targets of ROS damage are the phospholipid-containing membranes of mitochondria as well as mitochondrial DNA.¹⁵⁻¹⁷

Damage of cellular structures by ROS occurs during aging, and this is caused by excess ROS production resulting in accumulation of mitochondrial and nuclear damage.¹⁵⁻¹⁸ Normally free-radical scavenging enzymes are present in cells to neutralize excess ROS and repair the enzymes that repair ROS-mediated damage.^{17,18} Some ROS production is important in triggering cell proliferation, gene expression and destruction of invading microbes,^{19,20} but with aging ROS damage accumulates and eventually impairs cellular function.¹⁵⁻¹⁸ Thus antioxidant enzymes and enzyme repair mechanisms along with biosynthesis cannot restore or replace enough of the ROS-damaged molecules to maintain function.^{15,16,20-22} Disease and infection can result in oxidative damage that exceeds the abilities of cellular systems to repair and replace damaged molecules,^{15,16,19} and this is also the situation in fatiguing illnesses.^{5,6}

In the case of fatigue, there is evidence that oxidative damage impairs mitochondrial function. For example, in chronic fatigue syndrome patients there is evidence of oxidative damage to DNA and lipids^{23,24} as well as the presence of oxidized blood markers, such as methemoglobin, indicative of excess oxidative stress.²⁵ In addition, oxidative damage to DNA and membrane lipids has been found in muscle biopsy samples obtained from chronic fatigue syndrome patients.²⁶ These authors also found increases in antioxidant enzymes, such as glutathione peroxidase, suggesting that this was an attempt to compensate for excess oxidative stress.²⁶ Chronic fatigue syndrome patients have sustained elevated levels of peroxynitrite due to excess nitric oxide, and this has been proposed to result in lipid peroxidation and loss of mitochondrial function as well as changes in cytokine levels that exert a positive feedback on nitric oxide production.²⁷ In addition to mito-

chondrial membranes, mitochondrial enzymes are also inactivated by peroxynitrite, and this could contribute to loss of mitochondrial function.^{28,29} Finally, although there are cellular molecules that counteract the excess oxidative capacity of ROS, such as glutathione and cysteine, these have been found at lower levels in chronic fatigue syndrome patients.³⁰

Replacement of damaged membrane components by Lipid Replacement Therapy

Critical targets of ROS damage are the genetic apparatus and cellular membranes.^{14,15,31} In the case of membranes, oxidation modifies lipid structure and can affect lipid fluidity, permeability and membrane function.^{32,33} Similar changes occur in fatiguing illnesses, such as chronic fatigue syndrome, where patients show increased susceptibility to oxidative stress and peroxidation.^{23,24} One of the most important changes caused by accumulated ROS damage during aging and in fatigue is loss of electron transport function, and this appears to be directly related to mitochondrial membrane lipid peroxidation,¹⁵ which induces permeability changes in mitochondria and loss of transmembrane potential.^{15,31}

Lipid Replacement Therapy (LRT) plus antioxidants have been used to reverse ROS damage and increase mitochondrial function in certain clinical disorders and conditions, such as chronic fatigue.^{14,34,35} LRT results in replacement of damaged cellular lipids with undamaged lipids to ensure proper structure and function of cellular structures, mainly cellular and organelle membranes.¹⁴ Damage to membrane lipids can impair fluidity, electrical properties, enzymatic activities and transport functions of cellular and organelle membranes.³¹⁻³³ During LRT lipids must be protected from oxidative and other damage, and this is also necessary during storage as well as during ingestion, digestion, and absorption in vivo. To be effective, LRT must result in delivery of high concentrations of unoxidized, undamaged membrane lipids in order to reverse the damage and restore function to oxidized cellular membranes. Combined with antioxidant supplements, LRT has proven to be an effective method to prevent ROS-associated changes in certain clinical conditions.¹⁴

LRT is possible because cellular lipids are in dynamic equilibrium in the body.¹⁴ Orally ingested lipids diffuse to the gut epithelium, and are bound and eventually transported into the blood and lymph using specific carrier lipoproteins and also by nonspecific partitioning and diffusion mechanisms.^{36,37} Within minutes, lipid molecules are transported from gut epithelial cells to endothelial cells, then excreted into and transported in the circulation bound to lipoproteins and blood cells where they are generally protected from oxidation.^{37,38} Once in the blood, specific lipoprotein carriers and red blood cells protect lipids

Table 1. Components of NTFactor[®], a Lipid Replacement Therapy dietary supplement[†]

NTFactor[®] is a nutrient complex that is extracted and prepared using a proprietary process that protects lipids from oxidation. In addition, nutrients, vitamins and probiotic microorganisms are added to the preparation. It contains the following ingredients:

Glycophospholipids: polyunsaturated phosphatidylcholine, other polyunsaturated phosphatidyl lipids, glycolipids and other lipids such as cardiolipin and sterol lipids.

Probiotics: *Bifido bacterium*, *Lactobacillus acidophilus* and *Lactobacillus bacillus* in a freeze-dried, microencapsulated form with appropriate growth nutrients.

Food Supplements, Vitamins and Growth Media: bacterial growth factors to support probiotic growth, including defatted rice bran, arginine, beet root fiber extract, black strap molasses, glycine, magnesium sulfate, para-amino-benzoate, leek extract, pantethine (bifidus growth factor), taurine, garlic extract, calcium borogluconate, artichoke extract, potassium citrate, calcium sulfate, spirulina, bromelain, natural vitamin E, calcium ascorbate, alpha-lipoic acid, oligosaccharides, vitamin B-6, niacinamide, riboflavin, inositol, niacin, calcium pantothenate, thiamin, vitamin B-12, folic acid, chromium picolinate.

[†] From reference 14. NTFactor[®] is a registered trademark of Nutritional Therapeutics, Inc., P.O. Box 5963, Hauppauge, NY 11788 (tel: +1-800-982-9158), Website: www.propax.com

throughout their passage and eventual deposition onto specific cell membrane receptors where they can be taken into cells via endosomes and by diffusion.³⁹ After binding to specific cell surface receptors that bring the lipids into cells, lipid transporters in the cytoplasm deliver specific lipids to cell organelles where they are taken in by specific transport proteins, partitioning, and diffusion.⁴⁰ The concentration gradients that exist from the gut during the digestion of lipids to their absorption by gut epithelial cells and their transfer to blood and then tissues are important in driving the unoxidized lipids into cells. Damaged or oxidized lipids can be removed by a reverse process that is mediated by lipid transfer proteins and enzymes that recognize and degrade damaged lipids.⁴⁰

Prevention of oxidative damage by Lipid Replacement/Antioxidant Therapy

The repair of damaged cellular and mitochondrial membranes as well as DNA are important in preventing loss of electron transport function and cellular energy.^{21,22} This can be accomplished, in part, by neutralizing ROS with various antioxidants or increasing free-radical scavenging systems. Thus dietary supplementation with antioxidants and some accessory molecules, such as zinc and certain vitamins, are important in maintaining antioxidant and free-radical scavenging systems.²³ In addition to zinc and vitamins, there are at least 40 micronutrients required in the human diet,⁴² and aging increases the need to supplement these to prevent age-associated damage to mitochondria and other cellular elements. Antioxidant use alone, however, may not be sufficient to maintain cellular components free of ROS damage. Thus LRT is important in replacing ROS-damaged membrane lipids and returning membrane function to normal.¹⁴

Dietary antioxidant supplementation has partially reversed the age-related declines in cellular antioxidants and mitochondrial enzyme activities, and prevented mitochondria from most age-associated functional decline. For example, in rodents fed diets supplemented with antioxidants, the antioxidants were found to inhibit the progression of certain age-associated changes in cerebral mitochondrial electron transport chain enzyme activities.^{43,44} Thus animal studies have shown that antioxidants can partially prevent age-associated changes in mitochondrial function. However, antioxidants alone cannot completely eliminate ROS damage to mitochondrial membranes, and this is why LRT is an important addition to antioxidant dietary supplementation.¹⁴ Dietary antioxidants may also modify the pathogenic processes of certain diseases.^{14,23,27,45} For example, antioxidant administration has been shown to have certain neuroprotective effects, such as prevention of age-related hearing loss.⁴⁶ The dietary use of antioxidants has been shown to be useful in preventing age-associated mitochondrial dysfunction and damage, inhibiting the age-associated decline in immune and other functions and prolonging the lifespan of laboratory animals.^{14,41,47}

Preclinical and clinical studies using Lipid Replacement/Antioxidant Therapy

Antioxidants and LRT results in replacement of damaged cellular and mitochondrial membrane phospholipids and other lipids that are essential structural and functional components of all biological membranes.¹⁴ One such LRT dietary supplement is NTFactor[®], and this supplement has been used successfully in animal and clinical lipid replacement studies.^{34,35} NTFactor[®]'s encapsulated lipids are protected from oxidation in the gut, and can be absorbed and transported into tissues without undue damage. NTFactor[®]

Table 2. Effects of NTFactor[®], a dietary LRT supplement, on fatigue scores in patients with chronic fatigue, chronic fatigue syndrome or fibromyalgia syndrome[†]

Subjects/patients	n	Average age (years)	Time on NTFactor [®]	Piper Fatigue Scale fatigue reduction (%)	Reference
Chronic fatigue	34	50.3	8 weeks	40.5**	34
Chronic fatigue	20	68.9	12 weeks	35.5*	35
CFS (and/or FMS) [†]	15	44.8	8 weeks	43.1*	48

[†] From reference 48 with permission. *P<0.001; **P<0.0001, compared to data without supplement. Data was collected using the Piper Fatigue Scale. [†] Chronic Fatigue Syndrome and/or Fibromyalgia Syndrome (5/15)

contains a variety of components, including phospholipids, glycopospholipids and other lipids, nutrients, probiotics, vitamins, minerals and plant extracts (Table 1).

NTFactor[®] has also been used to reduce age-related damage in laboratory animals. In aged rodents, Seidman et al.⁴⁶ found that NTFactor[®] prevented hearing loss associated with aging, and shifted the threshold hearing from 35-40 dB in control aged animals to 13-17 dB. They also found that NTFactor[®] preserved cochlear mitochondrial function, and prevented aging-related mitochondrial DNA deletions found in the cochlea.⁴⁶ Thus LRT was successful in preventing age-associated hearing loss and reducing mitochondrial damage in rodents.

In clinical studies LRT has been used to reduce fatigue and protect cellular and mitochondrial membranes from damage by ROS.^{34,35} Propax[®] containing NTFactor[®] has been used in a dietary LRT study with severe chronic fatigued patients to reduce their fatigue.³⁴ Using the Piper Fatigue Scale¹² for measurement of fatigue we found that fatigue was reduced by approximately 40.5% (P<0.0001), from severe to moderate fatigue, after eight weeks of supplementation with Propax[®] containing NTFactor[®] (Table 2). In more recent studies we examined the effects of NTFactor[®] on fatigue in moderately and mildly fatigued subjects and determined if their mitochondrial function, as measured by the transport and reduction of Rhodamine-123 and fatigue scores, improved with administration of NTFactor[®].³⁵ Oral administration of NTFactor[®] for 12 weeks resulted in a 35.5% reduction in fatigue, respectively (P<0.001) (Table 2).³⁵ In this clinical trial there was good correspondence between reductions in fatigue and

gains in mitochondrial function. Within 8 weeks of LRT with NTFactor[®], mitochondrial function was significantly improved (P<0.001), and within 12 weeks of NTFactor[®] supplementation, mitochondrial function was found to be similar to that of young healthy adults.³⁵ In contrast, after a 12-week wash-out period fatigue and mitochondrial function were intermediate between the initial starting values and those found after eight or 12 weeks on supplement.³⁵ The results indicate that in moderately to severely fatigued subjects dietary LRT can significantly improve and even restore mitochondrial function and significantly improve fatigue. Similar findings have been observed in chronic fatigue syndrome and fibromyalgia syndrome patients on LRT plus antioxidants for 8 weeks (Table 2). In this case LRT with Propax[®] containing NTFactor[®] reduced moderate to severe fatigue by 43.1%.⁴⁸

Lipid Replacement/Antioxidant Therapy for patients undergoing cancer therapy

LRT plus antioxidants has proven useful for patients undergoing cancer chemotherapy. For example, Propax[®] with NTFactor[®] has been used in cancer patients to reduce the adverse effects of cancer therapy, such as chemotherapy-induced fatigue, nausea, vomiting, malaise, diarrhea, headaches and other side effects.⁴⁹ Two studies were conducted by Colodny et al⁴⁹ on patients with advanced colon, pancreatic or rectal cancer, receiving identical 5-FU/methotrexate/Leukovorin therapy on a 12-week schedule. In the unblinded part of the study the effectiveness of Propax[®] with NTFactor[®] administered before and during chemother-

Table 3. Effects of Propax[®] with NTFactor[®] on the adverse effects of chemotherapy in a cross-over trial[†]

First arm	Second arm	Average % of patients on test supplement [§]		
		improvement	no change	worsening
Placebo	Propax [®] (+NTFactor [®])	57	22	21
Propax [®] (+NTFactor [®])	Placebo	70	6	24

[†] Data from reference 49. * The same regimen of 5-FU/methotrexate/leukovorin was used for colon, pancreatic or rectal cancers. [§] The percentage of patients reporting self adverse effects was averaged with the percentage of patients with adverse effects reported by a research nurse.

apy was determined by examining the signs/symptoms and side effects of therapy. This quality of life evaluation was conducted by a research nurse, and it was determined that patients on Propax[®] supplementation experienced fewer episodes of fatigue, nausea, diarrhea, constipation, skin changes, insomnia and other effects. In contrast, no changes or a worsening were noted in the occurrence of sore throat or other indications of infection. In the open label part of the trial, 81% of patients demonstrated an overall improvement in quality of life parameters while on chemotherapy.

In the double-blinded, cross-over, placebo-controlled, randomized part of the study of Colodny et al⁴⁹ on advanced cancers, the patients on Propax[®] LRT showed improvements in signs/symptoms associated with chemotherapy but only in the arm of the trial where the supplement was administered.⁴⁹ LRT with Propax[®] resulted in improvement from fatigue, nausea, diarrhea, impaired taste, constipation, insomnia and other quality of life indicators. Following cross-over from the placebo arm to the Propax[®] supplement arm, 57-70% of patients reported rapid improvements in nausea, impaired taste, tiredness, appetite, sick feeling and other quality of life indicators (Table 3).⁴⁹ Although preliminary, this clinical trial demonstrated the usefulness of LRT and antioxidants given during a 12-week schedule of chemotherapy.

Since the success of cytotoxic cancer therapy depends to some degree on free radical oxidation damage to cancer cells, LRT plus antioxidants should not be administered at the same time of day as chemo- or radiotherapy. The primary use of LRT plus antioxidants is to prevent damage to normal cellular structures, and this can be accomplished by administering the supplement at different times than the therapy to salvage normal cellular structures and diminish the adverse side effects of therapy.

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