Finally an Answer to the Most Common Complaint: Fatigue

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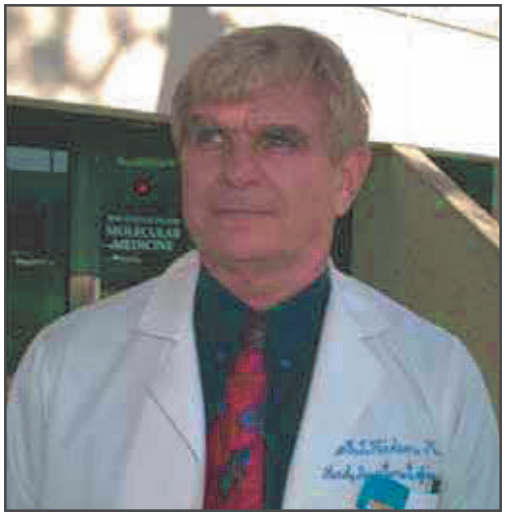
Abstract

The most common complaint of patients seeking general medical assistance is fatigue. Fatigue occurs naturally during aging and in most degenerative diseases, including neurological, respiratory, coronary, musculoskeletal, metabolic and gastrointestinal diseases as well as infections and cancer, and it is characterized at the cellular level by diminished mitochondrial function through loss of efficiency in the electron transport chain. Lipid Replacement Therapy administered using an all-natural nutritional supplement containing membrane glycophospholipids and antioxidants can reduce or prevent fatigue and membrane oxidative damage and restore mitochondrial function. Recent clinical trials using patients with chronic fatigue have shown the benefit of Lipid Replacement Therapy in restoring mitochondrial electron transport function and reducing moderate to severe chronic fatigue.

Introduction

Chronic or intractable fatigue that is not reversed by sleep is the most common complaint of patients seeking medical care.[1, 2] It is also an important secondary condition in many degenerative diseases and occurs naturally during aging.[1] The phenomenon of fatigue has been defined as a multidimensional sensation, and clinical studies have determined the extent of fatigue in various medical conditions and its possible causes.[3-5] Many diseases are associated with fatigue, including neurological, respiratory, coronary, musculoskeletal, metabolic and gastrointestinal diseases as well as infections and cancer.[2-7]

Most patients understand fatigue as a loss of overall energy and inability to perform even simple tasks without exertion. At the cellular level fatigue is related to cellular energy systems found primarily in the cells' mitochondria. Damage to mitochondrial components, especially mitochondrial membranes, occurs mainly by oxidation, and this can result in increased ion leakage across mitochondrial membranes and impair the ability of mitochondria to produce high-energy molecules needed for survival and growth.[8] During aging and most chronic diseases the production of oxidative molecules, such as Reactive Oxygen and Nitrogen species (ROS/RNS), can cause oxidative stress and cellular damage, resulting in oxidation of lipids, proteins and DNA.[9-11] When oxidized, these molecules are structurally and sometimes functionally changed. Important targets of ROS/RNS damage are mitochondria, mainly their phospholipid-containing membranes, as well as cellular and mitochondrial DNA.[9-11]



One of the most important changes in tissues and cells during aging and in chronic degenerative diseases is accumulated oxidative damage due to ROS/RNS. ROS/RNS are oxidative and free radical oxygen- and nitrogen-containing molecules, such as nitric oxide, oxygen and hydroxide radicals and other molecules.[9] Critical targets of these cellular oxidants are the genetic apparatus and cellular membranes,[8,9,] and in the case of cellular membranes oxidation can affect lipid fluidity, permeability and membrane function.[12,13] Similar damage occurs in fatiguing illnesses, such as chronic fatigue syndrome (CFS), where patients have intractable fatigue for at least six months and show increased susceptibility to oxidative stress and peroxidation.[14, 15]

In this brief review I will concentrate on recent clinical trials that have shown the effectiveness of lipid replacement therapy (LRT) plus antioxidants in the treatment of certain clinical disorders and conditions, such as chronic fatigue.[6, 7] LRT is not just the dietary substitution of certain lipids with proposed health benefits; it is the actual replacement of damaged cellular lipids with undamaged (unoxidized) lipids to ensure proper function of cellular

structures, mainly cellular and organelle membranes. [6, 7] 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.[6] LRT must result in the cellular delivery of unoxidized, undamaged membrane glycophospholipids in order to replace damaged lipids and restore function to oxidized cellular membranes. Combined with antioxidant supplements, LTR has proven to be an effective method to prevent ROS/RNS-associated changes in cellular activities and functions and for use in the treatment of various clinical conditions.[7]

Lipid Supplements and Health Benefits

Dietary supplements made up of mixtures of lipids have been used to improve general health.[16, 17] They have also been used as adjunct treatments in various clinical conditions. For example, n-3 fatty acids have been used in the adjunct treatment of cardiovascular diseases and inflammatory disorders.[17-20] Most studies have documented the value of dietary lipid supplements that favor certain types of lipids, such as n-3 polyunsaturated fatty acids (mainly fish- or flaxseed-derived) relative to n-6 lipids.[16-20] However, not every clinical study has found health benefits from lipid dietary supplementation.[21]

Lipid replacement is possible because in the body cellular lipids are in dynamic equilibrium.[6] Orally ingested lipids diffuse to the gut epithelium and are bound and eventually transported into the blood and lymph using specific carrier alipoproteins and also by nonspecific partitioning and diffusion mechanisms.[22, 23] Within minutes, lipid molecules are transported from gut to endothelial cells, then excreted into and transported in the blood circulation bound to lipoproteins and blood cells where they are generally protected from oxidation. Once in the circulation, specific lipoprotein carriers and red blood cells protect lipids throughout their passage and eventual deposition onto specific cell membrane receptors where they can be taken into cells via endosomes and by diffusion.[24, 25] 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, partitioning, and diffusion.[26] The concentration gradients that exist from the gut to the tissues are important in driving lipids into cells. Similarly, damaged lipids are removed by a similar reverse process that may be driven by lipid transfer proteins and by enzymes that recognize and degrade damaged lipids.[6, 26]

Oxidative Damage to Mitochondria and Chronic Fatigue

Excess ROS/RNS production can result in lifetime accumulation of mitochondrial and nuclear oxidative damage.[9-11] On the other hand, cellular free-radical scavenging enzymes neutralize excess ROS/RNS and repair the enzymes that reverse oxidation-mediated damage.[11, 27]

Although some ROS/RNS production is important in triggering cell proliferation, gene expression and destruction of invading microbes,[28, 29] with aging oxidative damage accumulates.[9-11, 27] When this occurs, antioxidant enzymes and enzyme repair mechanisms along with biosynthesis cannot restore or replace enough damaged molecules.[9-11, 29-31]

Disease and infection can result in excess oxidative damage that exceeds the abilities of cellular systems to repair and replace damaged molecules,[10, 15, 28] and this also occurs in fatiguing illnesses, such as Fibromyalgia Syndrome and CFS.[14, 15] In CFS patients there is evidence of oxidative damage to DNA and lipids,[14, 15, 32] as well as the presence of blood markers that are indicative of excess oxidative stress.[33] CFS patients also have sustained elevated levels of the RNS molecule peroxynitrite due to excess nitric oxide, and this results in lipid peroxidation and loss of mitochondrial function as well as changes in cytokine levels that exert a positive feedback on nitric oxide production.[34] In addition to mitochondrial membranes, mitochondrial enzymes are also inactivated by peroxynitrite, and this could also contribute to loss of mitochrondrial function.[35, 36] In addition, cellular molecules that could counteract the excess oxidative capacity of ROS/RNS, such as glutathione and cysteine, have been found in lower levels in CFS patients.[37]

Antioxidants Help Prevent Oxidative Damage

Preventing oxidative damage of cellular and mitochondrial membranes and DNA are important in preventing loss of cellular energy.[6, 14, 31, 38] This can be accomplished, in part, by neutralizing ROS/RNS with various antioxidants or increasing free-radical scavenging systems that neutralize ROS/RNS. Thus dietary antioxidants and some accessory molecules, such as zinc and certain vitamins, are important in maintaining antioxidant and free-radical scavenging systems.[14] In addition to zinc and vitamins, there are at least 40 micronutrients required in the human diet,[39] and aging increases their need 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/RNS damage, and it cannot reverse the damage once it occurs. Thus, LRT is necessary to replace oxidation-damaged membrane lipids.[6, 7]

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.[40, 41] These animal studies have shown that antioxidants can partially prevent age-associated changes. However, antioxidants alone cannot completely eliminate oxidative damage to mitochondria, and this is why LRT is an important addition to antioxidant supplementation.[6, 7]

Dietary antioxidants can also modify the pathogenesis of certain diseases.[6, 7, 14] For example, antioxidant administration has been shown to have certain neuroprotective effects.[42] The dietary use of antioxidants has been shown to prevent age-associated mitochondrial dysfunction and damage, inhibit the age-associated decline in immune and other functions and prolong the lifespan of laboratory animals.[42-44]

LRT in Preclinical and Clinical Studies

Replacing damaged cellular and mitochondrial membrane phospholipids and other lipids is an important role of lipid replacement therapy (LRT).[6, 7] One LRT dietary supplement is NTFactor®, which has been used successfully in animal and clinical lipid replacement studies.[45, 46] Its encapsulated lipids are protected from oxidation in the gut and can be absorbed and transported into tissues without oxidative damage. This dietary supplement contains a variety of components, including phospholipids, glycophospholipids and other lipids, nutrients, probiotics, vitamins, minerals and plant extracts.[6]

In animal studies this LRT supplement has been used to prevent hearing loss associated with aging.[47] Seidman et al.[47] found that this LRT supplement prevented hearing loss associated with aging and shifted the threshold hearing from 35-40 dB in control aged animals to 13-17 dB in the treatment group (P<0.005). They also found that it preserved cochlear mitochondrial function, increasing mitochondrial function by 34%. It also prevented aging-related mitochondrial DNA deletions found in the cochlear.[47]

LRT has also been successfully used in clinical studies to reduce fatigue and protect cellular and mitochondrial membranes from oxidative damage.[45, 46] For example, this dietary supplement has been used in a vitamin and mineral mixture in cancer patients to reduce the effects of cancer therapy, such as chemotherapy-induced fatigue, nausea, vomiting and other side effects associated with chemotherapy.[48] This double-blinded, cross-over, placebo-controlled, randomized trial on cancer patients receiving chemotherapy showed that LRT improved fatigue, nausea, diarrhea, impaired taste, constipation, insomnia and other quality of life indicators.[48]

NTFactor® has been used in a study with severely chronic fatigued patients to reduce their fatigue.[45] Using the Piper Fatigue Scale5 we found that fatigue was reduced approximately 40.5% (P<0.0001), from severe to moderate fatigue, after eight weeks of LRT supplementation with NTFactor®.[45] Recently we examined the effects of this form of lipid replacement therapy on fatigue in moderately and mildly fatigued subjects and to determine if their mitochondrial function improved.[46] Use of this LRP dietary supplement® for 8 or 12 weeks resulted in a 33% or 35.5% reduction in fatigue, respectively (P<0.001).46 In this clinical trial there was good correspondence between reductions in fatigue and gains in mitochondrial function.

After only 8 weeks of LRT, mitochondrial function was significantly improved (P<0.001), and after 12 weeks LRT supplementation, mitochondrial function was found to be similar to that of young healthy adults.[46] After 12 weeks of supplement use, subjects discontinued the supplement for an additional 12 weeks, and their fatigue and mitochondrial function were again measured.
After the 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, indicating that continued dietary LTR is probably required to show improvements in mitochondrial function and maintain lower fatigue scores.[46]

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 results were found with CFS and/or Fibromyalgia Syndrome patients indicating that LRT plus antioxidants for 8 weeks reduced moderate to severe fatigue by 43.1%.7

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Lipid Replacement Therapy: a Functional Food Approach with New Formulations for Reducing Cellular Oxidative Damage, Cancer-Associated Fatigue and the Adverse Effects of Cancer Therapy

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Abstract

Background:
Cancer-associated fatigue and the chronic adverse effects of cancer therapy can be reduced by Lipid Replacement Therapy (LRT) using membrane phospholipid mixtures given as food supplements.

Methods:
This is a review of the published literature on LRT and its uses.

Results: LRT significantly reduced fatigue in cancer patients as well as patients suffering from chronic fatiguing illnesses and other medical conditions. It also reduced the adverse effects of chemotherapy, resulting in improvements in incidence of fatigue, nausea, diarrhea, impaired taste, constipation, insomnia and other quality of life indicators. In other diseases, such as chronic fatigue syndrome, fibromyalgia syndrome and other chronic fatiguing illnesses, LRT reduced fatigue by 35.5-43.1% in different clinical trials and increased mitochondrial function.

Conclusions: LRT formulations appear to be useful as non-toxic dietary supplements for direct use or placed in functional foods to reduce fatigue and restore mitochondrial and other cellular membrane functions. Formulations of LRT phospholipids are suitable for addition to various food products for the treatment of a variety of chronic illnesses as well as their application in anti-aging and other health supplements and products.

Keywords: nutritional supplements, NT factor®, Coenzyme Q_{10}, cancer fatigue, mitochondria,

Background

Nutritional supplements are often taken to maintain health and prevent disease, but cancer patients routinely take multiple dietary supplements to prevent recurrence of cancer, reduce the adverse effects of cancer therapy and to improve quality of life [1-4]. Indeed, one of the most common changes in behavior among cancer patients is initiation of the use of multiple dietary supplements [3].

Studies conducted on the routine use of dietary supplements by cancer patients as well as cancer survivors indicate that there is often little consideration as to their safety, efficacy and potential negative effects [5, 6]. In fact, some data suggest that higher than recommended doses of some vitamins and minerals might result in enhancement of carcinogenesis, changes in survival in some cancers and interference with therapy or prescription medications [5, 6]. In cancer patients several potentially beneficial effects of dietary supplements have been documented, including reductions in the risk of cancer carcinogenesis and tumor progression, enhancement of immune responses against cancer or immune systems in general, improvements in nutrition and general health, and reductions in the adverse effects of cancer therapy [3-5, 7-14]. Here we will focus on one of the most troublesome aspects of cancer and its therapy: cancer-associated fatigue.

Introduction

One of the most common symptoms in cancer that can add considerably to cancer morbidity is cancer-associated fatigue [13-16]. It exists in all types of cancers from the least to the most progressed cancers [15, 16]. Along with pain and nausea, it is one of the most common and troublesome symptoms of cancer [16, 17]. Cancer-associated fatigue is especially apparent in advanced cancers where the systemic adverse effects of cancer therapy are almost always present [17-19].

In advanced cancer patients receiving adjuvant therapies the prevalence of cancer-associated fatigue is reported to be as high as 95% [20]. Thus cancer-associated fatigue is a problem before, during and after therapy, and it can continue to be a problem years after cancer treatment has stopped [16, 19]. Cancer-associated fatigue has a very strong negative effect on quality of life; therefore, addressing and reducing cancer-associated fatigue should be an important consideration in the treatment of cancer [14, 19].

Although not well understood, cancer-associated fatigue is thought to be a combination of the effects of having cancer plus the effects of cancer treatments [16, 19]. Unfortunately, cancer-associated fatigue is rarely treated, and is often thought to be an unavoidable symptom [15, 16]. Cancer-associated fatigue can be considered to be the product of a variety of contributing factors [21]. In addition to a decrease in the availability of cellular energy, such as

provided by mitochondria, there exist psychological and medical factors that determine states of fatigue. The psychological factors include depression, anxiety, sleep disturbances, among others, and the medical factors include anemia, endocrine changes, poor nutritional status and release of inflammatory cytokines [11-14, 19-23]. All of these factors can all contribute to cancer-associated fatigue [12-14].

Cancer-associated fatigue does not occur as an isolated symptom. Cancer patients usually have a variety of symptoms, including cancer-associated fatigue. Cancer-associated fatigue occurs as one of multiple symptoms that are present at all stages of cancer, with exception of the very earliest stages. Cancer-associated fatigue is similar to many other symptoms in cancer patients, in that the severity of cancer-associated fatigue usually correlates with decreased functional abilities [24].

Cancer therapy also contributes in an important way to cancer-associated fatigue [19-21]. In fact, the most commonly found and disabling effect of cancer therapy is fatigue [20, 24, 25]. During cancer therapy fatigue problems can vary, from mild to severe, and excess fatigue during cancer therapy is an important reason given by patients when they discontinue therapy [26]. When Manzullo and Escalante [23] reviewed the literature on the effects of cancer therapy on cancer-associated fatigue, they found that 80-96% of patients receiving chemotherapy and 60-93% receiving radiotherapy experienced moderate to severe fatigue. Fatigue not only was a significant problem during cancer therapy, but it continued for months to years after the therapy ended [23]. Thus in cancer patients suppressing cancer-associated fatigue as well as controlling therapy-induced fatigue are important in supportive cancer care [27].

Recent research on cancer-associated fatigue has been directed at understanding and treating cancer-associated fatigue as well as developing ways to distinguish between depression and cancer-associated fatigue [15]. Depression is a common complaint of cancer patients. Both cancer-associated fatigue and depression have multidimensional and heterogeneous qualities. For example, they both possess physical, cognitive and emotional dimensions, and there is a certain degree of overlap across these dimensions [15, 20].

Fatigue or loss of energy is a core symptom in diagnosing depression. Thus both fatigue and depression are often diagnosed together. This is usually accomplished by self-assessment, where fatigue and depression are considered to be part of a clinical symptom cluster, co-morbidity or syndrome [28, 29]. There are procedures, however, that can distinguish between cancer-associated fatigue and depression by removal of fatigue-associated assessments from an analysis of depression [30, 31]. Criteria have been established when assessing fatigue or cancer-associated fatigue that take depression into consideration, and these two symptoms can thus be separated from one another by considering unshared properties [32].

Chronic fatigue lasting more than 6 months that is not reversed by normal sleep is the most common complaint of patients seeking general medical care [33, 34]. Fatigue occurs naturally during aging, and it is also an important secondary condition in many clinical diagnoses [34, 35]. Most patients understand fatigue as a loss of energy and inability to perform even