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.

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

simple tasks without exertion. Many medical conditions are associated with fatigue, including respiratory, coronary, musculoskeletal, and bowel conditions as well as infections [33-35]. Fatigue is the most common complaint made by the overwhelming majority of cancer patients [16, 19-21].

Fatigue and its Relationship to Oxidative Stress and Damage to Mitochondria

An important phenomenon associated with cancer and its progression as well as aging and age-related degenerative diseases is oxidative stress [36-39]. Oxidative stress is caused by an intracellular excess of reactive oxygen (ROS) and nitrogen (RNS) free radical species over intracellular antioxidants. When this imbalance occurs, it results in oxidation of cellular structures, such as membrane lipids and proteins; it also causes mutation of mitochondrial and nuclear DNA [39-42]. The free radicals ROS and RNS are naturally occurring cellular oxidants that are usually present in low concentrations; they are important cellular regulators and are involved in gene expression, intracellular signaling, cell proliferation, antimicrobial defense and other normal cellular processes [43-45]. However, when ROS/RNS are in excess over cellular antioxidants, oxidative damage can occur to cellular structures [39, 44-46]. Recently Maes [47] proposed a link between excess oxidative stress and activation of ROS/RNS pathways, which is in turn linked to fatigue and fatiguing illnesses.

Cellular antioxidant defenses usually maintain ROS/RNS at appropriate concentrations that prevent excess oxidation of cellular structures [48-50]. Some of the endogenous cellular antioxidant defenses are mediated by glutathione peroxidase, catalase and superoxide dismutase, among other enzymes [51, 52]. There are also low molecular weight dietary antioxidants that can affect anti-oxidant status [53, 54]. Some of these dietary antioxidants have been used as natural chemopreventive agents to shift the excess concentrations of oxidative molecules down to more physiological levels [55, 56].

Excess oxidative stress and its mediators (ROS/RNS) within cancer cells have been linked to promotion and progression of cancer malignancy (metastasis) [57-61]. To demonstrate this oxidative stress and antioxidant status have been examined in various malignant cancers, such as breast [58-62], prostate [63, 64], colorectal [65, 66], renal [67, 68], and other cancers [69-71]. In all of these different cancers ROS/RNS were in excess of cellular antioxidant concentrations, resulting in excess oxidative stress. Therefore, these cancers could have been induced as a consequence of excess ROS/RNS and oxidative damage to the genetic apparatus [37, 39, 72]. Even more likely than carcinogenesis is the progression of tumors that might not evolve to malignancy in the absence of excess oxidative stress [11-14].

Excess Oxidative Stress and Severe Fatigue Caused by Cancer Therapy

Cancer therapy, such as chemotherapy, can result in the generation of excess ROS/RNS [reviewed in 8, 9, 11, 12]. Thus cancer therapy and the resulting production of excess oxidative stress can damage biological systems other than tumors [8, 9, 11, 12]. During chemotherapy the

highest known levels of oxidative stress are generated by anthracycline antibiotics, followed in no particular order by alkylating agents, platinum-coordination complexes, epipodophyllotoxins, and camptothecins [8, 9]. The primary site of ROS/RNS generation during cancer chemotherapy is the cytochrome P450 monooxygenase system within liver microsomes. Enzyme systems, such as the xanthine-xanthine oxidase system, and non-enzymatic mechanisms (Fenton and Haber-Weiss reactions) also play a role in creating excess oxidative stress during chemotherapy [8, 9]. The very high levels of oxidative stress caused by anthracyclines is also related to their ability to displace coenzyme Q_{10} (CoQ_{10}) from the electron transport system of cardiac mitochondria, resulting in diversion of electrons directly to molecular oxygen with the formation of superoxide radicals [reviewed in 8, 9].

Anthracyclines and other chemotherapeutic agents cause generation of high levels of ROS/RNS, but not all chemotherapeutic agents generate excess oxidative stress. Some agents generate only modest amounts of ROS/RNS. Examples of this are: platinum-coordination complexes and camptothecins, taxanes, vinca alkaloids, anti-metabolites, such as the anti-folates, and nucleoside and nucleotide analogues [8, 9, 11, 12]. However, most chemotherapeutic agents generate some oxidative stress, as do all anti-neoplastic agents when they induce apoptosis in cancer cells [8, 9]. Drug-induced apoptosis is usually triggered by the release of cytochrome c from the mitochondrial electron transport chain. When this occurs, electrons are diverted from NADH dehydrogenase and reduced CoQ_{10} to oxygen, resulting in the formation of superoxide radicals [8, 9, 73].

Chemotherapeutic agents used to treat cancer cause oxidative stress, which produces side effects, and among the most common side effects is chronic fatigue [8, 9, 11, 12]. Chronic fatigue caused by cancer therapy can reduce therapeutic efficacy [12, 13]. Although many anti-neoplastic agents have clearly established mechanisms of action that are not dependent upon the generation of ROS/RNS, these drugs can only mediate their anticancer effects on cancer cells that are exhibiting unrestricted progression through the cell cycle. They must also have intact apoptotic pathways. Thus oxidative stress interferes with cell cycle progression by inhibiting the transition of cells from the G_0 to G_1 phase, slowing progression through S phase by inhibition of DNA synthesis. This results in inhibition of cell cycle progression of the G_1 to S phase, and it also results in inhibition by checkpoint arrest [74-78].

Chemotherapeutic agents can also activate DNA repair systems. DNA repair of damage caused by alkylating agents and platinum complexes results in resistance to these drugs, and checkpoint arrest during oxidative stress can enhance the repair processes and diminish the efficacy of treatment [79-81]. Abolishing checkpoint arrest produces the opposite effect and enhances the cytotoxicity of anti-neoplastic agents. By reducing oxidative stress, antioxidants counteract the effects of chemotherapy-induced oxidative stress on the cell cycle and enhance the cytotoxicity of antineoplastic agents [8, 9].

Important intracellular signal transduction pathways that are necessary for the action of some antineoplastic agents can also be affected by oxidative stress [8, 9, 82, 83]. There are two

major pathways of drug-induced apoptosis following cellular damage by anti-neoplastic agents: (1) The mitochondrial pathway, initiated by release of cytochrome c; and (2) the CD95 death receptor pathway, initiated by CD95L binding to its death receptor [8, 9, 81]. Oxidative stress during chemotherapy results in the generation of highly electrophilic aldehydes that have the ability to bind to the nucleophilic active sites of caspases as well as the extracellular domain of the CD95 death receptor. This inhibits caspase activity and the binding of CD96L ligand, resulting in impairment of the ability of anti-neoplastic agents to initiate apoptosis [82-84].

Similar to chemotherapy, radiotherapy also results in generation of oxidative stress and excess ROS/RNS [85, 86]. The principal target of radiation in cancer cells is DNA, and DNA can be directly damaged by radiation. However, genetic damage is also mediated by excess ROS/RNS [86, 87]. Recently the principal source of excess ROS/RNS during radiotherapy has been shown to be mitochondrial [87, 88]. Thus the initial cytotoxicity of radiation is now thought to be due to excess ROS/RNS, which triggers apoptosis via alteration of mitochondrial metabolism. This causes transiently opening of mitochondrial permeability transition pores, which increases the influx of calcium ions into the mitochondrial matrix. The influx of calcium ions stimulates mitochondrial nitric oxide synthase and generation of nitric oxide, which then inhibits the respiratory chain and eventually stimulates excess ROS/RNS free radicals that initiate apoptosis [88, 89].

Cancer Therapy, its Adverse Side Effects and Damage to Cellular Mitochondria
Cancer therapy is associated with several adverse side effects. One of the most difficult side effects is caused by chemotherapeutic drug (or radiotherapeutic) damage to mitochondria [8, 9, 11, 12]. Cardiac mitochondria are especially sensitive to certain chemotherapy agents, such as anthracycline antibiotics [8, 9]. Anthracycline-induced cardiac toxicity is characterized by acute, reversible toxicity that causes electrocardiographic changes and depressed myocardial contractility and by chronic, irreversible, dose-related cardiomyopathy [9, 90]. The selective anthracycline-induced toxicity to cardiac cells is due to damage to cardiac mitochondria. The sensitivity of cardiac cells to anthracyclines, such as doxorubicin, has been found to be due to the unique properties of cardiac mitochondria, which possess a Complex I-associated NADH dehydrogenase in the inner mitochondrial membrane facing the mitochondrial cytosol [91, 92].

Small molecules can penetrate the outer mitochondrial membrane; thus doxorubicin as a relatively small molecule can readily penetrate the outer mitochondrial membrane [90, 93]. However, because it is hydrophilic and cannot partition into the lipid membrane matrix, it cannot penetrate the inner mitochondrial membrane [93]. Thus, it cannot participate in oxidation-reduction reactions with the type of inner matrix-facing, electron transport chain dehydrogenases found in most types of cells, including most tumor cells [90, 93]. But in heart cells doxorubicin can interact with the mitochondrial cytosolic-facing NADH dehydrogenase that is unique to this tissue [94, 95]. This interaction produces doxorubicin aglycones, which are highly lipid soluble

and readily penetrate the inner mitochondrial membrane [90, 93]. At this location they can displace CoQ_{10} from the electron transport chain [90, 94].

The displacement of CoQ_{10} from the electron transport chain during doxorubicin treatment results in decreased CoQ_{10} in cardiac muscle [96]. This occurs as the plasma concentration of CoQ_{10} increases [97]. CoQ_{10} normally accepts electrons from Complexes I and II and transfers them down the electron transport chain, resulting in the formation of water. However, the presence of aglycones in the inner mitochondrial membrane and inner matrix results in the transfer the electrons directly to molecular oxygen, resulting in the formation of superoxide radicals [98]. Thus, doxorubicin generates a high level of oxidative stress in cardiac mitochondria, causing acute cardiac toxicity and damage to mitochondrial DNA [90, 95, 99].

Cardiac cells that are damaged by anthracyclines cannot sustain their function, and changes in their structure, mostly disruption of mitochondria, eventually results in apoptosis [90, 100]. This produces cardiac insufficiency and an inability to respond to pharmacological interventions, resulting ultimately in cardiac failure. However, if CoQ_{10} is administered during anthracycline chemotherapy, damage to the heart is prevented by decreases in anthracycline metabolism within cardiac mitochondria and by competing with aglycones for the CoQ_{10} sites within the electron transport chain [8, 9, 90]. Thus, CoQ_{10} administered concurrently with anthracyclines can maintain the integrity of cardiac mitochondria and prevent damage to the heart, and at the same time enhancing the anti-cancer activity of anthracyclines [8, 9, 90].

In addition to chemotherapy, radiotherapy also produces damage to tissues other than cancer tissues. Agents that protect tissues against radiation effects have been used to reduce unwanted damage [88, 101]. Such radioprotective agents that have been used to decrease the adverse effects of radiotherapy are: antioxidants, free radical scavengers, inhibitors of nitric oxide synthase and anti-inflammatory and immunomodulatory agents [88, 101]. The most effective of these target mitochondria, such as proteins and peptides that can be transported into mitochondria and plasmids or nucleotide sequences. For example, agents that target and stimulate mitochondrial manganese superoxide dismutase genes can be used as radioprotective agents [88].

Molecular Replacement of Mitochondrial Components During Cancer Therapy

Replacement of CoQ_{10} during chemotherapy dramatically prevents development of anthracycline-induced cardiomyopathy and histopathological changes in heart tissue [9, 90]. Administering CoQ_{10} can also prevent changes in electrocardiograms (EKG) characteristic of anthracycline-induced heart damage [102]. In animals the administration of CoQ_{10} resulted in increased survival, improvement in their EKG patterns, and reduced heart histopathological changes [103]. These preclinical data, along with clinical data [discussed in 11, 12, 90] support the contention that CoQ_{10} protects the heart tissue from anthracycline-induced damage.

During chemotherapy with anthracyclines in some institutions cancer patients have received concurrent administration of CoQ_{10} to prevent both chronic and acute cardiotoxicity [9,

11, 12, 90]. For example, the importance of administering CoQ_{10} on the development of doxorubicin-induced cardiotoxicity in patients with lung cancer has been studied by Judy et al. [104]. Doxorubicin given alone without CoQ_{10} caused marked impairment of cardiac function with a significant increase in heart rate and a substantial decrease in ejection fraction, stroke index and cardiac index. In contrast, doxorubicin administered along with CoQ_{10}, did not cause cardiotoxicity, and cardiac function remained unchanged [104]. Other studies have confirmed these results and have shown that CoQ_{10} can reduce the cardiac toxicity of doxorubicin in adults [105, 106] and also in children [107, 108]. Thus in preclinical and clinical studies the data indicate that CoQ_{10} protects the heart from the cardiotoxicity of anthracyclines.

Cancer-Associated Fatigue and Other Adverse Effects of Therapy
The most common complaint of patients undergoing anti-neoplastic therapy is fatigue, but there are also other complaints of patients that are undergoing cancer therapy [13, 14]. These include: pain, nausea, vomiting, malaise, diarrhea, headaches, rashes and infections [23, 106, 108]. Other more serious problems can also occur, such as cardiomyopathy, peripheral neuropathy, hepatotoxicity, pulmonary fibrosis, mucositis and other effects caused by therapy [23, 26, 106, 108]. In terms of their cancer-associated fatigue, most patients feel that cancer therapy-caused fatigue is an untreatable symptom [25]. Although fatigue is usually the most commonly reported adverse symptom during cancer therapy, up until recently there was little effort directed at reducing fatigue before, during or after cancer therapy [109]. The perception that cancer-associated fatigue is an untreatable symptom has changed recently [12, 14].

Reducing cancer-associated fatigue and fatigue associated with cancer therapy are now considered important therapeutic goals. Psychological, physical, pharmaceutical and nutraceutical methods have been undertaken to reduce fatigue and improve the quality of life of cancer patients [14, 23, 111]. Such treatments are based mainly on suppressing fatigue but also on controlling co-morbid or related symptoms, such as pain, anemia, cachexia, sleep disorders, depression and other symptoms [14, 23, 111-115].

Unfortunately, there is no standard protocol related to treating cancer-associated fatigue and related symptoms. In reviewing the types of supportive measures used to control fatigue and related symptoms, the data suggest that graded exercise, nutritional support, treatment of psychological problems (such as depression with certain anti-depressants or psycostimulants), treatment of anemia with hematopoetic growth factors and control of insomnia with cognitive behavioral therapy or pharmacological and nonpharmacological therapies all have a role to various degrees in controlling cancer-associated fatigue [110-115]. Some of these approaches, such as the use of pharmacological drugs and growth factors, have been systematically meta-analyzed in 27 studies [116]. In this limited analysis, only a psycostimulant (methylphenidate) and hematopoetic growth factors (erythropoietin and darbopeitin) were more effective than placebo treatments. Other treatments were no better than placebo in the treatment of cancer-related fatigue 116].

Cancer-Associated Fatigue, Aging and Mitochondrial Membrane Damage

As discussed above, cancer-associated fatigue has been defined as a multidimensional sensation [14, 35, 112, 113, 116]. Most patients understand fatigue as a loss of energy and inability to perform even simple tasks without exertion [116, 117]. Cancer-associated fatigue has been described as the dysregulation of several interrelated physiological, biochemical and psychological systems [112, 113], but at the tissue and cellular levels fatigue is related to reductions in the efficiency of cellular energy systems, mainly found in mitochondria [13, 14, 118]. Damage to mitochondrial components, mainly by ROS/RNS oxidation of membrane phospholipids, can impair mitochondrial function, and this can also result in oxidative damage to other cellular structures [reviewed 36, 42, 44]. Mitochondrial membranes and DNA are major targets of oxidative stress, and with aging ROS/RNS mitochondrial damage can accumulate [80, 119].

During aging and in certain medical conditions oxidative damage to mitochondrial membranes impairs mitochondrial function [80, 119, 120]. For example, in chronic fatigue syndrome patients evidence of oxidative damage to DNA and lipids exists [120, 121] as well as oxidized blood markers [122] and muscle membrane lipids [123] that are indicative of excess oxidative stress [124]. In chronic fatigue syndrome patients also have sustained elevated levels of peroxynitrite due to excess nitric oxide, which can 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, increasing the rate of membrane damage [126].

Lipid Replacement Therapy of Oxidized Membrane Components and its Effect on Fatigue

In cancer patients mitochondrial membranes as well as other cellular membranes are especially sensitive to oxidative damage by ROS/RNS, which occurs at high rates in cancer [65, 66, 68-71, 124]. Oxidation of membrane phospholipids alters their structure, affecting lipid fluidity, permeability and membrane function [124, 126, 127]. One of the most important events caused by ROS/RNS damage is loss of electron transport function, and this appears to be related to mitochondrial membrane lipid peroxidation. Membrane oxidation induces permeability changes in mitochondria, and this can cause loss of mitochondrial transmembrane potential, an essential requirement of oxidative phosphorylation [128, 129].

Lipid Replacement Therapy (LRT) has been used to reverse the accumulation of damaged phospholipids in mitochondria and other cellular membranes by replacing them with unoxidized phospholipids [13, 14, 130]. LRT plus antioxidants has been show to reverse ROS/RNS damage and increase mitochondrial function in certain fatiguing disorders, such as chronic fatigue, chronic fatigue syndrome and fibromyalgia syndrome [118, 131]. LRT has been found to be effective in preventing ROS/RNS-associated changes and reversing mitochondrial damage and loss of function [reviewed in 14, 131].

LRT with unoxidized phospholipids and antioxidant supplements has been effective in replacement of damaged cellular and mitochondrial membrane phospholipids and other lipids that are essential structural and functional components of biological membranes [reviewed in 14, 131]. NTFactor®, a LRT oral supplement containing phospholipids, phosphoglycolipids and other membrane lipids, has been used successfully in animal and clinical LRT studies [13, 14, 118, 131, 132]. NTFactor's encapsulated lipids are protected from oxidation in the gut and can be absorbed and transported into tissues via lipid carriers without oxidation. Once inside cells the membrane lipids naturally replace oxidized, damaged membrane lipids by natural diffusion, and carrier proteins pick up the damaged lipids for degradation, transport and excretion [134].

In preclinical studies NTFactor® lipids have been used to reduce age-related functional damage, such as hearing loss associated with aging in rodents. NT Factor® lipids prevented hearing loss associated with aging and shifted the threshold hearing from 35-40 dB in control, aged rodents to 13-17 dB [134]. They also found that NT Factor® lipids preserved cochlear mitochondrial function and prevented aging-related mitochondrial DNA deletions found in the cochlear [134]. Thus NT Factor® lipids were successful in preventing age-associated hearing loss and reducing mitochondrial damage and DNA deletions in rodents [134].

In clinical studies LRT has been used to reduce fatigue and protect cellular and mitochondrial membranes from oxidative damage by ROS/RNS [reviewed in 13, 14, 131]. A LRT-vitamin mixture containing NT Factor® (Propax^{TM} with NT Factor®) was by used by Ellithorpe et al. [132] in a study of patients with severe chronic fatigue and was found to reduce their fatigue by approximately 40.5% in 8 weeks. In these studies fatigue was monitored by use of the Piper Fatigue Scale to measure clinical fatigue and quality of life [135]. In a subsequent study we examined the effects of NT Factor® on fatigue and mitochondrial function in patients with moderate to severe chronic fatigue [118]. Oral administration of NT Factor® for 12 weeks resulted in a 35.5% reduction in fatigue and 26.8% increase in mitochondrial function; whereas after a 12-week wash-out period fatigue increased and mitochondrial function decreased back towards control levels [118]. Thus in fatigued subjects dietary LRT can significantly improve and even restore mitochondrial function and significantly decrease fatigue. Similar findings were observed in chronic fatigue syndrome and fibromyalgia syndrome patients [131]. Recently a new formulation of NT Factor® plus vitamins, minerals and other supplements (Revacel^{TM} with NT Factor®) resulted in a 36.8% reduction in fatigue within one week [136] (Table 1).

Lipid Replacement Therapy in Conjunction with Cancer Therapy
LRT has been used to reduce the adverse effects of chemotherapy in cancer patients [reviewed in 14]. For example, a vitamin-mineral mixture with NTFactor (Propax^{TM} with NTFactor®) has been used in cancer patients to reduce some of most common adverse effects of cancer therapy, such as chemotherapy-induced fatigue, nausea, vomiting, malaise, diarrhea, headaches and other side effects [137]. In two studies on patients with advanced metastatic colon, pancreatic or rectal

cancers receiving a 12-week chemotherapy treatment schedule of 5-florouracil/ methotrexate/leukovorin LRT was used to reduce adverse effects of chemotherapy [137].

Table 1. Effects of dietary LRT supplement NTFactor on Piper Fatigue Scale scores.[1]

Subjects/patients	n	Av age	Time on LRT	Piper Fatigue Scale fatigue reduction (%)	Reference
Chronic fatigue[2]	34	50.3	8 wks	40.5**	Ellithorpe et al. [132]
Aging, chronic fatigue[3]	20	68.9	12 wks	35.5*	Agadjanyan et al. [118]
Chronic fatigue syndrome (and/or fibromyalgia syndrome[#])[2]	15	44.8	8 wks	43.1*	Nicolson & Ellithorpe [131]
Obesity, fatigue[4]	35	42	8 wks	24*	Nicolson et al. [138]
Aging, chronic fatigue[5]	67	57.3	1 wk	36.8*	Nicolson et al. [136]

[1]Modified from Nicolson [14]
[2]Propax[TM] with NT Factor®
[3]NT Factor®
[4]Healthy Curb[TM] with NT Factor®
[5]Advanced Physician's Formula[TM] or Revacel[TM] with NT Factor®
**P<0.0001, *P<0.001 compared to without NT Factor®
[#]5/15 fibromyalgia syndrome; 3/15 chronic fatigue syndrome plus fibromyalgia syndrome

In the first unblinded part of the clinical study the effectiveness of NTFactor in a vitamin-mineral mixture (Propax[TM] with NTFactor®) administered before and during chemotherapy was determined by examining signs and symptoms, and in particular, the side effects of therapy. A quality of life evaluation was conducted by a research nurse, and it was determined that patients on NTFactor supplementation experienced significantly fewer episodes of fatigue, nausea, diarrhea, constipation, skin changes, insomnia and other side effects [137]. In this open label trial 81% of patients demonstrated an overall improvement in quality of life parameters while on chemotherapy with LRT [137]. In the double-blinded, cross-over, placebo-controlled, randomized part of the study on advanced cancers the patients on chemotherapy plus LRT showed improvements in signs/symptoms associated with the adverse effects of chemotherapy [137]. Adding LRT resulted in improvements in the incidence of fatigue, nausea, diarrhea, impaired taste, constipation, insomnia and other quality of life indicators. Following cross-over from the placebo arm to the LRT arm, 57-70% of patients on chemotherapy reported improvements in nausea, impaired taste, tiredness, appetite, sick feeling and other quality of life

indicators [137] (Table 2). This clinical trial and other data clearly demonstrated the usefulness of LRT given during chemotherapy to reduce the adverse effects of cancer therapy [reviewed in 14].

Table 2. Effects of LRT (Propax^{TM} with NTFactor®) on the adverse effects of cancer chemotherapy in a cross-over clinical trial.[1,2]

First arm	Second arm	Average % patients on test arm[3]		
		improvement	no change	worsening
placebo	Propax^{TM}+NT Factor®	57	22	21
Propax^{TM}+NT Factor®	placebo	70	6	24

[1]Table modified from Nicolson [14].

[2]The same regimen of 5-flurouracil/methotrexate/leukovoran was used for colon, pancreatic or rectal cancers.

[3]The percent of patients' self-reporting adverse effects was averaged with the percent of patients with adverse effects reported by a research nurse.

Potential New Lipid Replacement Therapy Products and their Possible Uses

In addition to use of LRT in cancer patients before, during and after their anti-cancer therapy, LRT has a number of other uses in many possible new products. Some of the possible new products containing LRT formulations are listed in Tables 3 and 4. For example, LRT formulations could have a variety of new uses as additives to functional foods (Table 3) or as condition-specific dietary supplements (Table 4). Some existing uses of LRT formulations in conditions other than cancer are as follows.

Table 3. Potential Functional Food products where LRT can be added.

Nutritional Products	Beverages	Dairy Products	Energy Foods
Fruit powders	Energy drinks	Yogurts `	Energy bars
Vegetable powders	Fruit drinks	Milk	Energy drinks
Protein powders	Vegetable drinks	Cheeses	Energy shots
Meal replacements	Soy milk	Sour cream	Antioxidant drinks
Cereals	Vitamin drinks	Cottage cheese	Cookies
Frozen foods	Probiotic drinks	Butter	Energy chews
Breads and bakery goods	Milk	Ice cream	Powders
Soups		Soy ice cream	
Pet foods			

Table 4. Potential condition-specific dietary supplements with added LRT.

Amino acid supplements	Herbal supplements
Anti-aging supplements	Hormone supplements
Bone and joint supplements	Liver health supplements
Brain health supplements	Urinary health supplements
Cellular support supplements	Mood relief supplements
Digestive support supplements	Prostate health supplements
Heart health supplements	Sports performance supplements
Fiber supplements	Weight loss supplements
Immune enhancement supplements	Multivitamin supplements
Inflammatory support supplements	Essential fatty acid supplements

LRT and Weight Loss

Many individuals have weight issues or are obese, and weight reduction regimens that use drugs or stimulants can result in increased fatigue. We have studied the use of LRT in a weight loss clinical trial using a NT Factor® mixture with an FDA-approved amaylase inhibitor (Healthy Curb™) [138]. The objective was to see if subjects could safely lose weight without increasing appetite or fatigue and without changing eating or exercise patterns or using drugs, herbs or caffeine. A 2-month open label clinical trial with Healthy Curb™ was initiated. Weight and measurements were taken weekly, appetite was assessed and fatigue was determined using the Piper Fatigue Scale [135]. We found that sixty-three percent of the participants lost an average of 6 pounds along with 2.5 and 1.5 inch reductions in waist and hip circumference, respectively, and the entire group of participants lost an average of 3 pounds with average reductions of 1.5 and 1 inch waist and hip circumference, respectively. Participants experienced gradual and consistent weight loss along with reductions in waist and hip measurements, body mass index (BMI) and basal metabolic rate (BMR) during the entire trial [138]. There was a 44% reduction in overall hunger with reduced cravings for sweets, and thus notable appetite suppression occurred during the trial. The entire test group showed an average of 24% decrease in overall fatigue. Blood lipid profiles generally improved, suggesting improved cardiovascular health, and no adverse effects were noted clinically or found in blood chemistries [138].

LRT and Fatiguing Illnesses

Fatiguing illnesses, such as chronic fatigue syndrome, fibromyalgia syndrome, Gulf War illness and other fatiguing illnesses can be successfully treated with LRT, such as NT Factor® and products containing NT Factor® (Table 1). In fatiguing illness patients use of products containing NT Factor® resulted in reductions in fatigue of approximately 35-43% (Table 1) [118, 131, 132, 136]. In addition to fatigue, use of LRT in fatiguing illnesses patients also

resulted in enhanced qualify of life and better mood, concentration, cognition and other symptoms [131, 132, 136], along with enhanced mitochondrial function [118].

LRT and Anti-Aging Products

LRT has the potential to reduce the effects of aging. In animal studies LRT reduced hearing loss and DNA mutations associated with aging [135]. In clinical trials using aged subjects (average age 68.9) LRT with NT Factor® significantly reduced fatigue by 35.5% in 12 weeks [118]. When mitochondrial function was assessed in these subjects, there was a 26.8% increase in mitochondrial function after LRT with NT Factor® to the levels found in much younger adults. After a 12-week wash-out period, fatigue increased and mitochondrial function decreased back towards control levels [118]. This indicated that LRT was effective in reversing some of the effects of aging, such as fatigue and loss of mitochondrial function. Anti-aging formulations, such as Healthy Aging[TM] with NT Factor®, have been used to repair damaged cellular membranes and reverse some of the other natural oxidative effects of aging.

LRT and Degenerative Diseases

Patients with neurodegenerative, neurobehavioral and metabolic illnesses all have problems with excess oxidation damage. For example, in the case of neurological diseases brain cells are particularly vulnerable to oxidative stress and damage caused by excess ROS/RNS. This is because of the brain's inability to withstand excess oxidative stress due to a high content of easily oxidized substrates (membrane phospholipids), relatively low levels of endogenous antioxidants, relatively high levels of endogenous generation of ROS and the endogenous generation of nitric oxide [139-141]. Antioxidant nutraceuticals (natural supplements, vitamins and minerals) have been proposed as a strategy to attenuate oxidative damage in neurological diseases [142]. In addition, LRT formulations, such as Healthy Aging[TM] with NT Factor®, contain a key brain phospholipid (phosphatidylserine) that improves brain "age-associated memory impairment," learning and cognitive performance that are impaired in dementing disorders like Alzheimer's disease [143]. LRT could also be used to repair oxidatively damaged brain structures, such as mitochondrial and cellular membranes, and reduce the damage caused by endogenous oxidation.

LRT and Respiratory Diseases

Asthma, chronic obstructive pulmonary disease and other respiratory conditions are characterized by inflammation and oxidative stress [144, 145]. Antioxidants have been proposed to attenuate the incidence and severity of respiratory attacks [145]. New products, such as Breathe Clear[TM] with NT Factor®, have been used to reduce the symptoms of allergic and respiratory inflammation. In addition to NT Factor®, Breathe Clear[TM] contains quercetin and other bioflavoids plus amino acids and L-taurine to reduce allergic inflammation and pulmonary

reactions. Quercetin is a flavonol that helps modulate the release of histamine by mast cells [146].

LRT and Cardiovascular Diseases
Mitochondrial oxidative stress has been implicated, along with other factors, in cardiovascular disease and heart attack [147, 148]. Aging is accompanied by accumulation of cardiac mitochondrial membrane oxidation, increased mitochondrial DNA mutations as well as decreased production of critical cardiac proteins [147]. Vitamins, minerals, antioxidants and other supplements have been suggested as dietary approaches to reduce the risk of myocardial infarction and coronary disease [149, 150]. LRT could play an important role in repairing cardiac mitochondrial and cellular membranes, an important role in cardiovascular health.

LRT, Metabolic Syndrome (Pre-Diabetes) and Type 2 Diabetes
One of the central defects in metabolic syndrome (a pre-diabetes, pre-cardiovascular disease syndrome) and its associated diseases (type-2 diabetes, vascular inflammation, atherosclerosis, among other diseases) is excess cellular oxidative stress [151, 152]. Nutritional supplements, vitamins, minerals, antioxidants and other supplements [151] as well as LRT with NT Factor are important new approaches, along with diet, weight management and lifestyle changes, for treating metabolic syndrome and preventing its associated diseases [151, 152].

Conclusions
Nutritional supplements have been used in a variety of diseases to provide patients with a natural, safe alternative to pharmacological drugs. In patients with cancer and other chronic illnesses nutritional supplements are often used for specific purposes or to improve quality of life. For example, cancer-associated fatigue is one of the most common symptoms in all forms and stages of cancer, but few patients receive assistance for their fatigue. Cancer-associated fatigue is associated with cellular oxidative stress, and during cancer therapy excess drug-induced oxidative stress can cause a number of adverse effects, including: fatigue, nausea, vomiting and more serious effects. Cancer-associated fatigue and the adverse effects of cancer therapy can be reduced with LRT using natural phospholipid supplements that replace damaged membrane lipids along with providing antioxidants and enzymatic cofactors. Administering dietary LRT supplements can reduce oxidative membrane damage and restore mitochondrial and other cellular functions. Recent clinical trials using cancer and non-cancer patients with chronic fatigue have shown the benefits of specific LRT nutritional lipid supplements in reducing fatigue and restoring mitochondrial function. Newer formulations of LRT supplements will prove to be important additions in the treatment of a variety of chronic illnesses as well as useful additions to anti-aging and other health products.

List of Abbreviations Used

CoQ$_{10}$, coenzyme Q$_{10}$; EKG, electrocardiogram; FDA, Food and Drug Administration; LRT, Lipid Replacement Therapy; RNS, Nitrogen Reactive Species; ROS, Reactive Oxygen Species

Competing Interests

The authors have no financial interests or conflicts of interest.

Authors' Contributions

Both authors contributed to this review.

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