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10

Nutritional Supplements for Cancer-Associated Fatigue and Cancer Therapy – A Molecular Basis for Restoring Mitochondrial Function

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1. Introduction

Cancer patients routinely take multiple – dietary supplements to prevent recurrence or chronic disease, to improve quality of life and overall health, or to reduce the adverse effects of cancer therapy (Gansler et al., 2008; Miller et al., 2009; Ströhle et al., 2010; Velicer & Ulrich, 2008). In fact, one of the most common behavior changes among cancer patients is the use of dietary supplements (Miller et al., 2009).

Although cancer patients routinely use dietary supplements, there is often little consideration as to their safety, efficacy and potential negative effects (Cassileth et al., 2009; Giovannucci & Chan, 2010). 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 (Cassileth et al., 2009; Giovannucci & Chan, 2010). Nonetheless, several potentially beneficial effects of dietary supplements have been recorded, including reductions in the risk of cancer carcinogenesis and tumor progression, enhancement of immune responses against cancers or immune systems in general, improvements in nutrition and general health, and reductions in the adverse effects of cancer therapy (Cassileth et al., 2009; Doyle et al., 2006; Isenring et all, 2010; Miller et al., 2009; Conklin, 2000; Nicolson & Conklin, 2008; Nicolson, 2010; Ströhle et al., 2010),

This review will concentrate on one particularly troublesome aspect of cancer and cancer therapy—cancer-associated fatigue.

2. The importance of cancer-associated fatigue

Cancer-associated fatigue adds considerably to cancer morbidity (Brown & Kroenke, 2009; Hofman et al., 2007). It exists in all types of cancers from the least to the most progressed cancers (Brown & Kroenke, 2009; Hofman et al., 2007). Along with pain and nausea, it is one of the most common and troublesome symptoms of cancer (Hofman et al., 2007; Prue et al., 2006), especially in advanced cancers (Curt et al., 2000; Prue et al., 2006; Respini et al., 2003).

In patients receiving adjuvant therapies the prevalence of cancer-associated fatigue is reported to be as high as 95% (Sood & Moynihan, 2005). Thus cancer-associated fatigue is a

problem before, during and after therapy and can continue to be a problem years after cancer treatment (Curt et al., 2000; Hofman et al., 2007). 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 (Curt et al., 2000; Nicolson, 2010).

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 (Curt et al., 2000; Hofman et al., 2007). Unfortunately, cancer-associated fatigue is rarely treated, and is often thought to be an unavoidable symptom (Brown & Kroenke, 2009; Hofman et al., 2007).

Cancer-associated fatigue can be considered to be the product of a variety of contributing factors (Ahlberg et al., 2003). In addition to a decrease in the availability of cellular energy, there are psychological factors, such as the presence of depression, anxiety, sleep disturbances, among others, as well as anemia, endocrine changes, poor nutritional status, release of inflammatory cytokines and cancer therapy that can all contribute to cancer-associated fatigue (Ahlberg et al., 2003; Gutstein, 2001; Manzullo & Escalante, 2002; Sood & Moynihan, 2005). Thus cancer-associated fatigue does not occur as an isolated symptom; rather, it occurs as one of multiple symptoms that are present in cancer patients. Similar to some other symptoms in cancer patients, the severity of cancer-associated fatigue correlates with decreased functional abilities (Given et al., 2001).

Cancer therapy also contributes to cancer-associated fatigue (Sood & Moynihan, 2005). In fact, the most commonly found and disabling effect of cancer therapy is fatigue (Given et al., 2001; Sood & Moynihan, 2005; Vogelzang et al., 1997). During cancer therapy fatigue problems can vary, from mild to severe, and excess fatigue during cancer therapy is a significant reason why patients discontinue therapy (Liu et al., 2005). Reviewing articles on the effects of cancer therapy on fatigue, it was noted that 80-96% of patients receiving chemotherapy and 60-93% receiving radiotherapy experienced moderate to severe fatigue, and fatigue continued for months to years after cancer therapy ended (Manzullo & Escalante, 2002). Therefore, in cancer patients controlling cancer-associated fatigue as well as therapy-induced fatigue are both important strategies (Marrow, 2007).

There have been efforts at understanding and treating cancer-associated fatigue as well as developing ways to distinguish between depression and cancer-associated fatigue (Brown & Kroenke, 2009). Both cancer-associated fatigue and depression have multidimensional and heterogeneous qualities, possessing physical, cognitive and emotional dimensions and a certain degree of overlap across these dimensions (Brown & Kroenke, 2009; Sood & Moynihan, 2005). In cancer patients fatigue or loss of energy is a core aspect of 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-morbitity or syndrome (Arnold, 2008; Bender et al., 2008). There are techniques, moreover, that can distinguish between these two different symptoms by removal of fatigue-associated assessments from an analysis of depression (Smets et al., 1996; Stone et al., 2000). When assessing fatigue or cancer-associated fatigue, criteria have been established that take depression into consideration, and these two symptoms can thus be separated out by considering unshared properties (Cella et al., 2001).

Chronic or intractable fatigue lasting more than 6 months that is not reversed by normal sleep is the most common complaint of patients seeking general medical care (Kroenke et al., 1988; Morrison, 1980). It occurs naturally during aging and is also an important secondary condition in many clinical diagnoses (Kroenke et al., 1988; McDonald et al., 1993).

Most fatigued 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 (Kroenke et al., 1988; McDonald et al., 1993; Morrison, 1980). However, this symptom is especially important in the overwhelming majority of cancer patients (Ahlberg et al., 2003; Curt et al., 2000; Hofman et al., 2007; Sood, & Moynihan, 2005).

3. Oxidative stress and damage to mitochondrial membranes – Relationship to fatigue

Another phenomenon associated with cancer and its progression as well as aging and age-related degenerative diseases is oxidative stress (Dreher & Junod,1996; Halliwell, 1996; Kehrer, 1993). 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, and mutation of mitochondrial and nuclear DNA (Abidi & Ali, 1999; Bartsch & Nair, 2004; Marnett, 2000; Stadtman, 2002). ROS and RNS are naturally occurring cellular free radical oxidants that are usually present in low concentrations and are involved in gene expression, intracellular signaling, cell proliferation, antimicrobial defense and other normal cellular processes (Castro & Freeman, 2001; Ghaffari, 2008; Johnson et al., 1996). However, when ROS/RNS are in excess over cellular antioxidants, damage can occur to cellular structures (Abidi & Ali, 1999; Castro & Freeman, 2001; Ghaffari, 2008; Maes & Twisk, 2009). Recently Maes (2009) has proposed a link between excess oxidative stress (and activation of ROS/RNS pathways and fatigue and fatiguing illnesses.

Under normal physiological conditions our cellular antioxidant defenses usually maintain ROS/RNS at appropriate concentrations that prevent excess oxidation of cellular structures (Barber & Harris, 1994; Fridovich,1995; Sun, 1990). Endogenous cellular antioxidant defenses include glutathione peroxidase, catalase and superoxide dismutase, among other enzymes (Jagetia et al., 2003; Seifried et al., 2003), and low molecular weight dietary antioxidants (Aeschbach et al., 1994; Schwartz,1996). Some of these dietary antioxidants have been used as natural chemopreventive agents to shift the excess concentrations of oxidative molecules towards more physiological levels (Prasad et al., 200; Tanaka, 1994).

Excess oxidative stress (or primarily its mediators—excess ROS/RNS) within cancer cells has been linked to promotion and progression of malignancy of cancers (Brown & Bicknell, 2001; Klaunig & Kamendulis, 2004; Ray et al., 2000; Tas et al., 2005; Toyokuni et al., 1995). Thus oxidative stress and antioxidant status have been examined in various malignant cancers, such as breast (Brown & Bicknell, 2001; Kang, 2002; Ray et al., 2000; Tas et al., 2005), prostate (Aydin et al., 2006; Sikka, 2003), colorectal (Otamiri & Sjodahl,1989; Oxdemirler et al., 1989), renal (Asal et al., 1990; Gago-Dominguez et al., 2002), and other malignancies (Batcioglu et al., 2006; Manoharan et al., 2005; Seril et al., 2003). In all of these cancers ROS/RNS were in excess of antioxidant concentrations, resulting in cellular oxidative stress. Thus these cancers could possibly have been induced as a consequence of excess ROS/RNS and oxidative damage to the genetic apparatus (Abidi & Ali, 1999; Dreher & Junod, 1996; Jaruga et al., 1992). Even more likely than carcinogenesis is the promotion of progression of tumors that might not evolve to malignancy in the absence of excess oxidative stress (Nicolson, 2010; Nicolson & Conklin, 2008).

4. Cancer therapy causes excess oxidative stress and severe fatigue

The most common therapies used against cancers, such as chemotherapy, can result in the generation of excess ROS/RNS (Conklin, 2000; 2004). Thus cancer therapy and the resulting production of excess oxidative stress can damage biological systems other than tumors (Conklin, 2004; Nicolson, 2010; Nicolson & Conklin, 2008). 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 (Conklin, 2004). 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. The very high levels of oxidative stress caused by anthracyclines are 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 (Conklin, 2000; 2004).

Although anthracyclines and other chemotherapeutic agents cause generation of high levels of ROS/RNS, 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 antifolates, and nucleoside and nucleotide analogues (Conklin, 2000; 2004; Nicolson & Conklin, 2008). Most chemotherapeutic agents do, however, generate some oxidative stress, as do all anti-neoplastic agents when they induce apoptosis in cancer cells. 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 (Betteridge, 2000; Conklin, 2000).

Use of chemotherapeutic agents to treat cancer causes oxidative stress that produces side effects, including fatigue. This can reduce the efficacy of therapy (Nicolson & Conklin, 2008; Nicolson, 2010). Many anti-neoplastic agents have clearly established mechanisms of action that are not dependent upon the generation of ROS/RNS; however, these drugs can only mediate their anticancer effects on cancer cells that exhibit unrestricted progression through the cell cycle and have intact apoptotic pathways. 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, inhibiting cell cycle progression of G_1 to S phase, and by checkpoint arrest (Balin et al., 1978; Gonzalez, 1992; Hauptlorenz et al., 1985; Kurata, 2000; Schackelford et al., 2000).

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 (Fojo, 2001; Wei et al., 2000; Zhen et al., 1992). Abolishing checkpoint arrest produces the opposite effect and enhances the cytotoxicity of antineoplastic 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 (Conklin, 2004).

Oxidative stress can affect important intracellular signal transduction pathways that are necessary for the action of some antineoplastic agents (Conklin, 2004; Hampton et al., 1998;

Shacter et al., 2000). There are two major pathways of drug-induced apoptosis following cellular damage by antineoplastic agents: the mitochondrial pathway, initiated by release of cytochrome c, and the CD95 death receptor pathway, initiated by CD95L binding to its death receptor (Fojo, 2001). 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, and this results in the impairment of the ability of antineoplastic agents to initiate apoptosis (Chandra et al., 2000; Hampton et al., 1998; Shacter et al., 2000).

In addition to chemotherapy, radiotherapy also results in generation of oxidative stress and excess ROS/RNS (Feinendegen et al., 2007; Greenberger et al., 2001). The principal target of radiation is tumor cell DNA, and this can be directly damaged by radiation. However, genetic damage is also mediated by excess ROS/RNS (Epperly et al., 2003; Feinendegen et al., 2007). Recently the principal source of excess ROS/RNS during radiotherapy has been shown to be the mitochondria (Epperly et al., 2003; Sabbarova & Kanai, 2007). The initial cytotoxicity of radiation is now thought to be due to excess ROS/RNS triggering of apoptosis via alteration of mitochondrial metabolism. This causes transiently opening of mitochondrial permeability transition pores, which increases the influx of calcium ions into the matrix. The influx of calcium ions stimulates mitochondrial nitric oxide synthase and generation of nitric oxide, which inhibits the respiratory chain and eventually stimulates excess ROS/RNS free radicals that initiate apoptosis (Leach et al., 2002; Sabbarova & Kanai, 2007).

5. Cancer therapy and mitochondrial damage

Cancer therapy is associated with several adverse side effects. One of the most difficult side effects is caused by chemotherapeutic drug damage to mitochondria (Conklin, 2000; Nicolson & Conklin, 2008). Cardiac mitochondria are especially sensitive to certain chemotherapy agents, such as anthracycline antibiotics (Conklin, 2004). 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 (Conklin, 2004; 2005). The selective anthracycline-induced toxicity to cardiac cells is due to damage of 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 in that they possess a Complex I-associated NADH dehydrogenase in the inner mitochondrial membrane facing the cytosol (Lehninger, 1951; Rasumssen & Rasmussen, 1985).

Doxorubicin is a relatively small molecule, and because of this property it readily penetrates the outer mitochondrial membrane. However, because it is hydrophilic and cannot partition into the lipid membrane matrix, it cannot penetrate the inner mitochondrial membrane (Conklin, 2005; Nohl, 1987). 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 (Conklin, 2005; Nohl, 1987). But in heart cells doxorubicin can interact with the mitochondrial cytosolic-facing NADH dehydrogenase that is unique to this tissue (Davies & Doroshow, 1986; Doroshow & Davies, 1986). This interaction produces doxorubicin aglycones, which are highly lipid soluble and readily penetrate the inner mitochondrial membrane (Conklin, 2005; Gille & Nohl, 1997). At this

location they can displace CoQ_{10} from the electron transport chain (Conklin, 2005; Davies & Doroshow, 1986).

The displacement of CoQ_{10} from the electron transport chain during doxorubicin treatment results in decreases of CoQ_{10} in cardiac muscle (Karlsson et al., 1986) as the plasma concentration of CoQ_{10} increases (Eaton et al., 2000). 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 (Papadopoulou & Tsiftsoglou, 1996). Thus, doxorubicin generates a high level of oxidative stress in cardiac mitochondria, causing acute cardiac toxicity and damage to mitochondrial DNA (Conklin, 2005; Doroshow & Davies, 1986; Palmeira et al., 1991).

Anthracycline-damaged cardiac cell mitochondria cannot sustain their function, and changes in their structure results in disruption of mitochondria and eventually apoptosis (Serrano et al., 1999; Conklin, 2005; Gille & Nohl, 1997). 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 decreasing anthracycline metabolism within cardiac mitochondria and by competing with aglycones for the CoQ_{10} sites within the electron transport chain (Conklin, 2005). 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 (Conklin, 2000; 2005).

In addition to chemotherapy, radiotherapy also produces damage to tissues other than cancerous tissues. Agents that protect tissues against radiation effects have been used to reduce unwanted damage (Brizel, 2007; Sabbarova & Kanai, 2007).

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 (Brizel, 2007; Sabbarova & Kanai, 2007). The most effective of these under development 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 to produce this important dismutase have been used as radioprotective agents (Sabbarova & Kanai, 2007).

6. Molecular replacement of mitochondrial components during cancer therapy

As discussed in Section 5, chemotherapy can displace important mitochondrial cofactors, such as CoQ_{10} (Conklin, 2000; 2005). During chemotherapy replacement of CoQ_{10} dramatically prevents development of anthracycline-induced cardiomyopathy and histopathological changes. It can also prevent changes in electrocardiograms (EKG) characteristic of anthracycline-induced heart damage (Domae et al., 1981). Indeed, the administration of CoQ_{10} to animals resulted in increased survival, improvement in the EKG patterns, and reduced heart histopathological changes (Usui et al., 1982). These preclinical data, along with clinical data (discussed in Conklin, 2004 and Nicolson & Conklin, 2008) support the contention that CoQ_{10} protects the heart tssue from anthracycline-induced damage.

During chemotherapy of cancer, patients have received concurrent administration of CoQ_{10}. This can affect both acute and chronic cardiotoxicity caused by anthracyclines (Conklin, 2004; 2005; Nicolson & Conklin, 2008). For example, Judy et al. (1984) studied the importance of administering CoQ_{10} on the development of doxorubicin-induced cardiotoxicity in patients with lung cancer. 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—cardiac function remained unchanged. Other studies have confirmed these results and have shown that CoQ_{10} can reduce the cardiac toxicity of doxorubicin in adults (Buckingham et al., 1997; Cortes et al., 1978) and children (Iarussi et al., 1994; Loke et al., 2006).

Thus in preclinical and clinical studies the data indicate that CoQ_{10} protects the heart from the cardiotoxicity of anthracyclines. The impact of CoQ_{10} on the anti-neoplastic efficacy of anthracycline-based chemotherapy, however, was not studied in these reports (Buckingham et al., 1997; Cortes et al., 1978; Iarussi et al., 1994; Loke et al., 2006).

7. Cancer-associated fatigue and other cancer-associated conditions

The most common complaint of patients undergoing anti-neoplastic therapy is fatigue, but there are also other complaints that include: pain, nausea, vomiting, malaise, diarrhea, headaches, rashes and infections (Buckingham et al., 1997; Loke et al., 2006; Manzullo & Escalante, 2002). Other more serious problems can also occur, such as cardiomyopathy, peripheral neuropathy, hepatotoxicity, pulmonary fibrosis, mucositis and other effects (Buckingham et al., 1997; Liu et al., 2005; Loke et al., 2006; Manzullo & Escalante, 2002). Due to misconceptions among patients and their physicians, most patients feel that cancer therapy-associated fatigue is an untreatable symptom (Vogelzang et al., 1997). 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 (Von Roenn & Paice, 2005). This has changed recently (Nicolson, 2010; Nicolson & Conklin, 2008).

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 (Borneman et al., 2007; Escalante et al., 2011; Nicolson, 2010). These treatments are based on suppressing fatigue but also on controlling co-morbid or related symptoms, such as pain, anemia, cachexia, sleep disorders, depression and other symptoms (Escalante et al., 2011; Mustian et al., 2007; Nicolson, 2010; Ryan et al., 2007; Watson & Mock, 2004; Zee & Acoli-Isreal, 2009).

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

(Escalante et al., 2011; Mustian et al., 2007; Nicolson, 2010; Ryan et al., 2007; Watson & Mock, 2004; Zee & Acoli-Isreal, 2009). Some of these approaches using pharmacological drugs and growth factors have been systematically analyzed in 27 studies (meta-analysis) by Milton et al. (2008). 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 (Milton et al., 2008).

8. Cancer-associated fatigue, aging and oxidative mitochondrial damage

Cancer-associated fatigue has been defined as a multidimensional sensation (McDonald et al., 1993; Milton et al., 2008; Mustian et al., 2007; Ryan et al., 2007). Most patients understand fatigue as a loss of energy and inability to perform even simple tasks without exertion (Levy, 2008; Milton et al., 2008). Cancer-associated fatigue has been described as the dysregulation of several interrelated physiological, biochemical and psychological systems (Mustian et al., 2007; Ryan et al., 2007), but at the tissue and cellular levels fatigue is related to reductions in the efficiency of cellular energy systems, mainly found in mitochondria (Agadjanyan et al., 2003; Nicolson, 2003; 2005). Damage to mitochondrial components, mainly by ROS/RNS oxidation, can impair mitochondrial function, and this can also result in oxidative damage (reviewed in Bartsch & Nair, 2004; Castro & Freeman, 2001; Kehrer, 1993). Mitochondrial membranes and DNA are major targets of oxidative stress, and with aging ROS/RNS mitochondrial damage can accumulate (Huang & Manton, 2004; Wei & Lee, 2002).

During aging and in certain medical conditions oxidative damage to mitochondrial membranes impairs mitochondrial function (Huang & Manton, 2004; Logan & Wong, 2001; Wei & Lee, 2002). For example, in chronic fatigue syndrome patients there is evidence of oxidative damage to DNA and lipids (Logan & Wong, 2001; Manuel y Keenoy et al., 2001) as well as oxidized blood markers (Richards et al., 2000) and muscle membrane lipids (Felle et al., 2000) that are indicative of excess oxidative stress (Dianzani, 1993). 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 (Pall, 2000).

9. Molecular replacement 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 (Batcioglu et al., 2006; Dianzani, 1993; Gago-Dominguez et al., 2002; Manoharan et al., 2005; Otamiri & Sjodahl, 1989; Oxdemirler et al., 1989; Seril et al., 2003). Oxidation of membrane phospholipids alters their structure, affecting lipid fluidity, permeability and membrane function (Dianzani, 1993; Nicolson et al., 1977; Subczynski & Wisniewska, 2000). 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 (Kanno et al., 2004; Radi et al., 1994).

Lipid Replacement Therapy (Nicolson, 2003; 2005; 2010) has been used to reverse the accumulation of damaged lipids in mitochondria and other cellular membranes. Lipid Replacement Therapy plus antioxidants can reverse ROS/RNS damage and increase mitochondrial function in certain fatiguing disorders, such as chronic fatigue, chronic fatigue syndrome and fibromyalgia syndrome. Lipid Replacement Therapy has been found to be effective in preventing ROS/RNS-associated changes and reversing mitochondrial damage and loss of function (reviewed in Nicolson, 2010; Nicolson & Ellithrope, 2006).

Lipid Replacement Therapy with unoxidized lipid 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 all biological membranes (reviewed in Nicolson, 2010; Nicolson & Ellithrope, 2003). NTFactor, a Lipid Replacement oral supplement containing phospholipids, phosphoglycolipids, cardiolipid precursors and other membrane lipids, has been used successfully in animal and clinical lipid replacement studies (Agadjanyan et al., 2003; Ellithorpe et al., 2003; Nicolson & Ellithorpe, 2006; Nicolson et al., 2010). 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 (Mansbach & Dowell, 2000).

In preclinical studies NTFactor has been used to reduce age-related functional damage. Using rodents Seidman et al. (2002) found that NTFactor prevented hearing loss associated with aging and shifted the threshold hearing from 35-40 dB in control, aged rodents to 13-17 dB. They also found that NTFactor preserved cochlear mitochondrial function and prevented aging-related mitochondrial DNA deletions found in the cochlear. Thus NTFactor was successful in preventing age-associated hearing loss and reducing mitochondrial damage and DNA deletions in rodents (Seidman et al. 2002).

In clinical studies Lipid Replacement Therapy has been used to reduce fatigue and protect cellular and mitochondrial membranes from oxidative damage by ROS/RNS (reviewed in Nicolson, 2003; 2005; 2010). A vitamin supplement mixture containing NTFactor was by used by Ellithorpe et al. (2003) 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 (Piper et al., 1987). In addition, in a subsequent study we examined the effects of NTFactor on fatigue and mitochondrial function in patients with chronic fatigue (Agadjanyan et al., 2003). Oral administration of NTFactor 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 (Agadjanyan et al., 2003). Thus in fatigued subjects dietary Lipid Replacement Therapy can significantly improve and even restore mitochondrial function and significantly decrease fatigue. Similar findings were observed in chronic fatigue syndrome and fibromyalgia syndrome patients (Nicolson & Ellithorpe, 2003). Recently a new formulation of NTFactor plus vitamins, minerals and other supplements resulted in a 36.8% reduction in fatigue within one week (Nicolson et al., 2010) (Table 1).

Subjects/patients	n	age	Average Time on NTFactor	Piper Fatigue Scale fatigue reduction (%)	Reference
Chronic fatigue	34	50.3	8 wks	40.5**	Ellithorpe et al., 2003
Aging, chronic fatigue	20	68.9	12 wks	35.5*	Agadjanyan et al., 2003
Chronic fatigue syndrome (and/or fibromyalgia syndrome#)	15	44.8	8 wks	43.1*	Nicolson & Ellithorpe, 2003
Aging, chronic fatigue	67	57.3	1 wk	36.8*	Nicolson et al., 2010

Modified from Nicolson (2010)
**P<0.0001, *P<0.001 compared to without NTFactor
#5/15 fibromyalgia syndrome; 3/15 chronic fatigue syndrome plus fibromyalgia syndrome
Ad

Table 1. Effects of dietary Lipid Replacement supplement NTFactor on Piper Fatigue Scale scores.

10. Lipid replacement therapy in conjunction with cancer therapy

Lipid Replacement Therapy has been used to reduce the adverse effects of chemotherapy in cancer patients (Nicolson, 2010). For example, a vitamin-mineral mixture 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 (Colodny et al., 2000). 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 Lipid Replacement Therapy was used to reduce adverse effects of chemotherapy.

In the first unblinded part of the clinical study the effectiveness of NTFactor in a vitamin-mineral mixture 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 (Colodny et al., 2000). In this open label trial 81% of patients demonstrated an overall improvement in quality of life parameters while on chemotherapy with Lipid Replacement Therapy (Colodny et al., 2000).

In the double-blinded, cross-over, placebo-controlled, randomized part of the study on advanced cancers the patients on chemotherapy plus Lipid Replacement Therapy showed improvements in signs/symptoms associated with the adverse effects of chemotherapy (Colodny et al., 2000). Adding Lipid Replacement 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 Lipid Replacement Therapy arm, 57-70% of patients on chemotherapy reported improvements in nausea, impaired taste, tiredness, appetite, sick feeling and other quality of life indicators (Colodny et al., 2000) (Table 2). This clinical trial and other data clearly demonstrated the usefulness of Lipid Replacement Therapy given during chemotherapy to reduce the adverse effects of cancer therapy (Nicolson, 2010).

First arm	Second arm	Average % patients on test arm# improvement	no change	worsening
placebo	Propax(+NTFactor)	57	22	21
Propax(+NTFactor)	placebo	70	6	24

Table modified from Nicolson (2010).
* The same regimen of 5-flurouracil/methotrexate/leukovoran was used for colon, pancreatic or rectal cancers.
#The percent of patients' self-reporting adverse effects was averaged with the percent of patients with adverse effects reported by a research nurse.

Table 2. Effects of Propax with NTFactor on the adverse effects of chemotherapy in a cross-over trial.

11. Summary – Cancer-sssociated fatigue and its treatment

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 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 Lipid Replacement Therapy, a natural lipid supplement formulation that replaces damaged membrane lipids along with providing antioxidants and enzymatic cofactors. Administering dietary Lipid Replacement Therapy 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 Lipid Replacement Therapy nutritional lipid supplements in reducing fatigue and restoring mitochondrial function.

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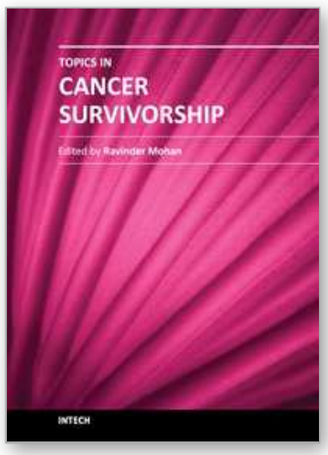
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Cancer is now the leading cause of death in the world. In the U.S., one in two men and one in three women will be diagnosed with a non-skin cancer in their lifetime. Cancer patients are living longer than ever before. For instance, when detected early, the five-year survival for breast cancer is 98%, and it is about 84% in patients with regional disease. However, the diagnosis and treatment of cancer is very distressing. Cancer patients frequently suffer from pain, disfigurement, depression, fatigue, physical dysfunctions, frequent visits to doctors and hospitals, multiple tests and procedures with the possibility of treatment complications, and the financial impact of the diagnosis on their life. This book presents a number of ways that can help cancer patients to look, feel and become healthier, take care of specific symptoms such as hair loss, arm swelling, and shortness of breath, and improve their intimacy, sexuality, and fertility.

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