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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).