

# **MEMBRANE LIPID REPLACEMENT AND ITS USE IN RESTORING MEMBRANE FUNCTION AND REDUCING FATIGUE, PAIN, AND OTHER SYMPTOMS IN CHRONIC CONDITIONS AND AGING**

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## **SUMMARY**

Membrane Lipid Replacement is the use of functional oral supplements containing cell membrane glycerolphospholipids and antioxidants to safely replace damaged membrane phospholipids that accumulate during aging and in various chronic and acute conditions. Most if not all clinical conditions and aging are characterized by membrane phospholipid damage, resulting in loss of membrane and cellular function. Our clinical trials have shown the benefits of Membrane Lipid Replacement supplements in replenishing damaged membrane lipids and restoring mitochondrial function, resulting in reductions in fatigue, pain and other symptoms in aged subjects and patients with a variety of conditions. Recent observations have indicated that Membrane Lipid Replacement can be a useful natural supplement strategy in a variety of conditions, such as unrelenting and chronic fatigue, found in many conditions and disorders;; obesity and metabolic condions; chronic pain, present in many conditons; chemical contamination and changes associated with normal aging. Membrane Lipid Replacement provides general membrane nutritional support during aging and various conditiions to improve membrane function and overall health without risk of adverse effects. It is an extremely safe alternative to pharmaceutical approaches to alleviating fatigue, pain, gastrointestinal problems and other symptoms associated with chronic and acute conditions and aging.

## **INTRODUCTION: MEMBRANE LIPID REPLACEMENT**

Membrane Lipid Replacement (MLR) is the oral supplementation of membrane phospholipids and antioxidants to provide replacement molecules that are damaged during chronic conditions and aging [1, 2]. Replacement membrane phospholipids are important for a variety of cellular and tissue functions and for general health [1, 3]. For example, membrane phospholipids form the matrix for all cellular membranes and provide separation of enzymatic and chemical reactions into discrete cellular compartments and organelles, while also being essential for the function of membrane enzymes and receptors. Phospholipids are also an important energy storage reservoir and provide precursors for bioactive molecules that function in cellular signalling and molecular recognition pathways [7, 8]. Thus MLR lipids are essential for general health [1-3].

Orally ingested phospholipids can be degraded into their constuent parts and absorbed; or they can be taken in as intact molecules without degradation as small phospholipid droplets and

micells [2]. When present in excess, most phospholipids in the gastrointestinal system are absorbed undegraded as phospholipid droplets [2]. The process is very efficient—over 90% of phospholipids are absorbed and transported into the blood within six hours [4]. In the blood circulation phospholipids are usually found in carrier molecules, such as lipoproteins, or cell membranes of erythrocytes or red blood cells. Eventually they are delivered to tissues and cells where they are transferred by membrane contact and carrier or transport proteins to various cellular and organelle membranes [2]. Along this pathway, and at their ultimate destination, glycerolphospholipids can be modified, for example by substitution of their fatty acid side chains, to reflect the specific compositions of the membranes at their final destination. The process appears to be driven by mass action (more is faster and better), so excess intact phospholipids have an advantage in being able to reach their final destination without being degraded (reviewed in [2]).

Patients with chronic conditions as well as aged individuals are often deficient in MLR phospholipids, because dietary sources usually cannot provide enough MLR lipids for maintenance of undamaged cellular membranes, and thus health can suffer [1, 2, 4]. To provide the necessary MLR glycerolphospholipids these lipids have been used as supporting molecules for health maintenance. Dietary lipids, such as essential phospholipids and fatty acids, are effective oral supplements, because they are successfully and efficiently absorbed in the upper small intestine within hours [2, 4].

In most if not all acute and chronic conditions cellular membranes are damaged by oxidative free radicals that are produced inside cells [1, 2]. During acute and chronic conditions the concentrations of free radical reactive oxygen species (ROS), such as superoxide anion radicals, hydroxyl radicals and hydrogen peroxide, and reactive nitrogen species, primarily peroxynitrite anion, are dramatically increased. The usual cellular antioxidants that normally neutralize these free radical oxidants are unable to neutralize all of them, and thus damage to cellular components occurs [2]. Membrane phospholipids and their unsaturated fatty acids are especially sensitive to oxidative damage by ROS and reactive nitrogen species [1, 2]. Thus oral supplementation of membrane lipids as MLR molecules for cellular membranes and other cellular structures has been used to restore cellular membranes in critical cellular structures, such as mitochondria [1, 2].

### **COMPOSITIONS OF MLR LIPID SUPPLEMENTS (NTFactor Lipids®)**

The lipid compositions of most MLR supplements are now available [1, 2]. For example, the lipid composition of one MLR supplement, NTFactor Lipids®, was recently disclosed [1]. NTFactor Lipids® is a mixture of glycerolphospholipids with unsaturated fatty acids and was developed based on mitochondrial lipid composition. It contains by weight a diverse mixture of glycerolphospholipids and fatty acids [1].

### **SAFETY OF MLR SUPPLEMENTS (NTFactor Lipids®)**

Extremely high doses of MLR phospholipids have been given to animals and humans with no apparent acute or chronic toxicities (reviewed in [2]). For example, in a long-term phase I/II clinical trial using patients with cardiovascular disease, phospholipid was given at doses over 5 grams per day with no adverse effects [5]. The phospholipid was shown to increase plasma

high-density lipoprotein and apolipoprotein A1 levels and reduce triglyceride levels without any evidence of toxicity [5].

The use of relatively high oral doses of MLR lipids has actually improved cardiovascular blood markers. In one study, older subjects (60.7 average age) received over 2 grams per day of oral glycerolphospholipids (NTFactor®) for over 6 months and showed no adverse effects of the MLR phospholipids [6]. In fact, cardiovascular blood marker levels, such as homocysteine, a blood marker for cardiovascular health, heart attack and hospitalization, improved significantly during this period without any evidence of any adverse effects from the MLR phospholipids [6]. In fact, there has never been any evidence of any toxicity or adverse events from the long-term use of MLR glycerolphospholipids [1-3, 5, 6]. Therefore, the U.S. Federal Drug Administration (FDA) has classified MLR phospholipids as ‘Generally Recognized as Safe’ or GRAS [7].

### **OTHER MLR LIPID SUPPLEMENTS**

Several oral dietary phospholipid supplements have been developed over the years that contain mixtures of the common membrane glycerolphospholipids and other lipid components [1-3, 5]. Of the commercially available oral phospholipid supplements, most are lecithin preparations that lack protection from oxidation and enzymatic destruction [1, 2]. However, some oral MLR supplements, such as NTFactor® and NTFactor Lipids®, are protected against oxidation and degradation and fulfill the requirements for convenience, efficacy and safety [1, 2]. The MLR lipids in NTFactor® and NTFactor Lipids® contain fructooligosaccharides (inulins) that protect the glycerolphospholipids from oxidation, bile and enzymatic destruction and temperature extremes [2]. Daily use of MLR supplements have been found to be safe in amounts of several grams of glycerolphospholipids per day [4, 5].

Recently dietary supplements have been developed that contain MLR phospholipids along with additional non-MLR ingredients. For example, some NTFactor lipid-containing supplements also contain probiotic bacteria, various vitamins and minerals and other components (Propax™ with NTFactor®, Advanced Physician’s Formula™, Healthy Aging™, Pro-Green Energy with NTFactor®, among others). A specific supplement for mitochondrial support contains NTFactor® and also NADH, Coenzyme-Q10, vitamin E,  $\alpha$ -ketoglutaric acid, L-carnitine, and other ingredients in order to overcome mitochondrial deficiencies other than damaged membrane phospholipids [8].

### **MITOCHONDRIAL FUNCTION AND FATIGUE**

The most common clinical use of MLR supplements is to treat fatigue [1, 2, 9]. Fatigue is the most common complaint of patients seeking general medical care, and it is associated with aging and most if not all chronic medical conditions [10]. Fatigue is considered a complex, multi-dimensional sensation that is not well understood but is perceived to be a loss of overall energy, mental or physical tiredness, a feeling of exhaustion or diminished endurance, and an inability to perform even simple tasks without exertion [9, 10]. Fatigue develops during aging and chronic diseases due to a variety of causes, including loss of mitochondrial function [1, 2, 9]. Indeed, moderate to severe fatigue has been directly related to loss of mitochondrial function and diminished production or leakage of high energy molecules, such as ATP [1, 2].

Many conditions associated with fatigue are closely related to loss of mitochondrial function [2, 11]. Chronic fatigue in various conditions is also closely related to loss of mitochondrial function or mitochondrial dysfunction. For example, certain mental conditions, such as schizophrenia, bipolar disease, among others, some cancers and other conditions may or may not be associated with mitochondrial dysfunction [11]. Mental and cancer patients are often characterized with moderate to severe depression, and depression is frequently related to mild fatigue states where it shows some physical, cognitive and emotional overlap with fatigue [11].

Loss of mitochondrial function has been directly related to oxidative damage to mitochondrial membrane lipids, especially in the inner mitochondrial membrane [2, 11]. Inner mitochondrial membrane (MIM) lipid damage increases proton and ion leakiness and lowers trans-membrane potential of the MIM, reducing the production of high energy molecules (ATP). The consequence of a loss in ATP production is reduced physical and mental performance, as seen with aging and disease. This is obviously seen in chronic fatigue syndrome patients, as these patients present with evidence of oxidative damage to their DNA and lipids, such as oxidized oxidized membrane lipids. These are indicators of excess oxidative stress [2, 12]. Thus patients have sustained, elevated levels of free radical oxidants, such as ROS and RNS, which can result in loss of mitochondrial function [12].

## **USE OF MLR SUPPLEMENTS TO REDUCE FATIGUE**

MLR supplements have been used in several clinical studies designed to support moderate to severe chronic fatigue in order to reduce fatigue scores (less fatigue) (Table 1). Although most of the studies in Table 1 were relatively small (less than 50 participants) and open-label (lacking placebo controls), there were highly significant outcomes in terms of fatigue reductions. One non-open label exception was a cross-over trial studying the effects of oral NTFactor<sup>®</sup> on fatigue in moderately to severely fatigued older subjects [14]. In this cross-over trial there was good correspondence between reductions in fatigue and gains in mitochondrial function, as assessed by MIM redox potential. After 8 weeks of MLR with 4 grams per day of NTFactor<sup>®</sup>, mitochondrial function improved significantly, and after 12 weeks of NTFactor<sup>®</sup> supplementation, mitochondrial function was found to be similar to that found in young healthy adults (26.8% increase,  $p < 0.0001$ ). In this study fatigue was reduced 35.5% ( $p < 0.001$ ) during this period [35]. After 12 weeks of supplement use, subjects were placed on placebo without their knowledge for an additional 12 weeks, and their fatigue and mitochondrial function were measured. After the 12-week placebo period, fatigue and mitochondrial function were intermediate between the initial starting values and those found after eight or 12 weeks on the supplement [14]. Similar results on the effects of NTFactor on fatigue were found in subjects with chronic fatigue syndrome (CFS/ME) and/or fibromyalgia, Gulf War illness and chronic Lyme disease (reductions from 26-43%, Table 1). Analyzed together, these clinical data indicate that MLR can be successfully used to reduce fatigue in individuals with different diagnoses but with moderate to severe fatigue.

Loss of mitochondrial function is not always exclusively linked to membrane lipid damage [11]. To overcome this problem supplements containing coenzyme Q10, L-carnitine, alpha-lipoic acid, NADH, along with MLR glycerolphospholipids, have been used as combination mitochondrial

supplements. As an example of a combination MLR supplement, ATP Fuel® has been used to treat long-term chronic illness patients with intractable fatigue [19, 20]. The patients in the ATP Fuel® clinical studies had been ill with moderate to severe intractable fatigue for an average of over 17 years, and they had been seen by multiple physicians (>15). In addition, they had taken an average of over 35 supplements or drugs with no effect on their fatigue [19, 20]. These patients responded to the MLR combination supplement, showing significant reductions in fatigue within 6 weeks ( $p < 0.0001$ ). The MLR combination supplement proved to be a safe and effective method to significantly reduce fatigue in patients, even after years of intractable fatigue [19].

## **MLR SUPPLEMENTS AND PATIENT SUPPORT**

In addition to fatigue in chronic illnesses, fatigue is one of the most common symptoms found in cancer patients. It occurs in the earliest forms of cancer to the most progressed metastatic states. Cancer-associated fatigue is not well understood, but it is thought to be due to a combination of the effects of cancer itself plus the effects of cancer treatments [18]. MLR supplements have been used to improve cancer-associated fatigue and the fatigue and other side effects of cancer therapy [18].

## **VARIOUS CLINICAL USES OF MLR SUPPLEMENTS**

MLR lipid supplements have been used in a variety of clinical conditions (Table 1). For example, MLR may modify metabolism through body mass reduction and appetite restraint [16]. In this study 30 obese but otherwise normal subjects took oral HealthyCurb®, a NTFactor® and alpha-amylase inhibitor formulation, 30 min before each meal. Over time subjects gradually lost weight, as shown by significant reductions in weight and waist and hip circumferences. They also showed reductions in body mass index (BMI) and basal metabolic rate (BMR) ( $p < 0.001$ ). Overall hunger was reduced during the trial by 44.5% ( $p < 0.001$ ), with decreased cravings for sweets and fats. There was also a 23.9% reduction in fatigue ( $p < 0.009$ ). Along with fatigue reduction subjects had a 26.8% enhancement in perceived improvements in cognition and increased abilities to concentrate, remember and think clearly ( $p < 0.004$ ) [16].

Improvements in mental clarity while on MLR lipid supplements have been examined in a preliminary study using NTFactor Lipids® [21]. A group of 29 subjects were given 0.6 grams of NTFactor Lipids® in a drink, and fatigue and mental focus were surveyed after three hours. At this time a self-reported survey instrument was given to the participants. A majority of the participants responded within one hour, and by three hours they reported improvements in cognition, mental clarity and focus along with reductions in perceived fatigue [21].

In another study NTFactor Lipids® was used to reduce pain, fatigue, gastrointestinal and other symptoms in chronic illness patients [22]. For example, in fibromyalgia patients NTFactor Lipids® reduced significantly ( $p < 0.001$ ) pain, fatigue, gastrointestinal symptoms and improved Quality of Life assessments within 8 days in an open label clinical trial [22]. This has now been followed by an NIH-approved (NCT03288389) randomized, placebo-controlled cross-over trial. Preliminary results that were used to justify the trial indicated similar to previous clinical studies that NTFactor Lipids® has significant positive effects on fibromyalgia and other fatigued patients.

Finally, MLR supplements containing NTFactor Lipids® have been used as anti-aging supplements to help aged subjects improve their quality of life. In addition to fatigue and other problems associated with aging, MLR supplementation will be useful to delay some of the functional decline seen in patients as they age. Future studies will concentrate on sensory improvements, cognition, memory loss and other factors associated with reductions of quality of life with age.

## **FINAL COMMENT**

The use of MLR formulations, such as NTFactor Lipids®, have proven to be safe and effective as daily supplements for replacing damaged membrane glycerolphospholipids and restoring membrane function. This has a positive effect on cellular function and health, such as mitochondrial function, and it has been demonstrated in various clinical trials. The positive effects of MLR lipids are also apparent in other membrane compartments, such as the plasma membrane, and additional studies will concentrate on the functional effects of MLR lipids on the plasma membranes of various cell types. Preliminary results indicate that MLR supplements like NTFactor Lipids® can attenuate nerve transmission. This may help explain the effects of NTFactor Lipids® in reducing widespread pain and gastrointestinal symptoms.

MLR natural lipid supplements are not drugs; thus the usual drug safety issues are not an issue with natural MLR supplements. Extremely high doses of MLR phospholipids have been given to animals and humans over long periods of time without any evidence of toxicity or adverse effects [2].

Daily use of MLR lipid supplements should improve health during aging and help support various conditions. Its use is completely justified because of the efficacy and safety of natural MLR supplements.

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## **Conflict of Interest Statement**

Garth Nicolson is a part-time consultant to Nutritional Therapeutics, Inc. of Hauppauge, NY; Resarched Nutritionals of Los Olivos, CA; Allergy Research Group of Alameda, CA; and Naturally Plus Japan. He currently serves on the Board of Directors of Univa NP Holdings, a corporation that markets hydrogenized water.

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**Table 1.** Effects of NTFactor® MLR supplements on fatigue scores.<sup>a</sup>

MLR Supplement	Subjects/patients	n	Av. age	Time (wks)	Fatigue Score reduction (%)	Reference
Propax/NTFactor®	Chronic fatigue	34	50.3	8	40.5 <sup>§</sup>	Ellithorpe et al. [13]
NTFactor®	Aging, chronic fatigue	22	68.9	12	35.5*	Agadjanyan et al. [14]
NTFactor®	CFS/fibromyalgia	15	44.8	8	43.1*	Nicolson & Ellithorpe [15]
Healthy Curb®	Obesity, fatigue	35	42	8	23.9*	Ellithorpe et al. [16]
APF/NTFactor® <sup>c</sup>	Aging, chronic fatigue	67	57.3	1	36.8 <sup>§</sup>	Nicolson et al. [17]
Propax/NTFactor®	Cancer, fatigue	35	50.7	8	30.1*	Nicolson [18]
ATP Fuel®/NTFactor®	CFS/ME	30	55.0	8	30.7 <sup>§</sup>	Nicolson et al. [19]
ATP Fuel®/NTFactor®	GW Illness, fatigue	16	42.2	8	34.6*	Nicolson et al. [19]
ATP Fuel®/NTFactor®	Lyme disease, fatigue	17	52.4	8	26.0*	Nicolson et al. [20]

<sup>a</sup>Modified from Nicolson [1]

<sup>c</sup>Advanced Physician's Formula with NTFactor®

<sup>§</sup>p<0.0001, \*p<0.001 t-test with/without NTFactor®