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Feature Article

Reducing Inflammation through Micronutrient Therapy for Chronic Kidney Disease

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Introduction

Approximately 350,000 individuals in the U.S. diagnosed with chronic kidney disease (CKD) undergo therapeutic maintenance hemodialysis (MHD) on a regular basis. However, an astonishing 20% of this population dies each year as a result of associated cardiovascular disease (1). Uremia, along with the high prevalence of protein-energy malnutrition (PEM) and systemic inflammation are thought to be major contributors to the soaring cardiovascular mortality rate in CKD patients. This is attributed mainly to oxidative stress (2). Uremia also interrupts the delicate balance of pro-inflammatory and inhibitory cytokines, disturbing proper immune function. This contributes further to inflammatory complications, such as infection (3,4). Current research indicates malnutrition-inflammation atherosclerosis correction in CKD patients is complicated and intervention may require a multi-pronged approach. It is believed that improving nutrition status and reducing chronic inflammation may significantly improve cardiovascular morbidity and mortality rates in dialysis patients (2). This article will explore the use of micronutrient therapies to potentially regulate chronic inflammation and bolster the immune response in MHD patients.

Factors Leading to Micronutrient Losses

Pre-MHD patients are often malnourished and frequently suffer from micronutrient deficiencies as a result of reduced dietary intake, as well as modified dietary intake during renal failure progression. Once on dialysis, micronutrient losses occur during the actual MHD process, particularly water-soluble vitamins and potentially some trace minerals (5). Additionally, PEM contributes to high circulating concentrations of inflammatory proteins; promoting protein catabolism, muscle wasting, diminishing appetite, and ultimately, a vicious cycle of oxidative stress and inflammation (6).

Oxidative Stress: Imbalanced Antioxidant - Reactive Oxygen Species Levels

Wratten, et al (2002), indicated that an imbalance of antioxidant defense in the body contributed to reactive oxygen species (ROS) production, resulting in oxidative stress (SOX), a pro-inflammatory condition. The researchers further indicated the process of MHD itself was a cause for metabolic disorders related to SOX. During MHD, ROS is activated by triggering an inflammatory response as cellular components are impaired, further reducing the antioxidant capacity. Chronic inflammation and continual formation of ROS is a major contributor to cardiovascular disease. Additionally, the use of synthetic dialysis membranes in the hemodialysis dialyzer, and toxins derived from the dialysate could trigger the immune-inflammatory response, continuing the chain-reaction of oxidation and magnifying SOX with subsequent MHD treatments (7).

Micronutrient antioxidants, such as vitamins C (VC) and E (VE), and trace minerals, selenium and zinc are mostly involved in scavenging free-radicals or by directly quenching the free-radical, by breaking the cascading oxidative reactions, reducing ROS concentrations, and repairing damaged cell membranes (8). An imbalance of free-radical scavenging antioxidants, such as VC and VE, through loss in MHD or via red blood cell (RBC) destruction can aggravate SOX.

Antioxidant Synergy: Recycling Activity of Vitamins C and E

Since the hemodialysis membrane is non-selective, water-soluble VC can be lost during MHD. Handelman (2007) indicated in a recent editorial that as much as several hundred milligrams of VC could be lost during a single session of MHD, resulting in VC deficiencies if not properly supplemented (9).

VC and VE function synergistically as antioxidants. Both VC and VE act by scavenging free-radicals often produced during lipid (especially, LDL) or RBC membrane oxidation. Typically, VE is the preferred chain-breaking antioxidant and acts by donating an electron, breaking the chain of LDL peroxidation. VC replenishes VE's oxidative activity and serves as a cofactor with various enzymes needed to suppress free-radical production. As a result, the immune response (cytokine production) is inhibited, reducing SOX activity.

RBC losses are common during MHD due to the stress of dialysis, and is one of the reasons CKD patients may be anemic. Supplementing with adequate VE helps to protect fragile RBC membranes with its free-radical quenching activity. VC combats epoietin hyporesponsiveness by assisting with iron absorption and promoting RBC synthesis along with hemoglobin production. VC is also essential in collagen synthesis and protects blood vessels from membrane impairment.

In a study done by Yang, et al (2006), the effects of VC infusion and a VE-coated dialyzer were tested on patients with MHD induced oxidative stress. Eighty end stage renal disease (ESRD) patients were randomly selected into either a control or one of four hemodialysis (HD) treatment groups: HD with VC infusion (VC); HD with VE-coated dialysis membrane (VE); HD with VC infusion + VE-coated membrane (VC+VE); and HD with neither VC, nor VE. Results of the study indicated that the VE-coated dialyzer effectively prevented RBCs from oxidative stress and had a partial effect in reducing ROS activity as a whole. However, VC infusions significantly diminished the MHD-induced SOX. This suggests a combination of VC infusion in the dialysate and a small amount of VE coated on the dialyzer could potentially reduce inflammation during MHD, and its antioxidant property could be recoverable (10).

Since a VE-coated dialyzer may not be readily available in a hemodialysis unit, supplementation with VE could potentially be beneficial. Therapeutic dosage between 300 to 700 IU/day is regarded as safe, and could prevent SOX-related complications (11).

European consensus indicates 50 mg/day of VC can be safely administered (12); however, since ascorbic acid could partially be broken down into oxalate, plasma oxalate levels should be monitored and VC dosage should be individualized (13).

Vitamin E and Selenium

Critically ill patients demonstrate systemic inflammation symptoms, frequently associated with low serum micronutrient levels as they are taken up in tissues and organs during protein synthesis and immune cell production (8). Selenium commonly functions with VE as an antioxidant especially during intradialysis iron infusion. Glutathione peroxidase (GSH-Px), a kidney-derived enzyme, acts as a free-radical protector within the cell cytosol and mitochondria, while VE maintains the cell membrane integrity (14).

Serum levels of GSH-Px have been shown to be deficient in patients undergoing renal replacement therapy in acute renal failure, and MHD in chronic kidney failure (15). Researchers have indicated SOX in uremic patients where selenium balances were disturbed and glutathione enzyme concentrations and activity were compromised (16). Conflicting studies suggest selenium may or may not necessarily be lost during dialysis (17,18), however poor dietary intake prior to MHD may strongly influence selenium deficiency. For this reason, CKD patients experiencing PEM warrant even closer monitoring of serum selenium levels. Uremic patients are highly susceptible to oxidative stress due in part to suppressed

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serum selenium levels. Both serum selenium levels and activity of the antioxidant enzyme was found to be depressed as kidney disease progressed to end stages, according to a 2004 study done by Zacchara, et al (19).

Serum selenium is most commonly found in the reduced state (GSH) to effectively serve as an antioxidant in GSH-Px reactions. In a recent study, selenium erythrocyte enzyme activity and serum GSH levels were observed in 29 hemodialysis patients against 20 control subjects for three months. Serum GSH levels and GSH-Px activity were found to be significantly lower in the hemodialysis patients compared to controls, indicating impaired antioxidant response (20).

Other metabolic alterations, such as selenium's role in the immune system, may also be compromised as a result of deficiency. Selenium has been found to potentially reduce carcinogenic effects after supplementing with moderate doses over a period of several years (21).

In healthy adults, DRI for selenium is 20-70 mcg/day, with dietary intakes of at least 40 mcg/day to maintain adequate GSH-Px activity. Although supplementation standards for CKD patients have not formally been established, MHD patients exhibiting selenium deficiency symptoms can be supplemented for 3-6 months, and monitored closely (22). Available renal multivitamin formulas including 70 mcg of selenium per tablet include Dialyvite 3000 and Renax, USA. Food sources of selenium are readily available; however, selenium content is not indicated on food labels. The daily value percent on the label is provided for one serving of the food and can be used as a guideline. A food containing 20% or more of the DV is high in selenium, 10% to 19% is considered good. Plant foods are major sources of selenium, but the amount is dependent upon the soil in which the plants are grown. Animal and seafood sources of selenium are derived from the plants the animals consume. In the U.S., Brazil nuts, meats and bread are good sources of selenium (14).

Zinc Supplementation and Immune Regulation and Response

Like selenium, zinc deficiencies can compromise the body's immune system, predisposing MHD patients to oxidative stress and inflammation (23). Zinc is an essential albumin-transported mineral found in practically every cell in the body. It is required for DNA synthesis, growth during pregnancy, childhood and adolescence, and catalyzes approximately 100 different enzyme activities in carbohydrate (and insulin) metabolism, alcohol metabolism, and lactic acid reduction (14). Although zinc deficiency is rare in western countries, food sources rich in zinc are often high in protein, which are limited in early stages of renal insufficiency and often avoided by patients during later CKD stages due to anorexia. Chronic uremic CKD patients commonly experience taste and smell dysfunction as a result of zinc deficiency, which amplifies anorexia and poor oral intake, intensifying PEM and chronic zinc insufficiency. Zinc absorption interactions can also occur in CKD patients on oral iron supplementation during erythropoietin therapy, or with use of calcium-based phosphate binders and corticosteroids. Chronic zinc deficiency manifests by increasing skin fragility, presenting peripheral neuropathy and compromising immune functions (24). Cell-mediated immunity has been shown to be suppressed in zinc deficiency, making CKD patients more susceptible to infections, intensifying malnutrition and inflammation, and increasing incidences of morbidity and mortality (25). In a recent randomized study, Jern, et al (2000), demonstrated that a daily 2.2 mg zinc sulfate supplementation can normalize serum zinc levels and reduce protein catabolism in MHD patients (26). Protein catabolism, commonly a result of cachexia in ESRD patients, has been found to promote inflammation, compromising the patient's immune system (14). Another randomized crossover study indicated 3 months of 50 mg of elemental zinc supplementation significantly increased serum zinc levels, normalized the protein catabolic rate, and improved serum cholesterol levels (27).

In healthy adults, DRI intakes of elemental zinc range from 8-15 mg/day. Again, since zinc supplementation standards have not been set, MHD patients experiencing zinc deficiency symptoms, and/or with chronic PEM should consider up to 50 mg/day of monitored zinc supplementation for 3 to 6 months until deficiency symptoms have subsided (22). Available renal multivitamin formulas with zinc include Dialyvite 5000 Rx, Dialyvite 3000 Rx, Dialyvite Rx + Zinc, Renax, Renax 5.5, Diatx Zn , NephPlex Rx, Dialyvite 800 + Zinc, and Renavit + Zinc.

Folic Acid, B12, and B6 – Controlling Uremia

Micronutrients vulnerable to loss during MHD and key in controlling uremia include specific B vitamins—folic acid, B_{12} and B_6. Kidney failure often results in abnormal homocysteine metabolism as a consequence of diminished glomerular filtration rate. Hyperhomocysteinemia, a uremic condition prevalent in MHD patients, activates inflammation and damages blood vessels contributing to the high incidences of cardiovascular disease in CKD patients (28).

In healthy individuals, adequate folic acid intake, along with sufficient vitamin B_{12} and vitamin B_6, is essential in maintaining normal homocysteine levels. Folic acid and vitamin B_{12} are required to convert homocysteine into methionine. With adequate levels of vitamin B_6, methionine can then be broken down into cysteine, which is then either reabsorbed for other metabolic needs or excreted in the urine (13).

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Table 1
Summary of Micronutrient Recommendations

Micronutrient	Therapeutic Dosage	Sources Include	Comments
Vitamin E	300 - 700 IU/day		Generally recognized as safe
Vitamin C	50 mg/day		Monitor plasma oxalate levels
Selenium	20-70 mcg/day	Dialyvite 3000 Rx Dialyvite 5000 Rx Renax Renax 5.5	70 mcg Se/tablet in these sources
Zinc	50 mg/day	Dialyvite Rx + Zinc Dialyvite 800 + Zinc Renavit + Zinc	Check for resolution of deficiency symptoms after three-six months
Folic Acid Vitamin B_6 Vitamin B_{12}	5 mg/day 50 mg/day 500 mcg/day	Dialyvite 5000 Rx Diatx Zn Folbee Plus	KDOQI Clinical Practice Guidelines Recommendations
Injectable Vitamin D	Individualized based on PTH, per NKF KDOQI recommendations	Calcitriol Doxicalciferol Paricalcitol	Follow NKF KDOQI goals to maintain PTH at 150-300 pg/mL

Renal vitamin information found at these sites accessed March 15, 2009: www.ritecare.com/prodsheets/asp/VTF-314002.asp, www.everettlabs.com/ever2/renax.asp, www.dialyvite.net/default.asp?edid=59, and www.folbeeplus.com.

In CKD patients, this normal process of homocysteine degradation is significantly impaired due to folic acid deficiencies, and potentially vitamin B_{12} and/or B_6 deficiencies. In a study conducted by Bernasconi, et al (2006), moderate and advanced stage renal failure subjects were given either 5 or 15 mg/day folic acid dosages. Results indicated both doses yielded a significant, yet similar reduction of plasma homocysteine levels, suggesting benefits for folic acid supplementation in MHD patients (29). Anemic MHD patients on erythropoietin therapy may require additional vitamin B_6 supplementation to alleviate hyperhomocysteinemia. In a 12-month cohort study including 37 patients on intermittent HD treatment, supplementation of 250 mg of B_6 was given three times per week along with 50 mg of folic acid, administered one time per week. The researchers found mean homocysteine levels significantly decreased in all of the patients. Twenty-nine out of the thirty-seven patients supplemented resulted in normal plasma homocysteine levels after the treatment, suggesting the combination of folic acid and B_6 provided an effective and safe means to normalize plasma homocysteine levels in chronic hemodialysis patients (30). Vitamin B_{12} was shown to decrease serum homocysteinemia by approximately 10% when 1 mg was administered on a monthly basis in ESRD patients (31). Incidentally, new research has indicated high doses of B-vitamins may not lower homocysteine levels, preventing CVD-related mortality in CKD patients. Between years 2001 and 2006, Jamison, et al, conducted a large randomized, double-blind, controlled trial on 2056 advanced CKD and ESRD patients with high homocysteine levels. The subjects were treated daily with either a placebo or with a supplement containing 40 mg folic acid, 100 mg vitamin B_6, and 2 mg of B_{12}. The subjects were followed quarterly for 3+ years. Results of the study indicated survival did not improve after several years of follow up, and there were no significant reductions in cardiovascular events (32). Such strong conflicting research recently published warrants further studies to determine long-term effectiveness of B-vitamin supplementation for CKD patients. However, due to diminished appetite and low dietary intake in these patients and in accordance with the KDOQI Clinical Practice Guidelines, it is prudent to recommend at least 5 mg of folic acid, 500 mcg of vitamin B_{12} and 50 mg vitamin B_6, to protect against cardiovascular disease induced by hyperhomocysteinemia, but also to elevate B-vitamin status in patients with poor dietary intake (33). Renal vitamins currently available with B-vitamins include Nephro-Vite, Nephrocaps, Dialyvite, Dialyvite 3000 Rx, Dialyvite 5000 Rx, Diatx Zn, and Folbee Plus.

Vitamin D

Uremic conditions often intensify endocrine dysfunction in CKD patients. In healthy individuals, optimal kidney function is essential to convert dietary vitamin D and vitamin D absorbed by the skin, into its active form, $1,25(OH)_2$-D_3, or calcitriol. Parathyroid hormone (PTH) and phosphorus also aid in calcitriol produc-

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tion. However, during renal failure, active vitamin D levels drop significantly. Consequently, phosphate levels become elevated and calcium levels drop, stimulating PTH to be released into the blood. High serum PTH levels stimulate calcium movement from the bones into the blood, reabsorption of calcium from kidneys, and accelerated absorption of calcium from the intestine; a condition known as hyperparathyroidism (13).

Reduced vitamin D synthesis also manifests itself as secondary hyperparathyroidism, a condition considered by researchers to be a "classical" cause of CVD-related mortalities in MHD patients (34). Research indicates that serum PTH level is correlated with the degree of secondary hyperparathyroidism. When PTH levels exceed 500 – 600 pg/mL, patients experience moderate to severe hyperparathyroidism. High levels of serum PTH along with low levels of calcitriol are associated with bone loss, cardiovascular disease, and increased mortality in patients with ESRD. In a 2005 large cohort study done by Teng, et al, researchers found that activated, injectable vitamin D (VD) (calcitriol or paricalcitol) increased patient survival. Between the beginning of 1996 and end of 1999, a total of 51,037 MHD patients received injectable VD while 13,864 did not. Survival rate of the treatment group was significantly higher than the control group, with approximately 75.6% of the treatment patients surviving throughout the three year period. Only 58.7% of the control group patients survived the three year period (35). According to the NKF KDOQI, initial dosing recommendations for injectable VD is dependent upon the type of VD sterol administered and the severity of secondary hyperparathyroidism and serum PTH levels. VD injection therapy should commence when PTH levels are greater that 300 pg/mL and should cease when PTH levels are less than 150 pg/mL (36).

Recently, researchers have begun to study the "non-classical" effects of VD, such as its antioxidant properties and immunocompetent properties. Studies with congestive heart failure patients with adequate serum VD levels have been shown to have reduced pro-inflammatory and enhanced inhibitory-cytokine activity versus VD deficient subjects (37). Research determining benefits of activated vitamin D as an antioxidant in MHD patients still needs to be conducted to determine appropriate therapy.

Conclusion

In uremic CKD patients, inflammation as a consequence of chronic oxidative stress is complex and often entangled with anorexia and PEM. Chronic inflammation commonly leads to further complications, frequently resulting in cardiovascular-related deaths prevalent in MHD patients. Although micronutrient therapies have been explored, recovering losses for various vitamins during hemodialysis along with micronutrient supplementation to reduce deficiencies from PEM can play a role in reducing oxidative stress. Antioxidant synergies between various micronutrients should be considered when supplementing; however, future studies need to be conducted to determine appropriate approaches and to set standards with goals of improving nutrition status and quality of life for those undergoing MHD. ◆

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