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## Micronutrient Metabolism in Hemodialysis Patients

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### 1. Introduction

Patients with end stage renal diseases (ESRD) that require long-term dialysis treatment still have high morbidity and mortality rates. Risk factors that are associated with outcomes and survival rates include long dialysis duration, medical complications, oxidative stress, infection, inflammation, and impaired immune responsiveness. Some studies have been investigated associations of disturbances of certain micronutrients in patients undergoing dialysis. However, the homeostasis of these micronutrients plays a critical role in the maintenance of antioxidant status and immune function, and the amelioration of infection. This chapter will focus on the associations between micronutrients (trace elements and vitamins) status and these risk factors and their potential therapeutic uses in hemodialysis patients. In addition, we review other special nutrients (substrates) that are essential for patient management.

### 2. Main risk factors: Inflammation & oxidative stress

ESRD patients who undergo long-term hemodialysis can develop cardiovascular diseases, anemia, protein-calorie malnutrition, infections and altered immune function, renal osteodystrophy, and skin disorders, which are common complications (Himmelfarb, 2005). These patients already have a high incidence of cardiovascular disease, and half of the deaths among these patients can be attributed to induced cardiovascular disease (Bevc et al., 2006). In view of the accelerated atherosclerosis, some traditional risk factors as well as non-traditional factors that occur in dialysis patients have been reported.

In contrast to cardiovascular disease, other complications can be partly explained by these known risk factors. Increasing evidence shows that patients on dialysis have oxidative stress and inflammation. Relative to healthy controls, these patients have significantly higher plasma concentrations of lipid peroxidation products expressed as thiobarbituric acid-reactive substances (TBARS), malondialdehyde (MDA)(Guo et al., 2010; Kirmizis et al., 2010), advanced oxidation protein products (AOPP)(Taki et al., 2006; Chen et al., 2011), and oxidative DNA products (8-hydroxydeoxyguanosine, 8-OHdG)(Morishita et al., 2011). Chronic inflammation in hemodialysis patients is characterized by elevated concentrations of inflammatory markers and cytokines, such as C-reactive protein (CRP), interleukin-1 $\beta$

(IL-1 $\beta$ ), IL-2, IL-6, and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ )(Guo et al., 2010; Kirmizis et al., 2010). Cytokines are also important mediators involved in systemic inflammatory diseases. Oxidative stress is closely associated with inflammatory status, and the maintenance of the redox balance is known to modulate immune system homeostasis in hemodialysis patients. Chronic inflammation can induce an increased production of free radicals that cannot be counterbalanced due to defective antioxidant capability; an altered redox state is responsible for the accelerated dialysis syndromes. Oxidative stress occurs at sites of active inflammation and as a part of the reaction to invasive microorganisms (Nihi et al., 2010). Increased oxidative stress is also markedly related to the retention of oxidized solutes, the dialyzer membrane, bacterial contaminants in the dialysate, mitochondrial dysfunction, and decreased levels of antioxidant enzymes, including superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx)(Dursun et al., 2002; Ward and McLeish, 2003; Himmelfarb, 2008).

Oxidative stress has been implicated in other long-term complications, including anemia, amyloidosis, malnutrition, and infection (Morena et al., 2005). Infection may aggravate micronutrient deficiencies by reducing nutrient intake, increasing losses, and interfering with utilization by altering metabolic pathways (Maggini et al., 2007). Poor nutritional status arises due to increased oxidative stress, and the latter may be related to alterations in micronutrients' homeostasis in hemodialysis patients. Overall, lowered micronutrients' status can promote oxidative stress and inflammatory responses may lead to suppressed immunity, which predisposes to infections and aggravates malnutrition.

### 3. Trace elements

#### 3.1 Zinc

Zinc (Zn), an essential trace element, is an integral part of many enzyme functions and is a cofactor in those signaling pathways involving Zn-requiring proteins (Ngom et al., 2011). Zn is also an antioxidant and has anti-inflammatory properties. For example, Zn plays a critical structural role for antioxidant enzyme SOD and can stabilize biological membranes to decrease their susceptibility to oxidative damage that can impair cell functions (O'Dell, 2000). Zn is also a part of Zn-fingers and increases metallothionein biosynthesis, which can act as an antioxidant.

Several studies have demonstrated that Zn homeostasis has a critical impact on the health of hemodialysis patients. These patients have significantly lower concentrations of Zn in the blood and leukocytes and have increased oxidative stress (Roosbeh et al., 2009; Dashti-Khavidaki et al., 2010). The possible causes of decreased Zn concentrations need to be clarified, although Zn removal during hemodialysis, decreased gastrointestinal absorption of Zn, inadequate Zn intake, and reduced Zn-binding proteins in these patients have been reported. Increased expressions of intracellular metallothioneins following oxidative damage can sequester plasma Zn, and up-regulation of Zn-importing proteins by pro-inflammatory cytokines can reduce the plasma concentrations of Zn (Liuzzi et al., 2005; Haase and Rink, 2009; Guo et al., 2011). CRP is considered to be a sensitive marker of the induction of inflammatory activity; an association between decreased plasma Zn concentrations with higher CRP levels in hemodialysis patients has been noted (Guo et al., 2010). Medications used by hemodialysis patients, such as calcium carbonate, calcitriol (Dashti-Khavidaki, 2010), and aluminum phosphate-binders (our unpublished results), may interfere with blood Zn concentrations.

Efficient immune function depends on the status of some micronutrients and an inadequate status may lead to depressed immune responses. Zn is an immune regulator with multiple functional activities for immune effector cells, such as natural killer cell activity, and chemotaxis of neutrophils and monocytes (Kreft et al., 2000). Disturbances in Zn homeostasis can lead to a shift in the Th1/Th2 balance towards a Th2 response. In hemodialysis patients with Zn deficiency, the percentages of circulating CD3 and CD4 T lymphocytes are significantly lower than in controls; plasma Zn concentrations are correlated with %CD3 and %CD4 T cells, and CD4/CD8 ratios (Guo et al., 2010). Zn deficiency has also been found to be associated with some uremic symptoms, such as anorexia, impaired taste sensation, and sexual dysfunction. On the other hand, depression is a common psychological problem encountered among ESRD patients. Chronic inflammation is known to play an important role in the pathophysiology of depression, and the concentrations of pro-inflammatory cytokines are increased in these patients (Bilgic et al., 2007; Maes, 2008). An association between Zn deficiency with depression in hemodialysis patients has been noted (Roosbeh et al., 2011). Recent investigations suggest a positive association between blood Zn concentrations and albumin, hematocrit and prealbumin, which suggests that better nutritional status is a reason for higher Zn status in dialysis patients (Grzegorzewska and Mariak, 2001; Navarro-Alarcon et al., 2006). In addition, Zn promotes insulin-like growth factor-1 (IGF-1), which plays a role in the regulation of hematopoiesis and osteoclastogenesis (Nishiyama et al., 1999; Yamaguchi et al., 2010). Thus, Zn status also seems to be related to hemodialysis bone disease and anemia. Zn supplementation can increase blood Zn concentrations, leading to an increased protein catabolic rate (Jern et al., 2000), decreased osmotic fragility and lipid peroxidation (Candan et al., 2002), and reduced CRP levels (Rashidi et al., 2009) in hemodialysis patients. Zn supplementation (50 mg of elemental Zn from Zn sulfate for 90 days) improved food intake and serum cholesterol status in hemodialysis patients (Chevalier et al., 2002). Furthermore, our unpublished results showed that hemodialysis patients who received 10 mg of elemental Zn (78 mg of Zn gluconate) for 2 months had increased plasma Zn concentrations, reduced oxidative stress, and improved immune function. Sexual dysfunction in chronic renal failure patients undergoing hemodialysis is also common. Zn administration (100 mg/day for 6 weeks) can significantly increase serum concentrations of Zn and testosterone (Jalali et al., 2010). Most maintenance hemodialysis patients suffer from anemia, and Zn-based polaprezinc (34 mg Zn/day for 21 days) has been confirmed to provide an improved response to erythropoietin and increase hemoglobin levels (Fukushima et al., 2009). In summary, low Zn status is likely to be more common and Zn supplementation would appear to be beneficial for Zn-deficient patients undergoing chronic hemodialysis. Zn status may alter the risk of complications of hemodialysis, which results from improved nutrition, antioxidant, and anti-inflammatory properties.

### 3.2 Copper

Copper (Cu) is an essential trace element that is required for a number of enzymes. Cu has vital roles in hemoglobin synthesis and immune function and is also a cofactor for SOD, cytochrome c oxidase, and ceruloplasmin (Maggini et al., 2007). Regarding the antioxidant enzyme SOD, Cu provides its catalytic activity. However, excess blood Cu, particularly the free fraction, may lead to tissue injury apparently due to its pro-oxidant effects and the depletion of anti-oxidant reserves.

Although the actual cause for changes in Cu concentrations and distribution remains to be elucidated, long-term dialysis patients have elevated concentrations of plasma Cu and increased oxidative stress compared to healthy controls (Navarro-Alarcon et al., 2006; Tonelli et al., 2009; Guo et al., 2010). The prescription of different phosphate binders did not have any observable effects on serum Cu status (Veighey et al., 2011). However, Zn deficiency may increase the absorption of intestinal Cu and Cu can significantly inhibit the influx of Zn across the intestinal brush border membrane. The release of Cu during inflammatory tissue damage also can explain the enhancement of blood Cu concentrations (Guo et al., 2009). Moreover, mitochondrial dysregulation affects Cu chaperone expressions (Granata et al., 2009), which may result in impaired Cu homeostasis and increased oxidative stress in hemodialysis patients.

An increased Cu concentration in erythrocytes or blood is accompanied by an increase in oxidative stress and an increased TBARS concentration in hemodialysis patients (Bober et al., 2007; Guo et al., 2010). In addition, chronic inflammation, as indicated by an increased concentration of serum ceruloplasmin, is related to elevated concentrations of CRP and Cu (Panichi et al., 2004). Previous studies have shown that higher concentrations of CRP, Cu, Cu/Zn ratio, and ceruloplasmin are related to inflammatory status (Bo et al., 2008; Ghayour-Mobarhan et al., 2008). Elevations in plasma Cu can increase protein kinase C activation due to oxidative stress and these are associated with inflammation and the progression of renal diseases (Davis et al., 2001).

Recently,  $\beta$ -2-microglobulin deposits in the form of amyloid fibrils were found in the musculoskeletal systems of dialysis patients as a result of kidney failure (Srikanth et al., 2009).  $\beta$ -2-microglobulin accumulation with resultant tumor formation is also a known, albeit rare complication of long-term hemodialysis (Mendoza et al., 2010).  $\beta$ -2-microglobulin has been reported to be markedly correlated with oxidative stress and inflammatory biomarkers in hemodialysis patients (Filiopoulos et al., 2009). However, Cu binding to  $\beta$ -2-microglobulin may precede amyloid formation (Srikanth et al., 2009).

Elevated serum and leukocyte Cu concentrations were associated with cardiovascular disease; Cu may directly affect atherogenesis and is a marker of inflammation associated with atherosclerosis (Kinsman et al., 1990; Ford, 2000). Higher blood Cu status may subsequently promote the development of breast cancer, and the adjusted odds ratios for breast cancer were 1.8, 1.0, 1.6, and 3.2, respectively, in the 4 quartiles of Cu distribution (Overvad et al., 1993). Whether or not Cu homeostasis has an impact on the development of atherosclerosis and some types of cancer in long-term dialysis patients remains to be established.

Variations in the distributions of both Cu and Zn can actually indicate oxidative stress, inflammation status, and immune dysfunction in dialysis patients. There is no question that disturbance in blood Cu remains a major problem and that Zn supplementation may benefit hemodialysis patients.

### 3.3 Selenium

Trace element selenium (Se) is required for the functions of a number of Se-dependent enzymes. Se bound to the active sites of antioxidant enzyme GPx plays an important role in protecting cell membranes and sub-cellular components from oxidative damage. Thus, Se is a potent antioxidant that acts as an anti-inflammatory agent and is required for immune system function (Rayman, 2000). Se can simulate Th1 immune responses against viral

infections and is involved in thyroid hormone synthesis (Kocabaş et al., 2006). Adequate Se status is necessary for maintenance of cell-mediated immunity and humoral immunity. In addition, the association of plasma Se concentrations with subsequent risk of cancer has been described. We are currently conducting clinical trials in our laboratory; the anti-angiogenesis effects of supranutritional levels of Se are consistently observed in three types of cancer.

The kidney accumulates the highest amounts of Se and is the major source of plasma GPx (Adamowicz et al., 2002). The plasma concentrations of Se and GPx activities are significantly lower in dialysis patients than in healthy controls (Zagrodzki et al., 2007; Tonelli et al., 2009; Pakfetrat et al., 2010; Fujishima et al., 2011a). Reduced intake of Se lowers the blood Se status of dialysis patients (Andrew et al., 2008). Increased inflammation may decrease the absorption of Se and result in low Se status (Walston et al., 2006). Blood Se status is also significantly associated with albumin concentration and the dialysis process (Fujishima et al., 2011a); lower Se status may be related to malnutrition in these patients.

Further, statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) also have antioxidant and anti-inflammatory properties, which can further reduce the numbers of inflammatory cells and CRP concentrations (Fermis, 2003). In hemodialysis patients who used statins, blood Se concentrations were significantly higher compared with untreated patients (Taccone-Gallucci et al., 2010). Thus, this raises the possibility that low Se concentrations may be attributed to diminished Se retention due to increased oxidative stress.

Patients undergoing hemodialysis have low Se status that may increase their risk of anemia and certain cancers (Viron, 2002). On the other hand, a population-based prospective cohort study has conducted among hemodialysis patients showed that low blood Se status may contribute to immune system dysfunction and an increased risk of death, especially death related to infectious disease (Fujishima et al., 2011b). Se status was significantly associated with decreased IL-6 concentrations and altered erythrocyte membrane fluidity in these patients (McGrath et al., 1995; Walston et al., 2006), and Se supplementation stimulated erythrocyte GPx enzyme activity and reduced NF- $\kappa$ B activation in HIV-infected patients (Kupka et al., 2004). A previous investigation also showed an association between CRP and low Se concentrations in dialysis patients (Guo et al., 2010). This suggests a relationship between the reduced concentrations of plasma Se and the increased inflammatory responses of hemodialysis patients.

Se supplements such as sodium selenate, sodium selenite, L-selenomethionine, and Se-enriched yeast, are available to counter potential deficiencies. However, organic forms of Se are more bioavailable and are found to be less toxic than inorganic Se. Se-containing yeast (150  $\mu$ g Se/day) supplementation, was effective for increasing blood Se concentrations in healthy adults, whereas the same amount of inorganic forms failed to raise blood Se concentrations (Schrauzer, 1979). For hemodialysis patients who received oral supplementations of sodium selenite (230  $\mu$ g Se/day) for 3 months, followed by 200  $\mu$ g/day for the next 3 months, their plasma Se concentrations increased until reaching a plateau similar to control levels (Saint-Georges et al., 1989). Hemodialysis patients who received supplements of 200  $\mu$ g of Se (as Se-rich yeast) per day for 3 months had significantly higher plasma Se concentrations and decreased leukocyte DNA damage (Zachara et al., 2010). Se-rich yeast supplementation (200  $\mu$ g Se/day for 3 months) for hemodialysis patients

significantly increased blood Se concentrations, but had no effect on plasma levels of GPx protein (Zachara et al., 2009). Rapidly increased plasma GPx activity was found following kidney transplantation (Whitin et al., 1998). Thus, the damaged kidney is unable to synthesize GPx, even after induction with Se. In contrast, erythrocyte GPx in the kidney is primarily synthesized in the proximal tubules (Whitin et al., 1998). Treatment with yeast-Se (900 µg of Se/week) caused an increase in Se concentrations and erythrocyte GPx activity (Zachara et al., 2001).

On the other hand, increased plasma Se is positively associated with indices of erythropoiesis and nutritional status (Zagrodzki et al., 2007). Significantly increased Se concentrations were seen after 4-months of recombinant human erythropoietin (rHuEpo) treatment (Celiker et al., 2001). In contrast, Se deficiency, particularly when combined with viral infection, can cause cardiovascular disease (DiSilvestro, 2005). Patients on hemodialysis have a higher prevalence of hepatitis C virus infection, may be attributed to the decreased plasma Se concentrations and GPx activities (our unpublished observations). Reduced serum Se and platelet GPx activity in hemodialysis patients are related to cardiovascular complications (Girelli et al., 1993). Se supplementation may help to prevent cardiovascular disease due to its antioxidant capacity, improvement in blood lipids, and the inhibition of platelet aggregation (Nève, 1996; Panicker et al., 2010; Rayman et al., 2011).

Se deficiency may alter immune function, increase oxidative stress, and increase the generation of inflammatory cytokines, which is complicating the clinical features in hemodialysis patients. The clinical manifestations of Se deficiency have a late onset; a deficiency may be present for a long time before these manifestations appear. Thus, there is a need for routine assessments of Se status and the efficacy of Se supplementation for hemodialysis patients.

## 4. Vitamins

### 4.1 Vitamin C

Vitamin C, also known as ascorbic acid, is a potent water-soluble antioxidant and co-enzyme in hydroxylation reactions and has anti-mutagenic properties. Vitamin C plays an important role in the synthesis of neurotransmitters that are critical for brain function and that are known to affect mood (see the web from the Linus Pauling Institute). Vitamin C is also required for the synthesis of collagen and carnitine.

Hemodialysis patients are particularly prone to vitamin C deficiency because of dietary restrictions, limited absorption, and poor nutritional status (Böhm et al., 1997; Richter et al., 2008). The dialysis process may decrease the blood concentrations of vitamin C (Deicher et al., 2005). Significantly decreased plasma vitamin C and increased oxidative stress were seen during hemodialysis, which could be exacerbated by intravenous iron treatment (Shi et al., 2005). Also, increased weekly hours of dialysis increase the loss of vitamin C (Coveney et al., 2010). Vitamin C homeostasis may have a significant impact on these patient outcomes.

Daily intake of 60-100 mg of vitamin C is sufficient to maintain health in the general population, but may not be adequate for dialysis patients (Richter et al., 2008). Although, short-term oral vitamin C supplementation (250 mg at 3 times/week for 2 months) did not alter oxidative stress and inflammatory markers in hemodialysis patients (Fumeron et al.,

2005). Every other day supplementation with 250 mg of vitamin C for 3 months increased blood vitamin C concentrations, decreased MDA, and improved LDL and total cholesterol concentrations (Abdollahzad et al., 2009). Several polypeptides associated with oxidative stress and inflammatory markers were also normalized after oral vitamin C supplementation (250 mg at 3 times/week) (Weissinger et al., 2006). For hemodialysis patients who were given 1,000 mg of vitamin C for 3 months (Washio et al., 2008) or for 1 year (Ramos et al., 2005), decreased LDL oxidation, increased plasma vitamin C and plasma SOD activity, but not SOD mRNA expression in leukocytes were noted. After intravenous administration of vitamin C, ESRD patients also showed increased paraoxonase activity and vitamin E, decreased AGE, isoprostanes, 8-OHdG and lipid peroxidation concentrations, and reductions in pro-inflammatory mediators (Chien et al., 2004; Tarng et al., 2004; Shi et al., 2005; Chan et al., 2006; Ferretti et al., 2008).

A high dietary intake and high circulating concentrations of vitamin C may protect against ischemic heart disease, possibly due to its antioxidant properties and anti-inflammatory effects (Wannamethee et al., 2006). Inverse relationships between vitamin C status with CRP, IL-6, fibrinogen, coagulation factors VII, VIII, and IX, and thrombin-antithrombin complexes have also been noted (Deicher et al., 2005). Therefore, low total vitamin C plasma concentrations may be an independent predictor of adverse cardiovascular outcomes for hemodialysis patients; vitamin C supplementation has been suggested to reduce cardiovascular disease risk.

Hemodialysis patients with functional iron deficiencies often develop resistance to rHuEpo. For these patients, anemia prevention relies primarily on supplemental EPO and intravenous iron. Improved vitamin C status and decreased inflammation could lead to better utilization of iron and EPO (Handelman, 2007). Plasma concentrations of vitamin C are positively associated with hemoglobin concentrations, and vitamin C status may help patients to utilize iron for erythropoiesis during anemia management (Attallah et al., 2006; Deved et al., 2009; Finkelstein et al., 2011). Anemic hemodialysis patients who received oral daily vitamin C at a dose of 500 mg/day had decreased ferritin concentrations and EPO dose requirements, while hemoglobin and hematocrit concentrations were increased (Sirover et al., 2008).

On the other hand, long-term dialysis patients have a decreased quality of life compared to healthy controls (Mydlik and Derzsiová, 2008). Increased malnutrition-inflammation scores may be significantly associated with depression, sleep disorders, and poor quality of life (Bilgic et al., 2007). Lower quality of life scores were positively related to decreased blood status of the antioxidants Zn, Se, and vitamin C (Raimundo et al., 2006). When health-related quality of life was assessed using Short Form 36 (SF-36) scale scores, associations between plasma vitamin C status, MDA and life quality were also found in EPO-treated hemodialysis patients (Guo, C-H., unpublished results). Hemodialysis patients who were treated with EPO and were supplemented over 3 months with vitamin B6 (20 mg/day), folic acid (10 mg/week), and vitamin C (60 mg/day), showed increased quality of life scores (Mydlik and Derzsiová, 2008).

Oral or parenteral iron administration is a common practice for hemodialysis patients. However, a major concern is that an oversaturation of transferrin and subsequent propagation of redox-active iron can occur with the recommended dose of iron (Ardalan et al., 2007). Redox-active iron is a potent pro-oxidant that triggers free-radical chain reactions. Vitamin C may also act as a pro-oxidant via the reduction of ferric ion. Hemodialysis



patients who received 100 mg of iron sucrose and vitamin C intravenously had an increase in oxidative stress comparable to patients given iron alone (Eiselt et al., 2006); however, this finding was not confirmed by Shi et al (2005). This suggests that combination treatment of high doses of iron and vitamin C by intravenously route, should be avoided in anemic hemodialysis patients.

In addition, hyperoxaluria due to vitamin C supplementation (500 mg/day for 3 months) for chronic dialysis patients was found (Sirover et al., 2008). A concern has been raised that high plasma oxalate concentrations may lead to deposition in soft tissues. Nevertheless, one study found that there was no evidence that vitamin C supplementation increased the risk of kidney stone formation (Curhan, 1999). An earlier study involving 45,251 peoples with no history of kidney stones and who were followed for 6 years found that those who had consumed 1500 mg or more of daily vitamin C had a reduced risk of kidney stones compared to those who consumed less than 250 mg daily (Curhan, 1996). Vitamin C supplementation may address the potential protective effects on the clinical outcomes; however, hemodialysis patients should also be advised not to ingest excess amounts of vitamin C supplements.

#### 4.2 Vitamin E

Vitamin E is a family of tocopherols (alpha-, beta-, gamma-, and delta-) and tocotrienols (alpha-, beta-, gamma-, and delta-). Vitamin E is a fat-soluble vitamin with a variety of cellular membrane stabilizing- antioxidant and non-antioxidant activities. Some studies have been suggested that vitamin E can be used as an erythropoietic agent for decreasing premature erythrocyte hemolysis by reducing membrane fragility and the oxidation of cell membrane polyunsaturated fatty acids (Jilani and Iqbal, 2011). Vitamin E also has anti-tumor effects and is anti-atherogenic due to its antioxidant effects. Vitamin E supplementation has shown anti-proliferative, pro-apoptotic, and cyclooxygenase-2- inhibiting effects (Wada, 2011). Vitamin E is a nutrient known for promoting optimal immune function. When given orally, vitamin E has been shown to significantly enhance both cell mediated and humoral immune functions in humans and animals (Pekmezci, 2011). Vitamin E supplementation increases IL-2 production by T cells, enhances Th1 responses, and decreases the production of IL-4, a stimulator of Th2 responses (Maggine et al., 2007).

The plasma concentrations of vitamin E in chronic renal insufficiency patients may be decreased or normal (Yukawa et al., 1999; Hodkova et al., 2006; Zwolinska et al., 2009; Guo et al., 2011). In addition, abnormal distributions of vitamin E in different lipoproteins have been reported (Yukawa et al., 1999). After hemodialysis, the concentrations of high density lipoprotein (HDL)-cholesterol, vitamin E, and the total antioxidant capacity are significantly decreased (Montazerifar et al., 2010). In comparison to control subjects, LDL from dialysis patients contained less amounts of vitamin E and the MDA of LDL was significantly increased (Yukawa et al., 1999). Two studies evaluated vitamin E (600 IU) or multiple vitamins (800 IU of vitamin E, 250 mg of vitamin C, 100 mg of vitamin B6, 250 µg of vitamin B12 and 10 mg of folate) for possible effects on oxidative stress and inflammation in chronic hemodialysis patients; however, neither of these studies found any of the expected effects (Hodkova et al., 2006; Kamgar et al., 2009). This may have been due to not investigating patients with increased oxidative stress. However, oral administration of vitamin E (400 IU) and sodium selenide (600 µg), taken 6 h before a dialysis session, markedly reduced

oxidative stress in hemodialysis patients who were receiving iron infusions (Ardalan et al., 2007).

Alpha-tocopherol (800 IU) taken daily for 12 weeks decreased the susceptibility of LDL to oxidation in dialysis patients (Islam et al., 2000). The SPACE study, which examined hemodialysis patients, reported that 800 IU/day of alpha-tocopherol significantly reduced cardiovascular disease endpoints and myocardial infarction (Boaz et al., 2000). Moreover, oral vitamin E supplementation (> 800 IU) for 20 weeks significantly decreased the concentrations of plasma F2-isoprostanes in hemodialysis patients with increased oxidative stress (Reed et al., 2009). This suggests that adequate supplementation of vitamin E is needed in hemodialysis patients.

By comparison, a dialyzer membrane modified with vitamin E provided more effective antioxidant defense than oral administration of 600 IU of vitamin E for hemodialysis patients (Mydlík et al., 2001). Vitamin E bound to a dialyzer membrane resulted in lowered plasma MDA and oxidized LDL and MDA-LDL, and significantly increased the plasma vitamin E concentrations (Mune et al., 1999; Morimoto et al., 2005; Mydlík and Derzsiová, 2008). Although treatment with a vitamin E-coated dialyzer significantly reduced the percentage increase in an aortic calcification index after 24 months (Mune et al., 1999), whether a vitamin E-coated dialyzer can prevent cardiovascular disease and other dialysis-related complications needs further exploration.

#### 4.3 Folic acid

Folic acid (folate) is a water-soluble vitamin essential for a number of critical metabolic pathways. The pteridine moiety of folate is the prosthetic group of many enzymes that are involved in the transfer of one-carbon unit in amino acid and nucleotide metabolism, mitochondrial protein synthesis, conversion of homocysteine to methionine, methylation of transfer RNA, and de novo purine nucleotide synthesis.

Folate is involved in the remethylation of homocysteine to methionine; therefore, a low folate status results in an accumulation of homocysteine. Hyperhomocysteinemia is recognized as an independent risk factor for atherosclerotic cardiovascular diseases, neurodegenerative conditions, osteoporosis, and cancers. Homocysteine and its by-products (homocysteine thiolactone) have been shown to damage the endothelial cells and exacerbate the cardiovascular injury (Jakubowski, 2008). Further, homocysteine increased the affinity of N-methyl-D-aspartate (NMDA) glutamate subreceptors, which indirectly caused the calcium influx (Obeid and Herrmann, 2006). Increasing evidence shows that homocysteine thiolactone induce protein unfolding and aggregation, and can lead to the formation of amyloid fibrils (Paoli et al., 2010). DNA methylation plays an essential role in maintaining cellular function, and reduced DNA methyltransferase may contribute to the development of certain cancers (Davis and Uthus, 2004). In addition, homocysteine increased bone resorption and stimulated p38 mitogen-activated protein kinase (MAPK) activity, and inhibited collagen cross-linking in bone may contribute to osteoporosis (Jamal et al., 2005; Koh et al., 2006).

Some studies have noted that a significantly lower plasma concentration of folate and a higher homocysteine concentration in these patients (Tamura et al., 1996; Stanford et al., 2000). The increased incidence of atherosclerotic vascular disease is correlated with the status of blood homocysteine in ESRD patients undergoing dialysis (Bachman et al., 1995; Heinz et al., 2009). Moreover, blood homocysteine concentrations were found to be

significantly above the cutoff of 13.5  $\mu\text{mol/L}$  in chronic dialysis patients, with or without vascular diseases (Leblanc et al., 2000; Tremblay et al., 2000). An increase in homocysteine concentration was also associated with increased mortality among dialysis patients who were not receiving vitamins (Heinz et al., 2009). In addition, mitochondria have higher levels of several folate forms and tetrahydrofolate-synthesizing enzymes; folate deficiency impaired nuclear DNA and mitochondrial DNA synthesis, mitochondrial folate uptake, and enhanced mitochondrial oxidative decay, which may occur in hemodialysis patients.

Several studies have shown that folate deficiency is not observed in all patients on chronic hemodialysis (Tremblay et al., 2000; Coveney et al., 2010); although, blood folate loss can occur during the hemodialysis process (Tamura et al., 1996; Leblanc et al., 2000; Heinz et al., 2008). An inverse correlation between blood folate and total homocysteine concentrations has been shown (Koulouridis et al., 2001). This relationship between homocysteine and folate suggests that the concentrations of folate within the reference interval are inadequate for dialysis patients.

With regards to decreasing plasma folate concentration, it is strongly associated with increased homocysteine, TBARS, pro-inflammatory cytokines, and CD4/CD8 lymphocyte ratios (our unpublished observations). Also, a reduced folate concentration is inversely associated with colon tumorigenesis in these patients (Kaji et al., 2011). Plasma homocysteine concentrations are higher in dialysis patients; however, no significant inverse correlation between homocysteine and bone mineral density is observed (Kayabasi et al., 2010). By contrast, increased concentrations of homocysteine are associated with an increased risk fracture in hemodialysis patients (Jamal et al., 2005).

Chronic renal disease is associated with a relative resistance to the lowering effects of low-dose folate supplementation on homocysteine (Bostom et al., 1997). Folic acid supplementation (1-5 mg/day) may normalize plasma homocysteine levels in moderately hyperhomocysteinemic individuals with normal renal function; however, a similar effect has not been observed in ESRD patients (Tremblay et al., 2000). Supplementation with high dose of folate (> 5 mg/day) significantly reduces plasma homocysteine in hemodialysis patients, with or without atherosclerosis (Stanford et al., 2000).

Hemodialysis patients who received daily supplements of 15 mg of folic acid for 2 months had markedly increased in plasma folate concentrations and decreased blood total homocysteine, irrespective of their 5,10-methylene-tetrahydrofolate reductase (MTHFR) C677T genotypes (Billion et al., 2002). In hemodialysis patients who received oral supplementations of 15 mg/day of folic acid, had significantly lower homocysteine concentrations and found no evidence of adverse effects (Bostom et al., 1996). Treatment with folic acid (10 mg/day) for 6 months have normalized plasma homocysteine concentrations, and significantly increased total plasma antioxidant capacity and decreased TBARS levels in these patients (Chiarello et al., 2003; Alvares Delfino et al., 2007). For hemodialysis patients who were given 15 mg/day of 5-methyltetrahydrofolate for 12 weeks, increased plasma folate concentration and improved endothelial dysfunction were observed (Baragetti et al., 2007). On the other hand, intravenous 5-methyltetrahydrofolate (50 mg/day for 2-5 years) reduced inflammation status and prolonged survival rate in ESRD patients undergoing hemodialysis (Cianciolo et al., 2008). Low-dose intravenous folinic acid (1 mg/day, 3 times/week) for 3 months significantly reduced plasma homocysteine and MDA concentrations (Apeland et al., 2002).

Routine supplementations of folic acid over long time periods should be considered in order to reduce homocysteine concentrations, may be more beneficial in minimizing uremic complications in hemodialysis patients.

#### 4.4 Vitamin B6

Vitamin B6, a water-soluble vitamin, is an essential coenzyme for numerous biochemical pathways and is a potent antioxidant. Vitamin B6 is involved in lipid metabolism, nucleic acid and protein biosynthesis, and helps to maintain normal nerve function and the formation of red blood cells (Hisano et al., 2010). Vitamin B6 is also critically required for absorption of vitamin B12 and synthesis of niacin. Moreover, it may inhibit platelet aggregation, and ameliorate the development of diabetic neuropathy (Metz et al., 2003; Kobzar et al., 2009). By contrast, vitamin B6 deficiency impairs lymphocyte maturation, growth and proliferation, and antibody production; it suppresses the production of Th1 cytokines and, thus, promotes Th2 responses (Maggini et al., 2007).

Pyridoxal-5'-phosphate, the active moiety of vitamin B6, is significantly depleted in most chronic hemodialysis patients without supplementation and high-efficiency hemodialysis contributes to its depletion (Leblanc et al., 2000; Tremblay et al., 2000; Busch et al., 2010). In addition, these patients need to consume more vitamin B6 for hemoglobin synthesis during rHuEPO treatment, which result in vitamin B6 deficiency (Mydlík et al., 1997). Hyperhomocysteinemia may be also caused by reduced vitamin B6 concentrations. Blood cystathionine status is major indicator for the trans-sulfuration pathway of homocysteine, which has been shown to be dramatically increased in hemodialysis patients due to the inhibition of cystathionine catabolism by low blood vitamin B6 contents (Herrmann and Obeid, 2005). On the other hand, high concentrations of homocysteine in blood associated with an increased risk of cardiovascular disease, but no significant difference in the pre-dialysis serum pyridoxal-5'-phosphate concentrations of patients with or without evidence of vascular disease (Leblanc et al., 2000).

There is increasing evidence that deficiency of vitamin B6 may cause hyperoxalemia and hyperoxaluria in dialysis patients; vitamin B6 treatment lower urinary oxalate excretion and inhibit calcium oxalate crystal formation (Chetyrkin et al., 2005; Mydlík and Derzsiová, 2010). In contrast, lower blood concentration of vitamin B6 was correlated with accumulation of the advanced glycation end-products (AGE) in hemodialysis patients (Busch et al., 2010). Increased oxidative stress by-product can induce calcium oxalate crystal aggregation and attachment in the renal tubules (Thamilselvan and Menon, 2005).

A previous study showed oral supplementation of folic acid (5 mg/day for 14 days), but not vitamin B6 (40 mg) or B12 (1 mg), was very effective in lowering total homocysteine in healthy subjects. However, in dialysis patients require much more aggressive B-complex vitamins therapy to achieve the effect of lowering total plasma homocysteine (Bostom et al., 1996). These patients treatment with vitamin B supplements (15 mg of folic acid, 100 mg of vitamin B6, and 1 mg of vitamin B12/day for 4 weeks), but not vitamin B6 alone, have significantly decreasing total plasma homocysteine. Vitamin B supplementation (40 mg of folic acid, 100 mg of pyridoxine hydrochloride, and 2 mg of cyanocobalamin) decreased plasma homocysteine concentrations, but did not improve survival or reduce the incidence of vascular disease in those patients (Jamison et al., 2007). Increased intake of B-complex vitamins (5 mg of folic acid, 20 mg of vitamin B6, and 50 µg of vitamin B12) given 3 times per week for an average of 2 years did not reduce mortality and had no significant effects on

the risk of cardiovascular events in patients with end-stage renal disease (Heinz et al., 2010). In contrast, high-dose intravenous B-complex vitamins (250 mg of vitamin B1, 250 mg of B6, and 1500 µg of B12; 3 times/week) reduced blood total homocysteine levels only when combined with 5 mg of folate given orally (Sombolos et al., 2002). Other results indicate that the folate (5 mg) and vitamin B6 (250 mg) supplementation, but not vitamin B6 alone, resulted in a reduction of homocysteine concentrations and improvement of the lipidemic profiles (LDL and HDL) in patients maintained with hemodialysis (Ziakka et al., 2001).

However, vitamin B6 (pyridoxine) supplementation (50 mg/day for 3-5 weeks) alone has been shown to improve the immune function of hemodialysis patients (Casciato et al., 1984). Vitamin B6 supplementation (60 mg/day for 4 weeks) was also effective in improving peripheral polyneuropathy symptoms of various etiologies, possibly because of the resistance to peripheral polyneuropathy that vitamin B6 provides for hemodialysis patients (Okada et al., 2000).

In summary, results above indicate that administrations of vitamin B6 and folic acid in combination are clinically beneficial for improving blood homocysteine status, lipid profile and peripheral polyneuropathy symptoms, and reducing calcium oxalate formation. The dose in 50 to 100 mg/day of vitamin B6 can be of great therapeutic value in hemodialysis patients. However, daily consumption of large amounts of vitamin B6 supplements (> 100 mg) should be carefully considered.

#### 4.5 Vitamin B12

Another essential micronutrient that is crucial for health is vitamin B12 (cobalamin), which is involved in one-carbon (methyl) metabolism. Two forms of vitamin B12, methylcobalamin and 5-deoxyadenosyl cobalamin, are commonly used by the human body. Cobalamin is required for the methionine synthase that catalyzes the conversion of homocysteine into methionine, and insufficient amounts will result in hyperhomocysteinemia (Green and Miller, 2007). In addition, cobalamin is required by L-methylmalonyl-CoA mutase that catalyzes the conversion of L-methylmalonyl-CoA to succinyl-CoA, thus maintaining methylmalonic acid within its normal range.

Vitamin B12 status is typically assessed by plasma or serum vitamin B12 concentrations. For adults, values below approximately 170-250 pg/mL indicate vitamin B12 deficiency (Institute of Medicine, 1998). An elevated homocysteine concentration (values >13 µmol/L) and increased methylmalonic acid also suggest vitamin B12 deficiency (De Vecchi et al., 2000; Andrès et al., 2007). In a vitamin B12-deficient state, the irreversible reaction that forms 5-methyl tetrahydrofolate results in a secondary folate deficiency with concomitant impairments in thymidine and purine synthesis, which can lead to alterations in immunoglobulin production (Maggini et al., 2007). Individuals with vitamin B12 deficiencies may also have anemia, gastrointestinal symptoms, or peripheral neuropathies (Marar et al., 2001). Evidence has accumulated in recent years that vitamin B12 supplementation has beneficial effects on cardiovascular disease, dementia and cognitive function, depression, and some cancers.

In chronic dialysis patients, markedly increased concentrations of methylmalonic acid and total homocysteine have been found (Herrmann and Obeid, 2005). Statistically significant correlations were observed between homocysteine and vitamin B12 concentrations (De Vecchi et al., 2000). The uptake of vitamin B12 by peripheral blood mononuclear cells from hemodialysis patients was lower than by cells from controls (Herrmann et al., 2001).

Treatment with vitamin B12 and folic acid, but not vitamin B12 alone, appears to be effective for lowering the total plasma homocysteine concentration in hemodialysis patients who have either normal vitamin B12 concentrations or a deficiency (Pastore et al., 2006). In addition, adding vitamin B12 to a folate supplement can further enhance the reduction of plasma homocysteine, as compared to treatment with folate alone (Stopper et al., 2008). Oral supplementation with 15 mg/day of folic acid together with 1 mg/day of vitamin B12 was more effective for reducing homocysteine concentrations (Azadibakhsh et al., 2009). Further, genomic damage in the peripheral blood lymphocytes of dialysis patients due to oxidative stress can be ameliorated by supplementation with folic acid and vitamin B12, which is thought to contribute to homocysteine reduction (Stopper et al., 2008).

Both folic acid and vitamin B12 supplements have desirable effects on blood homocysteine levels. However, a poor response to treatment with erythropoietin for renal anemia is common. Infections, oxidative stress, and inflammation have been shown to reduce the responsiveness to erythropoiesis-stimulating agents by increasing the release of pro-inflammatory cytokines (Stenvinkel, 2003). Oxidative stress and inflammation can be attenuated by vitamin B12 and folate supplementation. Whether vitamin B12 alone or in combination with folate is beneficial for altering erythropoiesis in hemodialysis patients may need further investigation.

## 5. Other nutrients (substrates)

### 5.1 EPA and DHA

A growing body of evidence suggests that the omega-3 fatty acids eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) have immune modulating, anti-inflammatory, lipid-lowering, anti-arrhythmic, and anti-hypertensive effects (Kris-Etherton et al., 2002). Both EPA and DHA are present in mitochondrial membranes and are essential for mitochondrial function. It has been reported that omega-3 fatty acids could decrease the production of homocysteine; thus, they had a cardioprotective effect in patients with normal renal function (Pooya et al., 2010). Fish oil sources of EPA and DHA have also shown renal protective effects that prevented against the progression to chronic kidney disease in older adults (Lauretani et al., 2009). These could also significantly reduce inflammation, fibrosis and oxidative stress following renal injury (Soumura et al., 2010; Peake et al., 2011). Moreover, fish oil supplements (900 mg of EPA and 600 mg of DHA/day for 1 month) may decrease urinary oxalate excretion and the risk of calcium oxalate crystallization attributable to an altered oxalate transporter activity (Siener et al., 2011).

Chronic hemodialysis patients reportedly have significantly low concentrations of EPA and DHA in the plasma and cell membranes (Saifullah et al., 2007; Nakamura et al., 2008; Madsen et al., 2011). This abnormal status may be attributed to the dialysis process, which can enhance oxidative stress and potentially increase omega-3 fatty acid peroxidation. In addition, these patients consumed lower amounts of dietary fish and, consequently, had suboptimal blood concentrations (Kutner et al., 2002; Friedman et al., 2006).

Short-term supplementation with fish oil (2.4 g of EPA and 1.2 g of DHA) could significantly increase the EPA and DHA contents in leukocytes phospholipids of hemodialysis patients within one week (Faber et al., 2011). After oral administration of EPA/DHA (2.7 g/day for 3 months), decreased lipid peroxidation and leukotriene B4 production in peripheral blood mononuclear cells were found for ESRD patients on hemodialysis (Taccone-Gallucci et al.,

2006). Patients who were administered supplements of fish oil (2.4 g/day) for 2 months had significantly decreased inflammation and increased insulin sensitivity, HDL-cholesterol, albumin, and hemoglobin (Perunicic-Pekovic et al., 2007; Rasic-Milutinovic et al., 2007). Significantly increased serum HDL-cholesterol and decreased triglyceride concentrations were also observed in hemodialysis patients who were administered fish oil (2.4 g) supplements for 3 months (Svensson et al., 2004).

Supplementation with fish oils (EPA+DHA, 2 g/day) also had a beneficial effect on plasma HDL and triglyceride concentrations in those patients with serum triglyceride levels > 200 mg/dl and total cholesterol > 220 mg/dl (Taziki et al., 2007). Further, EPA (1.8 g/day) or fish oil (1.3 g/day) treatments for 3 months remarkably reduced the increased plasma concentrations of remnant lipoproteins and triglycerides and prevented the peroxidation of LDL in dialysis patients (Ando et al., 1999; Saifullah et al., 2007). When hemodialysis patients were given low doses of fish oils (1.6-1.7 g/day), however, there were no significant improvements in their blood lipid profiles (Pouliou et al., 2011), lipoprotein (a) (Beavers et al., 2009), or homocysteine concentrations (Rasmussen et al., 2010).

Uremic pruritus, also known as the renal itch, is quite common in patients undergoing hemodialysis or peritoneal dialysis (50-90%). The pathological processes that lead to uremic pruritus remain poorly understood, and there is no definitive treatment. Administration of fish oil (6 g/day for 8 weeks) could significantly decrease erythropoietin requirements (Jones and Kaiser, 2002) and improved the severity and distribution of uremic pruritus among hemodialysis patients (Peck et al., 1996). These authors speculated that the anti-inflammatory and anti-proliferative effects of fish oils may have contributed to these symptoms' reversal.

Abundant evidence suggests that EPA/DHA exhibit powerful lipid-lowering and anti-inflammatory capabilities, and are consequently involved with reduced uremic complications and an enhanced nutrition status in hemodialysis patients.

## 5.2 Coenzyme Q10

Coenzyme Q10 is a member of the ubiquinone family of compounds, which is found in virtually all cell membranes, mitochondria, and lipoproteins. Coenzyme Q10 is a vitamin-like substance that plays a crucial role in energy metabolism and in free radical scavenging (Thomas and Stocker, 2001). It is also recognized as an obligatory cofactor for the functions of uncoupling proteins (Echtay et al., 2000).

Coenzyme Q10 has a direct anti-atherogenic property; oral coenzyme Q10 supplementation was shown to ameliorate cardiac contractility and endothelial dysfunction in patients with chronic heart failure (Littarru and Tiano, 2007). In addition, a recent study identified coenzyme Q10-sensitive genes that were regulated by peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ) and were involved in cholesterol synthesis, lipoprotein metabolism, and inflammation (Schmelzer et al., 2010).

There is evidence to support the safety and efficacy of coenzyme Q10 in congestive heart failure, diabetes, atherosclerosis, hypertension, cardiomyopathies, migraine, and Parkinson's disease (Rosenfeldt et al., 2007; Nahas, 2008). Coenzyme Q10 supplementation may result in increased concentrations of coenzyme Q10 within circulating lipoproteins and increase the resistance of human LDL to oxidation (Littarru and Tiano, 2007). Coenzyme Q10 supplement (200 mg/day) improved blood pressure, and the endothelial functions of the conducting arteries of the peripheral circulation in dyslipidemia patients with type 2

diabetes (Hodgson et al., 2002; Watts et al., 2002). A combination of orally given fenofibrate and coenzyme Q10 (200 mg/day) was effective for improving the endothelium-dependent and endothelium-independent vasodilator functions of the forearm microcirculation (Playford et al., 2003). Further, coenzyme Q10 attenuated elevated blood pressure, renal membrane phospholipid degradation, and enhanced renal phospholipase A2 due to its antioxidant and anti-inflammatory actions (Okamoto et al., 1991; Ishikawa et al., 2011).

Evidence has shown that high coenzyme Q10 contents in human renal tissues (Dallner and Sindelar, 2000). However, the plasma coenzyme Q10 and coenzyme Q10/LDL-cholesterol ratios in both conservative therapy and hemodialysis populations were markedly lower (Lippa et al., 2000). Plasma coenzyme Q10 concentrations were significantly decreased and MDA concentrations were increased (Gazdikova et al., 2000); reduced coenzyme Q10 status probably due to renal impairment and removal by dialyses. However, statins are widely used cholesterol-lowering medications that may decrease the endogenous synthesis of coenzyme Q10, and are consequently involved with reduced mitochondrial respiration and perhaps mitochondria and cell death (De Pinieux et al., 1996; Colquhoun et al., 2005).

Hemodialysis patients always have an impaired mitochondrial respiratory system, and this may contribute to enhance oxidative stress (Granata et al., 2009). It has been reported that coenzyme Q10 administration suppressed oxidative stress in hemodialysis patients (Sakata et al., 2008). Supplementation with coenzyme Q10 (100 mg/day) for 3 months reduced the serum lipoprotein (a) in hemodialysis patients who were treated with statins (Shojaei et al., 2011); decreased serum lipoprotein (a) attributed to inhibition of expression of lipoprotein(a) receptor by coenzyme Q10 (Singh and Niaz, 1999). Coenzyme Q10 supplementation (90-120 mg/day) significantly improved the peripheral circulation and decreased the plasma concentrations of TBARS and carbonyl protein in patients on hemodialysis or peritoneal dialysis (our unpublished observations), although we were unable to determine coenzyme Q10 status at baseline. There was significantly lower salivary secretion in hemodialysis patients (Gavaldá et al., 1999); administered supplemental coenzyme Q10 (100 mg/day for 1 month) to these patients can improve salivary secretion (Ryo et al., 2011). Nahas (2008) indicated that a typical dose of 60 to 120 mg 1-3 times daily was not associated with any serious risks. In fact, the toxicity of higher doses of coenzyme Q10 has not been encountered in clinical use.

Low coenzyme Q10 status and increased oxidative stress in chronic dialysis patients may be ameliorated by coenzyme Q10 administration, which, therefore, can be considered as a complementary treatment. Although promising, administrations of coenzyme Q10 may improve peripheral circulation status and lipid profile, prevent against cardiovascular disease and neurodegenerative disease in patients undergoing hemodialysis require further study.

### **5.3 Probiotics, prebiotics and synbiotics**

Chronic gastrointestinal symptoms are the most common in ESRD patients who are treated by hmodialysis or peritoneal dialysis. Disturbances in gastric and small intestinal motility, small intestine bacterial overgrowth, gastric hypochlorhydria, diarrhea, abdominal pain, and irritable bowel syndrome are symptoms typically seen in these patients (Cano et al., 2007). The pathogenesis of these symptoms is probably multifactorial, and has also been attributed to changes in the small intestine microflora (Strid et al., 2003). It has been suggested that uremic toxins, commonly used medications, complications, and changes in dietary patterns have major influences on the microflora of the small intestine (Evenepoel et



al., 2009; Shu et al., 2009). Further, an abnormal distribution of microflora in the gastrointestinal tract can result in gastrointestinal permeability and inflammation. Oxidative stress and malnutrition frequently occur in people who suffer from gastrointestinal disturbances.

In addition to these considerations, uremic toxins include low-molecular weight solutes, medium-sized molecules (peptides and proteins), and protein-bound, low-molecular weight solutes. With regard to the latter, such as indoxyl sulfate and p-cresyl sulfate (originating from intestinal bacterial fermentation end-products of tyrosine and tryptophan), these cannot be efficiently removed by hemodialysis, even with a high-flux membrane (Niwa, 2011). Accumulation of these uremic toxins induces free radical production, and increases the expressions of transforming growth factor- $\beta$ 1, tissue inhibitor of metalloproteinase-1 and pro $\alpha$ 1(I) collagen; therefore, they play an important role in the development of cardiovascular disease and can promote the progression of renal dysfunction (Niwa, 2010). Some studies in humans have indicated the potential efficacy of probiotic, prebiotic, or synbiotic preparations for gastrointestinal diseases (Madsen et al., 2001). Probiotics are defined as viable micro-organisms for which sufficient quantities can reach the intestine in an active state and exert beneficial health effects. Prebiotics are non-digestible food ingredients that are metabolized by the probiotics. Synergistically acting combinations of probiotics and prebiotics are designated synbiotics.

The reported beneficial effects of these preparations include stimulation of intestinal motility and intestinal immunity, recovery of a disturbed gut mucosa barrier, elimination of toxins and potential pathogens, the release of nutrients, antioxidants and growth factors, stimulation of mineral absorption, and reduced colonic transit times via the normalization of altered intestinal microflora (Madsen et al., 2001; Singhi and Baranwal, 2008). In recent years, the prebiotic oligo-fructose-enriched inulin was shown to reduce urinary p-cresyl sulfate excretion in healthy volunteers (De Preter et al., 2007). The same authors also demonstrated that oligo-fructose-inulin significantly reduced p-cresyl sulfate generation rates and serum concentrations in hemodialysis patients (Meijers et al., 2010).

However, an oral preparation of lactic acid bacteria did not reduce serum p-cresol concentrations in hemodialysis patients (Hida et al., 1996). Interestingly, the results of our preliminary study showed that synbiotics may be beneficial for decreased bacterial overgrowth and normal motility patterns in patients undergoing peritoneal dialysis and hemodialysis.

Intestinal therapeutic interventions with probiotics and prebiotics have provided some clinical benefits, but these have not been exhaustively studied in ESRD patients on hemodialysis or peritoneal dialysis. Nonetheless, it will be important to determine which probiotic genera and species possess beneficial traits, in addition to finding the optimal doses and possible synergistic combinations.

## 6. Conclusion

Renal dialysis patients appear to be prone to certain degrees of deficiencies for a number of micronutrients (Zn, Se, vitamin C, E, folate, B6, and B12) and nutritional substrates (coenzyme Q10 and EPA/DHA). This could be due to the significant losses of these factors in these patients or to their high needs. Increased oxidative stress and pro-inflammatory cytokines are important targets for nutritional and pharmacologic therapy for ESRD patients

who are undergoing hemodialysis; prolonged oxidative stress and pro-inflammatory cytokine production can exacerbate the severity of uremic complications and inadequacy residual renal function. These clinical features may be ameliorated by the use of supplements of these micronutrients. Probiotics and prebiotics may also provide benefits to these patients. Their use is not always a standard of care for hemodialysis patients. Therefore, uncertainty has arisen as to whether or not nutraceutical interventions are needed by hemodialysis patients.

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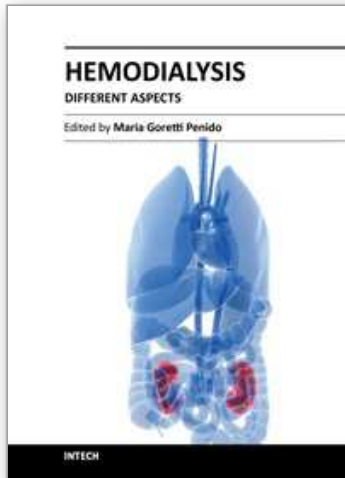
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Edited by Prof. Maria Goretti Penido

ISBN 978-953-307-315-6

Hard cover, 321 pages

**Publisher** InTech

**Published online** 14, November, 2011

**Published in print edition** November, 2011

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Chih-Hung Guo, Chia-Liang Wang and Pei-Chung Chen (2011). Micronutrient Metabolism in Hemodialysis Patients, Hemodialysis - Different Aspects, Prof. Maria Goretti Penido (Ed.), ISBN: 978-953-307-315-6, InTech, Available from: <http://www.intechopen.com/books/hemodialysis-different-aspects/micronutrient-metabolism-in-hemodialysis-patients>

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