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Feature Article: The Impact of Alternative Medicine Therapies on the Nutrition and Well-being of the Chronic Kidney Disease (CKD) Stage 5 Patient

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This article has been approved for 2 CPE units and the CPEU insert can be accessed in the Members Only Section of the website from the CPEU Inserts link.

Introduction

There are limited studies available on the use of alternative medicine therapies in CKD stage 5 patients, and little known about the effects of botanical medicines in this population. In these patients, malnutrition has been linked with both depression and cardiovascular disease. The purpose of this article is to examine how depression and cardiovascular disease may have ties to the malnutrition in this population, and review possible alternative medicine therapy options.

Depression in the CKD Stage 5 Population

Depression is the most common psychological problem in dialysis patients, and is associated with increased mortality in this group (1-3). Studies have evaluated quality of life scores from patient self

assessments, and have found them to be lower than those of healthy populations (1-3).

Kalender et al. studied quality of life in CKD patients, and found that when compared to control subjects, patients on dialysis had lower scores on all dimensions of quality of life (2). Twenty-four percent of patients had depression (2). The researchers concluded that lower quality of life scores were associated with higher serum C-reactive protein (CRP, an inflammatory marker); specifically, serum CRP levels were 1.52 +/- 2.72 for patients with depression compared to 0.62 +/- 1.29 in patients that did not have depression. Patients with depression also had lower albumin levels with a mean albumin of 3.48 +/- 0.56 versus 3.75 +/- 0.51 in non-depressed patients (2).

Micozkadioglu studied the relationship between a depressive affect and the Malnutrition Inflammation Complex Syndrome (MICS) in hemodialysis patients (3). He found that patients with a depressive affect had higher malnutrition-inflammation scores, and surmised that the cytokine response may lead to depression. Cytokines may also stimulate an inflammatory response and increase protein catabolism, thereby exacerbating malnutrition (3).

Alternative Medicine Therapies in the Treatment of Depression

Many alternative medicine treatments including the use of botanical medicines have been explored for the treatment of depression. Two botanical medicines that have been researched extensively in the treatment of depression are S-adenosyl-L-methionine (SAMe) and St. John's Wort (SJW). While these botanical medicines have

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not been studied specifically in CKD stage 5 patients, they have shown positive results in the general population.

S-adenosyl-L-methionine (SAME)

Brown and Gerbarg reviewed 16 open, uncontrolled trials, 13 randomized, double-blind, placebo-controlled trials and 19 double-blind trials comparing SAME to other antidepressants such as imipramine, amitriptyline, chlorimipramine, nomifensine, minaprine, and desipramine (4). All but one study showed SAME to be more effective than placebo and equivalent to the comparison antidepressant in treating major depression (4). Pancheri et al. found that SAME exhibited similar potency to the use of imipramine in treating depression, but SAME had fewer side-effects (5). Delle Chiaie et al. reported the results of two large multicenter trials comparing SAME to imipramine, and found similar results (6). In a study by Alpert et al., SAME was used as an adjunct therapy for resistant depressive disorder (7). In 30 patients treated with selective serotonin reuptake inhibitors (SSRIs) or venlafaxine who were given 800 to 1600 mg of SAME over 6 weeks, the researchers found that patients treated with SAME had a response rate of 50% and a remission rate of 43% (7).

It has been suggested that there may be a link between depression and folate deficiency. Fugh-Berman and Cott reviewed several studies on depressed patients and found that up to 35% of these patients had a folate deficiency (8). Folate is necessary for the synthesis of SAME. The most serious side effect of SAME is the reported appearance of manic symptoms in some bipolar patients (8). Other side effects are mild and may include headaches, anxiety, insomnia, diarrhea, and nausea (4). Some studies suggest SAME helps lower levels of homocysteine (4), which is an independent risk factor for cardiovascular disease. Research on the use of SAME in chronic kidney disease patients is scant, and the maximum safe dosage in CKD stage 5 patients is unknown.

St. John's Wort (SJW)

St. John's Wort (*Hypericum perforatum*) holds great promise in the treatment of mild to moderate depression. Kasper et al. conducted a double-blind, randomized placebo controlled multi-center clinical trial to assess the

efficacy of SJW extract, using 600 mg and 1200 mg doses (9). Using the Hamilton Rating Scale, SJW extract was determined to be more effective than placebo in treating mild to moderate depressive disorder after 6 weeks of treatment (9). Similarly, Szegedi et al. conducted a double-blind, randomized study comparing the effectiveness of SJW to paroxetine (10). Fugh-Berman and Cott reviewed the data from 23 clinical trials and found that SJW improved depressive symptoms, and was significantly more effective than placebo (8).

The side-effect profile of SJW appears to be better than that of standard anti-depressants such as SSRIs. Insomnia, weight gain and sexual dysfunction have been reported in patients taking SSRIs. In patients taking tricyclic antidepressants, increased heart rate, blurred vision, and urinary difficulties have been reported (11). In their review of clinical trials, Fugh-Berman and Cott reported that 19.8% of patients randomized to treatment with SJW reported side effects compared to 52.8% of those on tricyclic antidepressants (8). Common side effects from SJW include nausea, heartburn, diarrhea, insomnia, fatigue and jitteriness (4). There are a few SJW-drug interactions that may be particularly relevant for dialysis patients. SJW may affect cyclosporine levels by lowering them by up to 50%. Cyclosporine is an immunosuppressive drug, which many kidney transplant patients may be prescribed. SJW may also interfere with warfarin, commonly prescribed to dialysis patients, which may lead to inadequate anticoagulation or bleeding problems (4). Lastly, the active ingredient in SJW, hypericin, is primarily excreted by the kidney. SJW should be used with caution in patients with kidney failure since they may not be able to clear its active ingredients (12).

Cardiovascular Disease in the Dialysis Population

CKD stage 5 patients are at extremely high risk for cardiovascular disease, and cardiovascular complications are the leading cause of death in patients with kidney failure (13). According to the United States Renal Data System, mortality rates due to heart disease, in CKD stage 5 patients between 45 to 64 years of age are more than three times greater than rates in the general population. The mortality rate for dialysis patients are 180.8 per 1000 patient years compared to 49.8 per 1000 patient years in the general population (14). Survival probability in the first year after a diagnosis of heart



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disease in dialysis patients is significantly lower than in the general population. After five years, dialysis patients have only approximately a quarter of the survival probability of the general population (14).

Known risk factors for cardiovascular disease include high serum lipids, elevated coagulation factors and increased platelet activation. Studies have also linked oxidative stress with cardiovascular disease (15).

Vascular calcification may be a major contributor to cardiovascular disease in dialysis patients. Calcification is an early feature of atherosclerotic plaque formation in the general population; however, it is speculated that because of calcium and phosphorus imbalances, dialysis patients experience calcification at a much earlier age and much more frequently than healthy counterparts (13). In recent years, malnutrition and inflammation have been linked to what is now referred to as malnutrition-inflammation syndrome. This syndrome is specific to the dialysis population and largely involves the process of atherosclerotic complications.

Malnutrition-inflammation complex syndrome has been associated with decreased quality of life, and higher rates of morbidity and mortality (3,16). There are many causes of inflammation in dialysis patients, some of them specific to dialysis including vascular access infections. Other causes of inflammation include chronic heart failure and coronary artery disease (16). The inflammatory state in dialysis patients may lead to a loss of appetite and lead to catabolism of lean body mass (16).

Alternative Medicine Therapies in the Treatment of Cardiovascular Disease

There have been many studies on the use of alternative medicine therapies in the prevention and treatment of cardiovascular disease. Some of these studies have been specific to the CKD stage 5 population, and provide healthcare practitioners with information which can be applied directly to these patients.

Omega-3 Fatty Acids (n-3 fatty acids)

The use of n-3 fatty acids may have a positive affect on albumin, cardiovascular events and mortality. Kutner et al. examined the eating habits of 216 dialysis patients for three years, and found that those who consumed fish at least once per three day period were less likely to die compared to those patients who were not fish eaters (17).

It was also found that individuals who consumed fish on a regular basis had higher albumin levels (17).

Svensson et al. studied n-3 fatty acid intake and incidence of cardiovascular events in 206 hemodialysis patients (18). The results indicated that n-3 fatty acids had no significant effect on all cause mortality and total cardiovascular events. However, n-3 fatty acids decreased the rate of myocardial infarction (MI) in the study population after a two year period. The reduction in MI was explained as a possible "antithrombotic, anti-inflammatory or antioxidative effect" of n-3 fatty acids (18).

Risks and side effects of fish oil intake in hemodialysis patients may include mild gastrointestinal episodes, adverse interactions with hypertensive medications, potentiated effect in combination with aspirin and other anti-coagulation problems. This is especially concerning if patients are concomitantly taking warfarin, aspirin, garlic or ginkgo biloba. The FDA states that the use of eicosahentaenoic (EPA) and docosahexaenoic acid (DHA) n-3 fatty acids as dietary supplements is safe as long as the amount of 3 g per day is not exceeded, but this dosage recommendation is not specific for the CKD stage 5 population (19).

Flaxseed is another rich source of long-chain n-3 polyunsaturated fatty acids. Plant derived n-3 fatty acids have been shown to reduce atherosclerotic lesions in animal models (20). It is recommended that flaxseed be taken with fairly large amounts of fluid; this may be problematic for dialysis patients who have fluid limitations (12). No studies to date have been done on flaxseed supplementation in dialysis patients.

Garlic

Garlic is another botanical medicine that may be helpful in the treatment of cardiovascular disease; unfortunately no studies have been done in the CKD stage 5 population at this time.

Budoff studied the effect of aged garlic extract on the atherosclerotic plaque burden from calcification (21). The results indicated that the plaque burden in the study group increased by only 7.5% in one year compared to 22.2% in the control group. In this study, both groups were already on statin therapy, suggesting a possible potentiated benefit of garlic (21). This is a significant study not only because it revealed the positive effect of garlic in reducing coronary calcification, but also because it demonstrated a trend in the reduction of homocysteine levels. Both

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coronary calcification and elevated homocysteine levels are known risk factors for coronary artery disease in dialysis patients. In a four year, double-blind, placebo controlled study, Koscielny et al. showed that 900 mg per day of garlic powder significantly decreased the rate of development of atherosclerosis (22). The reduced rate of plaque development ranged from 5% to 18% (22). Garlic is not recommended for patients with diabetes who have widely fluctuating blood glucose levels, as it might elicit a hypoglycemic effect (23). Garlic should also be used with caution in patients taking warfarin since garlic may increase bleeding time (12). Patients on dialysis also receive heparin during dialysis treatments, so the addition of garlic supplements can be of concern.

Soy Protein

Hyperlipidemia contributes to the high rates of cardiovascular disease in patients with CKD stage 5. The U.S. Food and Drug Administration has approved the statement that 25 grams per day of soy protein, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease (19).

Studies have shown positive results in lowering cholesterol associated with soy protein intake in dialysis patients. One study evaluated the effect of soy protein on serum lipid profiles in hyperlipidemic and normolipidemic patients on dialysis. Researchers administered either 30 grams of isolated soy protein or milk protein to dialysis patients daily for 12 weeks. The soy protein intake was found to significantly lower total cholesterol by 18.6%, triglycerides by 43.1%, LDLs by 25.8% and increased HDLs by 17% (24). Similarly, a short-term study by Siefker and DiSilvestro showed that providing 25 grams of soy protein, four times per week for four weeks to 17 hemodialysis patients produced no harmful effects (25). In addition it was suggested that soy protein may potentially be beneficial as an antioxidant and anti-inflammatory agent (25). The results also indicated that soy protein intake was associated with reduced plasma values for oxidized low-density lipoprotein, a known risk factor for cardiovascular disease (25). They recommended further studies in this group with longer therapy intervention periods. Finally, a study by Fanti et al. demonstrated that soy protein could reduce serum CRP levels, thereby reducing the risk of the inflammatory response in hemodialysis patients (26).

However, because soy foods tend to be high in both

potassium and phosphorus, adjustments may need to be made in the prescribed nutrition plans of dialysis patients who consume large amounts of soy foods.

Green Tea

Research has shown that intake of green tea may lower cholesterol and triglycerides (27). Catechin, the antioxidant present in green tea, may have a protective effect against atherosclerosis by reducing smooth muscle cell plaque proliferation (27). In dialysis patients, atherosclerosis is a prominent feature of the malnutrition-inflammation complex syndrome. Green tea may hold some promise in the hemodialysis population; however, the recommended dosage of green tea necessary to exert the cardiovascular protective effects has usually been five to six cups per day (28). This would usually exceed the recommended fluid limitation prescribed for hemodialysis patients. The extract of green tea may be a more reasonable approach in this population. Although green tea extract may have possible drug interactions with anti-coagulants such as warfarin, therefore caution with tea extract and anti-coagulants needs to be exercised (12). In addition, a high dose of the extract for extended periods has been found to be unsafe. This can be problematic for individuals who adhere to the adage "if a little is good then more is better."

Special Issues with Alternative Medicine Therapies in CKD Stage 5 Patients.

The use of alternative medicine therapies has not been well studied with dialysis patients. Most dialysis patients usually have a long list of prescribed medications, and it may be challenging to identify all the potential botanical medicine-drug interactions. Dialytic clearance of botanical medicines is largely unknown (29). Dahl reports that the "unpredictable pharmacokinetics" of botanical medicines in patients with kidney failure is of great concern (30). Additionally, since botanical medicines lack standardization, they pose a special problem for dietitians and other clinicians in determining safe dosages for kidney failure (30). Some botanical medicines may be adulterated with toxic levels of lead, cadmium, mercury, and even arsenic or additives such as aluminum and magnesium. Other adulterated products that have been found in botanical medicines include hormonal and glandular extracts which may negate any potential benefits of a given



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botanical. These may be extremely dangerous due to the lack of clearance by the kidney. For most of the botanical medicines and several dietary supplements discussed in this review, the safe dosage for CKD stage 5 patients is unknown since most of the research has been conducted in the general population. Many of these studies have been conducted with relatively small populations, making the statistical significance and extrapolation of the research findings to the dialysis patient challenging and difficult.

Conclusion

This article has provided a review of the relationship between alternative medicine therapies and malnutrition as it relates to the treatment of depression and cardiovascular disease in the CKD stage 5 patient. Specific concerns associated with alternative medicine therapy use in dialysis patients have also been discussed. After reviewing the clinical studies, there may be indications for the use of alternative medicine therapies in the treatment of depression. Depression has been shown to be the most common psychological problem of patients with kidney failure. There is strong evidence for the use of SJW and SAME in the treatment of mild to moderate depression. No clinical trials on SJW and SAME have been conducted in the CKD stage 5 population, but there have been many successful clinical trials in the general population. Dialysis patients on warfarin and transplant patients on cyclosporine should exercise caution due to possible drug-botanical medicine interactions. The side effects of SAME and SJW have been reported as mild, therefore these two botanical medicines show promise in the dialysis population. Further studies should be conducted specifically with CKD stage 5 patients and the associated potential renal clearance concerns.

With regards to cardiovascular disease, this is a very significant problem and poses a high risk for mortality in the dialysis population. This review focused on the potential benefits of fish oils, flaxseed, garlic, soy protein and green tea in the treatment of various cardiovascular disease risks. There have been some studies done with dialysis patients on fish oils and soy in particular. Most of these studies demonstrated positive results on cardiovascular risk factors in the dialysis population but with certain limitations. It has been suggested that both can probably be safely recommended in dialysis patients as an adjunct therapy in the treatment of cardiovascular

disease. Garlic, flaxseed and green tea have not been tested in clinical trials in the dialysis population; however, clinical trials in the general population have shown positive results in the treatment of cardiovascular disease. These dietary supplements and botanical medicines could possibly be used in dialysis patients.

Finally, more research needs to be done on the topic of alternative medicine therapies such as botanical medicines in the CKD stage 5 population. Some botanical medicines may have promise in the improvement of nutritional status and well-being in the dialysis population. More research in this area and expanded use of botanical medicines could lead to an improved life expectancy and a better quality of life for those patients debilitated by malnutrition. 

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