Nutritional Interventions to Reduce Cardiovascular Risk in Chronic Renal Failure

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INTRODUCTION

Despite advances in the understanding of uremia and management of its complications, patients with end-stage renal disease (ESRD) continue to face mortality rates of 23% per year[1]. Atherosclerotic vascular disease accounts for half of these deaths, and is also a major source of morbidity[1]. The etiologic basis of atherosclerosis in chronic renal failure is multifactorial, including classical risk factors such as diabetes, hypertension and disordered lipid metabolism, and factors related to the uremic state, such as malnutrition, inflammation, increased oxidative stress, endothelial dysfunction and homocysteinemia.

CASE

A 63 year old Mexican-American woman with ESRD secondary to diabetic nephropathy on maintenance hemodialysis for the past 2 years was admitted to the hospital with a clotted right forearm vascular access graft. She underwent successful percutaneous angioplasty of the venous anastomosis. After the procedure was completed, she reported substernal chest pain associated with nausea and radiation down the left arm.

Her past medical history includes long-standing type II diabetes, hypertension, peripheral vascular disease manifested by a right plantar foot ulcer, obesity, and a positive tuberculin skin test treated with isoniazid. She was taking amlodipine 10 mg daily and calcium acetate 1300 mg with meals. She is a life-long non-smoker, does not consume alcohol, is retired from pre-school teaching, and lives with her husband of 41 years. Her physical exam is significant for a blood pressure of 165/85, a heart rate of 75 beats per minute, diminished pedal pulses, and mild peripheral edema. Laboratory data as follows.

Table 1. Laboratory values and clinical indicators preceding admission.

	Albumin,gm/dl	CRP, mg/l	Ferritin, ng/ml	Hematocrit, %	Total Cholesterol, mg/dl	Erythropoietin dose, Units	Weight, Kg
March	4.3		550	35	175	2000	87
June	3.9		736	35	168	2400	85.5
September	3.7		912	33	145	2900	83
December	3.2	10.4	983	35	153	3500	79

Electrocardiogram (ECG) recorded at the time of chest pain revealed new ST segment depressions in the lateral leads. The pain and ECG findings resolved with one dose of sub-lingual nitroglycerin. She remained in the hospital overnight and underwent coronary angiography the next day. Angiography revealed diffuse atherosclerotic disease in all coronary vessels.

Effective strategies for reducing cardiovascular events require integrated targeting of multiple biologic mechanisms underlying atherogenesis. Substantial advances in the pharmacologic treatment of atherosclerosis and its risk factors have been made. They include the use of angiotensin converting enzyme inhibitors, beta-adrenergic blockers, peroxisome-proliferator-activated receptor antagonists, and lipid-lowering drugs. Well-designed clinical trials of these agents have confirmed their benefits in patients with normal renal function. As exemplified by the patient presented, atherosclerosis frequently presents in ESRD in the setting of weight loss with overt evidence of chronic inflammation (elevated C-reactive protein, high ferritin, and increased erythropoietin requirements). After treatment of the acute illness, and establishing a pharmacological regimen, what nutritional strategies can be employed to mitigate further vascular disease?

Traditionally, nutritional interventions for cardiovascular risk reduction have centered on lipid-lowering diets. These diets are mildly efficacious in primary and secondary prevention studies in the general population but are limited by practical issues such as adherence [2]. The fluid, electrolyte, mineral, and energy requirements of the renal diet provide additional challenges to dietary interventions,

especially in ESRD patients who frequently have normal total cholesterol levels. Nutritional supplementation with vitamins or 'medical foods' as a means of reducing cardiovascular risk is another strategy undergoing investigation in the general population. The purpose of this review is to discuss the role of nutritional interventions in reducing cardiovascular risk in patients with renal disease.

PROTEIN AND ENERGY SUPPLEMENTATION

Serum albumin is commonly used as a marker of nutritional status in ESRD. A low serum albumin concentration is a strong independent predictor of mortality and cardiovascular disease in patients with ESRD[3-5]. Protein malnutrition, inflammation, and external protein losses (especially in peritoneal dialysis) all play a role in reducing serum albumin levels. In fact, it appears that both protein malnutrition and inflammation are required for serum albumin to drop markedly. Malnutrition, inflammation, and cardiovascular disease are tightly linked and foster each other. Stenvinkel et al describes two types of malnutrition in renal disease[6]. Type 1 is related to the anorexia associated with uremia. It is characterized by a modest reduction in serum albumin and a relative lack both of co-morbidity like congestive heart failure (CHF) and of significantly elevated inflammatory markers. Type 2 is notable for the frequent presence of other causes of morbidity and is termed "malnutrition, inflammation, and atherosclerosis", or MIA. In Type 2 malnutrition there are profound decreases in serum albumin, elevated pro-inflammatory cytokines, and increased oxidative stress. Clinically speaking, most patients with renal disease have components of both types of malnutrition, but the relative contribution of the two syndromes to reducing serum albumin varies among patients.

It is feasible to increase serum albumin in ESRD by augmenting protein and caloric intake; however, there are no clinical trials demonstrating the cardiovascular benefits of doing so. The literature on the impact of protein-energy supplementation on mortality and cardiovascular morbidity in renal

patients is at best inconclusive, and limited by the lack of prospective randomized clinical trials. With respect to clinical utility, the most extensively studied protein and energy intervention in hemodialysis has been intradialytic (administered during hemodialysis) parenteral nutrition (IDPN). Faulty experimental design, such as the lack of a control group has hampered many studies. A recent review concluded that there is not enough evidence to support the effectiveness of IDPN in achieving improved nutritional status or clinical outcomes[7]. In any case, all patients with ESRD require the help of a skilled renal dietitian to avoid protein-calorie malnutrition.

NUTRITIONAL STRATEGIES FOR COUNTERING INFLAMMATION: Fish Oil and Omega-3 Fatty Acids

The critical role of inflammation and cytokine elevations in the viscous cycle of malnutrition and cardiac disease is illustrated by recent studies of the connection between cytokine-driven markers of inflammation and cardiovascular outcomes. An elevation in C-reactive protein (CRP), a marker of acute phase response that reflects a rise in interleukin (IL)-6, is associated with an increase in mortality and cardiovascular morbidity in both the general elderly and dialysis patients, as well as with an increased incidence of atherosclerosis in predialysis patients[6]. Other serum proteins that are elevated in the acute phase response, including fibrinogen and Lp(a), a lipoprotein regulated by several hepatocyte-specific IL-6 responsive elements, are risk factors for cardiovascular disease in ESRD[8]. In 109 pre-dialysis patients, those with lower a nutritional status as assessed by an array of biochemical and subjective assessments had higher CRP and fibrinogen levels and an increase in carotid artery intima-media area by ultrasound compared with well-nourished patients[9], similar to findings in ESRD patients [10]. The increase in area of intima-media is presumed to reflect atherosclerosis.

Recent studies have demonstrated the clinical effectiveness of omega-3 polyunsaturated fatty acids (such as those found in fish oil) in reducing the inflammatory response in patients with ulcerative colitis and rheumatoid arthritis, and in the IL-6-related cachexia in pancreatic cancer patients. Similarly, the ingestion of omega-3 polyunsaturated fatty acids may reduce the incidence of atherosclerotic disease. The underlying mechanisms of omega-3 fatty acid vascular protection have not been entirely elucidated, but those that have been suggested include anti-inflammation, anti-oxidation, and regulation of hepatic gene transcription of three key lipid-metabolic pathways. Membrane stabilization that decreases cardiac arrhythmias and promotion of parasympathetic tone are other demonstrated cardiac benefits.

Observational studies of large populations have shown that dietary intake of fatty fish, a source of omega-3 fatty acids, correlates inversely with the incidence of cardiovascular disease. A significant association between fatty fish intake or fish oils and lower risk of heart disease has been shown in several longitudinal studies, such as the observational cohort of the Multiple Risk Factor Intervention Trial (MRFIT), the Honolulu Heart Program, and in secondary prevention trials such as the Diet and Reinfarction Trial (DART) [11]. In an open label controlled trial in 11,324 post-MI patients, omega-3 fatty acids (850 mg/d) but not vitamin E (300 mg/d), a naturally occurring antioxidant, significantly reduced the combined end-point of death, non-fatal myocardial infarction, and stroke by 15%. A clinical trial of a "Mediterranean diet" rich in anti-oxidants and omega-3 fatty acids was associated with a risk ratio of 0.28 compared to a control group for composite cardiac death and non-fatal MI over 46 months[12].

ANTI-OXIDANTS

The link between inflammation and atherosclerosis is mediated by oxidative stress, an important cofactor for endothelial dysfunction and atherogenesis. Oxidative stress contributes to atherosclerosis primarily through oxidation of low-density lipoprotein (LDL) particles. The presence of oxidized LDL within the arterial wall accelerates the formation of fatty streaks, the precursor lesions of atherosclerosis. LDL from hemodialysis patients has increased susceptibility to oxidation as measured by in vitro assays, reflecting in part the low LDL vitamin E concentration that results from vitamin E removal by dialysis[13]. Excessive production of free radicals and lipoprotein oxidation in uremia are enhanced by bioincompatibility of the hemodialysis membrane. Malnourished patients with chronic renal failure have more biochemical evidence of oxidation than well-nourished ones, a consequence of increased inflammation along with nutritional deficiencies of anti-oxidant vitamins. While elevated CRP levels correlated directly with increased carotid intima-media area in malnourished pre-dialysis patients, vitamin E levels demonstrated an inverse correlation with this surrogate of atherosclerosis[9].

Some forms of anti-oxidant therapy have the potential to counter the pro-atherogenic effects of oxidized LDL. Vitamin E is a potent, naturally occurring antioxidant and is often used safely in pharmacologic doses for its antioxidant effects. It protects human LDL against oxidation in vitro[14]. In hypercholesterolemic animals, vitamin E reverses endothelial dysfunction and increases resistance to oxidant-mediated injury. Supplementation in humans appears to inhibit platelet aggregation, decreases monocyte-enothelial adhesion, and prevents intra-arterial thrombus formation[15]. The Nurses Health Study, an eight-year follow-up of 88,000 women aged 34-59, found that in women in the top quintile of vitamin E intake the relative risk of major coronary events was 0.66 compared with women whose consumption ranked in the lowest quintile. Similar findings were reported in studies of 34,000 post-menopausal women and in 40,000 male health care professionals[14]. Several clinical trials of vitamin E for primary or secondary prevention of cardiovascular disease in the general population have either

shown a small benefit or have been inconclusive[14]. A large, randomized placebo-controlled trial of vitamin E (400 IU/d) as primary prevention in 10,000 patients followed for 4.5 years was unable to demonstrate a benefit of treatment[16]. Investigations of anti-oxidant therapy in the ESRD population have revealed promising effects on markers of atherogenic risk such as LDL oxidative susceptibility. Initial clinical trials of the cardiovascular benefits of vitamin E in dialysis patients have had positive results. A recent placebo-controlled trial of vitamin E (800 IU/d) for secondary prevention of cardiovascular events in dialysis patients (n= 196, follow-up 515 days) disclosed a greater than 50% reduction in myocardial infarction in the treatment group[17]. The use of vitamin E coated cellulose dialyzers in 2-year controlled study of 50 dialysis patients led to a significant reduction in levels of oxidized LDL and slowed the rate of aortic calcification by radiographic assessment[18]. Though these findings are encouraging, more work is needed to determine if this biochemical evidence of improved oxidative status translates into cardiovascular benefits in renal patients.

L-ARGININE

Nitric Oxide (NO) mediates vasodilation and angiogenesis and is an important anti-atherogenic molecule[19]. It is formed from L-arginine by NO synthase. Biologic activities of NO include mediating a reduction in endothelial release of vasoconstrictor and inflammatory proteins, a fall superoxide ion concentration, inhibition of platelet aggregation, and prevention of leukocyte adhesion to endothelial cells. Endothelial dysfunction in ESRD is linked to elevated asymmetrical dimethylarginine (ADMA), an inhibitor of NO synthase.

Dietary supplementation with the L-arginine is a promising nutritional strategy for ameliorating endothelial dysfunction in chronic renal failure. By increasing substrate availability and antagonizing endogenous ADMA, L-arginine increases NO production by cultured endothelial cells in vitro in a dose-

dependent fashion and enhances systemic and vascular NO production in vivo[19]. In vivo L-arginine administration may promote NO-mediated effects on vasodilation, angiogenesis, and antithrombosis. In addition, L-arginine exerts NO-independent effects via action as an anti-oxidant, inhibitor of angiotensin-converting enzyme, stimulant of fibrinogenolysis, and regulator of lipid metabolism[20].

A growing body of evidence suggests that dietary supplementation of L-arginine improves endothelial dysfunction in humans with cardiovascular risk factors and cardiac disease. Short-term intravenous L-arginine infusion (0.2 mg/kg) or oral L-arginine (7g three times a day for 4 weeks) increases endothelium-dependent blood flow and arterial dilation of the forearm in hypercholesterolemic patients. Among patients with congestive heart failure, oral L-arginine (5.6-12.6 g/d for six weeks) reduced plasma levels of endothelin-1and improved arterial compliance and overall functional status. Similarly, L-arginine is efficacious in improving cardiac function, reducing cardiac ischemia, and increasing exercise tolerance in individuals with coronary artery disease[20]. In a recent randomized study of 26 patients with non-obstructive coronary disease, oral L-arginine supplementation for six months reduced coronary endothelial dysfunction in response to acetylcholine (150% improvement in coronary blood flow), decreased endothelin-1 levels by 30%, and improved symptoms compared with placebo. Complementary to these hemodynamic effects in human subjects, evidence that dietary L-arginine inhibits atherogenesis is emerging from animal studies. Oral L-arginine for 6 months prevented xanthoma development and inhibited atherogenesis in LDL receptor knockout mice. Oral L-arginine also inhibited intimal lesion formation in hypercholesterolemic rabbits[21]. Two potential drawbacks of NO enhancement in patients with kidney disease include the promotion of injury in immune-mediated-glomerulonephritis and the possible association of NO and hypotension during hemodialysis. Whether L-arginine supplementation can improve cardiovascular health and reduce mortality in the general population and ESRD patients must be answered by prospective clinical trials.

DIETARY SODIUM AND FLUID COMPLIANCE

Restriction of sodium and fluid intake to prevent extracellular volume overload is mainstays of treatment of patients with renal insufficiency and ESRD. Fluid-related complications, especially pulmonary edema, are common in ESRD. It is estimated that 75% of patients with ESRD have left-ventricular hypertrophy[22], an important risk factor for CHF. The high prevalence of malnutrition in patients with primary cardiac failure raises the possibility that CHF is a causes nutritional wasting (cardiac cachexia). This appears to be mediated by pro-inflammatory cytokines, which rise in chronic heart failure seemingly as a result of tissue hypoxia, hypoperfusion, and congestion. In ESRD patients, inflammation from acute and chronic infection, the dialysis procedure itself, and other sources combine with CHF to increase the generation of cytokines[8]. This emphasizes the importance of extracellular volume control. Clinical trials of agents such as ACE inhibitors in ESRD are warranted.

FOLIC ACID, VITAMIN B6 AND VITAMIN B12

Homocysteine, a non-protein forming sulfur-containing amino acid, is under scrutiny as a risk factor for cardiovascular disease. Extensive case-control and cross-sectional studies support a strong association between hyperhomocysteinemia and atherosclerotic disease; however, this relationship is not consistent in prospective, population-based studies. The mechanism by which homocysteine contributes to atherogenesis is not entirely clear, but may include promotion of oxidative endothelial damage, oxidation of low-density lipoprotiens, promotion of thrombogenicity, and proliferation of smooth muscle cells. Serum homocysteine rises in parallel with serum creatinine during the course of chronic renal failure. In ESRD, mean levels are generally found to be around 30 umol/l where as levels around 13umol/l are considered the upper limit of normal in the general population.

Supplementation with folic acid, vitamin B6 and vitamin B12 has the potential to reduce or normalize high homocysteine levels in normal and uremic individuals, even in the absence of baseline vitamin deficiency, and may be an effective means for preventing cardiovascular disease. Among these vitamins, folic acid is the most powerful homocysteine-lowering agent. A recent meta-analysis of studies in the general population found that folate alone (0.5-5 mg/d) reduces homocysteine levels approximately 25%, while addition of vitamin B12 provides an additional 7% reduction but addition of vitamin B6 has no significant effect[23]. Higher doses of these vitamins seem necessary to overcome the metabolic abnormalities underlying the elevated plasma homocysteine so prevalent in patients with renal failure. A controlled study in dialysis patients using 15 mg/d folic acid plus 200 mg/d vitamin B6 reduced plasma homocysteine by a mean 28%, although only one-third of patients achieved normal levels with treatment[24]. Folic acid and vitamin B6 also have been shown to increase RBC and plasma glutathione levels, a potential benefit on anti-oxidant stress[25]. Large randomized trials addressing the impact of vitamin therapy to decrease homocysteine on cardiovascular outcomes in general and uremic populations are currently in progress.

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UPCOMING MEETINGS

World Congress of Nephrology. The American Society of Nephrology and the International Society of Nephrology. October 12-17, 2001 at the Moscone convention Center in San Francisco, CA, USA.

Second Annual Conference on Arteriosclerosis, Thrombosis, and Vascular Biology. Sponsored by the American Heart Association's Council on Arteriosclerosis, Thrombosis and Vascular Biology, the North American Vascular Biology Organization, and the National Heart, Lung and Blood Institute. Mays 11-13, 2001 at the Crystal Gateway Marriott, Arlington, VA, USA.

55th Annual Fall Conference & Scientific Sessions of the Council for High Blood Pressure Research. Sponsored by the American Heart Association's Council for High Blood Pressure Research. September 22-25, Hyatt Regency, Chicago, IL, USA

ABSTRACT-1

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Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial

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BACKGROUND: Excess cardiovascular mortality has been documented in chronic haemodialysis patients. Oxidative stress is greater in haemodialysis patients with prevalent cardiovascular disease than in those without, suggesting a role for oxidative stress in excess cardiovascular disease in haemodialysis. We investigated the effect of high-dose vitamin E supplementation on cardiovascular disease outcomes in haemodialysis patients with pre-existing cardiovascular disease. METHODS: Haemodialysis patients with pre-existing cardiovascular disease (n=196) aged 40-75 years at baseline from six dialysis centres were enrolled and randomised to receive 800 IU/day vitamin E or matching placebo. Patients were followed for a median 519 days. The primary endpoint was a composite variable consisting of: myocardial infarction (fatal and non-fatal), ischaemic stroke, peripheral vascular disease (excluding the arteriovenous fistula), and unstable angina. Secondary outcomes included each of the component outcomes, total mortality, and cardiovascular-disease mortality. FINDINGS: A total of 15 (16%) of the 97 patients assigned to vitamin E and 33 (33%) of the 99 patients assigned to placebo had a primary endpoint (relative risk 0.46 [95% CI 0.27-0.78], p=0.014). Five (5.1%) patients assigned to vitamin E and 17 (17.2%) patients assigned to placebo had myocardial infarction (0.3 [0.11-0.78], p=0.016). No significant differences in other secondary

endpoints, cardiovascular disease, or total mortality were detected. INTERPRETATION: In haemodialysis patients with prevalent cardiovascular disease, supplementation with 800 IU/day vitamin E reduces composite cardiovascular disease endpoints and myocardial infarction.

ABSTRACT-2

(From ASN September, 2000)

[A0927] Effects of a Vitamin E Coated Dialyzer Membrane on Lipid Peroxidation and Dialysis Adequacy

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Oxidative damage due to lipid peroxidation is implicated as a causative factor in the high incidence of vascular disease in hemodialysis (HD) patients. Recent clinical trials have reported that a new vitamin E coated dialysis membrane (VEM) may decrease plasma lipid peroxidation that occurs during HD. The purpose of this study was to determine the effects of a VEM on dialysis adequacy for the trial based on a consistent HD history with urea reduction ratio (URR) of 70% using a Polysulfone membrane (PSM). URR was measured (1) before the trial (2) after the first HD visit using the VEM and (3) after 6 weeks on the VEM. Creatinine and phosphate clearance were also determined after the first visit and compared to manufacturers specifications. Plasma lipid peroxidation was determined by measuring plasma cholesterol hydroperoxides. One patient was withdrawn due to excessive clotting with another patient requiring increased fragmin. URR was significantly lower in patients on the VEM compared to the PSM after the first HD visit (73.9 ± 2.3 vs 69.0 ± 2.8, $p<0.001$)and after 6 weeks on the VEM (68.0 ± 2.1, $p<0.001$). Creatinine and phosphate clearance was similar to the membrane manufacturer'sspecifications. Target fluid removal was reached in six of the patients. Plasma cholesterol hydroperoxides were significantly lower after six weeks using the VEM (12.4 nM ± 1.3 vs 6.2 ± 1.5, $p<0.001$). These data show that there are antioxidant benefits associated with the use of a vitamin E dialysis membrane, however, changes in dialysis prescription would be required to maintain dialysis adequacy.