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Cardiovascular Primary Care in End Stage Renal Disease

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Special interests: Primary care in chronic kidney disease, end stage renal disease and renal transplantation.

This is to acknowledge that Dr. Penfield has no financial interests or other relations with commercial concerns related directly to this program. During this presentation there will be discussion of off label uses of medications and procedures.

Introduction

End stage renal disease can be defined as loss of renal function to the point that renal replacement therapy is necessary. Renal replacement therapy includes hemodialysis, peritoneal dialysis and renal transplantation. Markedly increased cardiovascular disease is prevalent in both dialysis patients and transplant patients. I will focus on cardiovascular disease in dialysis patients with emphasis on uremia (loss of renal function) as the cause.

The incidence of end stage renal disease is steadily increasing over the last three decades[1]. This increased incidence is mainly due to the increase in older patients while the incidence in the younger population is staying the same as shown in figure 1. The cause of end stage renal disease is also changing over time with diabetes now surpassing hypertension in African American patients in the United States as the leading cause of end stage renal disease. Diabetes now accounts for 50% of the cause of end stage renal States.

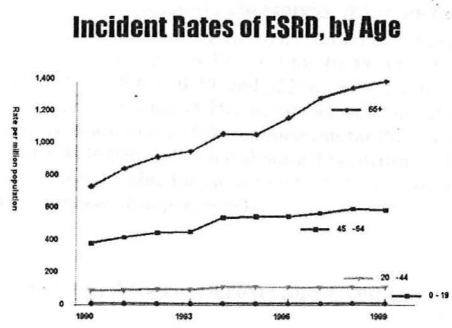


Figure 1

The rate of transplantation is not keeping up with the incidence of end stage renal disease because it is dependent on the number of available donors in the U.S population. Therefore the prevalence rate of dialysis patients is markedly increasing and is expected to double by the year 2010. Unfortunately the number of nephrology sub specialists is expected to stay the same. This excess of dialysis patients combined with the shortage of nephrologists is expected to result in a nephrology manpower crisis by the end of this decade[2]. The primary care of dialysis patients will therefore be left to primary care physicians instead of nephrologists.

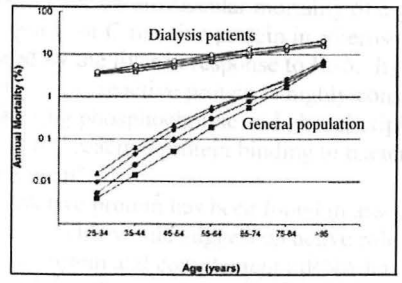


Figure 2

With this increase in older patients and diabetes, there is an increase in cardiovascular morbidity and mortality at initiation in end stage renal disease patients[1]. However, the prevalence of cardiovascular morbidity and mortality is also markedly increased in younger diabetic patients. Figure 2 shows the cardiovascular

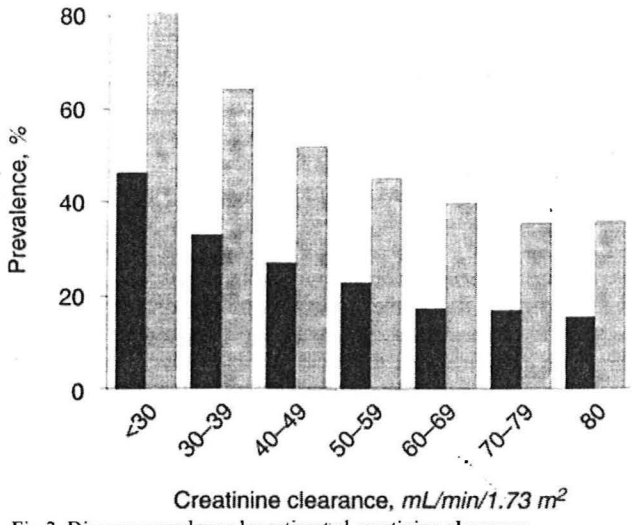


Fig.3. Disease prevalence by estimated creatinine clearance. (N = 145 for <30; 423 for 30-39; 1051 for 40-49; 1426 for 50-59; 1354 for 60-69; 769 for 70-79; and 622 for 80 mL/min/1.73 m2). Clinical disease () includes CHD and stroke; subclinical disease () includes ankle-arm index <0.9, common carotid IMT in upper quintile, left ventricular hypertrophy, and abnormal/borderline left ventricular ejection fraction. P value for linear trend <0.001 for both clinical and subclinical disease. (Shilpak, ref#4)

mortality for dialysis patients compared to the normal population. At all ages the cardiovascular mortality is increased. As a comparison the, mortality of a dialysis patient aged 25 to 34 has the same cardiovascular mortality as a patient aged 75-84 in the general population[3].

The cause of this increased cardiovascular mortality is now thought to be related to the effects of uremia as shown in figure 3. As loss of renal function progresses, the incidence of cardiovascular morbidity increases[4]. This uremic induced cardiovascular disease has many causes that will be outlined in this protocol.

Inflammation, Atherosclerosis and Uremia

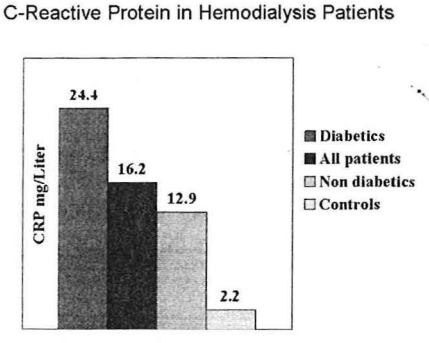
Atherosclerosis is considered to be an inflammatory lesion[5]. This is based on the finding of monocytes, foam cells and numerous inflammatory cytokines in atherosclerotic plaques. A marker of inflammation is C reactive protein. This marker was originally used as a marker for inflammatory diseases such as rheumatoid arthritis or vasculitis. It is now been used as a marker for cardiovascular mortality[6, 7]. A single level can determine the cardiovascular mortality of a group of patients over several years[7].

The role of C reactive protein in atherosclerosis is not clear. This protein is mainly secreted by the liver in response to IL-6. It has a role in the innate immunity. The structure of C reactive protein is highly conserved over many species. It functions by recognizing phosphocholine and phsopholipids and binding complement to them. This results in C reactive protein binding to bacteria and damaged cells and then activating complement[8].

C reactive protein has been found in association with complement in atherosclerotic plaques[9]. This would suggest an active role in causing the atherosclerotic plaque. C reactive protein and complement mRNA has also been seen in atherosclerotic plaques in association with macophages[10]. This association suggested that inflammatory cells in the atherosclerotic plaque are synthesizing C reactive protein in response to the

atherosclerosis. This would support the theory that C reactive protein is generated in atherosclerotic plaques and leaks into circulation making it merely a marker of atherosclerosis.

Dialysis patients have markedly elevated C reactive protein levels that correlate with cardiovascular mortality similar to non dialysis patients. The difference is that the levels are much higher. The cutoff value used by Lindahl in non dialysis patients to be a marker for a significant increase in mortality was 10[7]. The average level in non-diabetic dialysis patients was 12. The level in diabetic dialysis patients was 24[11]. A Level of less than 2 is normal and a level of 24 in non dialysis patients is seen only in severe inflammation such as seen in severe trauma, bacterial sepsis or vasculitis. One could consider the elevated C reactive protein in dialysis patients as a marker of increased atherosclerosis and/or as a marker of significant inflammation that causes atherosclerosis.



Zimmerman, etal. (1999) Kidney Int 55(2): 648-58.

Figure 4

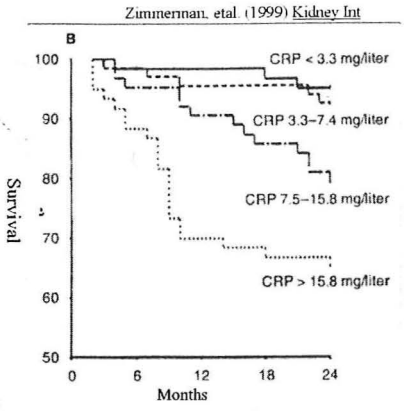


Figure 5

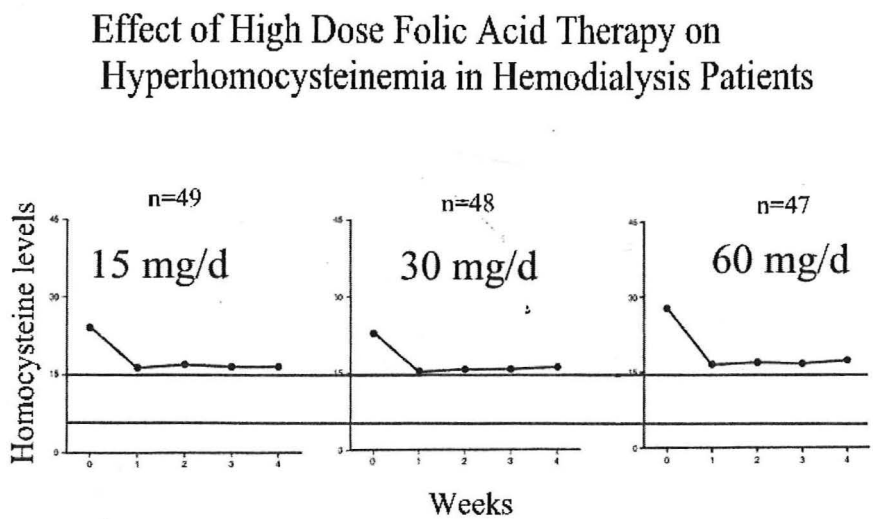
Other markers of inflammation that are elevated in dialysis patients and also associated with atherosclerosis include tumor necrosis factor-ά, interleukin-6, tissue growth factor-β, intercellular adhesion molecule-1 (ICAM), vascular cell adhesion marker (VCAM), monocyte chemoattractant protein-1 (MCP-1), among others[12].

Homocysteine

Homocysteine like C reactive protein has also been used as a marker for increased cardiovascular mortality in dialysis patients[13]. Levels in dialysis patients are also markedly elevated compared to the general population and higher levels correlate with higher cardiovascular mortality in dialysis patients[14, 15]. Researchers have looked for ways to decrease homocysteine levels in both the general population[13, 16] and in dialysis patients[17]. Folate can convert homocysteine into methionine by donating a methyl group with vitamin B12 as a cofactor. Alternative pathways include trimethylglycine (betaine) as a methyl donor. This pathway does not require B12 and can be upregulated in folate deficiency. Vitamin B6 can also metabolize homocysteine into cysteine. All of these dietary supplements have been tried in the general population, but folate seems to be the most successful[18]. Folate is an appropriate supplement to use in dialysis patients because

it is a water soluble vitamin that is lost during dialysis, rendering dialysis patients folate deficient.

For this reason several studies have looked at folate replacement as a way to improve the homocysteine levels in end stage renal disease. Various combinations of B12, B6 and betaine have been used and folate has been given both orally and intravenously. The dose of folate has varied from 1 mg per day to 60 mg per day. The result in most of these studies is that homocysteine can be lowered by about 25 percent using 1-5 mg per day. However the homocysteine levels never reach the normal level. Higher doses do not are no more effective in lowering homocysteine levels[14, 17].



SUNDER-PLASSMANN,et.al. J Am Soc Nephrol, Vol 6, 2000, 1106-16.

Figure 6: Homocysteine levels improve with folate therapy, but do not reach normal levels (lines). Higher doses of folate do not decrease the homocysteine levels

The reason for the inability to normalize homocysteine levels with pharmacological doses of folate has been attributed to uremic inhibition of enzymes involved in homocysteine metabolism in addition to folate deficiency. Therefore trying to force methylation with an excess supply of folate is not successful.

In all of the studies using folate supplementation, none have looked at cardiovascular endpoints. A current VA cooperative trial is ongoing which will look at not only homocysteine but also cardiovascular endpoints, including access clotting. This trial is using 40 mg of folate per day. The decision to use a pharmacological dose in this trial is based on the theory that folate may improve arteriosclerosis independent of its homocysteine lowering properties. This maybe related to folate's ability to act as a methyl donor in other metabolic pathways with potential anti-oxidant properties[18].

Uremic Dyslipidemia

Uremia is associated with an abnormal dyslipidemic state that is quite different from the lipid profile of non dialysis patients. Similar to homocysteine, this is related to uremic inhibition of various enzymes. In uremic dyslipidemia, the enzymes have been identified and can account for these changes.

Lipoprotein lipase is one of these enzymes. It is bound to the cell surface of peripheral cells and breaks down the triglycerides from lipoproteins into diglcerides and free fatty acids for uptake into the cell. Lipoprotein lipase metabolizes chylomicrons and very low density lipoproteins (VLDL). Hepatic lipase is also inhibited in uremia. Hepatic lipase is bond to hepatocytes and hepatic endothelial cells and breaks down triglycerides of IDL and converts it to low density lipoprotein (LDL). The result of the inhibition of these two enzymes leads to elevated triglycerides, chylomicrons, VLDL and IDL, but normal LDL levels in end stage renal disease[19].

Even though the LDL level is normal, it is modified in uremia into much more pro-atherogenic LDL particles. The abnormal lipoprotein metabolism produces small dense LDL. This small dense LDL is not recognized by the normal LDL receptor and therefore its clearance and time of exposure is increased. This increased exposure along with the increased oxidative stress of uremia results in accumulation of oxidized LDL and glycated LDL. These modified LDLs are not recognized by the normal LDL receptors of peripheral cells and hepatocytes and instead are taken up by the LDL scavenger receptor of macrophages[20]. This increased uptake by macrophages results in the formation of foam cells seen in atherosclerotic lesions[21].

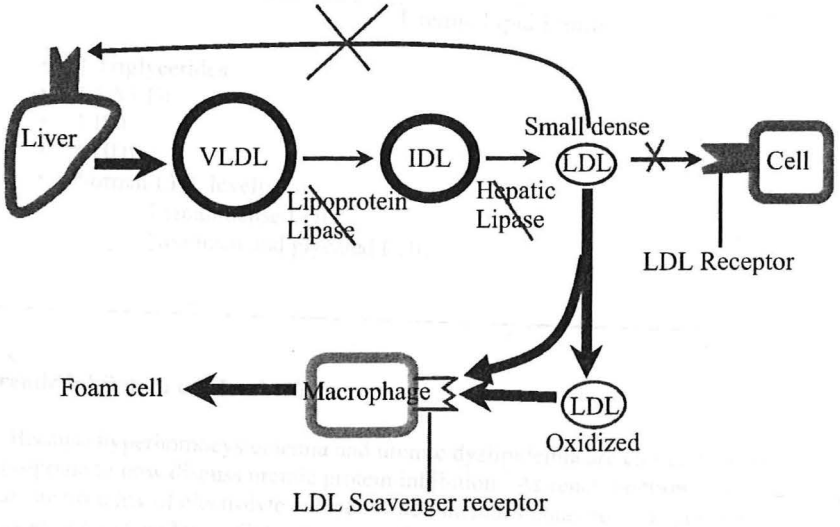


Figure 7: Uremic LDL metabolism. See text for details

Uremia also affects high density lipoprotein metabolism. Inhibition of lipoprotein lipase prevents formation of an HDL sub fraction resulting in reduced HDL. Uremic inhibition of lecithin cholesterol acetyl transferase (LCAT) also results in the decreased HDL[19]. LCAT deficiency prevents the maturation of nascent preβ-HDL into α-HDL resulting in poorly lipidated HDL particles that undergo rapid catabolism resulting in low plasma HDL levels[22].

On the other hand, uremic inhibition of hepatic lipase[23] and cholesterol ester transfer protein (CETP) tend to increase the levels of HDL[24, 25]. This effect on raising HDL does not counterbalance the HDL lowering effect of lipoprotein lipase and LCAT deficiency, so that the net effect of uremia on HDL is to lower HDL levels. However, this disrupted metabolism of HDL inhibits the flow of reverse cholesterol transport. Decreased activities of hepatic lipase and CETP have both been associated with an increased risk of atherosclerosis independent of the HDL levels. This decrease in reverse cholesterol transport causes prolongation of its half-life. This prolonged exposure results in oxidation of HDL[26], similar to LDL. This oxidation is exacerbated by the uremic inhibition of paraoxonase[27]. Paraoxanase is a protein that associates with HDL and prevents its oxidation[28]. Oxidation of HDL can convert it to a pro-atherogenic substance[29].

The net result of these uremic effects on the lipid profile of dialysis patients is an increase in triglycerides, VLDL, and IDL and a decrease in post prandial clearance of chylomicrons along with a decreased level of HDL and a normal LDL. There is also an increase in oxidized HDL, and oxidized LDL and small dense LDL[19].

Uremic Lipid Profile

- ↑ Triglycerides
- ↑↑ VLDL
- ↑ IDL
- ↓ HDL
- Normal LDL levels
  - ↑ small dense LDL
  - ↑oxidized and glycated LDL

Uremic Inhibition of Metabolism

Because hyperhomocysteinemia and uremic dyslipidemia are caused by uremia, it is appropriate to now discuss uremic protein inhibition. As renal function deteriorates there is an abnormality of electrolyte balance which includes potassium, magnesium, calcium, phosphorus and acidosis. Calcium metabolism is disturbed by the elevated parathyroid hormone and absence of vitamin D. Water soluble vitamins are also decreased in dialysis patients because of clearance on dialysis. The kidney also functions in metabolism of various substances in addition to its function in clearance. And finally there is a build up

of uremic toxins. The "uremic toxin" is not an identifiable set off compounds. Instead it is an accumulation of many different water soluble products of metabolism that inhibit protein function.

Dialysis is unable to clear these toxins because of the limited nature of dialysis. The clearance of uremic toxins is based on the glomerular filtration rate and is not dependent on size as long as the molecule is small enough to pass through the glomerular basement membrane. If the glomerular filtration rate is 100 ml/min, then the clearance per week is 1008 liters/week. In comparison, the weekly clearance of urea is only 210 liters per week based on standard dialysis settings. As the size of the molecule goes up, the clearance goes down. Creatinine clearance is only 183 liters per week and B12 clearance (considered a marker of middle molecule clearance) is only 122 liters per week. The reason for the decreased clearance of larger molecules is that dialysis clearance is based on diffusion based on differences in concentration across a semi-permeable membrane. Larger molecules move slower and can therefore not equilibrate as quickly as small molecules resulting in decreased clearance as the size increases.

Even with this markedly decreased clearance per week based on these calculations, this clearance is not as efficient because it is intermittent instead of continuous. This is illustrated by the fact that an equivalent weekly creatinine clearance on continuous ambulatory peritoneal dialysis is only 75 liters per week versus the 183 liters per week shown above for thrice weekly intermittent hemodialysis. Even with these calculations, in order to equal the urea clearance of the kidney, hemodialysis would have to be performed 8.5 hours per day 7 days per week. In order to match the middle molecule clearance of the kidney, hemodialysis would have to be performed 14 hours per day 7 days per week.

Advanced Glycation Endproducts and Oxidation

Advanced glycation end products (AGEs) are elevated in diabetics and contribute to the many of the complications of diabetes[30]. AGEs have also been noted to be markedly elevated in dialysis patients[31]. Misselwitz showed that even in pediatric dialysis patients AGEs are elevated, excluding the influence of age and diabetes in the adult population[32]. Surprisingly, Schwedler showed that these elevated AGEs in dialysis patients do not incur an increased mortality[31] like homocysteine and c-reactive protein. The increased AGEs are thought to be a result of the increased oxidative potential associated with uremia and AGEs in turn can be cause of oxidative stress[30].

An example of the increased oxidative state in uremic patients is the finding of increased levels of malondialdehyde (an example of lipoperoxidation) and pentosidine (an example of glycoxidation) in the myocardium of dialysis patients[33]. Several other examples of increased oxidative stress have been shown in dialysis patients[26, 34-36]. This increased oxidative stress is felt to contribute to the increased atherosclerosis and cardiac dysfunction seen in uremia[33].

Calcium, Phosphorus and Hyperparathyroidsim

Dialysis patients have significant disturbances in mineral metabolism that result in several cardiovascular complications. Hyperparathyroidism is of course induced by hypocalcemia. It is also induced by hyperphosphatemia which is a significant problem in

end stage renal disease. Patients are instructed to eat a high protein diet for adequate nutrition, but most protein containing foods are rich in phosphorus. Compliance with four large pills of phosphate binders per meal is also difficult to manage. In addition to these two mineral abnormalities, uremia itself also stimulates parathyroid hormone secretion[37]. Hyperparathryoidism can be treated with vitamin D analogues, but in order to prevent low turnover bone disease, the PTH goal is rather high at 1.5 to three times the upper limit of normal (100-200 if the upper limit of normal is 65). Because of hyperphosphatemia, the average level is around 400-500 and levels of greater than 2000 are not uncommon.

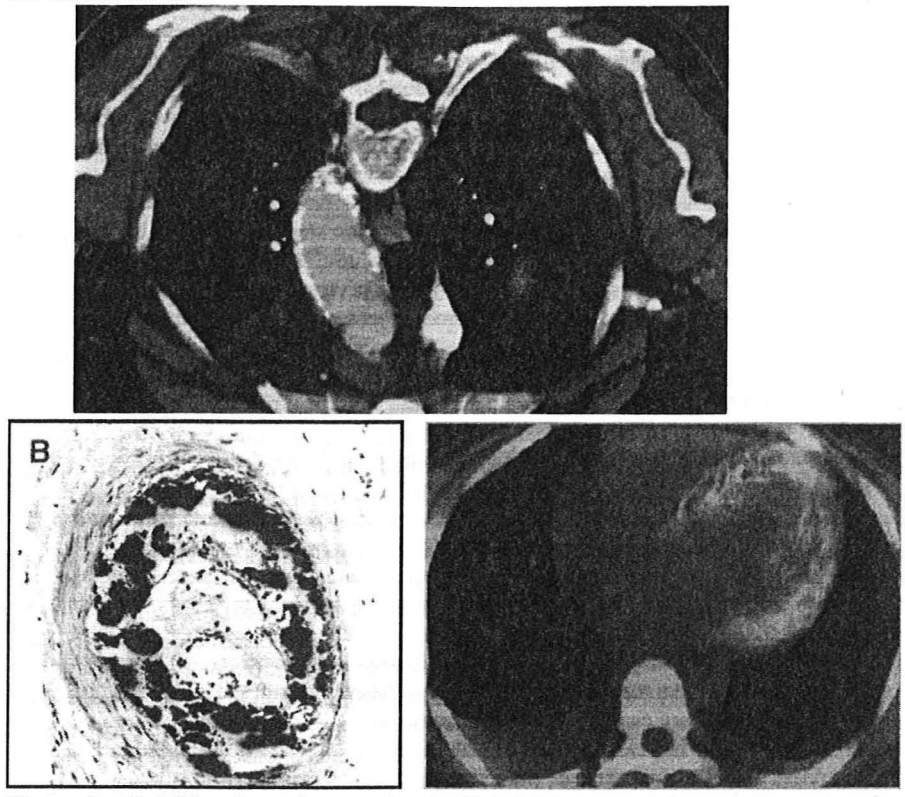
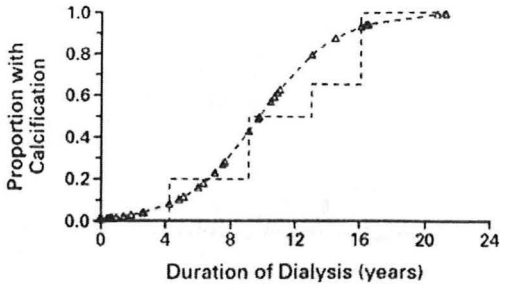


Figure 8: Calcification of aortoa(top). Calciphied artery in calciphylaxis (bottom left). Calcified left ventricle and septum (bottom right)

The result of this hyperparathyroidism is an increase in hypertension thought to be caused by calcium uptake into the endothelial cells[38, 39]. There is loss of calcium from bone and it ends up depositing in extra-skeletal locations. It is seen in the endothelium of arteries, the aorta and in the myocardium. This cardiovascular calcification results in exacerbation of hypertension, cardiac hypertrophy and fibrosis, and increased athersoclerosis[40]. Goodman showed that there is an increase in coronary artery

Coronary-Artery Calcification in Young Adults with End-Stage Renal Disease Who Are Undergoing Dialysis



Goodman, et al. (2000) N Engl J Med.[41]

Figure 9.
Prevalence of coronary-artery calcification among 39 patients with End-Stage Renal Disease, according to the duration of treatment with dialysis. Coronary-artery calcification was assessed by electron-beam computed tomography.

calcification that correlated with time on dialysis, the phosphorus level and the calcium-phosphorus product. At twenty years the percentage of patients with coronary calcifications was 100 per cent. It was remarkable considering that all of the patients in the study were pediatric patients or young adults less than thirty years of age[41].

Angiotensin and Sympathetic Nerve Activity

Another source of increased risk for cardiovascular disease in end stage renal disease is an elevated level of angiotensin II. This has been recognized for many years and is related to the secretion of renin by the failing kidney[42]. After nephrectomy, renin activity and circulating angiotensin II levels fall with a marked improvement in hypertension[42, 43]. There may still be small amounts of renin activity patients with bilateral nephrectomy from the adrenal glands or endothelium[44]. This small amount of renin can be sequestered from the circulation and concentrated in the myocardium and endothelium to upregulate local angiotensin II by tissue renin-angiotensin system activity[45]. Endothelin-1 is also elevated in end stage renal disease[46].

This elevated angiotensin II and endothelin-1 activity in uremia results in release of several markers of inflammation related to athersoclerosis via nuclear factor-κB(NF-κB). These markers include chemokines, cell adhesion molecules, and stimulators of macrophage activation, thrombosis and fibrosis (see table 2). NF-κB also causes upregulation of angiotensin type 1 receptor (AT1 receptor) that acts as a positive feedback loop[47]. Angiotensin II also stimulates an increase in reactive oxidation species (ROS) through NADPH oxidase[48, 49]. This increase in ROS further increases the activation of NF-κB and also stimulates vascular smooth muscle proliferation.

To illustrate the above effects: Increased renin-angiotensin system in end stage renal disease attracts macrophages, binds them to the endothelium, and activates them to form inflammatory foam cells. The increased thrombosis from PA1 in conjunction with the damaged endothelium and the increase in vascular smooth muscle proliferation results in thrombosis and infarction and TGF induces fibrosis.

Angiotensin II induced cytokine release
– MCP- (Monocyte Chemoattractant Protein-1)
– VCAM (Vascular Cell Adhesion Molecule)
– ICAM (Inducible Cell Adhesion Molecule)
– TNFα (Tumor Necrosis Factor-α)
– IL-6 (Interleukin-6)
– PAI1 (Plasminogen Activator Inhibitor-1)
– TGFβ (Transforming Growth Factor β)

Table 2

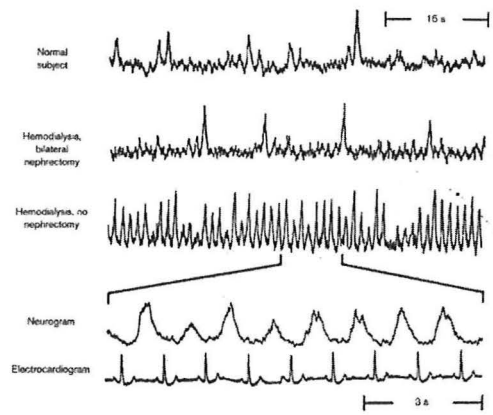


Figure 10:
Recordings of sympathetic nerve discharge to the leg muscles in a normal subject and in two patients receiving hemodialysis, one with and one without bilateral nephrectomy.The rate of sympathetic nerve discharge was much higher in the patient undergoing hemodialysis who had not had a nephrectomy than in the patient undergoing hemodialysis who had had a bilateral nephrectomy, with the rate in the latter being indistinguishable from that in the normal subject. Despite the elevated rate of sympathetic nerve discharge, the sympathetic nerve activity retained its normal relation to the cardiac cycle.
Converse R, et al, N Engl J Med (1992)[51]

Increased sympathetic activity as measured by circulating norepinephrine levels in patients in the general population has been associated with increased mortality[50]. End stage renal disease has also been associated with an increase in sympathetic nerve activity[51, 52]. This increase is seen in hemodialysis patients who still have their remnant kidneys but not in patients with bilateral nephrectomies, similar to renin, angiotensin II and endothelin levels. The etiology of this increased activity has been attributed to both the stimulation by angiotensin II[53] and the afferent nerve stimulation of the failing kidneys[54, 55]. This increased sympathetic over activity can be inhibited with the use of ACE inhibitors[53].

Sleep Apnea

Sleep apnea is very common in dialysis patients and has an estimated frequency of 21-45%[56] which is 12 times higher than that in the general population[57]. In patients with a sleep complaint the incidence is as high as 71 percent[58]. Sleep apnea has been established as a marker of cardiovascular disease and mortality in the general population[59] as well as in dialysis patients[60]. LVH and autonomic dysfunction has been related to sleep apnea in dialysis patients[61, 62]. No data is available regarding improvement in mortality in dialysis patients treated with continuous positive airway pressure (CPAP) and the improvement in the mortality of non dialysis patients is weak[63]. However, there is significant improvement in daytime somnolence and sleep with the use

of CPAP in dialysis patients. The benefit on mortality is currently being evaluated in patients with CHF in the general population[64].

Thrombosis & Bleeding

End stage renal disease has a paradoxical increase in both bleeding and thrombosis. This is not unique to end stage renal disease as it is also seen in disseminated intravascular coagulation(DIC) or heparin induced thrombocytopenia thrombosis (HITT). Originally dialysis patients were thought to have an increased risk of bleeding without an increase in thrombosis. This was based on uremic platelet dysfunction[65], the dosing of heparin (typically 8000 units three times per week), the increased incidence of gastrointestinal bleeding[66] and early autopsy studies showing a very low incidence of pulmonary embolism in comparison to the general population[67]. These autopsy findings were challenged by the recognition of pulmonary embolus in dialysis patients and a recent publication showed that the incidence of hospitalization for pulmonary embolus was 2.1 times greater in hemodialysis patients as compared to the general population[68]. Procoagulatory and fibrinolytic activity determined by measurements of partial thromboplastin time, prothrombin fragments F1 + 2, thrombin-antithrombin complexes and D- dimer concentrations were measured in a group of dialysis patients and found to be elevated compared to controls. The hemodialysis procedure itself further increased these procoagulatory indices and was only partially reversed with heparin[69]. Inflammation, oxidation and uremic protein interaction are again implicated in this uremic complication.

Atrial fibrillation is frequent in dialysis patients[70] and requires a determination of whether the increased risk of bleeding or the increased risk of thrombosis is more important. Many trials demonstrating the superiority of coumadin in preventing embolic strokes have been done in the general population[71]. However, all of these trials excluded dialysis patients and patients with renal insufficiency because of their derangements in coagulation [72]. There are only two retrospective trials that looked at the incidence of cerebral embolic events in dialysis patients and the results were contradictory. The first trial published in the American Heart Journal showed that hemodialysis patients had a 9.4 percent incidence of persistent atrial fibrillation and that 35 percent of these patients had thromboembolic events (stroke, transient ischemic attacks or peripheral emboli) versus 4 percent of the patients with normal sinus rhythm. Patients with atrial fibrialltion tend to be older with more cardiac disease, but this study claimed that atrial fibrillation was the only significant variable through multiple regression analysis. The authors recommended the use of coumadin in dialysis patients with atrial fibrillation, similar to the general population[72].

The second study was published one month later in the American Journal of Nephrology. This trial showed no difference in stroke risk between hemodialysis patients with atrial fibrillation and those with normal sinus rhythm. And surprisingly this trial showed a statistically significant increase in the stroke rate in patients that were anticoagulated with aspirin or warfarin versus those patients that were not anticoagulated. This result may have been related to cerebral hemorrhage instead of embolism. On the other hand, since this was a retrospective study, the patients on anticoagulation may have been a much higher risk group for stroke and were pre-selected for anticoagulation. The

authors recommended against anticoagulation claiming that hemodialysis patients were already anticoagulated because of uremic platelet dysfunction and the dosing of heparin thrice weekly[73].

These two papers constitute all of the studies done on the risk of stroke in dialysis patients with atrial fibrillation. Unlike the trials in the general population, no evaluation of the risk of bleeding was done. In addition, there is no data on whether the strokes were embolic, thrombotic or hemorrhagic in either study. Because of this lack of data specific to atrial fibrillation, we must consider data regarding anticoagulation for vascular access to help us decide on the need for anticoagulation in atrial fibrillation.

Vascular access can either be a native vein fistula where an artery (usually the radial or brachial artery) is anastomosed to an insitu vein (usually the cephalic vein in the forearm or cephalic or basilic vein in the upper arm), or a graft of synthetic material that has a separate radial and venous anastomosis. Grafts tend to clot much more frequently then fistulas and this is usually due to stenosis of the venous anastomosis. Full dose coumadin was used in the early days of dialysis to prevent clotting of external Scribner shunts but resulted in a significant increase in the incidence of hemorrhage[74]. Low dose coumadin with an INR goal of 1.4-1.9 was used in a recent trial to prevent clotting of PTFE grafts. Not only did it show no benefit in access patency, it also showed a significant increase in the risk of clinically important major bleeding[75]. Because of this increased risk of bleeding with coumadin in hemodialysis patients, warfarin use should be very conservative.

Aspirin use also has its problems in hemodialysis patients. Aspirin with dipyridamole versus either alone and placebo were used in a trial evaluating synthetic graft patency. Surprisingly it showed a decreased incidence of graft clotting with dipyridamole versus placebo and a trend towards increased thrombosis with the use of aspirin, though the results were not statistically significant[76]. These results were followed up by studies showing that low dose aspirin in cell culture (0.03 mmol/l) can cause an increase in PDGF induced vascular smooth muscle cell proliferation[77] and that dipyridamole inhibits it[78]. With higher doses of aspirin in cell culture (5 mmol/l) vascular smooth muscle cell proliferation was inhibited[79, 80]. For reference, a dose of 330 mg per day of aspirin results in levels of 0.1 mmol/l and 1000 mg per day results in 0.2 mg per day[80]. Therefore the correct dose of aspirin to prevent vascular smooth muscle cell proliferation is not clear. The use of aspirin in dialysis patients may not have the same benefit in cardiovascular disease as in the general population since part of the benefit of aspirin is related to platelet inhibition[81] which is already inhibited in dialysis patients[82]. However, there may be benefit from the anti-inflammatory properties of aspirin therapy[83]. Unfortunately there are no trials looking at cardiovascular mortality in dialysis patients taking aspirin.

Because of the marked differences in the mechanisms and risks between dialysis patients and the general population it would be difficult to extrapolate data from anticoagulation trials in the general population. Because of the increased risk of bleeding I recommend very conservative use of warfarin in dialysis patients, even in patients with atrial fibrillation. In contrast, since dialysis patients have a marked increase in inflammation and aspirin has proven cardiovascular properties related to its anti-inflammatory properties, I do recommend aspirin therapy in dialysis patients. There is evidence that higher doses are required to prevent vascular smooth muscle proliferation[84]. Smaller doses may only have the benefit of platelet inhibition which is already inhibited

in uremia. Therefore I recommend at least 325mg of aspirin per day if aspirin is going to be used. One possible risk with the use of aspirin is thrombosis of a synthetic PTFE graft as mentioned above[76].

Treatment

The risk of cardiovascular disease in end stage renal disease is markedly elevated because of the risk factors discussed above. The treatment for these patients though is based on the treatment of some of these risk factors involves the same therapy used in the general population.

Lipid lowering therapy

Uremic dyslipidemia is prevalent in dialysis patients. The mainstay of treatment is HMG-coenzyme A reductase inhibitors (statins), though the treatment goals are different. A low HDL with elevated triglyceride levels is predominant with a normal LDL. Therefore most dialysis patients are not treated with a drug that primarily treats LDL. This is illustrated in a recent study by Seliger[85]. He reviewed data from the USRDS (United States Renal Data System) on dialysis patients that were treated with statins. Only 10 percent of dialysis patients were treated with statins, yet there was a 32 percent decrease in mortality over a two period with a 0.63 relative risk of cardiovascular mortality favoring the use of statins. Even though dialysis patients have an elevated triglyceride, the use of fibrates in this study had no effect on mortality. Nicotinic acid has been used in to raise HDL levels in dialysis patients but there is no data on mortality benefit.

This improvement in mortality can be related to many of the properties of statins that affect the abnormal markers seen in dialysis patients. Statins, but not fibrates or nicotinic acid, have been shown to lower IDL which is elevated in dialysis patients. Statins have also been shown to decrease C reactive protein and oxidized LDL which are both elevated in dialysis patients. Statins also have anti inflammatory properties and tend to decrease oxidation. Statins can also lower LDL levels in patients with normal or low LDL before treatment, similar to the general population.

ACE Inhibitors

As mentioned above, renin, angiotensin II and aldosterone are markedly elevated in dialysis patients. Therefore treatment with an ACE inhibitor would seem to be indicated. ACE inhibitors have been shown to lower blood pressure in dialysis patients[86]. This blood pressure lowering effect is related mainly to the decrease in angiotensin II.. Possible alternative mechanisms for the blood pressure lowering affect is the increase in vasodilators associated with ACE inhibition, but this is unlikely because angiotensin receptor blockers also decrease blood pressure in dialysis patients[87].

Ace Inhibitors have many other benefits in dialysis patients other than blood pressure control. Ace inhibitors can reverse left ventricular hypertrophy(LVH) in dialysis patients in doses that do not lower blood pressure[88]. LVH is seen in 74 percent of dialysis patients at initiation of dialysis[89] and it has been associated with increased mortality.

LVH has also been associated with increased norepinephrine levels in dialysis patients, a marker of increased sympathetic nervous activity[90]. ACE inhibitors also decrease norepinephrine levels, so the reduction in LVH with ACE inhibitors maybe related to inhibition of sympathetic activity[53]. Metoprolol has also been used in dialysis patients with an improvement in LVH[91] further emphasizing the effect of sympathetic activity on LVH in end stage renal disease.

Hyperdipsia in endstage renal disease can result in excessive weight gains between hemodialysis treatments and the inability to adequately remove volume with resultant hypertension and cardiac dilatation. ACE inhibitors can improve the hyperdipsia associated with end stage renal disease[92]. The mechanism maybe related to inhibition of angiotensin II[93] or cerebral ACE activity[94-96].

ACE inhibitors have also been shown to prevent thrombosis of synthetic PTFE arteriovenous access grafts. The benefit maybe related to the inhibition of vascular smooth muscle proliferation and myoinitimal proliferation[97]. ACE inhibitors are thought to be anti-inflammatory[98, 99] and to decrease oxidation[49, 100], and decrease oxidized LDL[101] similar to statins.

One potential side effect of ACE inhibitors and angiotensin receptor blockers usage in hemodialysis patients is hyperkalemia[102]. It is probably related to inhibition of aldosterone stimulated secretion of potassium in the stool and sweat as it is seen regardless of the presence or absence of residual renal function.

Folate Therapy

Folate and vitamin supplementation should be standard in all dialysis patients because of the loss of water soluble vitamins during dialysis. The benefit of pharmacological doses of folate up to 15 mg per day in lowering homocysteine levels has been demonstrated. The non homocysteine lowering effects of 40 mg per day on cardiovascular outcome is still pending. A minimum of 1 mg of folate is recommended until this information is available.

Nocturnal Dialysis

Nocturnal dialysis is an alternative to standard dialysis. The main difference and benefit is the time per week spent on dialysis. Dialysis is done while the patients sleep for eight hours, six to seven nights per week. This results in a clearance of urea that is at least twice that of conventional dialysis with an improvement also in large molecule clearance[103]. Because the number of dialysis patients are small and finding an appropriate control is difficult, data on mortality is not available for nocturnal dialysis[104]. However, there is an improvement in many of the cardiovascular markers.

Homocysteine levels are lower in patients undergoing nocturnal hemodialysis compared to conventional dialysis patients and reach normal levels in 50 percent[105]. Blood pressure is markedly reduced in nocturnal dialysis patients with an improvement in LVH[106] and ejection fraction[107]. Phosphate removal improves to the point that phosphate binders are no longer needed[108]. In fact Na Phosphate must be added to the dialysate to prevent hypophosphatemia in some centers. Sleep apnea has also improved with the use of nocturnal hemodialysis[109].

Recommendations

Several recommendations are necessary for dialysis patients that are different than those necessary for non dialysis patients. I recommend treatment with more frequent dialysis such as nocturnal hemodialysis or short daily hemodialysis, restriction of fluid and sodium intake, control of blood pressure, maintain a normal hemoglobin, control phosphorus to less than 5.5 mg/dl, PTH at 100-200, avoid hemodialysis catheters and synthetic arteriovenous grafts in favor of native vein fistulas and transplant appropriate candidates as soon as possible. All of these recommendations are of course not for primary care physicians and many of these are impossible because of the patient's clinical situation. Also many of these recommendations require patient compliance.

For physicians providing primary care, the following recommendations are appropriate:

1. Uremic dyslipidemia: Statins should the preferred treatment for this disorder because of the improved mortality with their use. Fibrates may seem appropriate because of the elevated triglycerides, but there was no mortality benefit with fibrates in a retrospective study of dialysis pateints[85]. Similarly, nicotinic acid may seem appropriate for the low HDL levels because they have been shown to raise HDL levels in dialysis patients, but no data is available on the improvement in cardiovascular outcomes with nicotinic acid. The LDL level tends to be normal in dialysis patients, so the level of LDL that would stimulate the use of a statin should be low. Any dialysis patient should be considered to be at a very high risk of atherosclerosis. Therefore an LDL level of less than 100 should be an appropriate goal, similar to diabetics or patients with proven cardiovascular disease. A lower LDL goal maybe appropriate in dialysis patients with proven cardiovascular disease. This should be studied in a prospective trial.
2. Folate deficiency: All dialysis patients should be on supplements of B vitamin with at least 1 mg of folate per day. There are many vitamin supplements made specifically for dialysis patients with this formulation. The benefit of higher doses of folate on cardiovascular outcomes is currently being studied.
3. Increased renin and sympathetic activity: Ace inhibitors should be used in all patients as first line drug therapy after control of excess volume is attempted. This should cover the majority of dialysis patients. For the minority of patients with normal blood pressure, ACE inhibitors would also be indicated for LVH or heart failure[88, 110]. Other indications include prevention of arteriovenous graft thrombosis[111] and treatment of hyperdispsia[92]. These indications would include almost all dialysis patients. The use of angiotensin receptor blockers also reduce blood pressure in dialysis patients[87] and maybe an alternative for ACE inhibitors, though there is not much data on other benefits. Beta blockers should be the second line drug in dialysis patients because of the increased sympathetic activity in dialysis patients[50, 52] and the benefits of cardiovascular protection in the general population. Data specific to dialysis patients is not available.
4. Sleep apnea: CPAP therapy is effective in treating the subjective symptoms of sleep apnea but its use in improvement of cardiovascular disease has not been studied, even in the general population. The use of CPAP should be used to treat

symptomatic patients. The use of CPAP to improve cardiovascular mortality in dialysis patients should, at least, wait for the results of trials in the general population[64].

5. Warfarin: Because of the markedly increased risk of bleeding in dialysis patients[74, 75] the use of warfarin should be used conservatively even in chronic atrial fibrillation. It maybe appropriate to use warfarin in patients with embolic events thought to be related to atrial fibrillation.
6. Aspirin: Aspirin should be used to prevent cardiovascular events in dialysis patients with cardiovascular disease[112]. Because of a trend towards arteriovenous graft thrombosis treated with aspirin and protection with dipyridamole in one study[76], patients with AV grafts may benefit from the use of dipyridamole when using aspirin. This combination is currently being studied by the NIH.

Conclusion

Cardiovascular disease in end stage renal disease is highly prevalent and is the leading cause of mortality followed by infection. This cardiovascular disease results in a marked increase in mortality. The cause of this increased cardiovascular disease is related to inflammation and oxidation induced by the uremic state. Treatment goals are quite different from the general population. Many of the treatments used in the general population need to be restudied in patients with end stage renal disease to confirm the benefit in these patients.

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