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Determinants of Cardiovascular Risk in Hemodialysis Patients Without Significant Comorbidities

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1. Introduction

Cardiovascular (CV) disease is a major cause of morbidity and mortality in patients with end-stage renal disease. Traditional risk factors for CV disease include hypertension, smoking, diabetes, dyslipidemia, left ventricular hypertrophy, advanced age and male sex in the general population. Although hemodialysis patients have a high prevalence of many of these factors, they also have nontraditional, or uremia-related, specific factors such as anemia, altered calcium-phosphorus metabolism, inflammation, oxidative stress, nitric oxide synthase inhibitors, hypoalbuminemia, carbamylation, abnormal lipoproteins and hyperhomocysteinemia (Parfrey, 2000; London&Drüeke 1997). So the risk markers that predict CV events in hemodialysis patients may differ from those in the general population.

This increased CV risk has often been attributed to 'accelerated atherosclerosis' in end-stage renal disease (Cheung, 2000; Kasiske et al., 2000). However, CV causes of death are most prominent in the first years of dialysis and are rare in patients who have been on long term dialysis – the reverse of what would be expected if dialysis itself caused 'accelerated atherosclerosis (Mailloux et al., 1991). Because many patients with end-stage renal disease already have one or more comorbidities and clinically evident vascular disease, it is difficult to determine from clinical or epidemiological studies whether traditional or non-traditional risk factors are more responsible for the high risk of CV events.

The presence of comorbid disease is an increasingly common problem, being much more prevelant in new patients started on dialysis today than previously (Godkin et al., 2003; Mailloux et al., 1996; Merkus et al., 2000; Miskulin et al., 2009; Wallen et al., 2001). Hemodialysis patients who are under 55 years of age and without diabetes, significant comorbid diseases and obesity are very rare in the general hemodialysis population. For this reason, fewer epidemiological studies which focus on the determinants of CV risk of a relatively 'healthy' hemodialysis population are available. However, it is increasingly appreciated that chronic kidney disease alone is an independent risk factor for the development of CV disease. In this topic review of available data, an overview is presented of CV risk factors in hemodialysis patients without significant comorbidities.

2. Markers of inflammation

Chronic inflammation is one of the well-known non-traditional cardiovascular risk factors in hemodialysis patients. Chronic kidney disease results in a chronic, low-grade inflammatory process that becomes evident even in the early stages of the disease. After the start of dialysis treatment, various factors associated with the dialysis procedure may also contribute to a stronger, more active inflammatory response. All available evidence suggests that chronic inflammation in hemodialysis patients may contribute significantly to the development and progression of CV disease (Filiopoulos&Vlassopoulos, 2009; Stenvinkel, 2006; Zimmermann et al., 1999).

Although few studies are available concerning the relationship between inflammatory status and CV risk in hemodialysis patients without co-morbid diseases, the studies that do exist in this area also support the role of inflammation.

2.1 C-reactive protein (CRP)

CRP is the best studied inflammation marker associated with CV events. It is the prototypical acute phase response protein produced by the liver under the control of various proinflammatory cytokines, namely interleukin-6, interleukin-1, and tumor necrosis factor-α. Its uniqueness is due to rapid (within 6 hours) and dramatic increases (up to 1000-fold) in circulating concentrations after a cytokine-mediated response to most forms of tissue injury, infection, and inflammation. Moreover, it was shown that plasma half-life (19 hours) and fractional clearance rates of CRP were nearly constant in normal subjects, as well as in patients with infectious, inflammatory, and neoplastic conditions. This marks CRP as a 'precise objective index' of overall inflammatory activity and a surrogate of underlying cytokine stimulus (Arici& Walls, 2001; Pepys&Baltz, 1983; Vigushin et al., 1993).

Several observations have demonstrated that in a significant proportion of hemodialysis patients CRP is elevated for no apparent reason. A wide variety of factors in hemodialysis patients may be responsible for this elevation. First, the uremic state is associated with an altered immune response and uremia per se may cause a proinflammatory status with ongoing acute phase response. Also, extracorporeal circulation of blood during each hemodialysis session may act as a fresh stimulus for acute phase response. Increased cytokine release, the role of dialysis membranes, the dialysate and the patient-specific processes, such as the type of vascular access or unrecognized infections, may also play a role in inciting an inflammatory response (Arici&Walls, 2001; Stenvinkel, 2002a, 2002b).

The predictive value of CRP in CV risk and mortality in hemodialysis patients was shown in numerous studies, and evidence from experimental and clinical studies showed that CRP may contribute directly to the pathogenesis of atherosclerosis and its complications through a variety of mechanisms (Arici&Walls, 2001; Yeun&Kaysen, 2000; Zimmermann et al., 1999).

So it has been suggested that this hepatic–derived protein is not only a marker, but also a mediator, of vascular disease (Lagrand et al., 1997; Torzewski et al., 1998). Although a wide variety of potential sources may be associated with elevated CRP in this patient population, underlying silent CV disease may be one of the possible links for this elevation. So the clear association between CRP and CV disease in the hemodialysis population has added CRP as a new predictive CV risk factor which may actually be in a midway position between traditional and uremia-related CV risk factors (Arici&Walls, 2001).

One of the studies investigated the associations of different risk factors with carotid artery intima-media thickness in non-diabetic hemodialysis patients who had no clinical evidence

of atherosclerosis and no comorbidities (Zumrutdal et al., 2005). Seventy-two patients (43 men, 29 women; mean age 34.5 ± 10.6 years, mean time on hemodialysis 47.9 ± 40.0 months) were included in the study. Patients without history or evidence of myocardial, cerebrovascular or peripheral vascular disease, those without diabetes mellitus, and those who had been stabilized on hemodialysis therapy for more than six months and were less than 55 years old were enrolled. Patients were excluded whose chest radiograph showed calcified plaques in the aortic arch, or who had ischaemic findings on electrocardiography and/or ventricular wall motility disorders or valvular calcifications on echocardiography. Additionally, patients with conditions known to be associated with acute-phase responses were excluded. The control group consisted of 40 age-and sex-matched healthy subjects, who had been recruited from hospital staff. Body mass index, triglycerides, lipoprotein (a), fibrinogen, CRP, haematocrit-corrected erythrocyte sedimentation rate, serum cardiac troponin I, beta2 microglobulin, and homocysteine levels were found to be significantly different in patients on hemodialysis compared with control subjects. The mean value of the right and left carotid intima media thickness was 0.59 ± 0.06 mm for patients and 0.53 ± 0.07 mm for control subjects. The difference was significant (p=0.002). The carotid intima-media thickness of patients was correlated with age, body mass index, CRP, haematocrit-corrected erythrocyte sedimentation rate, beta2 microglobulin, serum cardiac troponin I, triglyceride, and fibrinogen. CRP, haematocrit-corrected erythrocyte sedimentation rate, serum cardiac troponin I, and fibrinogen were significantly correlated with each other, but not with beta2 microglobulin. The only parameter correlated with beta2 microglobulin was time on hemodialysis. The mean carotid intima-media thickness was significantly greater in patients with both left ventricular hypertrophy and a CRP level > 6.0 mg/L than it was in those with a CRP level ≤ 6.0 mg/L. In that study, multivariate regression analysis showed that age, CRP, beta2 microglobulin, and left ventricular hypertrophy were independent predictors of carotid artery intima-media thickness. The results of that study supported the hypothesis of an 'accelerated atherogenesis' in the hemodialysis population, even if those patients do not have clinical evidence of atherosclerosis. And CRP was found to be one of the independent predictors of early-onset atherosclerosis.

Most investigations of CV risk in patients on hemodialysis have been cross-sectional in nature and representative of the general hemodialysis population. In the previous study, the same subgroup of hemodialysis patients was followed up over the course of one year and the determinants of the progression of carotid artery intima-media thickness were assessed again (Zumrutdal et al., 2006). Fifty-four of the 72 patients completed the study and re-tested under the same standardized conditions after 12 months. The findings at 12 months showed that carotid artery intima-media thickness had progressed in 75.9 % patients. Age, CRP, beta2 microglobulin and left ventricular hypertrophy were independently related with baseline carotid artery intima-media thickness. At 12 months, age and CRP were found to be independent variables related with carotid artery intima-media thickness. The independent risk factors related with the change in carotid artery intima-media thickness from baseline to 12-month stage were age and male sex.

According to those results, age and male sex were related to progression of carotid artery intima-media thickness as unavoidable risk factors in this subgroup of the hemodialysis population. That agreed with the results of major clinical and epidemiological studies of the general population. The independent relation between CRP and carotid artery intima-media thickness both at baseline and 12 months supports the additional role of non-specific inflammation in hemodialysis patients without comorbidities.

2.2 Hematocrit-corrected erythrocyte sedimentation rate (Hct-corrected ESR)

Although ESR is widely used in the general population as an inflammation marker, it was judged to be of no clinical utility in chronic hemodialysis patients in the mid-1980s. So ESR has seldom been studied in patients on hemodialysis. However, in 2001, it was proposed that after correction of ESR values according to Hct levels in hemodialysis patients, Hct-corrected ESR could serve to select the inflammation-afflicted hemodialysis patients from those without this comorbid state (Borawski& Mysliwic, 2001). Supporting that study, while no relationship between ESR and carotid artery intima-media thickness was found, a relationship in hemodialysis patients without comorbidities was found between Hct-corrected ESR and carotid artery intima-media thickness, beyond other inflammatory markers, CRP, and fibrinogen. Although larger additional studies are needed to determine the potential value of Hct-corrected ESR as an inflammatory marker for early-onset atherosclerosis, this relationship may again reflect the role of non-specific inflammation in CV risk of the 'healthy' hemodialysis patients (Zumrutdal et al., 2005).

2.3 Fibrinogene

In the normal population, increased activity of procoagulant proteins including factor VII and fibrinogen is associated with coronary risk. Factor VII coagulant activity and markers of thrombin activation are elevated in patients with chronic renal failure and correlate positively with serum triglycerides and the acute phase reactants interleukin 6 and fibrinogen and negatively with serum albumin (Tomson, 2000). The presence of generalized endothelial dysfunction in uraemic patients is also suggested by higher plasma levels of fibrinogen, endothelin and other factors. The relationship between carotid artery intima-media thickness and fibrinogene in hemodialysis patients without comorbidities may reflect the role of fibrinogene in early-onset atherosclerosis as one of the best-studied inflammation markers (Zumrutdal et al., 2005).

3. Cardiac markers

3.1 Left ventricular hypertrophy

Left ventricular hypertrophy is a well-known potent predictor of CV mortality in patients on renal replacement therapy (Ma et al., 1992). This may result either from pressure overload, causing increased tensile stress, or from volume overload, causing increased shear stres (Tomson, 2000). Recently published results demonstrated that even with good control of hypertension and anaemia, conventional hemodialysis is associated with significant left ventricular hypertrophy. And high prevalence of CV disease was positively associated with left ventricular hypertrophy in hemodialysis population.

In the study assessing the predictive markers of CV risk in asymptomatic hemodialysis patients, in total, 113 hemodialysis patients were included. Demographic, anthropometric, clinical, and laboratory data were collected. Silent myocardial damage was defined by elevated cardiac troponin I values above cutoff values. Cardiac troponin I concentrations were below cutoff value in 103 (91.2%) patients (group 1), whereas 10 (8.8%) patients (group 2) had elevated concentrations. Group 1 patients had higher levels of hemoglobin and high-density lipoprotein cholesterol and lower C-reactive protein and tumor necrosis factor-alpha levels, as well as less incidence of left ventricular hypertrophy, when compared to group 2 patients. Diabetes mellitus, left ventricular hypertrophy, uncontrolled blood pressure, normalized protein equivalent of total nitrogen appearence, hemoglobin and tumor necrosis

factor-alpha were found to be independently associated with silent myocardial damage (Afsar et al., 2009).

In hemodialysis patients without comorbidities, mean carotid intima-media thickness, which reflects generalized atherosclerosis and CV risk, was significantly greater in patients with left ventricular hypertrophy, than it was in patients without left ventricular hypertrophy. Mean carotid intima-media thickness in subjects in the heathy control group was significantly lower than it was in hemodialysis patients both with and without left ventricular hypertrophy. The mean serum cardiac troponin I level in the control group was significantly lower than it was in patients both with and without left ventricular hypertrophy. The mean serum cardiac troponin I level was significantly higher in patients with left ventricular hypertrophy than it was in those without left ventricular hypertrophy (Zumrutdal et al., 2005). The relationship between carotid artery intima-media thickness, serum cardiac troponin I levels and left ventricular hypertrophy may demonstrate that subclinical atherosclerotic changes and/or adaptation may occur along with cardiac alterations. So it may be reasonable to apply early strategies for prevention and treatment of left ventricular hypertrophy in hemodialysis patients before clinically evident CV disease.

3.2 Cardiac troponins

Cardiac troponins are the most specific biomarkers for myocardial damage, although they may be elevated in situations other than acute coronary syndrome. Hemodialysis patients often have raised cardiac troponin I and T levels in the absence of acute ischaemic symptoms. The source of this increase has been a point of confusion over the past decade. At the beginning, some authors suggested that this might be related to the cardiac expression of troponins, while others argued for the skeletal muscle as a possible extracardiac source of abnormally elevated cardiac troponins in hemodialysis patients (Bodor et al., 1997; Kals et al., 2011; McLaurin et al., 1997).

In initial experience with two troponin subunits, serum troponin T was elevated more frequently than troponin I in patients with renal failure, and that led the clinicians to question its specificity for the diagnosis of myocardial infarction. Additionally, the poorer specificity of troponin T was attributed to subclinical myocardial injury in the setting of left ventricular hypertrophy or to uremia-induced skeletal muscle expression of the cardiac isoform of troponin T, while cardiac troponin I has been exclusively of cardiac origin and does not express in the skeletal muscle at any developmental stage. Thus, troponin I was proposed to be a better marker of myocardial injury in renal failure than T (Yeun&Kaysen, 2000). However, subsequent studies reported the absence of extracardiac cardiac troponin T expression in truncal skeletal muscle biopsy specimens from patients with end-stage renal failure at the RNA and protein levels (Haller et al., 1998). Another study, based on the electromyographic evaluation of 50 chronic hemodialysis patients, investigated the relationship between increased cardiac troponin T levels and uremic myopathy. Proximal-extremity muscles-deltoid, biceps, vastus laterali-, which were the most common targets of uremic myopathy, were studied. Five of 50 patients (10%) had a positive troponin T test, but only 1 of those patients had characteristic electromyographic findings. Totally, 4 of 50 patients (8%) had electromyographic findings characteristic of uremic myopathy. Positive troponin test results were not associated with calcium, phosphate, parathormone levels. There was no association between serum cardiac troponin T levels and uremic myopathy (Zumrutdal AO et al., 2000).

Subsequent studies showed that frequently positive T test results in hemodialysis patients were likely due to use of the older and less specific troponin T assay with some cross-reactivity to skeletal muscle (Yeun&Kaysen, 2000). And with the use of the latest generation assays, accumulated data from groups of renal failure patients have suggested that elevated levels of both troponin T and I in asymptomatic hemodialysis patients could be associated with added CV risk, including general mortality. Most of the recent studies supported the troponin tests as predictive markers of asymptomatic atherosclerosis and silent myocardial damage in hemodialysis patients (Kanderian& Francis, 2006; Kanwar et al., 2006).

The carotid artery intima-media thickness measurement has been proposed as a method for establishing risk stratification for CV events. To the best of our knowledge, we were the first to examine the relationship between serum cardiac troponin I level and early onset atherosclerosis in a selected subgroup of hemodialysis patients without any clinical evidence of either atherosclerosis or comorbidities. Based on those results, the increased serum cardiac troponin I level was positively correlated with the carotid intima-media thickness and seemed to be a valuable predictive marker for the assessment of CV risk in asymptomatic hemodialysis patients (Zumrutdal et al., 2005). Also, a possible association was found between elevated serum cardiac troponins and inflammatory markers such as CRP, fibrinogen and Hct-corrected ESR. The association between carotid intima-media thickness, serum cardiac troponin I levels and inflammatory parameters needs to be clarified with further studies. Although the underlying pathophysiology of elevated cardiac troponins is still not clearly understood, it may reflect ongoing, often subclinical, myocardial damage or microinfarctions that are partially independent of acute ischaemic injury. So serum cardiac troponin elevations might be very effective in elucidating cardiac risks of hemodialysis patients without any clinical evidence of atherosclerosis and comorbidities.

In conclusion, in addition to traditional risk factors such as age and male sex, non-specific inflammation may play a key role in the progression of atherosclerosis in patients on hemodialysis without comorbidities. Although it is well-established that end-stage renal failure is a state of chronic systemic inflammation, both nondialysis-related factors and the dialysis procedure per se may be responsible for this high risk. Beta2 microglobulin and serum cardiac troponins may be the potential new additions for CV risk in this group of patients. Further studies are needed to determine whether there is a causal relationship.

4. Metabolic markers

4.1 Beta 2 microglobulin

Elevated plasma beta2 microglobulin is a well-known characteristic of chronic renal failure, and among uremic toxins in the middle molecule range, it is certainly one of the most studied compounds. Beta 2 microglobulin is a key component in the genesis of dialysis-associated amyloidosis. The source of the elevated serum beta2 microglobulin has not been explained absolutely in hemodialysis patients. There is controversy as to whether elevated levels are caused predominantly by increased synthesis of beta2 microglobulin, the use of membranes in hemodialysis with different clearance capacities, or diminished renal elimination (Drüeke et al., 2009). Use of middle and high-flux biocompatible membranes was shown to be associated with a notable reduction in beta2 microglobulin and, in some other studies, the systemic inflammatory response, in the general hemodialysis population. However, the role of proinflammatory monocytic cytokines, such as interleukin-1 and

interleukin-6, in the pathogenesis of elevated beta2 microglobulin, and its role as a potential initiator of the inflammatory response were discussed (Vraetz et al., 1999; Xie & Yi, 2003).

Recently, a study comparatively evaluated the effect of hemodialysis and peritoneal dialysis on oxidative stress and inflammatory biomarkers and the associated factors. It found similar degrees of inflammaton and oxidative stress activation in both groups. In that study, beta2 microglobulin was one of the parameters which correlated to oxidative stress and inflammatory biomarkers. It was negatively correlated both with total antioxidant capacity in hemodialysis patients and with superoxide dismutase in peritoneal dialysis patients (Filiopoulos et al., 2009).

Previously, for what was probably the first time in the available literature, we provided data about the association between beta2 microglobulin and early-onset atherosclerosis in hemodialysis patients without comorbidities (Zumrutdal et al., 2005). In our study, the only parameter correlated with beta2 microglobulin was time on hemodialysis therapy. At that time, we speculated that the relationship we found might be casual (inflammatory) or just an epiphenomenon, and added that further follow up studies were needed to elucidate the importance of beta2 microglobulin as a new nontraditional cardiovascular risk factor in hemodialysis patients. Subsequently, few studies have evaluated the association of beta 2 microglobulin levels with clinical outcome in dialyzed patients. The patients were divided into two groups according to their serum beta2 microglobulin levels (lower beta2 microglobulin group, n=245 and higher beta2 microglobulin group, n=245) and followed-up. During the follow-up period of 40±15 months, there were 91 all-cause deaths, and out of them, 36 were from CV disease. All cause mortality in the higher beta2 microglobulin group was significantly higher compared to that in the lower beta2 microglobulin group. And serum beta2 microglobulin level was a significant predictor of mortality in hemodialysis patients, independent of hemodialysis duration, diabetes, malnutrition and chronic inflammation (Okuno et al., 2009).

A few studies also supported the correlation between serum beta2 microglobulin levels and various cardiovascular risk factors, including CRP, in hemodialysis patients (Kuragano et al., 2010). And recently, beta2 microglobulin has been suggested to be a novel biomarker of peripheral arterial disease and an independent predictor of aortic stiffness in atherosclerosis, in the general population (Wilson et al., 2007). Additionally, higher serum beta2 microglobulin levels were proposed to be a novel marker to distinguish levels of risk in acute heart failure patients with creatinine ≤ 3mg/dl (Kawai et al., 2010).

All of those findings strongly support the role of beta2 microglobulin in CV risk of hemodialysis patients, and it seems it will be a potential new CV risk marker in the future. Further studies are needed to clarify the importance of beta2 microglobulin as a CV risk factor in hemodialysis patients without comorbidities.

5. Determinants of cardiovascular risk in nondiabetic hemodialysis patients

Diabetes is not only a traditional risk factor for CV disease, but also one of the most common causes of end-stage renal disease. While a decline in CV deaths has occurred in the general population, a similar trend has not been observed in dialysis patients. This discrepancy is in part due to the demographics of patients about to be started on dialysis: about 40 percent are diabetic. Also, the average age of hemodialysis patients is approximately 60 years and about 20 percent are over 75 years, and many patients have underlying cardiac disease

(Mailloux, 2010). Thus, epidemiologic studies concerning the predictive factors of CV disease in nondiabetic hemodialysis patients are less available.

5.1 Association with traditional and nontraditional risk factors

In a study of the CV assessment of 75 nondiabetic hemodialysis patients, the main cause of renal failure was hypertension. Compared with normal controls, the patients were found to have increased inflammatory cytokines such as interleukin- 6, tumor necrosis factor alpha, and intercelluler adhesion molecule, as well as a high frequency of carotid intima media thickening, left ventricular hypertrophy, and aortic calcifications (Kunstmann et al., 2009).

Mortality predictors among 84 diabetic and 161 nondiabetic patients undergoing hemodialysis were investigated for two years. Forty-three diabetic patients and 30 nondiabetic patients died. Among diabetic patients, oliguria, elevated CRP, and elevated D-dimer levels predicted all-cause mortality. Oliguria was the most important predictor, particularly for infectious disease-related death. Among nondiabetic patients elevated cardiac troponin T levels, elevated D-dimer levels, and low cholesterol levels predicted all-cause mortality rates. Subdivision of the causes of death among nondiabetic patients revealed that cardiac troponin T levels predicted CV mortality rates. According to those results, mortality predictors among hemodialysis patients differed between diabetic and nondiabetic patients (Hocher et al., 2003).

In one comparison, two groups of nondiabetic hemodialysis patients (both groups n=30) matched for age and sex, were selected according to the absence or presence of symptomatic atherothrombotic vascular disease affecting the coronary, cerebral, or peripheral arteries. The two groups were identical regarding primary renal disease, duration of hemodialysis, and Epo treatment. The presence of hypertension, lipoprotein (a), and fibronectin levels were independent predictors for the presence of atherothrombotic CV disease which may contribute to the high prevalence of CV risk. Smoking was not a predictor. (Tzanatos et al., 2009).

Left ventricular hypertrophy: Left ventricular hypertrophy is one of the strongest predictors of CV mortality in the general dialysis population. It is an independent predictor of survival in patients with chronic renal failure and it is present in a large number of patients on hemodialysis. In 30 nondiabetic hemodialysis patients, predictive factors associated with left ventricular hypertrophy at baseline and in the follow-up period (at 0, 12, and 24 months) were studied. Systolic blood pressure, residual glomerular filtration rate and serum albumin levels were the predictive factors for left ventricular mass index at initiation of hemodialysis. Systolic blood pressure, human atrial natriuretic peptide, and hemoglobin levels were independent risk factors for left ventricular mass index, after 24 months. Systolic blood pressure, human atrial natriuretic peptide, and hemoglobin levels were also predictive factors for left ventricular mass index after initiation of hemodialysis (Io et al., 2010). Better management of hypertension and anaemia may be priorities for preventing or improving CV risk in these patients.

Carotid intima-media thickness: Carotid intima-media thickness is a strong predictor of CV events in the general population. The predictive value of carotid intima-media thickness in 99 nondiabetic hemodialysis patients was investigated. During a follow-up of 42.4±19.5 months, 33 patients died, 19 (57.6%) of them of CV causes. In those 19 patients carotid thickness was significantly higher than in those who survived. So carotid intima-media thickness was an independent predictor of CV death in nondiabetic hemodialysis patients (Ekart et al., 2005). Asymptomatic atherosclerosis and major risk factors in 104 nondiabetic patients with different stages of chronic kidney disease (stage 1-5) were also investigated. Carotid intima-media

thickness and plaque occurrence were compared with 40 healthy control subjects. Nondiabetic patients with chronic kidney disease showed advanced atherosclerosis, intima-media thickness, and plaque occurrence, and their numbers increased directly with the level of renal dysfunction. Another important risk factor was hypertension (Ekart et al., 2008).

Vascular calcification: The uremic state is associated with numerous metabolic abnormalities and endocrine disturbances primarily involving calcium and phosphorus metabolism. Vascular calcification is highly prevelant in dialysis patients and increases CV mortality. The presence and progression of vascular calcification in hemodialysis patients have been significantly associated with chronic inflammation, malnutrition, and disorders of mineral metabolism. Through a review of the literature examining vascular calcification in end stage renal failure patients, hyperphosphatemia is significantly associated with vascular calcification in nondiabetic patients, while it may not be a significant risk factor for vascular calcification in diabetic patients. In diabetic patients vascular calcification occurs long before the initiation of dialysis therapy and and the factors associated with vascular calcification in non-uremic diabetics appear to be hyperglycemia and related metabolic disorders, such as increased glycation and oxidative stress. In diabetic end stage renal failure patients, hyperglycemia is also suggested to be a significant factor associated with the progression of vascular calcification. Thus, the importance of glycemic control in diabetic and phosphate control in nondiabetic end stage renal failure patients is suggested (Ishimura et al., 2008).

The accumulating data demonstrate the role of abnormalities of calcium, phosphorus, vitamin D, and parathyroid hormone in CV disease and the importance of phosphate control is suggested for preventing vascular calcification and CV risk (Andress, 2008; London et al., 2000).

Diabetes mellitus and ethnicity are known factors that affect the extent of CV calcifications. The extent of CV calcifications was assessed in non-diabetic Caucasian hemodialysis patients by a novel composite calcification score. Body mass index, cholesterol, triglycerides, intact PTH, and serum levels of fetuin-A and uncarboxylated matrix Gla protein were not associated with CV calcifications. Age, male gender, dialysis vintage, smoking, calcium-phosphate product, CRP, and lower Kt/V were independent risk factors for CV calcifications (Schlieper et al., 2009). Increasing dialysis efficiency and lowering calcium-phosphate product can reduce CV calcifications. Generally, a calcium X phosphate product of less than 55 is the therapeutic optimum and it is possible that even lower levels offer further survival advantage. However, no prospective randomized studies have demonstrated a CV benefit and/or a survival advantage with any of the current therapeutic options. But observational studies have shown improved survival in hemodialysis patients treated with active vitamin D analogues (Levin&Li, 2005).

Metabolic abnormalities: Chronic kidney disease is associated with complex metabolic changes including insulin resistance, and insulin resistance is associated with increased CV risk (O'Sullivian&Kelly, 2007). In contrast to the general population, a higher body mass index is associated with better survival among hemodialysis patients. Theoretically, high energy supplementation in nondiabetic hemodialysis patients might adversely affect insulin resistance, and with this goal in mind, the effects of high energy supplementation on nondiabetic hemodialysis patients was investigated. According to the results, body fat mass and CRP were the primary determinants of insulin resistance in nondiabetic hemodialysis patients. High energy supplementation, increased adiposity, and inflammation exacerbated insulin resistance. However, long term metabolic effects of this strategy were unclear (Hung & Tang, 2009).

Another study on nondiabetic hemodialysis patients showed that liver fat, visceral adiposity, and sleep disturbances contributed to the development of insulin resistance and glucose intolerance. However, further studies in the long term are still needed to clarify whether interventions that improve insulin sensitivity improve clinical outcomes and CV risk in nondiabetic hemodialysis patients (Sakkas et al., 2008). The study comparing fasting glucose levels and impaired fasting glucose levels with malnutrition and inflammatory parameters in nondiabetic hemodialysis patients demonstrated that fasting glucose levels predict one-year all-cause mortality in non-diabetic hemodialysis patients. And they also showed that basal fasting glucose levels, or the presence of impaired fasting glucose, plays an important role in inflammation, malnutrition and short term mortality (Lin-Tan, 2007).

Diabetes mellitus and deficiency in n-3 long-chain polyunsaturated fatty acids are known to increase the incidence of CV disease. The study investigated the relationship between n-3 long-chain polyunsaturated fatty acids and the pulse wave velocity from the brachium to the ankle, which was measured as a marker of atherosclerosis in 54 diabetic and 93 nondiabetic hemodialysis patients. The mean pulse wave velocity in diabetic patients was significantly higher than that of nondiabetic patients. There was a significant inverse association between pulse wave velocity and docasahexaenoic acid levels and docasahexaenoic acid/aracidonic acid ratios in nondiabetic patients. It was concluded that n-3 long-chain polyunsaturated fatty acids may be a negative risk factor for CV disease in nondiabetic hemodialysis patients (Hamazaki et al., 2009).

Numerous abnormalities of lipid and lipoprotein metabolism are described in renal disease. These abnormalities are caused by complex alterations in several pathways of lipoprotein metabolism. In addition, nonenzymatic modification of lipoprotein particles enhances their atherogenicity without affecting the measured levels of cholesterol, triglycerides, or the HDL, LDL and very-low-density lipoprotein fractions (Tomson, 2000). Dyslipidemia may be present in more than 90 % of hemodialysis patients and has been reported to correlate with CV disease in some, but not all, cross sectional studies of nondiabetic patients on hemodialysis. Among other lipid parameters, low HDL cholesterol was one of the independent determinants of coronary artery disease in nondiabetic hemodialysis patients (Zumrutdal et al., 2007). However there are limited data concerning the effectiveness of lipid lowering with statins in decreasing CV outcomes in patients on hemodialysis.

Coagulation defects: In 68 nondiabetic hemodialysis patients, the probable association of circulating levels of plasminogen activator inhibitor type-1 and the expression of plasminogen activator inhibitor type-1 in internal iliac artery walls with atherosclerotic disease was investigated. Fifty age- and sex-matched healthy normotensive controls participated in the study. Atherosclerotic disease in both groups was assessed by measuring carotid intima-media thickness. Compared with control subjects, hemodialysis patients had significantly increased carotid thickness. Atherosclerotic plaques were detected in 61.7% of hemodialysis patients and 4% of controls. Carotid intima-media thickness was correlated with age, systolic blood pressure, low-density lipoprotein, CRP, and interleukin-6. In hemodialysis patients, a close correlation was found between serum plasminogen activator inhibitor type-1 level, CRP, and interleukin-6 level. Also, carotid intima-media thickness and plaque score were correlated with circulating levels of plasminogen activator inhibitor type-1 and with the expression of it in internal iliac artery walls. The circulating levels of plasminogen activator inhibitor type-1 and the expression of plasminogen activator inhibitor type-1 in internal iliac rtery walls were statistically associated with CRP, interleukin-6, and low density lipoprotein cholesterol. With all of those correlations, authors have suggested that increased circulating plasminogen

activator inhibitor type-1 and an upregulated expression of plasminogen activator inhibitor type- 1 in the vasculature could indicate a chronic endothelium activated state and that may identify the risk of atherothrombosis related with inflammation in nondiabetic hemodialysis patients (Peng et al., 2008). Among nondiabetic patients, generalized endothelial dysfunction is associated with an increase in CV risk.

Gene polymorphisms: Cytokine gene polymorphisms have been implicated as potential genetic risk factors for CV disease. The study assessed the role of cytokine gene polymorphisms in carotid intima-media thickness and left ventricular mass index, as surrogate markers for CV risk, in nondiabetic hemodialysis patents. Carotid intima-media thickness and left ventricular mass index progression for 2 years were detected at higher levels in patients with high-producer genotypes than in the patients with the low-producer genotype during the study period. The TNF-alpha-308 G/A polymorphism was closely associated with CRP. So polymorphisms in inflammatory genes could be additional factors affecting inflammation and CV risk in non diabetic hemodialysis patients (Yilmaz et al., 2010).

Synthesis of nitric oxide by endothelial nitric oxide synthase plays a key role in the atherosclerotic process. Several polymorphisms of the gene encoding endothelial nitric oxide synthase are known and have been investigated with respect to their influence on CV disease risk in the general population. The association between endothelial nitric oxide synthase gene polymorphism and CV events in nondiabetic Japanese hemodialysis patients was also investigated. Three endothelial nitric oxide synthase polymorphisms were genotyped for the patients and two endothelial nitric oxide synthase polymorphisms were found to be associated with major cardiac, cerebrovascular, or peripheral vascular events (Asakimori et al., 2004).

5.2 Coronary artery disease in nondiabetic hemodialysis patients

It is increasingly appreciated that chronic renal failure alone is an independent risk factor for the development of coronary artery disease. For evaluating the determinants of coronary artery disease in nondiabetic hemodialysis patients, among 312 consecutive patients on regular hemodialysis, 26 nondiabetic patients with angiographically defined coronary artery disease were compared with a subject group of nondiabetic hemodialysis patients of the same gender, smoking status, and hypertension with similar ages and body mass indexes, who had normal electrocardiography and myocardial perfusion scintigraphy. Demographics, CRP, ESR, Hct-corrected ESR, beta 2 microglobulin, cardiac troponin I, parathyroid hormone, albumin, calcium X phosphorus, and lipid profiles were compared between the groups. The nondiabetic patients with coronary artery disease had higher CRP, higher cardiac troponin I, and lower HDL-cholesterol levels than the patients without coronary artery disease. Backwards stepwise logistic regression analysis revealed that high CRP and troponin I levels and low HDL cholesterol levels were independently related with coronary artery disease in nondiabetic hemodialysis patients (Zumrutdal et al., 2007).

The predictive value of CRP in CV risk and mortality in hemodialysis patients was previously shown in numerous studies, and underlying coronary artery disease may be one of the possible links for this elevation. Additionally, even small elevations of serum cardiac troponin I concentration, at levels lower than those traditionally used for the diagnosis of acute events, were independently associated with the presence of coronary artery disease in asymptomatic hemodialysis patients. Thus, small and non-specific increases in cardiac troponin I levels may reflect underlying coronary artery disease in nondiabetic hemodialysis patients.

6. Conclusion

All hemodialysis patients, diabetic or nondiabetic, are at markedly increased CV risk, with chronic renal disease alone currently considered a coronary heart disease risk equivalent. A large number of risk factors for CV disease and decreased survival that are related or unrelated to the dialysis procedure have been identified. Since no data are available about the outcome comparing hemodialysis patients with comorbidities with those without, it is not possible to suggest increased benefits for survival for hemodialysis patients without comorbidities. Cardiovascular risk factor modification should be undertaken for all dialysis patients with or without comorbidities, given that they are considered a coronary heart disease equivalent.

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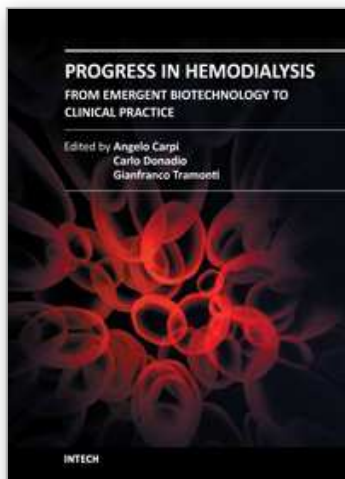
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