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Letters to the Editor / Cartas al Editor

RENAL DISEASE AND CARDIOVASCULAR RISK: A GLOBAL VIEW

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To the Editor:

There is a progressive increase of chronic kidney disease patients in the modern societies, probably associated to the reduction in cardiovascular mortality, as well as the increase in general population life spam. Consequently, current prevalence of chronic kidney disease is around 11-17% in developed countries.

On the other hand, it has been documented that the mortality secondary to cardiovascular disease is 10-30 times higher in chronic kidney disease patients than in the general population. This situation has been attributed to a significant increase in the prevalence of several cardiovascular risk factors: arterial hypertension, diabetes mellitus, dyslipidemia, anemia, altered calcium-phosphorus metabolism, malnutrition, and sedentary life style among the main ones, in chronic kidney disease patients[1-3].

Additionally, the sort of cardiovascular diseases that chronic kidney disease patients suffer depends not only on the prevailing cardiovascular alterations but also on the degree of their kidney dysfunction: pre-dialysis, dialysis or kidney transplant since preventive treatment can prevent more damage prevention in early chronic kidney disease stages than in dialysis one, as is it happens with dyslipidemia treatment[3-5].

Due to all the above mentioned reasons is very important for nephrologists, as well as for cardiologists who assist renal patients, to know the particular characteristics that cardiovascular risk have in nephropathy patients.

Cardiovascular risk factors

Arterial Hypertension. Hypertension is frequently found in chronic kidney disease (CKD) (85%) where it causes left ventricular hypertrophy (LVH), and acceleration of nephropathy progression (glomerulosclerosis). Arterial stiffness secondary to arteriosclerosis is common in CKD, and it is clinically characterized by an increased systolic pressure and widening of the pulse pressure, which are both closely correlated with LVH[2-6]. Besides, it was observed that systolic blood pressure, diastolic blood pressure, pulse pressure, and mean arterial pressure might have the strongest association with end-stage renal disease incidence among individuals with reduced glomerular filtration rate (GFR)[7-11]. It has been recommended to maintain blood pressure below 130/80 mmHg in CKD patients, and below 120/70 mmHg in those who also suffer from diabetes mellitus. However, blood pressure and mortality have a "U shape" curve relation in dialysis patients who suffer from dilated cardiomyopathy with low systolic function (reverse epidemiology)[2,12]. CKD progression reduces the kidney capability of keeping the sodium and water body balances, thus a low sodium diet and loop diuretics can be necessary in order to avoid volume overload, hypertension, and their consequences: LVH, coronary disease, cardiac insufficiency, and sudden death. Because of the above mentioned, converting enzyme inhibitors, angiotensin receptor blockers (used for treating CKD progression - proteinuria - LVH), loop diuretics (used for handling volume overload), and beta blockers (used for treating LVH) are among the main recommended drugs for treating hypertension in these patients[2,4,5,8]. In the Tassin center, where long dialysis sessions (8 hours) are prescribed, a normal blood pressure is achieved without medication in 85% of their patients[13,14]. Besides, some drugs, such as corticosteroids and calcineurin inhibitors (cyclosporine and tacrolimus), as well as graft artery stenosis, or graft dysfunction can elevate blood pressure in kidney transplant patients[15].

Diabetes Mellitus. Diabetic patients have higher risk of suffering from acute coronary syndromes than non diabetic ones. Tight glycemic control is an important aim in renal patients since it has been proven that this control leads to a reduction in microvascular

disease. Thus, it has been recommended to keep glycosylated hemoglobin below 7%, as well as fasting serum glucose between 70-120 mg/dl. For this purpose low carbohydrate diet, oral hypoglycemic drugs and different sort of insulin can be used. Uncontrolled glycemia has been associated with increased mortality in dialysis patients[2,9,16,17].

Diabetes mellitus is the most common cause of end-stage renal disease leading to transplantation, and diabetes mellitus is the most important risk factor for post-transplant cardiovascular disease. Approximately 20% of non-diabetic patients develop hyperglycemia after transplantation, and 5% to 10% require therapy with oral hypoglycemic agents and insulin. Elderly, obese, and patients with a strong family history of diabetes are at higher risk for developing post-transplant diabetes. Corticosteroids and calcineurin inhibitors (tacrolimus more than cyclosporine) contribute to glucose intolerance[15].

Dyslipidemia . Dyslipidemia is a very frequent disorder in CKD (prevalence>60%). In end-stage CKD patients the relationship between total serum cholesterol and low density lipoprotein cholesterol (LDL), and mortality has a "U shape" curve: patients with serum LDL cholesterol levels higher than 100 mg/dl have a major risk of suffering a cardiovascular adverse event. However, patients with very low serum LDL cholesterol levels (probably a malnutrition marker) present higher mortality rates. Regarding hypertriglyceridemia, serum triglyceride levels higher than 200 mg/dl, is present in around 30% of end-stage CKD patients, especially in those on high carbohydrate diet, beta blockers, cardiac failure (due to hepatic hypoperfusion), peritoneal dialysis (due to peritoneal glucose absorption). These high serum cholesterol levels are recognized cardiovascular risk factors, as well as glomerular (mesangial tissue) damaging ones; and hypertriglyceridemia ($\geq$ 500 mg/dl) can induce pancreatitis[2,3,17,18]. It has been demonstrated that lipid lowering therapy (statins and/or ezetimibe) decreases cardiac death and atherosclerosis mediated cardiovascular events in CKD patients. Besides, it has also been reported that rosuvastatin reduces all cause mortality among both gender moderate CKD patients with LDL-cholesterol < 130 mg/dl, and elevated high-sensitivity C-reactive protein ($\geq$ 2 mg/l). Neither atorvastatin nor rosuvastatin had statistically significant effect on cardiovascular death, non fatal myocardial infarction, and stroke in patients with diabetes mellitus receiving hemodialysis[19-23]. Regarding kidney transplant patients, causes of dyslipidemia are: immunosuppressant drugs (corticosteroids, sirolimus, cyclosporine, tacrolimus), high fat diet, genetic predisposition, proteinuria, and decrease renal function[15]. General recommendations for handling dyslipidemia in nephropathy patients are a low fat diet, and statins and fibrates prescription which are the main means for achieving serum lipid aids in this population: total cholesterol: $\leq$ 200 mg/dl, LDL cholesterol: $\leq$ 100 mg/dl, triglyceride: $\leq$ 200 mg/dl. However, it has been reported that statin decrease mortality and cardiovascular events in persons with early stages of CKD, they have little or no effect in persons receiving dialysis, and have uncertain effects in kidney transplant recipients[2,17,18,24,25].

Anemia. LVH increases significantly in CKD patients as the level of hemoglobin falls below 10 g/dl. In dialysis patients, worsening anemia is associated with progressive left ventricular dilatation (LVD), and with the development of the novo heart failure. Anemia correction by erythropoietin can prevent or reverse LVH but has little effect after it has progressed to LVD. Additionally, anemia has been pointed out as one of the CKD progression factors. Then, intravenous iron, and subcutaneous erythropoietin are used for treating anemia in CKD, in order to achieve the following hematologic aids: serum ferritin > 300 ng/ml, saturated transferrin > 25%, and hemoglobin: 10-11 g/dl[2,25,26]. However, in dialysis centers which base their treatment on long dialysis sessions (Tassin center) only 75% of their patients are on erythropoietin with an average dose that is 50% of the dose usually used[27].

Calcium-phosphate metabolism (CPM). CPM derangements has been associated to cardiovascular disease (LVH, vascular and cardiac valves calcifications), and renal damage progression in CKD patients. Additionally, high serum phosphorus level stimulates hyperparathyroidism which constitutes one of the uremic cardio-toxicity mechanisms.

The expected levels of serum CPM parameters in stage V-CKD are: calcium 8.4 - 9.5 mg/dl, phosphorus 3.5 - 5.5 mg/dl, parathyroid hormone: 100 - 300 pg/dl, and phosphorus-calcium product $\leq$ 55 mg2/dl2.Hyperphosphatemia can be solved by reaching an adequate dialysis dose, low phosphate diet, and phosphorus binders (calcium carbonate, sevelamer, and lanthanum). Regarding hyperparathyroidism, it can be handled by using calcitriol, cinacalcet, or parathyroid surgery[2,28,29]. However, in dialysis centers which base their treatment on long dialysis sessions (Tassin center) only 35% of their patients are on phosphorus binders, with an average serum phosphorus level of 4 mg/dl[30].

Nutrition and Life style . A general recommendation for CKD patients is to follow a low sodium, potassium, fat and phosphate diet which has to be under the supervision of a nutritionist. Regarding fat diet content, it is as follows: 25-35% of the whole calories coming from fat (20% unsaturated, 10% polyunsaturated, and less than 7% saturated). Regarding phosphate diet content, it should be around 800-1000 mg/day. Besides, a sodium bicarbonate supplement can also be added to the diet in order to avoid protein catabolism secondary to renal metabolic acidosis. For this reason, aimed serum bicarbonate levels should be 22 mmol/L. In regards to calcium intake, it should be 1500-2000 mg/day in order to reduce the risk of vascular calcification. Even though there are no studies which demonstrate that cessation of smoking improves the outcomes of CKD, it seems reasonable to extrapolate data from the general population that indicates reduction of cardiovascular risk over time after stopping smoking. Alcohol consumption is also not recommended while regular physical exercise is (at least 40 minutes, three times per week)[2,3,31].

Studies report that smoking is as prevalent in renal transplant recipients as it is in general population, and it is linked to cardiovascular disease in the late post-transplant period[13].

Other factors. Many factors increase the oxidative stress such as inflammation, malnutrition (reduced antioxidant vitamins), uremic toxins, etc. If vitamin C and E can reduce myocardial infarction rates is controversial, while there is some more data supporting N-acetilcysteine in this sense. Regarding the chronic inflammatory process (high reactive protein C levels), it has also been proposed as a cardiovascular risk factor, thus removal of the inflammatory focus (infected clotted vascular access, hidden abscesses, etc.), and or anti-inflammatory drugs (aspirin, statin) prescription has been recommended if a causative focus is detected. Hyperhomocysteinemia (Hcy), it is much more frequent in dialysis patients (prevalence: 80%) than in the general population, where Hcy is an independent

risk factor for cardiovascular events, and it is frequently associated with folic acid and vitamin B deficit. Thus, these vitamins are suggested for treating it[2,3,32,33]. With regards some renal parameters, it has been documented that a reduced glomerular filtration rate, and a increased albuminuria are both risk factor for all-cause mortality and cardiovascular disease mortality particularly in type II diabetes mellitus-affected individuals, independently from subclinical cardiovascular disease[34].

In kidney transplant patients, allograft dysfunction is an independent risk factor for cardiovascular disease, and it has been proposed that inflammatory response associated to rejection may contribute to the pathogenesis of cardiovascular disease. Additionally, a number of epidemiologic studies implicate various infections, including cytomegalovirus infection in the pathogenesis of cardiovascular disease in this group[15].

Cardiovascular diseases.

Left ventricular hypertrophy (LVH). LVH is present in a significant proportion of CKD patients: 20-40% in pre-dialysis, and 50-75% in dialysis ones; and LVH in the latter group is an independent mortality risk factor. Myocardial hypertrophy is an adaptive process which occurs in response to a long-term augment in myocardial work due to left ventricular pressure or volume overload. Initially, these myocardial changes are beneficial but then become maladaptive, resulting in myocytes death due to diminished myocardial capillary density with reduced subendocardial perfusion, myocardial rearrangement, and development of myocardial fibrosis. The latter can be exacerbated by many factors such as male gender, ageing, ischemia, angiotensin II, aldosterone, catecholamines, and parathyroid hormone. As a consequence myocardial changes, electrophysiologic abnormalities and impaired diastolic filling appear in this population. There are many factors which contribute to the development of LVH through inducing pressure overload: hypertension, arterial stiffness (arteriosclerosis), aortic stenosis; and through inducing volume overload: increased extracellular volume, arteriovenous fistula, and anemia[2,3,35].

Ischemic cardiomyopathy . Coronary artery disease is very prevalent in CKD patients (17-73%) since uremic milieu (platelet function derangement, prothrombotic factors, increased oxidative stress, inflammation), and their associated co-morbidities (hypertension, diabetes mellitus, dyslipidemia, abnormal calcium-phosphorus metabolism) favors coronary artery wall damage. Coronary atherosclerotic plaque in CKD patients usually has severe calcium deposition which contributes to its high rate of complication. The degree of this calcification is directly associated to a long dialysis duration, hyperparathyroidism, hyperhocysteinemia, old age, high calcium-phosphorus product, and high reactive C protein serum levels. There are a group of CKD patients who suffer from ischemic symptoms (25-50%) without critical coronary artery stenosis, which have microvascular disease and underlying cardiomyopathy. In LVH myocardial oxygen demand may not receive an adequate coronary flow, and consequently it induces a reduced cardiac transmural perfusion leading to subendocardial ischemia[2,3,25,36,37]

Arrhythmias. There is an increased risk of developing arrhythmias in CKD, which are secondary to the presence of LVH and coronary heart disease in this population. Besides, characteristic abnormal serum electrolytes levels in CKD patients (hyperkalemia, hypocalcemia, and/or hypermagnesemia), rapid electrolyte fluctuation during dialytic treatment can affect their cardiac conduction. Atrial fibrillation is the most frequent arrhythmia in the general population, as well as in the dialysis one, especially in those patients who have left atrial dilatation. Ventricular arrhythmias have been documented in up to 30% of dialysis patients, and they are usually more prevalent and severe in old age, dialysis hypotension, myocardiopathy, and/or digoxin therapy. Sudden cardiac death represents 60% of the cardiac death in dialysis patients. Antiarrhythmic therapy is much more difficult in patients with CKD since choice of therapy is narrowed due to the altered pharmacokinetics of many drugs resulting from renal failure, neurotoxicity of certain drugs and their complex interactions. Cardiac pacing is a common method of treatment for symptomatic bradiarrhythmias[2,3,37,38].

Valvular and pericardial disease. Most common valvulopathy in nephropathy is the aortic disease (prevalence in dialysis: 55%), which is usually the consequence of dystrophic calcification of the valvular annulus and leaflets. A valve can evolve in 6 weeks from sclerosis to hemodinamically significant stenosis, with a worsening of LVH, and subsequent symptoms: angina, cardiac failure, and syncope. Among the main aortic stenosis risk factors are: old age, years of dialyses, hyperphosphatemia, and high serum calcium-phosphorus product levels. Mitral valve calcification is also frequent in CKD but less than aortic one. The former has been associated with cardiac conduction defects, and valvular insufficiency. Even though, altered calcium-phosphorus metabolism is its main risk factor, additional ones are: left atrial dilatation, systolic hypertension, and years of CKD. Besides, acute and subacute endocarditis is another relatively frequent cardiologic complication observed in hemodialysis patients[39-41]

The most frequent pericardial disorder in CKD patients is the acute pericarditis associated to dialysis. Its main causes are inadequate dialysis dose, or staphylococcus sepsis. Chronic constrictive pericardial disease can also be observed in this population. Acute (cardiac tamponade) and chronic (cardiac constriction) pericardial disease can lead to significant hypotension, and even to simulate a congestive cardiac failure. Pericardial disorders have an incidence of 20% in nephropathy patients[2,3].

Cardiac insufficiency. LVH is very prevalent in CKD patients, and it induces left ventricular diastolic dysfunction, and consequently an increase in left ventricular stiffness in this population. All these changes predispose CKD patients to symptomatic pulmonary edema during fluid overload, but simultaneously, they lead them to a large fall in left ventricular pressure during volume contraction states, and consequently to symptomatic hypotension. Around 15% of dialysis patients have systolic myocardial contractility reduction secondary to an overload cardiomyopathy. In this population, systolic dysfunction can be associated not only to ischemic heart disease, but also to a reversible manifestation of severe uremia which can improve with dialysis. It should also be taken into account that an arterio-venous fistula hypertrophy, mainly a brachial one, can induce a high output cardiac insufficiency in dialysis patients. Additionally, it has been reported that kidney transplant can normalize cardiac systolic dysfunction in dialysis patients[3,35].

Conclusion: Cardiovascular diseases and their associated risk factors are the same in chronic kidney disease patients as in the general

population, although they are more prevalent and difficult to be handled in the former at any period of their nephropathy: predialysis, dialysis and kidney transplant.

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