Review article

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Cardiorenal continuum: A proposal for the prevention of cardiovascular and renal disease

El continuo cardiorrenal: una propuesta para la prevención de las enfermedades cardiovasculares y renales

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Abstract

Cardiovascular risk factors such as arterial hypertension, type 2 diabetes mellitus (DM2) and dyslipidemia are commonly involved with chronic kidney disease (CKD) and its contribution to long-term cardiovascular morbidity. Diffuse endothelial dysfunction and atherosclerosis are believed to be part of the common pathophysiology in diabetic and non-diabetic CKD, particularly in the elderly. Age is the main determinant of glomerular filtration rate (GFR) and effective renal plasma flow and it has been reported that the presence of hypertension at baseline enhances the yearly decline in creatinine clearance. Dyslipidemia may directly affect the kidney by causing deleterious renal lipid disturbances (renal lipotoxicity), as well as indirectly through systemic inflammation and oxidative stress, vascular injury, hormones change and other signaling molecules with renal action. Several cross-sectional studies found that impaired glucose tolerance, as well as the presence of left ventricular hypertrophy, is associated with an increase in the slope of the inverse relationship between age and GFR in subjects with never-treated essential hypertension. Most of the drugs used to reduce the burden of risk factor on cardiovascular disease also benefit the renal function. So, we propose the cardiorenal continuum as a preventive strategy to protect both organs and reduce the deleterious impact of the cardiovascular risk factors on the renal function considering both organs as a functional and physiopathological binomial.

Keywords: Cardiorenal continuum, cardiovascular disease, chronic kidney disease, albuminuria, risk factors, hypertension, dyslipidemia, diabetes.

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Resumen

Los factores de riesgo cardiovascular (FRCV) como hipertensión arterial (HTA), diabetes mellitus tipo 2 (DM2) y dislipidemia suelen estar involucrados con la enfermedad renal crónica (ERC) y su contribución a la morbilidad cardiovascular.

La disfunción endotelial difusa y la aterosclerosis están conceptualizadas como La disfunción endotelial difusa y la aterosclerosis están conceptualizadas como parte de la fisiopatología de la ERC en diabéticos y no diabéticos, particularmente en ancianos.

La edad es el principal determinante de la tasa de filtración glomerular (TFG) y flujo plasmático renal efectivo y se ha reportado que la presencia de HTA favorece la declinación en la depuración de creatinina. La dislipidemia puede afectar directamente el riñón causando trastorno renal lipídico (lipotoxicidad renal) e indirectamente a través de la inflamación sistémica y estrés oxidativo, agresión vascular y cambios humorales y de otras moléculas de señalización con acción renal. Varios estudios transversales han encontrado que el deterioro a la tolerancia glucosada y la presencia de hipertrofia ventricular izquierda están asociados con un aumento en la pendiente de la relación inversa entre edad y TFG en sujetos con HTA no tratada.

La mayoría de las drogas empleadas para reducir la carga de los FRCV también son beneficiosas para la función renal. De tal forma que se propone al continuo cardiorrenal como una estrategia preventiva para proteger ambos órganos y reducir el impacto deletéreo de los FRCV sobre la función renal partiendo del punto de vista de un binomio funcional y fisiopatológico.

Palabras clave: continuo cardiorrenal, enfermedad cardiovascular, enfermedad renal crónica, albuminuria, factores de riesgo, hipertensión arterial, dislipidemia, diabetes.

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Introduction

It is well known that the worldwide incidence of cardiovascular and kidney diseases tends to increase, mainly due to the greater longevity of the population and the increase in cases of type 2 diabetes mellitus (DM2) and arterial hypertension (AHT). The latter represents the greatest burden as it causes a high proportion of morbid events related to the cardiovascular, cerebrovascular and renal spheres, with a greater weight within the countries with middle and low income.[1]

Epidemiological and observational studies have allowed us to know that there is a close relationship between renal and cardiac function, where the major cardiovascular risk factors affect both organs equally. However, little importance has been given to this link.

In the series of 4102 patients hospitalized for heart failure published by Amsalem *et al.*,[2] 57% were bearers of kidney failure, but in almost 50% of them it was unknown since the serum creatinine levels were within normal values and they only presented alteration in the urinary albumin to creatinine ratio, which indicates renal damage.

Cardiorenal syndrome (CRS) is a clinical situation conditioned by the involvement of the heart and the kidney, where the damage to each of these organs potentiates the other in an accelerate way, feeding back each other with a high percentage of mortality after a few years[3]; this is a situation where there is rarely going back.

On the contrary, the cardiorenal continuum is a concept for the early preventive approach that aims to avoid damage to both organs, with which it distances itself from the CRS, given that this long-term vision implies a more proactive and more dynamic activity in the short-term to ensure the preservation or prolongation of the optimal functioning of both organs.[4]

As indicated by its name, the cardiorenal continuum is nothing more than a succession of events where it is clearly possible to intervene in order to prevent damage to both organs. It is not a clinical entity like CRS, but rather a more effective form of intervention by the physician.[4]

The elementary conception of the kidney as a simple filtering organ undergoing the onslaughts of an insufficient pump has been displaced by the understanding of a complex and robust interaction between the heart and the kidney. The above is put in evidence by Guyton,[5] who established that both one and the other are regulators of vital functions such as, for example, blood pressure (BP), vascular tone, diuresis, natriuresis, circulating volume homeostasis, peripheral perfusion and tissue oxygenation. They also have endocrine functions (related to calcium/phosphorus balance and glucose absorption/excretion) and are capable of cellular and humoral signaling.[6]

Cardiorenal continuum and interaction between cardiovascular risk factors and kidney damage

Current literature establishes that the hemodynamic regulation of the heart and the kidney is a complex and dynamic system in which changes in the function of an organ can lead to a spiral of dysfunction of both through the alteration in the balance of nitric oxide and reactive oxygen species, systemic inflammation, activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), major cardiovascular risk factors (AHT, dysglycemia, dyslipidemia, smoking and obesity) and the influence and interaction of several substance such as cytokines, growth factors, chemotactic factors, endothelin, prostaglandins, vasopressin, and natriuretic peptides.[4,7] (Figure 1).

In fact, the contribution of non-invasive imaging techniques has been essential to know that almost two thirds of patients with chronic kidney disease (CKD) are bearers of subclinical atherosclerosis, which progresses, in just 24 months, in more than half from them.[8,9] Moreover, a significant correlation has been described between the estimated glomerular filtration rate (eGFR) and an increase in the carotid intima-media thickness in subjects with normal or near normal renal function.[10,11]

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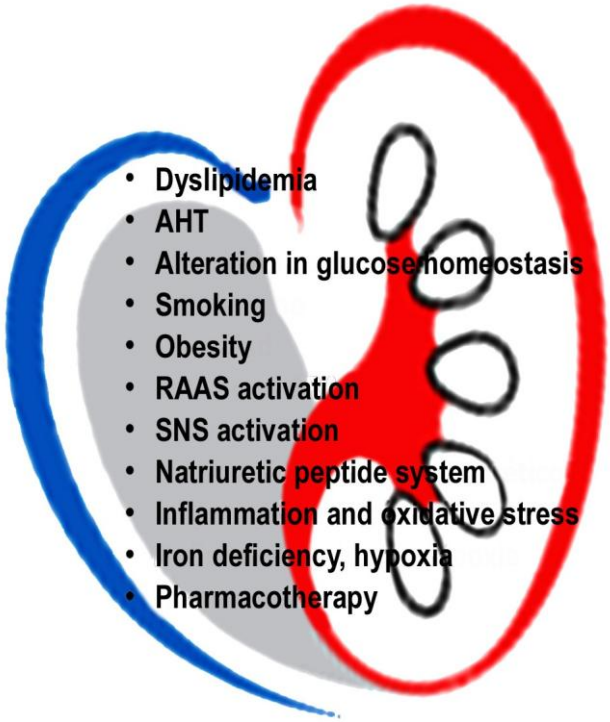

Figure 1. Dynamic and complex interactions between the heart and the kidney. AHT: Arterial hypertension; RAAS: Renin-angiotensin-aldosterone system; SNS: sympathetic nervous system. *Source: Own elaboration.*

Traditionally, it has been recognized the leading role of hypertensive disease and DM2 regarding the impact on endothelial function (vascular and renal), whose deleterious effect is expressed early in both pathologies,[12,13] especially when other cardiovascular risk factors (CVRF) such as dyslipidemia, smoking or obesity, which favor the progression of atherosclerosis and deterioration in the function of both organs are present.[14,15] The high prevalence of AHT and atherogenic dyslipidemia in patients bearers of DM2 and CKD is well known, which further darkens the prognosis of these patients[16] and obliges to an earlier, intensive and thorough management in these cases.

The updated versions of the guidelines for treatment of AHT by the American College of Cardiology/American Heart Association (ACC/AHA)[17] and the European Society of Cardiology (ESC)[18] have established blood pressure values for patients with CKD lower than in previous editions:

• ACC/AHA: <130/80 mmHg

• ESC: 130 to 139/70 to 79 mmHg

Both guidelines are highly influenced by the results of the Systolic Blood Pressure Intervention Trial (SPRINT),[19] in which it was documented that intensive treatment aiming at the goal of systolic blood pressure <120 mmHg reduces the risk of cardiovascular disease and mortality in non-diabetic adults with high cardiovascular risk, many of whom were bearers of CKD. However, its results are questioned by the methodology used in the measurement of blood pressure, so it is worth mentioning that although intensive treatment can reduce clinical events, it does not slow the progression of the CKD.

As for the alterations in glucose homeostasis (prediabetes and established diabetes), the importance of the impact of the duration of exposure to hyperglycemia in the prevention of DM2 or, at least, in the delay in its appearance is recognized today; in fact, subjects who become diabetic before 50 years of age have a higher cardiovascular and renal risk than those who remain normoglycemic,[20,21] being that the increase in 18 mg/dL above 106 mg/dL in blood glucose is associated with an increase in the risk of cardiovascular death of 11%, of major coronary events of 10%, of ischemic stroke of 8%, of vascular occlusive disease of 8% and an increase in the risk of intracerebral hemorrhage of 5%.[22] as a consequence, it is not risky to state that elevated values in plasma fasting glucose are associated with an increase in the GCVR in non-diabetic subjects.

Dyslipidemia is an important factor for progression of CKD that increases the risk of developing atherosclerosis and its complications. The participation of oxidized low-density lipoproteins that promote greater endothelial damage in the glomerular capillary, the decrease in the concentration of high-density lipoproteins and their functional capacity for the reverse cholesterol transport, the increase in the concentration of triglyceride-rich lipoproteins, the atherosclerosis of extra and intra-renal arteries, the accumulation of lipoproteins in the mesangium, and the tubular reabsorption of filtered proteins that induce fibrosis in

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the renal interstitium[14,23-25] had been proposed among the mechanisms responsible for the kidney damage.

It is worth highlighting that more than a third of hypertensive patients are also bearers of atherogenic dyslipidemia, which is why it is reasonable to think that the association of both entities produces greater kidney damage.

For several years and due to the excessive increase in overweight/obesity rates in the world population, the impact of these diseases on the cardiorenal continuum has been evidenced, especially because they are important conditioning factors in the development of AHT and DM2, a trilogy of fatal consequences that feeds back and leads to severe heart, renal and arterial lesions. In fact, McMahon *et al*.[26] state that the risk of CKD is 1.71 times higher in obese individuals than in general population (95% CI: 1.14-2.59) and Chang *et al*.[27] demonstrate that the rate of decline in eGFR is more accelerated as higher the body mass index.

As it would be expected in a very complex condition where numerous actors of first, second and third order intervene, the explanation of the pathophysiological mechanism(s) becomes more difficult to clarify. However, briefly, it can be said that the state of sodium retention; the hyperinsulinemia/insulin resistance/ lipotoxicity; intraglomerular hypertension, glomerular hypertrophy with or without secondary focal segmental glomerulosclerosis; the increase in glomerular functional demand with hyperfiltration and albuminuria, and the activation of the humoral machinery of the adipocyte with greater production of angiotensin II and stimulation of pro-inflammatory cytokines intervene in the cardiovascular continuum.[28-30]

In relation to the metabolically normal obese, there is a very particular phenotype that apparently protects these subjects from the metabolic complications of obesity but not from the risk of kidney damage,[31,32] thus, obesity, independently of the metabolic status, is an important risk factor for the deterioration of kidney function.

As for smoking, there is no doubt about the systemic harmful effect of cigarette smoke, in addition, the information related to the impact on the kidney is similar to that observed in the cardiovascular system, thus becoming the most important modifiable risk factor for both systems.

It is clear that the risk of increased urinary albumin excretion is higher in smokers. The data from the study conducted by Kuller *et al*.[33] indicate that, at least in men, smoking increases the risk of end-stage kidney disease; in fact, it is accepted that smoking is «nephrotoxic» in older adults, in hypertensive and/or diabetic subjects and in those with pre-existing kidney disease. The magnitude of the impact of the adverse renal effect of smoking is independent of the underlying kidney disease[34] and can be exerted by the following mechanisms:

- Nicotine induces apoptosis of the podocytes through the generation of reactive oxygen species and the consequent promotion of oxidative stress associated with downstream signaling of mitogen-activated protein kinases (MAPKs).[35,36]
- Nicotine favors the proliferation and hypertrophy of mesangial cells via neuronal and non-neuronal nicotinic acetylcholine receptors.[35-37]
- Blood pressure rises, especially in hypertensive patients, during and after each cigarette.

Clinical relevance of the cardiorenal continuum

It has been briefly exposed the solid connection between the CVRFs and kidney damage, which as such is the basis of this proposal to conceptualize the cardiorenal continuum (Figure 2) as a form of approach of early intervention in cardiovascular and renal protection to reduce the morbidity and mortality derived from the involvement of both organs, since pathophysiological alterations in one lead to deterioration in the function of the other.[4] In other words, "*when the heart suffers, the kidney cries and vice versa*.»

The fundamental goal of prevention is to avoid the appearance of the CVRFs in the general population. Once they are present, they influence the development and progression of endothelial

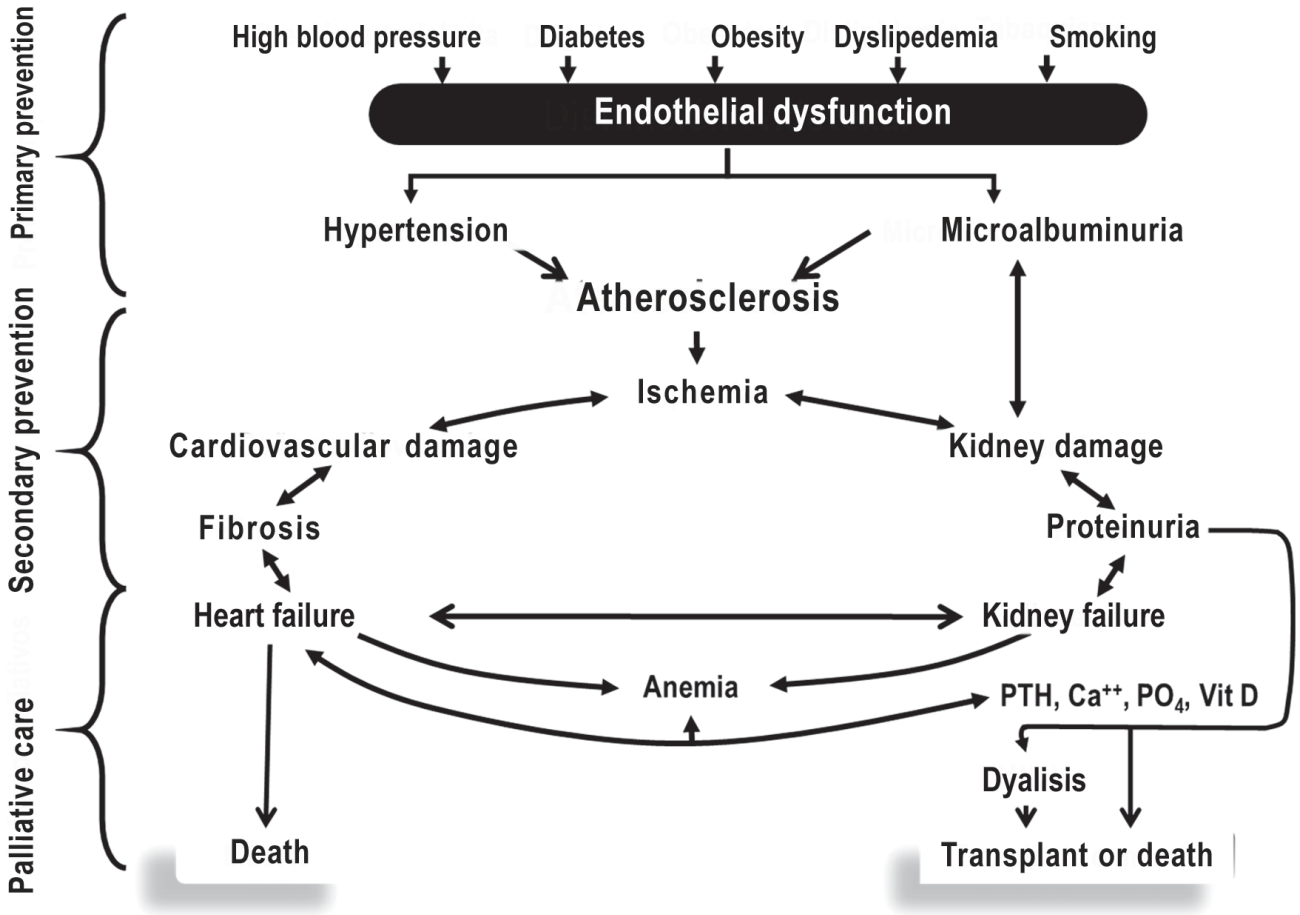

Figure 2. Vision of the cardiorenal continuum. PTH: parathyroid hormone; Ca++: calcium; PO4: phosphate; Vit D: vitamin D. *Source: Elaboration based on Arocha & Amair.*[4]

dysfunction, which could be expressed by accentuation of the elevated BP or by albuminuria, with which atherosclerosis is favored and begins the cycle of cardiac and renal damage until developing heart failure or kidney failure, two conditions that interact with a high mortality.

The actuation windows had been placed in the left margin: primary prevention on the CVRFs and secondary prevention to delay cardiac and renal damage and palliative care in the last evolutionary phase.

The major risk factors for the development of cardiovascular diseases are: obesity, AHT, DM2, dyslipidemia and smoking, which are also the main producers of kidney damage and acceleration of the progression of the kidney disease; therefore, they are fundamentals of the cardiorenal continuum for renal protection.

The presence of kidney disease is included as an independent risk factor for cardiovascular disease in various guidelines for the management of AHT.[17,18,38] In fact, the percentage of patients with kidney disease who die during follow-up due to cardiovascular complications is very high compared to those who progress to renal replacement therapy.[39]

In the studies conducted by Ruilope *et al.*[40] and Mann *et al.*,[41] patients with plasma creatinine between 1.3 and 1.4 mg/dL showed a significantly

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higher incidence of primary cardiovascular events and cardiovascular and global mortality compared to those who had normal renal function; therefore, a small elevation of creatinine (even taking into account its imprecision, since to increase the plasma creatinine concentration, renal function must decrease by 50%) indicates evident kidney damage and an increased risk of cardiovascular disease.

Relationship between renal function and cardiovascular morbidity and mortality

The interconnection between kidney damage and cardiovascular morbidity and mortality is notable and increasing as the deterioration of renal function progresses, to the point that cardiovascular mortality in dialysis patients is 500 times higher than that of the general population.[42]

Go *et al*.,[43] in a large database with more than 1.1 million adults, studied the relationship between the glomerular filtration rate estimated by the Modification of Diet in Renal Disease formula and the risk of mortality, cardiovascular events and hospitalization. After adjusting for age, gender, race, comorbidity, and socioeconomic status, the authors evidenced an increased risk of any of these three outcomes as glomerular filtration rate decreased.

Meanwhile, Keith *et al*.[44] conducted a longitudinal follow-up study of 27,998 patients with a glomerular filtration rate <90 mL/min/1.73 m^2 in two determinations and pointed to the AHT, the coronary heart disease and congestive heart failure as the entities most associated with CKD.

The follow-up study conducted by Cerasola *et al*.[45] demonstrated the close relationship between the abdominal circumference and the systolic blood pressure with early deterioration of kidney function in hypertensive patients without repercussion on target organs. For their part, Hemmelgarn *et al*.,[46] in another community-based observational study aimed at analyzing the relationship between deterioration of eGFR, proteinuria, and clinical outcomes in nearly 1 million patients, concluded, after a 35-month follow-up, that the risks of death, myocardial infarction, and progression to renal failure were associated with a given level of eGFR (<60 mL/min/1.73 m^2) and increased independently in patients with a higher level of proteinuria.

Therapeutic strategies in cardiorenal protection

Because it is a very extensive and well-known topic, this review supports that the therapeutic measures widely recognized and used in cardiovascular medicine – such as antihypertensive agents, RAAS inhibitors, beta-blockers, statins, platelet antiaggregants and proprotein convertase subtilizing/kexin type 9 inhibitors have also demonstrated to be nephroprotective.[47-51]

Consequently, it is essential to insist that they should be used at the correct dose, early and for a prolonged or indefinite period to guarantee adequate protection of both organs and to remember that clinical and therapeutic inertia is responsible for the failure of early intervention and/or dose adjustment with the consequent vascular and kidney damage.[4]

Conclusions

The heart-kidney interrelationship constitutes a pathophysiological and clinical reality with multiple common etiological factors and complications that interact with each other, hence its integration in the cardiorenal continuum allows, in the one hand, to understand the need for early and energetic control and treatment of the common risk factors and, on the other, to intervene since the earliest stages (primordial prevention and primary prevention) to avoid the development and progression of cardiovascular and renal damage, especially in high risk groups such as the population over 60 years of age, prediabetics (including those with metabolic syndrome) and diabetics, hypertensive patients and subjects with obesity.[4,7,14,17,18]

Early evaluation of renal function in all patients belonging to the aforementioned higher risk categories allows early detection and intervention

to reduce the risk of cardiovascular events, kidney failure and death. Furthermore, it is clear that all those interventions aimed at slowing the progression of renal function deterioration pay off by reducing cardiovascular risk and vice versa.

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Conflict of interest

None declared by the authors.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

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Contribution of the authors

Both authors contributed equally in the search for bibliographic material, writing and review of the manuscript.

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