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Editorial

Towards a better prevention in cardio-kidney metabolic syndrome: Role of aldosterone and albuminuria

Hacia una mejor prevención del síndrome cardiorrenometabólico: papel de la aldosterona y la albuminuria

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Pharmacological treatment of patients with hypertension and elevated cardiorenal risk has been classically based on the chronic blockade of the renin–angiotensin-system (RAS), with either angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB). If necessary, other antihypertensive drugs have been commonly added, mainly diuretics and calcium antagonists. Theoretically, this approach prevents the development and progression of albuminuria and retards the progressive decay in renal function while acting positively on the simultaneous increased cardiovascular risk. Albuminuria is an established risk factor for the simultaneous development of chronic kidney disease (CKD) and cardiovascular disease. All this has promoted the concept and the clinical use of cardiorenal disease that more recently has been expanded as the new concept of cardio-kidney-metabolic (CKM) syndrome.[1]

Although the beneficial effects of chronic RAS blockade have been largely recognized, it is also evident that a residual risk remains for both CKD and cardiovascular disease development and progression. Indeed, we have observed that the classical scheme of antihypertensive treatment described above was unable to completely prevent the development of new onset albuminuria and its progression, as well as the accompanying cardiorenal risk.[2] Additionally, the role of aldosterone in CKM syndrome has been recently recognized and the use of antialdosterone drugs considered.[3] In fact, some individuals show elevated plasma aldosterone levels under chronic RAS blockade, known as aldosterone escape phenomenon.[4] However, the excessive secretion of aldosterone plays a crucial role in the progression of cardiorenal disease. Unfortunately, despite its strong relevance, it remains clinically underappreciated. In fact, the need to measure plasma and urine aldosterone levels has been stressed.[5] In recent trials of new drugs in diabetic patients treated with the classical scheme blocking RAS plus antihypertensive and antidiabetic drugs, high and very high albuminuria and cardiovascular damage were already present.[6–8] These trials have demonstrated that counteracting aldosterone was protective for the renal and cardiovascular damage in type 2 diabetes mellitus (T2DM). A deleterious role of aldosterone in different clinical situations under CKM context is already present even in the early stages of cardiorenal disease particularly, but not exclusively, in people with obesity and T2DM, thus facilitating the development of arterial hypertension, CKD, and heart failure (HF).[3]

The role of aldosterone in arterial hypertension was initiated decades ago by the description of primary aldosteronism and the possibility of curing hypertension with surgery. Medical treatment of primary aldosteronism initially included the administration of spironolactone. The prevalence of this secondary cause of hypertension was considered as very low, but nowadays, we know that primary aldosteronism is much more frequently present.[9] A higher prevalence led to the conclusion that, in the hypertensive population, an adequate blood pressure control requires an adequate recognition and treatment of aldosterone excess.[10] Other aspects of interest relating aldosterone and blood pressure are the fact that high plasma aldosterone concentration is accompanied by a worse ambulatory blood pressure monitoring profile and higher prevalences of masked uncontrolled hypertension[11,12] and resistant hypertension.[13,14]

On the other hand, new data related to the spectrum of dysregulated aldosterone secretion with a low renin phenotype has been described in patients with early stages of essential hypertension as well as in normotensive individuals relating the development of hypertension, CKD and cardiovascular disease.[15] This dysregulated aldosterone production is apparently prominently influenced by adrenocorticotropic hormone (ACTH), and could be accompanied by high-normal albuminuria (values between 10 and 30 mg/g of

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creatinine).[3] This multifactorial situation requires, first, an adequate identification of alterations in the renin-angiotensin-aldosterone system (RAAS) in clinical practice, and second, the demonstration of the benefit of administration of aldosterone blockers in individuals with low renin. Although evidence is lacking from prospective clinical studies of albuminuria, this indicates that plasma aldosterone concentration and the aldosterone/renin ratio may serve as potential therapeutic targets for the early prevention of CKM disease. And also, potentially of even greater importance is the recent finding that high serum aldosterone levels in patients with CKD are independently associated with an increased risk for kidney disease progression, irrespective of the presence of T2DM.[3]

In conclusion, clinical situations characterized by an increased activity of aldosterone are more prevalent than previously considered, and they extend from mildly elevated blood pressure accompanied by low renin to hypertension due to primary aldosteronism and/or resistant hypertension. The ability of aldosterone to damage the cardiovascular and renal systems is particularly elevated in the presence of CKM syndrome particularly in patients with obesity and/or T2DM. Therefore, the need to determine renin and aldosterone levels in plasma in clinical practice needs to be expanded, as well as the potential use of aldosterone blockers. In this sense, new drugs counteracting the effects of aldosterone, such as non-steroidal mineralcorticoid receptor antagonists and aldosterone synthase inhibitors have been developed and are being increasingly used in clinical practice.[16,17] Therefore, it is highly recommended the search for urine albumin measurement and if possible the determination of aldosterone levels in patients at all the stages of CKM syndrome. Individuals with both albuminuria and elevated aldosterone levels could be candidates for such aldosterone inhibition as a relevant treatment of the CKM syndrome progression.

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