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CARDIOPULSE

Global spotlights

Use of chronic kidney disease blind spot to prevent cardiorenal outcomes

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Chronic kidney disease (CKD) is one of the fastest growing causes of death, predicted to become the fifth global cause of death by 2040 and the second before the end of the century in some countries where longer lifespan.[1] CKD and arterial hypertension are intimately ligated and blood pressure (BP) elevates in parallel with the progressive decay of renal function.[2] The diagnosis of CKD requires the demonstration of pathological albuminuria and/or an estimated glomerular filtration rate (eGFR) $<$60 mL/min/1.73 m^2, albeit the concept of mildly decreased renal function (60–90 mL/min/1.73 m^2) is recognized by KDIGO Guidelines.[2]

The elevation in BP must be counteracted to avoid an accelerated decay in renal function usually accompanied by a more rapid progression of the cardiovascular disease accompanying CKD. Before any of the parameters defining CKD (albuminuria or decreased eGFR) attains the threshold to diagnose the patient as having CKD, the presence of early kidney damage is a real situation not well recognized nor treated in clinical practice. In this regard, an eGFR $<$60 mL/min/1.73 m^2 implies that $>$50% of the functioning kidney mass has been lost. Thus, the process of kidney damage starts well before, even decades before a diagnosis of CKD is made. The obvious implication is that CKD is being diagnosed and treated late. KDIGO tried to limit the negative consequences of a delayed diagnosis by setting diagnostic criteria that involve evidence of kidney damage, such as albuminuria or imaging, even when kidney function was preserved.[2] However, as defined by KDIGO, pathological albuminuria is still a late event that maybe absent until late in the course of CKD. In polycystic kidney disease, imaging may allow a diagnosis of CKD several decades earlier than albuminuria or eGFR criteria. This illustrates a concept, the so-called CKD blind spot, similar to the rear-view mirror blind spot in cars: CKD is present, but we lack the tools necessary to diagnose it until later on, losing precious time needed for earlier and more effective therapy (*Figure 1A–C*).[3] Thus, diagnostic tests should be developed that identify CKD from different causes as early as imaging does in polycystic kidney disease.

The presence of high-normal albuminuria,[4] and the existence of a fall in eGFR $\geq$5 mL/min/year2 are parameters indicating the existence of early kidney damage albeit better indicators are required. Work is ongoing on the identification of earlier biomarkers of CKD, mainly through the analysis of urine that is thought to be able to represent early kidney events better than plasma or serum.[5] However, the most promising biomarkers imply expensive techniques that will not be routine in the clinic until cost decreases dramatically. An alternative is to use already existing clinical and laboratory data to identify early CKD or persons at risk of progression to CKD. The recent development of risk prediction equations from $>$5 million individuals in 34 multinational cohorts has shown high discrimination and variable calibration in diverse populations.[6] Two formulas are being considered, one to calculate the probability of incident eGFR $<$60 mL/min/1.73 m^2 and the second to define the time to kidney failure. Further study is needed to determine whether the use of these equations improves patient outcomes, but probably the most adequate way to detect early kidney damage and to predict the evolution of CKD will be obtained by using big data and its complementary tools like machine and deep learning (*Figure 2*).

Human ageing is associated with progressive loss of nephrons and eGFR. This may be intimately related to the occurrence of hypertension as in a German necropsy study of young persons that died in accidents, individuals with primary hypertension had roughly half the number of nephrons than those without hypertension.[7] A low nephron number may be congenital, as a consequence of genetic factors, low birth weight or prematurity, or acquired. Individuals with a clinical history of preterm births and low body weight at birth that frequently go together are at risk of earlier development of CKD where the risk is secondary to a decreased nephron number[8] which facilitates the development of albuminuria and of high BP. Later on, the usual cardiovascular risk factors and the coexistence of obesity, hypertension and diabetes facilitate the progression of CKD and simultaneous

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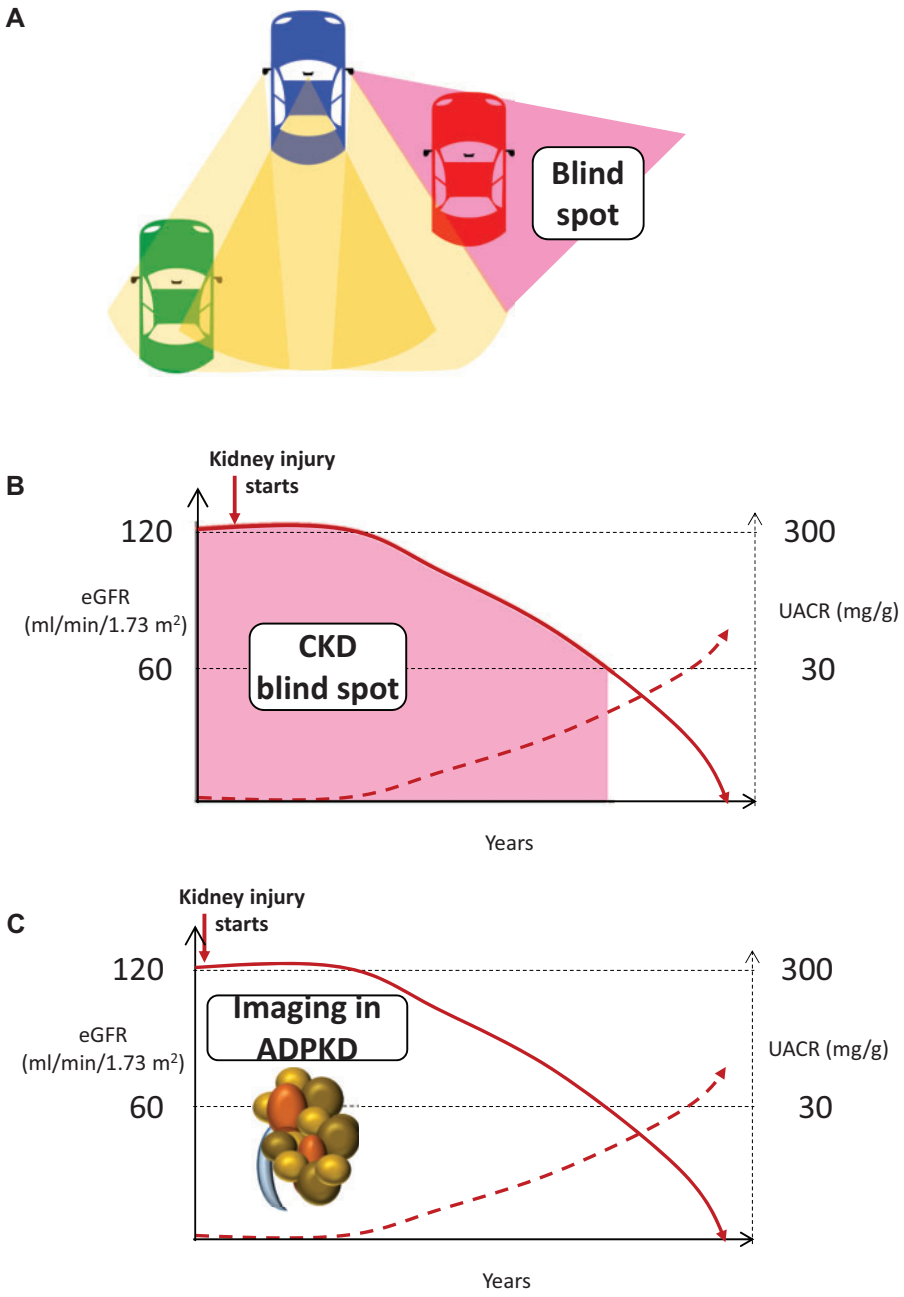

Figure 1 The chronic kidney disease blind spot and the role of big data and artificial intelligence. (*A*) Car rear-view mirror blind spot. (*B*) Chronic kidney disease blind spot. The most frequently used diagnostic and staging criteria for chronic kidney disease, based on glomerular filtration rate (GFR) and urinary albumin: creatinine ratio (UACR) are late events, allowing a blind spot, that may last years to decades, characterized by progression of undiagnosed kidney injury. (*C*) Imaging addresses the blind spot in autosomal dominant polycystic kidney disease, allowing the diagnosis of chronic kidney disease decades before GFR or UACR. A key research priority is the search for novel criteria that allow closing the blind spot in other causes of chronic kidney disease. Adapted from Sanchez-Niño *et al.*[3]

cardiovascular disease.[1] Age, race, gender and genetics contribute to increase the risk of CKD together with the existence of primary renal disease (*Figure 2*).

The goal of BP control in CKD differs in the American and European Hypertension Guidelines and the KDIGO Guidelines[9] that recently proposed a systolic BP target of <120 mmHg in most subpopulations of people with CKD. More clinical trials looking jointly to cardiovascular, renal, cognitive and mortality outcomes are needed but the recommendation of the US Preventive Task Forces of screening for high BP adults aged 18 years or older[10] will facilitate, through an adequate control of BP, the simultaneous prevention of renal and cardiovascular disease from the early stages of both processes.

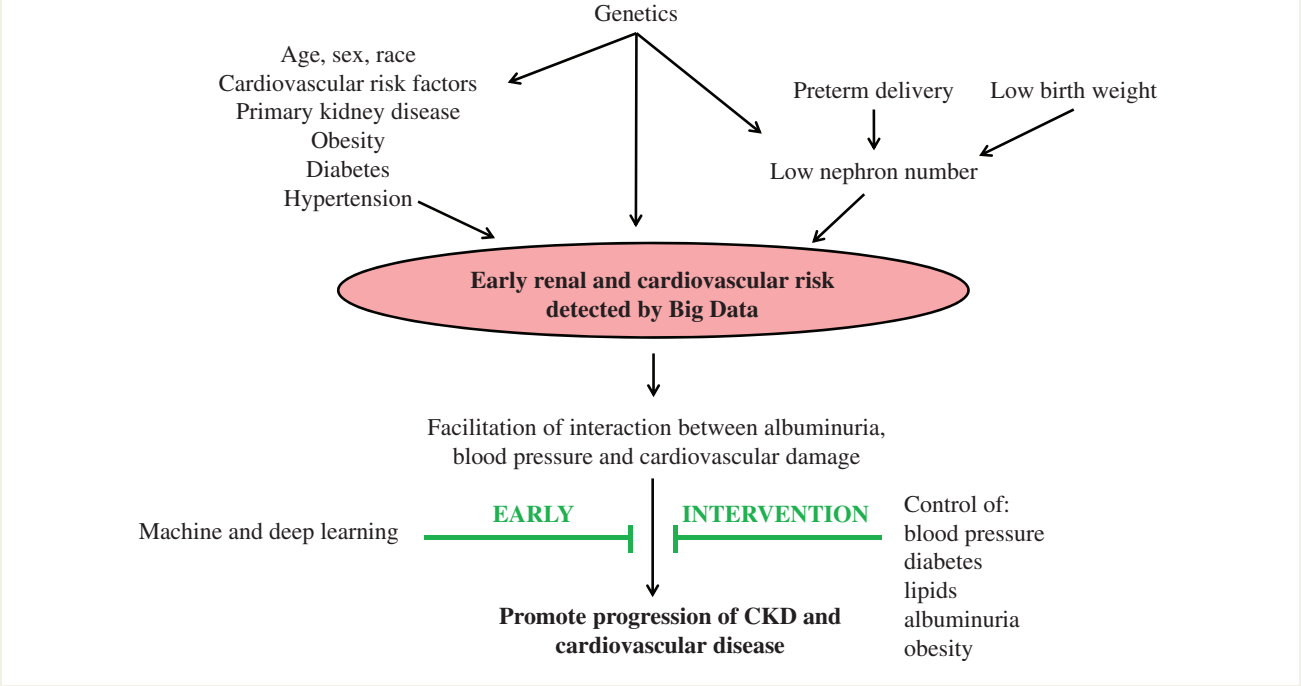

Figure 2 Analysis of big datasets with machine and deep learning may identify information on electronic health records that integrated into dynamic algorithms helps predict in real time the risk or even the presence of chronic kidney disease and thus, allow and early diagnosis and intervention or recruitment of high-risk individuals for studies aimed at identifying biomarkers of early chronic kidney disease that avoid the current blind spot in chronic kidney disease diagnosis.

Finally, once we know the content of CKD blind spot, the data of out of office BP that will be more used in the near future will contribute to better identify elevated BP at early stages of CKD. Besides hypertension, higher degrees of albuminuria and sodium intake associate with accelerated decline of eGFR rate regardless the primary cause of renal damage.[2] Hence, the use of antihypertensive drugs with antiproteinuric effect, the control of dietary salt and or the use of diuretics are particularly recommend even in the absence of hypertension.

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