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Preclinical Cardiorenal Interrelationships in Essential Hypertension

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Commentary

By Professor Richard Glassock

This scholarly and detailed review of cardiac and renal manifestations of 'essential hypertension' suffers mainly from the lack of rigor in definition exactly what compromises a 'preclinical' state.

Certainly 'hypertension' itself is not 'preclinical' and the evidence is very strong that the 'essential' variety is mostly caused by subtle renal abnormalities, even though elevated blood pressure over time can induce progressive renal changes. The 'cut points' for defining 'hypertension' can and should vary according to individual patient characteristics. One might take the view that in approaching the definition of 'hypertension' that 'one size does not fit all'. Nevertheless, as clearly pointed out by Tsioufis and coworkers, certain organ-based abnormalities can precede or accompany 'essential hypertension' in otherwise asymptomatic individuals. These include left ventricular hypertrophy (LVH), decreased glomerular filtration rate (GFR) and small increases in urinary albumin excretion. The origins of these 'preclinical' manifestations are complex and bidirectional in terms of the kidney and the heart, and very difficult to disentangle from each other. The authors use the term 'preclinical cardiorenal syndrome' to distinguish the subject of their review. To include hypertension in a 'preclinical' syndrome seems to me to be an arguable semantic mistake. To claim that hypertension is the second leading cause of chronic kidney disease seems to discount all of the evidence that the reverse is more likely to be a true statement. Certainly LVH, depressed GFR, and albuminuria are commonly found in 'hypertensive' subjects. Underlying microvascular injury (endothelial cell damage and dysfunction), indolent expansion of the extracellular volume, inflammation, activation of the neurohumoral axes, and alteration of cellular signals for growth, apoptosis and autophagy seem to be responsible for these 'preclinical' manifestations as the authors point out. One needs to be very careful in assigning causation based on observational epidemiological associations since directionality cannot be determined in this type of studies. Using 'preclinical' abnormalities to risk stratify individuals for adverse cardiovascular (CV) events can be misleading, and studies have shown that the addition of albuminuria or GFR to standard CV risk classification scores (such as the Framingham Risk Score - see http://www.framinghamheartstudy.org/risk/index.html) do not improve the accuracy of prediction very much at all. It is generally agreed, however, that any level of albuminuria above normal is a non-specific marker of generalized microvascular dysfunction, just as elevation of C-reactive protein is a marker of inflammation.

In the final analysis, a 'preclinical cardiorenal syndrome' syndrome exists, even in the absence of 'hypertension', and it can be defined by markers such as subtle albuminuria, alterations in GFR and changes in left ventricular structure, geometry and function. These abnormalities are of a reciprocal nature and very difficult to disentangle one from another. Better understanding of their genetic, cellular, biochemical and molecular nature may lead to better therapeutic and preventative measures.

This paper raises issue about what is the best definition of 'preclinical cardiorenal syndrome' and how its recognition might lead to treatment programs directed to alleviate the underlying patho-physiological disturbances. Of course, a randomized clinical trial would be required to provide proof that interventions at the preclinical stage would have lasting benefits for meaningful patient outcomes at acceptable risks. No such data is currently available.

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