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Abstract

Objective: A continuous association between albuminuria and cardiorenal risk exists further below moderately increased albuminuria ranges. If only based in albumin to creatinine ratio (ACR) higher than 30 mg/g, a significant percentage of individuals may be out of the scope for therapeutic management. Despite epidemiological outcomes, the identification of biochemical changes linked to early albuminuria is underexplored, and normoalbuminuric individuals are usually considered at no risk in clinical practice. Here, we aimed to identify early molecular alterations behind albuminuria development.

Methods: Hypertensive patients under renin-angiotensin system (RAS) suppression were classified as control, (ACR < 10 mg/g) or high-normal (ACR = 10-30 mg/g). Urinary protein alterations were quantified and confirmed by untargeted and targeted mass spectrometry. Coordinated protein responses with biological significance in albuminuria development were investigated. Immunohistochemistry assays were performed in human kidney and arterial tissue to in situ evaluate the associated damage. **Results:** A total of 2663 identified proteins reflect inflammation, immune response, ion transport and lipids metabolism (P value ≤ 0.01). A1AT, VTDB and KNG1 varied in high-normal individuals (P value < 0.05), correlated with ACR and associated with the high-normal condition (odds ratio of 20.76, 6.00 and 7.04 were found, respectively (P value < 0.001)). After 12 months, protein variations persist and aggravate in progressors to moderately increased albuminuria. At tissue level, differential protein expression was found in kidney from individuals with moderately increased albuminuria and atherosclerotic aortas for the three proteins, confirming their capacity to reflect subclinical organ damage. **Conclusion:** Early renal and vascular damage is molecularly evidenced within the normoalbuminuria condition.