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Editorial Comment

EDITORIAL COMMENT

Evidence of chronic kidney injury in patients not meeting KDIGO criteria for chronic kidney disease

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ABSTRACT

Subjects not meeting KDIGO criteria for chronic kidney disease (CKD), i.e. normoalbuminuric (urinary albumin:creatinine ratio, UACR <30 mg/g) individuals with an estimated glomerular filtration rate >60 mL/min/1.73 m^2, are considered at no increased cardiovascular or kidney risk associated with kidney disease, but the incidence of subclinical atherosclerosis, cardiovascular events and CKD progression is already increased in the high-normal UACR range (10–30 mg/g). Earlier intervention in this subclinical pre-CKD stage may diminish cardiorenal risk. However, tools to predict albuminuria development and to identify those subjects who will benefit most from intervention are limited. Recent data have identified urine molecular changes within the normoalbuminuria condition, consisting of an altered urinary peptidome, proteome and metabolome, which represent subclinical organ damage and processes such as inflammation, oxidative stress, tricarboxylic acids cycle deregulation, impaired fatty acids β-oxidation or defective tubular reabsorption.

Keywords: albuminuria, cardiorenal risk, cardiovascular risk, chronic kidney disease, fatty acids oxidation, metabolomics, proteomics, tubular reabsorption

Chronic kidney disease (CKD) is projected to become the global fifth cause of death by 2040 due to unmet needs in the early diagnosis and treatment of the condition [1]. Urinary albumin:creatinine ratio (UACR) in the moderately increased range (i.e. 30–300 mg/g) is an indicator of subclinical organ damage and an established risk factor of cardiovascular morbi-mortality and renal disease progression at any stage of kidney function as assessed by the estimated glomerular filtration rate (eGFR). UACR 30 mg/g is a current cut-off point for the clinical diagnosis of CKD. CKD can also be diagnosed based on eGFR <60 mL/min/1.73 m^2. Equations for renal risk prediction have been developed recently, aiming for earlier identification of patients at increased risk of CKD progression. In this line, high albuminuria was associated with the predicted 5-year absolute risk of CKD defined by eGFR <60 mL/min/1.73 m^2, regardless of the presence of diabetes [2]. Subjects not meeting KDIGO criteria for CKD (normoalbuminuric subjects with eGFR >60 mL/min/1.73 m^2) are usually considered at no increased cardiovascular or kidney risk related to kidney disease, but epidemiological evidence clearly supports a continuous association between albuminuria and cardiorenal risk starting with UACR levels below 30 mg/g. The incidence of subclinical atherosclerosis [3, 4], cardiovascular events [5] and heart failure [6] is increased in the high-normal range of normoalbuminuria (UACR = 10–30 mg/g).

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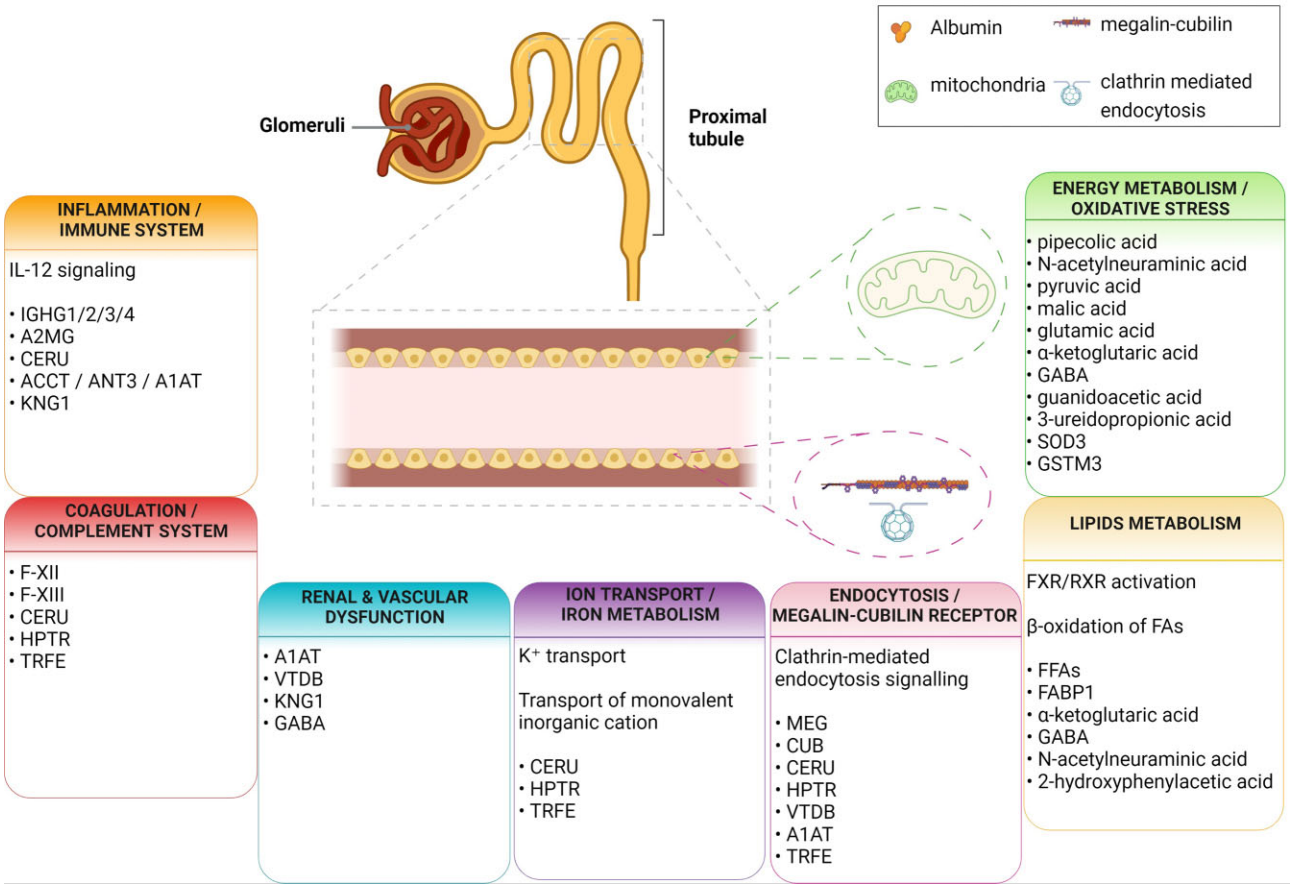

FIGURE 1: The main biological pathways and molecular alterations identified in normoalbuminuric hypertensive subjects with UACR in the high-normal range (10–30 mg/g) despite RAS blockade, as compared with UACR <10 mg/g [8, 11, 12].

In this clinical scenario, earlier intervention to slow down albuminuria progression and diminish associated cardiorenal risks would be desirable already in the subclinical stage of normoalbuminuria with preserved kidney function. However, biomarkers are needed to identify higher-risk patients within this population for referral from primary care to cardiovascular risk or nephrology clinics. In this sense, there is a big gap between evidence and established therapeutic intervention, which may improve outcomes in a wider population. Thus, subjects not meeting KDIGO criteria for CKD are commonly outside the scope for therapeutic intervention if no other traditional risk factors exist, but may still develop cardiovascular disease and renal function decline in the medium-long term. This is in part a consequence of the limited tools available with which to anticipate (predict) albuminuria progression.

An earlier pharmacological intervention with kidney and cardioprotective drugs would be justified in subjects in the early stages of cardiorenal risk if clinical trials demonstrated improved outcomes. However, the success of such clinical trials would depend on the enrichment of participants at higher risk of progression and on a better understanding of molecular events that explain why albuminuria progression rates differ between subjects categorized in the same clinical group on the basis of baseline UACR, diabetes, hypertension or eGFR.

The existence of these unsolved questions may in part be traced to an insufficient understanding of molecular events associated with albuminuria development. Within this complex scenario, the characterization of molecular events may aid in stratifying cardiorenal risk at early stages and in deciphering the molecular mechanisms leading to albuminuria progression. While molecular studies in normoalbuminuric subjects with preserved kidney function are scarce, recent systems biology approaches have shed some light in this area.

In hypertensive subjects with normoalbuminuria under chronic renin–angiotensin system (RAS) blockade, >2500 urinary proteins were identified by untargeted mass spectrometry. The urinary protein pattern differed in patients with normoalbuminuria in the high-normal range (UACR 10–30 mg/g) from those with UACR <10 mg/g [7]. Alpha-1 antitrypsin (A1AT), kininogen-1 (KNG1) and vitamin D-binding protein (VTDB) were differentially present in urine and also differentially expressed in human kidney and aorta samples, suggesting that early renal and vascular damage may be molecularly reflected in the urine of patients with normoalbuminuria. The unparalleled value of proteomics was also evidenced by the characterization and clinical development of CKD273, a CKD risk score based on the measurement of 273 urinary peptides that independently predicted future development of microalbuminuria in type 2 diabetic patients with normoalbuminuria as well as loss of GFR in patients with normoalbuminuria and eGFR above 60 mL/min/1.73 m^2, i.e. in patients not fulfilling current criteria to diagnose CKD [8, 9].

The urinary concentration of metabolites 3-ureidopropionate, oxaloacetate and guanidoacetate decreased, while malate increased in patients with microalbuminuria: and in patients with normoalbuminuria within the high-normal albuminuria range compared with those with lower albuminuria (UACR <10 mg/g) [10]. Nine metabolites previously associated with cardiorenal risk were also altered in the high-normal albuminuria range: 2-hydroxyphenylacetic acid, glutamic acid, N-acetylneuraminic acid, pipecolic acid, pyruvic acid and scyllo-inositol increased, and α-ketoglutaric acid, γ-aminobutyric acid and N-acetylalanine decreased [11]. The presence of these metabolites in urine together with increased levels of fatty acids and fatty acid binding protein-1 (FABP1), and alterations in clathrin-mediated endocytosis signalling, is consistent with defective tubular reabsorption and tubular damage caused by fatty acid overload, impaired mitochondrial β-oxidation, peroxisome proliferator activated receptor (PPAR) activation or tricarboxylic acid cycle dysregulation (Figure 1). These findings fit well with evidence that proximal tubular injury induced by glucose overload, albumin and its ligands, or other stressors, leads to CKD progression [12, 13]. In proteinuric conditions, albumin-bound fatty acids may contribute to proximal tubule fatty acid overload, favouring lipotoxicity, oxidative stress and impaired proximal tubule function [14]. In this line, increased urinary fatty acids were strongly correlated with tubulointerstitial injury and proteinuria [15].

Albuminuria is both a marker of glomerular dysfunction and a contributor to proximal tubular cell injury [16]. However, specific tubular injury markers (kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), (FABP) and N-acetyl-β-D-glucosaminidase (NAG)) did not add to the risk stratification for CKD progression over the information provided by UACR and eGFR in adult patients with eGFR 20–70 mL/min/1.73 m^2 and UACR 53.0 mg/g [interquartile range (IQR) 5.6–503.1] [17]. This would suggest that UACR itself may already provide information on tubular cell injury contribution to CKD progression that is not further improved by assessing other biomarkers of tubular injury. However, in children with eGFR 30–90 mL/min/1.73 m^2 and UACR 57.8 mg/g (IQR 8.8–312), urinary EGF, KIM-1, monocyte chemoattractant protein-1 (MCP-1) and α-1 microglobulin were associated with CKD progression after multivariable adjustment [18]. This suggests that urinary markers of tubular cell injury may add information to that provided by albuminuria in an earlier prediction window (younger age and higher eGFR).

In conclusion, within the clinical condition of normoalbuminuria, further stratification of risk may be possible through the use of novel biomarkers identified through system biology approaches. These markers are consistent with tubular cell injury, inflammation, altered immune responses and oxidative stress. Multicentric large clinical cohorts should validate these biomarkers, and this should be followed by clinical trials that enrol normoalbuminuric patients with preserved kidneys but at high risk of cardiorenal risk based on novel biomarkers and randomize them to early intervention or placebo. Only such a detailed clinical development effort will allow the early identification and intervention necessary to turn the tide on the increasing global burden of CKD and its associated adverse cardiovascular outcomes.

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CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or in part.

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