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NEPHROLOGY – LETTER TO THE EDITOR

Tubular secretion in chronic kidney disease staging: a new proposal

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Editor,

Chronic kidney disease (CKD) prognosis is currently determined mainly by obtaining the patient's glomerular filtration rate (GFR) (measured or estimated) and his/her albuminuria–proteinuria (24-h or spot urine sample) level. These are proper variables for predicting CKD evolution, since the GFR is the cornerstone of the renal depurative function, and the albuminuria–proteinuria has direct effect of tubular damage. Consequently, CKD staging is currently based on these two variables, resulting in a score which consists of five CKD stages (I–V) with different alternative subtypes, depending on the patient's GFR and his/her albuminuria–proteinuria level, respectively (Table 1) [1].

However, it should be pointed out that renal physiology is not just represented by glomerular function (GFR) but also by tubular (secretion and reabsorption) and interstitial (erythropoietin synthesis, etc.) functions [2].

In this sense, the crucial role that tubular secretion has in the excretion of several "uremic toxins" which are not excreted by GFR is currently recognized [3, 4]. This is one of the main reasons why a significant residual diuresis matters in dialysis patients and justifies its preservation [5, 6]. Therefore, it makes sense that CKD staging should incorporate an additional variable for evaluating the patient's renal secretion capability.

For many decades, a high dose of cimetidine (1200–1600 mg/day) has been used for evaluating the GFR in an accurate, noninvasive and secure way. Since the creatinine excreted in the urine is a combination of the creatinine filtered by the glomerulus and secreted by the proximal tubule, and creatinine proximal tubule secretion can be blocked by high dose of cimetidine, then creatinine clearance aided with cimetidine (CAC) is equivalent to GFR, being the CAC/GFR ratio: 1.1 ± 0.02 [7]. Additionally, there is a classical principle in renal physiology which states that the ratio between creatinine clearance (CC) and CAC (CC/CAC) can be used for evaluating the magnitude of the tubular secretion activity since a CC/CAC > 1 means the existence of net creatinine secretion, while a CC/CAC $= 1$ means its deficit [2]. This CC/CAC ratio could be based on 24-h or spot urine samples, in order to simplify the procedure. Besides, the CC/CAC ratio could be useful for establishing different degrees of tubular secretion capability, such as (S1): CC/CAC $= 1$, (S2): CC/CAC > 1 but <1.5, (S3): CC/CAC ≥ 1.5 and <2, and (S4): CC/CAC ≥ 2 [2, 7, 8]. In addition, CC/CAC ratio constitutes an adequate means for exploring completely the tubular secretion capability since even though cimetidine is mainly secreted by cationic organic transporters, it is also secreted by anionic organic transporters [4]. Thus, it would be very interesting to include the degree of tubular secretion activity in the current CKD staging system, and this categorization could be performed as follows. For instance: if a CKD patient has a GFR: 25 ml/min/1.73 m^2, albuminuria: 500 mg/day, and CC/CAC: > 1.5 but <2, this patient could be classified as stage 4, A2, S3. Even, the documented patient's tubular secretion capability (e.g., S3) could be registered at the intersection place between his/her GFR and albuminuria–proteinuria level in the CKD stages chart (Table 1).

Perhaps, at the same level of proteinuria, a low GFR with a high tubular secretion (Stage 3b-S4) could have a better prognosis than a relatively high GFR without tubular

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Table 1 Proposed chronic kidney disease triple functional evaluation: glomerular filtration rate, albuminuria–proteinuria, and tubular secretion

Albuminuria (mg/day)	GFR (ml/min/1.73 m^2)	A1a <10	A1b 10–29	**A2** 30–299	A3a 300–1999	A3b ≥2000
Stages						
Stage 1	>105	S	S	S	S	S
	90–104	S	S	S	S	S
Stage 2	60–89	S	S	S	S	S
Stage 3a	45–59	S	S	S	S	S
Stage 3b	30–44	S	S	S	S	S
Stage 4	15–29	S	S	**S3**	S	S
Stage 5	<15	S	S	S	S	S

GFR, glomerular filtration rate; S, secretion capability or CC/CAC ratio; CC, creatinine clearance; CAC, creatinine clearance aided with cimetidine

S1: 1, S2: >1, S3: ≥1.5, S4: ≥2

Table 2 Potential advantages and disadvantages of including tubular secretion capability (based on cimetidine) in the chronic kidney disease (CKD) evaluation

Advantages	Disadvantages
More complete renal functional evaluation	More complex renal functional evaluation
Low cost medication (cimetidine)	CKD evaluation increased cost
Low adverse effects (cimetidine)	CKD evaluation more adverse effects
Pharmacological handling of tubular secretion	–
Tubular secretion equation could be obtained for simplifying the CKD staging	–

secretion (Stage 2-S1). This is an intriguing hypothesis which deserves at least to be explored.

Regarding the advantages of evaluating the renal secretion capability using the CC/CAC ratio, it could make the current CKD clinical evaluation more complete, and based on a low cost, easy to obtain (it requires just cimetidine premedication) and reliable marker which has very few adverse effect reported [8, 9]. Even more, a tubular secretion equation could be mathematically created in order to simplify this tubular functional evaluation. It should take into account that to explore the significance of evaluating the tubular secretion capability in CKD patients, it not only could confirm the suspicion of its potential prognosis value but also could give nephrologists the opportunity of learning how to handle it pharmacologically, with the consequent increase in the patient's uremic toxins urinary excretion capability (Table 2). However, the disadvantages of including this functional tubular marker in CKD staging should also be considered, such as an increase in the evaluation costs (extra analyses and cimetidine value), risks (cimetidine adverse effects), and complexity (Table 2).

As long as we know, there are no studies which have explored this new proposed CKD staging model, so it should be challenged by future clinical studies in order to evaluate its usefulness and reliability, but it might explain why CKD patients with similar level of GFR and albuminuria have a different clinical evolution of their nephropathy. Perhaps, this phenomenon could be explained by their different tubular capability for secreting uremic toxins. In this sense, it could perform a cohort study consisting on following up CKD patients of different gender, age and chronic nephropathy stage, including the periodic measurement of not only the GFR and albuminuria–proteinuria but also the CC/CAC ratio, in order to evaluate the patients' clinical evolution and their CKD progression measured as patient's overall mortally, and GFR worsening, respectively.

In conclusion, a new model for staging CKD is here proposed, which consist of including the tubular secretion evaluation using for this purpose the CC/CAC ratio. A prospective cohort study should be performed in order to explore the validity and utility of this proposal.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

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