

TOO MUCH NEPHROLOGY? THE CKD EPIDEMIC IS REAL AND CONCERNING. A CON VIEW

Pierre Delanaye

Department of Nephrology-Dialysis-Transplantation, University of Liège (ULg CHU), CHU Sart Tilman, Liège, Belgium
Correspondence and offprint requests to: Pierre Delanaye;

ABSTRACT

The prevalence of chronic kidney disease (CKD) clearly depends on its definition, and the definition used most often is the one proposed by the Kidney Disease: Improving Global Outcomes guidelines in 2012: 'CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.' Abnormality of kidney function is a glomerular filtration rate (GFR) <60mL/min/1.73 m², and the most frequently used marker of kidney damage is the presence of albuminuria [albumin excretion rate >30 mg/24 h or albumin/creatinine ratio (ACR) >30 mg/g (or 3 mg/mmol)]. However, two major aspects of this definition could explain why CKD prevalence is, in our view, overstated in most epidemiological studies. First, the fixed threshold at 60 mL/min/1.73 m² is questionable because normal GFR decreases with age. This and the profound consequence it has on CKD epidemiology will be illustrated. The second aspect of the definition is the criterion of chronicity, which is ignored by the vast majority of epidemiological studies. In other words, confirming CKD (low GFR and/or high ACR) is mandatory. Indeed, a large proportion of subjects with a low first GFR level has a normal GFR level when tested a second time. The prevalence of CKD may hence, in fact, be considerably lower although still neither negligible nor irrelevant.

KEYWORDS: chronic kidney disease, chronicity, epidemiology.

Introduction

Too much nephrology? Answering 'yes' to this provocative question with persuasive arguments and still being an enthusiastic nephrologist is quite challenging. Although the increase in disease prevalence cannot be viewed as 'good news' in itself, there is a high and natural temptation to consider relevant diseases as being frequent. The debate is not only scientific or philosophical, but also pragmatic. When discussing funding for research in nephrology with health authorities or other sources, the high(est) chronic kidney disease (CKD) prevalence might be of some assistance. However, we are (at least try to be) scientists and these considerations (even if important) are beyond the scope of this debate. At the heart of the debate of 'Too much nephrology?' is the definition of CKD [1]. The Kidney Disease: Improving Global Outcomes (KDIGO) definition is clearly the one that is used most often [1]: 'CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health.' Abnormality of kidney function is defined as a glomerular filtration rate (GFR) <60mL/min/1.73 m². Markers of kidney damage are multiple (e.g. urine sediment abnormalities or structural abnormalities), but what counts the most in epidemiology is the presence of albuminuria [albumin excretion rate > 30 mg/24 h or albumin/creatinine ratio (ACR) >30mg/g]. A staging system (Figure 1) is proposed. The word 'or' is important in the KDIGO definition as it means that every subject with a GFR <60mL/min/1.73 m² will be considered to have CKD even in the absence of albuminuria (Stage A1, ACR <30 mg/g). With this definition, the CKD prevalence is 10-14% [2-5].

Two aspects of the KDIGO definition will be discussed: one that is systematically used in epidemiological studies, but which we disagree with, and the other that we fully agree with

although it is never or very rarely considered.

CKD: the definition matters (first aspect, which we disagree with)

The first aspect is the unique threshold at 60mL/min/1.73 m² that we disagree with for defining CKD [1]. It must be acknowledged that this unique cut-off is useful as a common, unified and simple definition of CKD. Simplicity is, however, not sufficient by itself to justify a definition, and (over) simplification can be dangerous in medicine. Consequently, this threshold has been debated extensively in the literature. This point was illustrated recently by a PRO/CON debate in *NDT*, where Richard Glasscock highlighted the arguments for an age-calibrated definition of CKD [6], based either on well-known GFR percentiles (the most scientific way in our opinion) [7] or on different age-adapted thresholds (75mL/min/1.73 m² <40 years, 60 mL/min/1.73 m² between 40 and 65 years and 45mL/min/1.73 m² >65 years) [8]. We agree with Dr Glasscock on every point [8]. First, it is clear from the literature that normal GFR values decrease with age, and that, after 60-65 years, a large part (up to 25%) of healthy people have GFR values <60mL/min/1.73 m² [7, 9, 10].

Figure 1: KDIGO 'heat maps' illustrating CKD stages and association with risk.

Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009)				Albuminuria stages, description and range (mg/g)				
				A1		A2		A3
				Optimal and high-normal		High		Very high and nephrotic
				<10	10-29	30-299	300-1999	>2000
GFR stages, description and range (ml/min per 1.73 m ²)	G1	High and optimal	>105					
			90-104					
	G2	Mild	75-89					
			60-74					
	G3a	Mild-moderate	45-59					
	G3b	Moderate-severe	30-44					
	G4	Severe	15-29					
	G5	Kidney failure	<15					

Secondly, the KDIGO justifies the 60mL/min/ 1.73 m² by 'the prognosis argument'; that is, people with a GFR <60 mL/min/1.73 m² have a higher risk of mortality/morbidity [11]. This assertion is based quite exclusively on the metaanalyses from the Chronic Kidney Disease Epidemiology (CKD-EPI) consortium [1, 11]. However, using the same database and prognostic argument as the consortium, another analysis could actually argue for the age-calibrated CKD definition [8]. Also, the vast majority of original epidemiological studies with available prognostic data showed that a GFR <60 mL/min/1.73 m² was associated with a higher risk only in the youngest individuals, whereas the threshold should be decreased to 45mL/min/1.73 m² in the oldest ones [12, 13]. Among these studies, the prospective Renal Risk in Derby (RRID) study is of particular interest. The authors followed 1741 subjects (mean age 72.9 ± 9.0 years) with confirmed Stage 3 CKD [14]. Most of the subjects had little or no albuminuria [median ACR: 30

(interquartile range: 0-150) mg/g]. The risk of mortality, end-stage renal disease (ESRD) and renal disease progression (defined as a 25% decline in GFR, coupled with a worsening of the GFR category or an increase in the albuminuria category) was very low, especially when the baseline albuminuria was normal. Regarding mortality, only patients at Stage 3b or 4 had a significantly higher risk of mortality. All of these data suggest that Stage 3a/A1 (i.e. a GFR between 45 and 60 mL/min/1.73 m² and no albuminuria) is not associated with higher ESRD or mortality risk in subjects >65 years of age.

An important question is the epidemiological relevance of proposals for an age-calibrated definition. The answer is not easy, as most epidemiological studies only consider the KDIGO staging. The KDIGO used data from the National Health and Nutrition Examination Survey (NHANES) III (1999-2006) and showed an overall CKD prevalence of 11.7%. When only the GFR criterion is considered [i.e. without Stage A2 (ACR between 30 and 300 mg/g) or A3 (ACR > 300 mg/g)], the CKD prevalence was 4.8%, and the majority of these CKD patients (3.6% of the total CKD prevalence) were at Stage 3a [1]. It is very clear from the literature that CKD prevalence increases with age [2-5], and more importantly, that the stage for CKD diagnosis changes with age: in young patients, the majority have CKD because they exhibit albuminuria, whereas at 60 years of age, most patients are diagnosed with CKD 'only' because they have an estimated GFR (eGFR) <60 mL/min/ 1.73 m² [15]. Three cohorts could help to better illustrate the impact of the proposal of an age-calibrated definition. The first is from the Maladie Rénale Chronique au Maroc (MAREMAR), which included 10 524 adults, who represent a randomized (voters list) and representative sample of the adult population. The authors clearly showed that nearly 50% of the patients classified as Stage 3a/A1 had a GFR <60 but above the third percentile for GFR distribution according to age. All of these subjects were >55 years of age [16,17]. The second one is our cohort of non-representative people from the general population of Liege, Belgium [18]. People were tested for creatinine and albuminuria on a voluntary basis by a 'health bus' that covered the area around Liege. There were 4189 subjects >50 years of age who were tested, and the prevalence of Stage 3a was 9.8% with the KDIGO threshold. With a simple age-adapted threshold (i.e. GFR <60 mL/min/1.73 m² for subjects <65 years of age and GFR <45 mL/min/1.73 m² for subjects >65 years), the CKD prevalence decreased to 4.4% (P. Delanaye, unpublished data). Lastly, the data obtained by random selection of 3870 subjects >40 years of age in northeastern Italy (Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints, INCIPLE study) [19] indicated that the prevalence of KDIGO Stage 3a/A1 was 4.6%. With the same simple age-adapted threshold, the prevalence decreased to 1.5% (G. Gambaro, unpublished data). Age calibration, therefore, clearly has a major impact on CKD prevalence.

CKD: the definition matters (second aspect, which we agree with)

A second aspect of the CKD definition warrants being underscored: the chronicity criterion [20]. All abnormalities must be confirmed and 'present for >3 months' [1]. The vast majority of epidemiological studies do not abide by this criterion as they calculate the CKD prevalence based on only a single measurement of creatinine and/or ACR [2,21]. Why is this criterion important or 'epidemiologically' relevant? The main goal of the chronicity criterion is to exclude all patients suffering from acute kidney injury from the CKD definition. This point is quite indisputable. Another reason is the intra-individual variation of measurements, and more generally, the risk of false-positive results with current diagnostic tools [20].

This point is particularly well known for ACR. Indeed, the intra-individual ACR variation (i.e. the variation that can be observed physiologically in a given subject when measurements are repeated under the same conditions) is very high and dependent on the ACR level (i.e. the lower the ACR, the higher the variation). False-positive results for albuminuria are also very frequent, and even more so when albuminuria is tested on random urine samples and/or by dipsticks. It is well known and recommended that all albuminuria results by dipstick, ACR or even 24-h urine collection must be confirmed by a second and perhaps a third measurement (if there is a discrepancy with the first results) [22]. The same limitations also apply to serum creatinine, and even more so to eGFR, because the biological and physiological variation of serum creatinine (~4.5%) are amplified in equations for GFR estimation, as an exponent is applied to creatinine and thus also to its variation [23, 24]. Irrespective of the reason why confirmation is important, one must consider whether confirmation impacts CKD prevalence. Table 1 summarizes studies where GFR estimation was tested twice, and it shows the impact on epidemiology [25-31]. In addition to these studies, the MAREMAR study is also very informative. Among the subjects identified as CKD, 78.9% ($n = 285$) had been re-tested after 3 months. Among the subjects diagnosed as Stage 3a and 3b at baseline, 32 and 7.4%, respectively, had a GFR >60 mL/min/1.73 m² at the second testing [16]. Similarly, to be included in the RRID prospective study, subjects needed to have an eGFR between 30 and 59 mL/min/ 1.73 m² and confirmed by at least two previous results in the course of clinical care. When the GFR was re-tested at baseline by the central lab, it was >60 mL/min/1.73 m² for 29% of them [14].

Table 1. Studies illustrating the impact of confirmed CKD on the CKD epidemiology

References	Context	Results
[25]	USA NHANES III Random sample of 98 patients with Stage 3a with a second examination (with a median delay of only 2 weeks)	23% moved to a higher CKD stage
[26]	Tasmania Retrospective laboratory data 369 098 subjects, and 60.4% had a second test	GFR <60 ml/min/1.73 m ² : First test: ♂: 12.1% ♀: 15.6% Second test: ♂: 5.8% ♀: 8%
[27]	UK Retrospective laboratory data 332 891 subjects with at least two measurements, at least 3 months apart	5.41% of subjects with GFR <60 mL/min/1.73 m ² and prevalence increased to 6.4% if only the last GFR result is considered
[28]	Italy Random selection of the general population (>4000), among them, 214 with CKD (including albuminuria) had a second test 4-6 months apart	10% of the subjects with GFR <60 mL/min/1.73 m ² at first test were >60 mL/min/1.73 m ² at the second test
[29]	USA Data from Veteran Affairs 26 080 results with two serum creatinine determinations, 3-6 months apart	20% of the subjects with GFR <60 mL/min/1.73 m ² at first test were >60 mL/min/1.73 m ² at the second test
[30]	Norway One lab in the city on the Arctic circle, 38 241 measurements, and among them, 6863 with Stage 3a, and 5337 were re-tested >3 months apart	40.7% of the subjects with GFR <60 mL/min/1.73 m ² at first test were >60 mL/min/1.73 m ² at the second test
[31]	UK 3205 participants aged >60 years from primary care, of these, 485 with two serum creatinine determinations (most of the time due to suspected CKD), at least 90 days apart	25% of the subjects with GFR <60 mL/min/1.73 m ² at first test were >60 mL/min/1.73 m ² at the second test

Conclusions: are we bad guys?

Although the recent data from the Global Burden of Disease (GBD) study are impressive, they share the limitations just discussed above (i.e. no CKD confirmation, no age-calibrated CKD definition) [5]. GBD data on the increased prevalence of CKD are particularly interesting, especially in developing countries where the increase in CKD prevalence is clear and driven by hypertension and diabetes. Are we thus shooting ourselves in the foot? Are we engaging in a type of 'scientific masochism'? Are we ultimately nihilists, promoting the *status quo* when so much remains to be done in diabetes or hypertension? Of course not. First, the situation is different in high-income countries, where the observed increased prevalence of CKD is mainly driven by ageing of the population [5].

If the increased CKD prevalence is due to the increased mean age of the population in Western countries, then it is not nihilism to say that (i) the real increase in prevalence could be less with

an age-adapted threshold definition, (ii) the CKD prevalence based on KDIGO will continue to increase in coming decades (at least as long as mean life expectancy increases) and (iii) all potential preventive or therapeutic actions on these 'CKD' subjects would have a limited impact, as ageing remains a non-modifiable risk factor.

We are definitively not nihilists, when favouring a more reasonable CKD prevalence. First, even if these recommendations lead to a significant decrease in the prevalence (from ~10 to ~5%), the prevalence remains high, requiring collaboration of nephrologists with other specialists and general practitioners in particular. Secondly, far from a call for inaction, our opinion of a decreased prevalence should allow health professionals worldwide, and maybe even more so in developing countries, to focus on patients genuinely at risk: hypertensive and diabetic patients. Finally, answering to the question 'Too much nephrology?' is probably less important than the answer to the question, 'how can nephrologists provide better nephrology?'

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CONFLICT OF INTEREST STATEMENT

None declared.

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