

**INVITED PAPER**

**C-K-D: MORE VASCULAR DAMAGE THAN KIDNEY DISEASE**

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**Abstract:** The perceived prevalence of Chronic kidney disease (CKD) is on the increase worldwide. This has led to considerable debate and controversy as some believe such an increase reflects a genuine increase in the incidence and prevalence of CKD whilst others perceive it to be the result of the ageing of the population with the inherent decline in kidney function associated with advancing age. This review tries to reconcile both views drawing attention to the fact that the age-related decline in kidney function may not be physiological but instead a manifestation of diffuse vascular ageing and atherosclerosis affecting a number of endorgans including the kidneys. Consequently, the so-call age-related chronic kidney disease (CKD) may be better defined as Cardio-Kidney-Damage (C-K-D).

**Keys words:** Chronic kidney disease, CKD, CVD.

*ESRD the scale of the problem:*

There is little doubt that the number of patients suffering from endstage renal disease (ESRD) and treated by renal replacement therapy (RRT) is increasing worldwide. It is estimated that by 2010 in excess of 2 million patients will be treated [1]. It is also abundantly clear that the great majority of those treated by RRT live in the West and in highly developed economies capable of affording the high cost of treatment. In most Western countries ESRD (CKD stage 5) accounts for around 0.1–0.2% of the general population but seems to consume more than 1–2% of the annual healthcare budget [1, 2]. Consequently, emerging countries with low and middle economies cannot afford such therapy,

leaving patients who reach ESRD to die. The inequalities of healthcare provision in the field of ESRD are massive and most unlikely to be addressed in the foreseeable future. This has triggered renewed interest in disease prevention to alleviate this global healthcare tragedy.

*CKD the scale of the problem:*

In order to effectively prevent the rising tide of ESRD, it has been reasoned that early detection and/or prevention of CKD would be effective. With that in mind, more effective ways of detection of CKD have been sought including the development of formulae that calculate glomerular filtration rate (GFR) with a serum creatinine value [3]. It is well known that serum creatinine can be within the normal range, whilst GFR is significantly reduced. A calculation of GFR would allow the early detection of CKD. This has also led to a classification of CKD based on GFR level [4] (Table 1).

Table 1 – Табела 1

*CKD KDOQI Classification*  
*CKD KDOQI класификација*

Stage	Description	GFR (ml/min/1.73 m <sup>2</sup> )
1	Kidney damage* with normal or increased GFR	≥ 90
2	Kidney damage* with mild decreased GFR	60–89
3	Moderate decreased GFR	30–59
4	Severe decreased GFR	15–29
5	Kidney failure	< 15 (or dialysis)

\* = Kidney damage as defined by the presence of albuminuria or haematuria.

The introduction of the GFR calculation formulae, the definition of CKD and its classification have raised considerable awareness of CKD and highlighted the fact that a considerable number of individuals within the general population may suffer from CKD; on average, in most detection studies, around 5–7% of the general population had CKD stage 1 and 2 based on the presence of microalbuminuria and around 3–4% had CKD stage 3 based on an estimated GFR of less than 60ml/min/1.73m<sup>2</sup> (5–14) (Table 2). This led to the alarming recognition that up to 10–16% of the general population may suffer from CKD.

Table 2 – Табела 2

*Representative Population-based Studies on CKD Epidemiology*  
*Репрезентативни студији за епидемиологија на ХББ врз основа*  
*на иследување на популацијата*

Study	Country	Design	N	Outcome (%)
NHANESIII (5)	USA	CS/L	15,626	CKD = 11.0, MA = 12.0
PREVEND (6)	Netherlands	CS/L	~ 40,000	MA = 7.0
NEOERICA (7)	UK	CS/Service-based	130,226	CKD = 10.6 (F); 5.8 (M)
HUNT II (8)	Norway	CS	65,181	CKD = 10.2 MA = 5.9
EPIC-NORFOLK (9)	UK	CS	23,964	MA = 11.8
MONICA/ (10) AUSBURG	Germany	CS	2,136	MA = 8.0
AUSDIAB (11)	Australia	CS	11,247	CKD = 9.7 MA = 6.0
Zhunan (12)	Taiwan	CS/L	462,293	CKD = 11.9
Beijing (13)	China	CS	13, 925	CKD = 13.0
Takahata (14)	Japan	CS	2,321	MA = 13.7

*(Outcome = Subjects with CKD or Microalbuminuria)*

**Abbreviations:** AUSDIAB = Australian Diabetes, Obesity and Lifestyle study, CKD = Chronic Kidney Disease, CS = Cross-sectional, GP = General population, F = Female, L = Longitudinal, MA = Microalbuminuria, M = male, N = Number of participants, NHANES = National Health and Nutrition Evaluation Survey, N = Number, NEOERICA = New Opportunities for Early Renal Intervention by Computerised Assessment, PREVEND = Prevention of Endstage Renal and Vascular Disease.

#### *CKD Detection: Limitations*

The fact that around 10% of the general population may be affected by CKD raises a number of questions and concerns.

1. Are the CKD detection methods accurate?
2. What is the impact of this high CKD prevalence?
3. Can CKD or its complications be prevented?
4. Can ESRD be prevented?

### 1. *Are the CKD detection methods accurate?*

As mentioned above, most studies relied on the detection of microalbuminuria to classify individuals into CKD stages 1 and 2. Unfortunately, this generates a number of false positive results and inflates the prevalence of CKD. First and foremost, most detection programmes tested urine once and therefore cannot ascertain chronicity. Secondly, microalbuminuria is often transient and secondary to a range of inflammatory and microvascular disease, from dermatitis, hepatitis, gingivitis to colitis and malignancies [15–22]! It is therefore a reflection of systemic inflammation and/or microvascular pathology rather than CKD specifically. This is also the case of its association with obesity and smoking [23, 24]. Thirdly, microalbuminuria is often associated with acute febrile conditions and readily reversible. Therefore to define CKD on the basis of microalbuminuria alone is a mistake.

The other variable used to define CKD 3, 4 and 5 is the calculated GFR. This most commonly relies on the MDRD formula that takes serum creatinine into consideration [3].

$$\text{eGFR(ml/min/1.73 m}^2\text{)} = 175 \times \left\{ \left[ \frac{\text{sCr}}{88.4} \right]^{-1.154} \right\} \times \text{age (years)}^{-0.203} \times 0.742 \text{ if F} \times 1.21 \text{ if B}$$

F = Female, B = Black individuals

This formula has been validated in the MDRD trial of dietary protein restriction in patients with CKD stages 3 and 4 [3]. It was not meant to be used to detect CKD in the general population where the GFR is expected to be > 60 ml/min. Consequently, it was found to be underestimated by up to 25–30% GFR in those individuals with GFR > 60. Furthermore, in that range of GFR the accuracy of the MDRD formula when compared to measured GFR is limited, decreasing as the GFR increase to become totally inaccurate above a GFR of 90 ml/min [25].

The fact that the MDRD formula underestimates the true GFR in those with GFRs between 50 and 60 ml/min would generate a large number of individuals with CKD3 solely on the basis of a defective calculation (26). This would also inflate the number of people with CKD.

Therefore, the current gestimate of a CKD prevalence of around 10% is likely to be well above the true prevalence of CKD. A figure of 3–5% may be more accurate.

### 2. *What is the impact of this high CKD prevalence?*

The presumed high CKD prevalence is mostly noticeable in the elderly. Most detection studies identify individuals over the age of 60 as suffering from

either microalbuminuria (CKD 1 and 2) or GFR < 60ml/min (CKD 3 or 4). This raises a number of questions and concerns. Firstly, it is important to remember that microalbuminuria increases with age to affect up to 30% of those over the age of 70 [9, 10]. Also, GFR falls with age and therefore the majority of the elderly have reduced GFR, thus labelling them as suffering from a chronic disease: CKD. Some have called this labelling the medicalisation of normality as they argued it is normal for GFR to fall with age and it is not a chronic disease?! This has been challenged by those who argue that not all elderly individuals have a progressive decline in GFR.

The true impact of CKD is not so much its progression to ESRD, as only a minority reaches ESRD, but the high cardiovascular disease (CVD) morbidity and mortality associated with CKD [27]. The impact of CKD on CVD outcomes is noticeable regardless of individuals' age and still detectable in the elderly [28]. This seems to be the major concern regarding a high prevalence of CKD in the community exacerbating the already high CVD death rate.

Of note, microalbuminuria is also associated with a poor CVD prognosis and increased related mortality [6, 9]. This may reflect the fact that microalbuminuria is a marker of diffuse vascular pathology and transcapillary leakage of albumin. This is reflected in the glomerular capillaries by albuminuria. In other words, the urine may be the mirror through which we identify those who have diffuse vascular pathology, such as age-related atherosclerosis, and whose capillaries are permeable to albumin.

### *3. Can CKD or its complications be prevented?*

Over the last decade, interest in disease prevention and detection has increased and taken centre-stage in a number of healthcare policies. However, the rationale of such disease prevention strategies has been challenged by those who argue that the risk- and cost-benefit of such approaches are far from proven [29]. This also applies to the early detection of CKD1 and 2; there is no evidence that these are progressive renal disorders nor that the cost and effort of their detection is warranted. Clearly, further research is needed to define the natural history of early CKD and those with isolated microalbuminuria.

### *4. Can ESRD be prevented?*

Advances made over the last 25 years in the management of progressive CKD, predominantly stages 3 and 4, have shown that with good blood pressure control, the reduction of proteinuria and the use of inhibitors of the renin-angiotensin-aldosterone system (RAAS), the rate of decline of established CKD can be slowed [30]. Guidelines have recommended target blood pressure levels

< 130/80mmHg, and even lower in those suffering from diabetic or proteinuric nephropathies [4, 31–34]. They have also recommended a reduction in proteinuria through blood pressure control and the use of RAAS inhibitors (Tables 3 and 4).

Table 3 – Табела 3

*Target Blood Pressure Control Recommendations*  
*Прејораки за контрола на целниот крвен притисок*

<b>Society</b>	<b>Recommendations</b>
<b>JNCVII [31].</b>	Treating SBP and DBP to targets < 140/90 mmHg to decrease CVD and renal morbidity and mortality in general population. In patients with Diabetes and Hypertension or CKD: Target BP < 130/80 mmHg.
<b>EBPG [32].</b>	General population: Target BP < 140/90 mmHg General Population & high CVD risk: Target BP < 130/80 mmHg
<b>BHS [33].</b>	Threshold for intervention BP $\geq$ 140/90 mmHg in high CVD risk individuals including CKD CKD: Target BP < 130/80 mmHg CKD + Proteinuria > 1g/24h: Target BP < 125/75 mmHg
<b>K/DOQI [4].</b>	CKD: target BP <130/80 mmHg. CKD with heavy proteinuria as well as diabetic CKD: lower target
<b>NICE [34].</b>	CKD: Target SBP < 140 mmHg (range 139–120); DBP < 90 mmHg. CKD & Diabetes or with Proteinuria > 1g/24h: Target systolic < 130 mmHg (range 129–120) and diastolic < 80 mmHg.

**Abbreviations:** JNCVII = The Seventh report of the Joint National Committee for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNCVII), BHS = British Hypertension Society, EBPG: European Best Practice Guidelines for the management of hypertension, K/DOQI = Kidney/Disease Outcomes Quality Initiative, NICE = UK National Institute of Health and Clinical Excellence

Table 4 – Табела 4

*Guidelines for Management of Hypertension and Proteinuria in CKD*  
 Упатствија за менаџирање на хипертензија и протеинурија кај ХББ

<i>Organisation</i>	<i>Recommendations</i>
<i>K/DOQI Guidelines(2004) [4]</i>	<ul style="list-style-type: none"> <li>• <b>Diabetic CKD:</b> ACEI/ARB preferentially Other agents to reduce CVD risk and reach BP target: Diuretic preferred, then BB or CCB.</li> <li>• <b>Non Diabetic CKD with urine Protein-to-Creatinine ratio (PCR) &gt; 200 mg/g:</b> same as diabetic CKD</li> <li>• <b>Non diabetic CKD with urine PCR &lt; 200 mg/g:</b> None preferred Other agents to reduce CVD risk and reach BP target: Diuretic preferred, then ACEI, ARB, BB or CCB.</li> <li>• <b>CKD in the transplant recipient:</b> None preferred Other agents to reduce CVD risk and reach BP target: CCB, Diuretic, BB, ACEI, ARB</li> </ul>
<i>NICE CKD guideline (2008) [34].</i>	<ul style="list-style-type: none"> <li>• <b>Diabetic CKD:</b> Preferentially started with ACEI/ARB.</li> <li>• <b>CKD + Hypertension + Proteinuria &gt; 0.5g/24h or ACR &gt; 30 mg/mmol):</b> Preferentially started on an ACEI/ARB.</li> <li>• <b>CKD + Proteinuria (&gt; 1g/24h) without hypertension:</b> Preferentially started on an ACEI/ARB [2].</li> </ul>

**Abbreviations:** NICE = National Institute of Health and Clinical Excellence (UK), K/DOQI = Kidney/Disease Outcomes Quality Initiative

#### *A unifying C-K-D Hypothesis*

As discussed above, CKD in the community appears to be a disease of the elderly; it is characterised by a high prevalence of microalbuminuria and reduced GFR in this age group. It is also associated with raised CVD morbidity and mortality. The unifying concept and explanation is that these elderly individuals suffer from progressive age-related atherosclerosis causing progressive and systemic damage to their vasculature and manifested as microalbuminuria and as progressive renal ischaemia and reduced kidney function. This is supported by clinical, functional and histological evidence; the elderly with progressive CKD are those with atherosclerosis detectable by increased carotid intima-media thickness, those with increased arterial stiffness as judged by raised vascular pulse wave velocity and those with histological evidence of renal

arterial and arteriolar sclerososis as well as glomerulosclerosis. Therefore, in this age group CKD should stand for diffuse Cardio-Kidney-Damage. All efforts should be made to identify those at risk and prevention. Those at risk of C-K-D are those elderly individuals who have had a lifecourse of exposure to systemic hypertension, diabetes, dyslipidemia and smoking; they develop C-K-D with age. Prevention, detection and control of these risk factors is the only viable healthcare strategy to reduce the global burden of C-K-D and its associated increased death rate (~ 25 million/year worldwide) [35]. The World Health Organisation (WHO) has made the reduction of the death rate associated with chronic non-communicable disease (NCD) one of its 21<sup>st</sup> century top priorities [35]. This should have a considerable beneficial impact on the reduction of the global burden of C-K-D.

So to conclude, it is most likely that CKD as chronic kidney disease may be overrepresented and overdiagnosed within our communities. However, C-K-D as Cardio-Kidney-Damage is likely to be a true global consequence of the ageing of populations and the consequent lifelong cardiovascular damage affecting the renal vasculature of those exposed to known risk factors such as hypertension, diabetes, dyslipidemia and smoking. The prevention of these factors should be a healthcare priority in all communities.

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## Резиме

**ХББ: ПОВЕЌЕ ВАСКУЛАРНО ОШТЕТУВАЊЕ  
ОТКОЛКУ БУБРЕЖНА БОЛЕСТ****El Nahas M., Bello AK.***Sheffield Kidney Institute  
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Забележано е дека преваленцата на хроничните бубрежни болести (ХББ) е во пораст ширум светот. Тоа доведе до значителна дебата и противречности бидејќи едни сметаат дека ваквото зголемување го рефлектира вистинскиот пораст во инцидентноста и преваленцата на ХББ, додека другите прифаќаат дека тоа е резултат на стареењето на популацијата со вродено намалување на бубрежната функција, поврзано со напредното стареење. Овој ревиски труд се обидува да ги усогласи двата погледа обрнувајќи внимание на фактот дека намалувањето на бубрежната функција во однос на возраста не мора да биде физиолошко, но наместо тоа, манифестацијата на дифузни васкуларни промени од стареење и атеросклероза, влијаат на голем број внатрешни органи, вклучувајќи ги и бубрезите. Последователно, т.н. ХББ поврзана со возраста може да биде подобро дефинирана како кардио-бубрежно оштетување (КБО).

**Клучни зборови:** хронична бубрежна болест – ХББ (CKD), КВБ (CVD).

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