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Chronic Kidney Disease (CKD) prevention or The urgency of a national policy of screening and early treatment

A prevenção da Doença Renal Crónica (DRC) ou A urgência de uma política nacional para o diagnóstico e tratamento precoces

Helena Oliveira Sá

Nephrology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
President of The National Commission for Monitoring Dialysis (Comissão Nacional de Acompanhamento de Diálise)

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Chronic kidney disease (CKD) is one of the chronic diseases of modern societies, such as cardiovascular, oncologic, respiratory and diabetic diseases that can be treated, though not always be cured. It is estimated that over 80% of deaths, in Europe, are caused by these chronic diseases, for which the best investment is prevention. Furthermore, in Portugal, strategies to promote health and prevent disease would be rational, at a time when severe austerity measures are decreed by the government. Health spending in Europe is estimated as being concentrated in treatment at approximately 97% and only 3% in prevention[1].

Key issues associated with CKD are: the high risk of developing cardiovascular events at almost all stages of the disease and the lower risk of progressing towards end stage renal disease (ESRD), with the subsequent need of dialysis or kidney transplantation[2,3]. Portugal has been characterized by the highest incidence and prevalence of ESRD treated by dialysis or kidney transplantation in the European Union (EU) (235.9 and 1575.9 per million population (pmp) in 2010 and 226.49 and 1661.9 pmp in 2011)[4]. Important reasons that may explain these figures are good survival rates, increased life expectancy and growing prevalence of diabetes in the Portuguese population. From a population younger than the EU27 average in the 1980s, Portugal has currently one of the older population structures in Europe and worldwide. These profound changes in our age profile took place primarily during the last decades[5]. Moreover, in 2011, Portugal had the highest prevalence estimates of diabetes, among OECD countries, in adults aged 20-79 years: 9.7%[6]. The only national study about prevalence of CKD in stage 5 and earlier (stages 3 and 4), published by Vinhas *et al.*, in 2011 with data collected in 2008, revealed a rate of CKD of 6.1% from a national representative sample, similar to what is observed in other Western countries[7]. The rate of ESRD patients (stage 5 D or T) for the same year of this study was significantly lower (0.14%), as expected, though higher than the average of EU countries[4,7].

End stage renal disease, as emphasized by Straube, despite its prevalence and high costs, is not generally recognized as having high importance by legislators, health care policymakers and the general public[8]. Fortunately, the number of patients with CKD that progress to ESRD is a minority[9]. Indeed, the

risk of cardiovascular events in patients with CKD and the risk of developing acute kidney injury (AKI) over CKD, as well as the increased mortality associated with this severe condition, challenge us to improve the earlier diagnosis and treatment of CKD and of its main complications. As occurs with "epidemic" chronic diseases, CKD is also highly influenced by unhealthy lifestyles (unbalanced diet, lack of physical activity, etc.) leading to a higher incidence of obesity, diabetes and hypertension. Thus, a requisite to decrease CKD incidence is to control those important risk factors. In Portugal, as in other countries, if we aim to decrease ESRD incidence, prevalence and high mortality associated with this condition, we have to focus on the control of CKD risk factors, which depends primarily on general public education and population behaviour *(primary prevention)*. This strategy might benefit from the initiative of other health organizations, such as those focusing on diabetes, hypertension and obesity control. The purpose of all these initiatives is the same: decreasing the risk of developing threatening chronic diseases by promoting healthy lifestyles.

The strategies for earlier diagnosis and treatment of CKD *(secondary and tertiary prevention)* are a great challenge for health systems, as opposed to giving the general population the responsibility for primary prevention. In Portugal, we have an efficient and high quality treatment of CKD at the tertiary level, since the patient suffering from severe CKD (stages 4 and 5) is referred to a Hospital or a Nephrology Department. The results of treatment of ESRD in Portugal in recent years, reassure us of the high level of health care on this subject, both with dialysis and kidney transplantation[10,11]. However, as regards secondary and tertiary prevention at early stages of CKD (1, 2 and 3), we must recognize the lack of a national health policy to help contain the outburst of this severe chronic disease. Nevertheless, it is known that early identification and management of CKD is highly cost-effective and can reduce the risk of kidney failure and cardiovascular disease by up to 50%[12]. The KDIGO's statement that all countries should have a screening programme for CKD must also apply to Portugal[13]. We have to discuss what kind of CKD screening programme best suits our population and our health care resources. Detection of CKD should not be limited to occasional cross-sectional screening studies; instead, it should be carried out continuously. The question of whom to select for CKD screening is a pertinent issue, as it has been proven that universal screening of unselected populations with no risk of CKD has not been shown to be cost-effective[20]. The problem of the earlier CKD diagnosis is also related to two other important analyses: firstly, the accurate definition of CKD, secondly the necessary involvement of primary care physicians. Only with a partnership between primary and secondary care, can this challenge be won. The main role in detecting and treating CKD ought to belong to primary care physicians[14]. Evidence-based guidelines demonstrate that the following have been effective in slowing the progression of CKD: early recognition of CKD; better treatment of hypertension, diabetes, hyperlipidemia, anaemia and abnormal bone mineral metabolism; discontinuation of NSAIDs; use of aspirin and ACE inhibitors or ARBs. In early stages of CKD, these recommendations should be followed by general practitioners in primary care centres. Regretfully there is considerable lack of awareness of the guidelines in primary care practices[15].

ACCURACY IN DEFINING CKD

Before 2002, the definition of CKD was not consensual and most physicians related to the main primary diagnosis or aetiology. In 2004, the Kidney Disease Improving Global Outcomes (KDIGO) adopted the five-stage classification system of CKD established by the US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K-DOQI)[16]. This new classification quickly entered the general consensus, mainly based in two renal markers: estimated GFR and presence of albuminuria/proteinuria. The first two stages (1 and 2) of the CKD classification, as defined by K-DOQI, might, indeed, be controversial: stage 1, which is characterized by isolated albuminuria, is typical of kidney involvement on endothelial systemic dysfunction, not a specific kidney **disease**. Stage 2 CKD, characterized by a decrease of eGFR between 60-89 ml/m/1.73m^2, dismisses the normal ageing decay of GFR (approximately 6-8ml/m/1.73m^2 per decade, or 1.0ml/m/1.73m^2 per year), thus considering some aged healthy people, chronic kidney patients (mostly elderly and female subjects with low eGFR who will be falsely identified as patients with kidney disease)[14,17]. As Glassock and Winearls proposed, the use of estimated GFR alone for classifying CKD is not justified and should not be applied globally to define CKD, particularly when the eGFR is

›60ml/m/1.73m². As said by the same authors "GFR can be estimated but diagnosis cannot and proper treatment requires precision in diagnosis"[18].

Talking about CKD secondary prevention strategies we should think if the diagnosis of earlier stages of CKD is cost-effective and worth the investment, particularly in what concerns high level of health care. It may happen that the new definition might contribute to the misclassification of a lot of patients as having *Chronic Kidney Disease* in the absence of clinically relevant kidney disease[19]. We may attempt to avoid the overdiagnosis risk that simply occurs when a screening test is ordered, or a pseudodiagnosis is established, that will not change clinical management and prognosis[20]. Indeed, subjects in the first stages of CKD, if simply referred to the nephrologist due to an isolated microalbuminuria or to a slight decrease of eGFR (higher than 60 ml/m/1.73m²), have an irrelevant risk of progressing to ESRD or, ultimately, of experiencing symptoms or early death due to kidney disease. Microalbuminuria has been associated with an increased risk of cardiovascular events, and this risk is independent of that induced by an impaired GFR. Therefore, microalbuminuria needs to be managed the same way as a cardiovascular risk factor or as a chronic vascular disease factor with renal involvement[19,21]. Still, measures of GFR were independently and significantly associated with cardiovascular events only in subjects ‹ 60 years of age. This supports the idea that the elderly and the very old, deserve careful analysis before they are considered as having chronic kidney disease based on GFR values alone, especially when estimated with methods with limited accuracy.

Numerous studies have shown that those who have an increased risk of ESRD, as well as of cardiovascular disease and mortality, are the individuals with detected proteinuria **and** impaired eGFR (even at high levels, such as ›60 ml/m/1.73m²), comparatively to patients in stage 3 with reduced eGFR but, **without** proteinuria. As pointed out by Winearls and Glassock: is there reliable a classification system in which a patient in stage 2 could progress worse than a patient in stage 3? Is there reliable a classification system in which CKD stages 3-4 are found to be more common in women, but stage 5 CKD is much more common in men?[22]

We need clinical judgment and critical analysis of the 2002 NKF classification of CKD, particularly when we are trying to select whom to submit to chronic kidney disease screening, or whom to treat early to avoid progression of CKD[16] After an important discussion of these matters Bauer *et al*[23] proposed a revised staging system for CKD that enables accurate, effective and timely communication with patients, primary care doctors and nephrologists. The main goal of the proposal is to identify those patients who will benefit from targeted screening and from effective and safe interventions. This new CKD staging system proposes that stages 1 and 2 be eliminated and stages 3, 4 and 5 be simply named moderate impairment, severe impairment and kidney failure, respectively. In addition, the authors proposed that age should be a modifying factor, especially in moderate kidney impairment. I might dare suggesting to combine this new proposal with the recommendations of UK Consensus Conference on Early Chronic Kidney Disease–6 and 7 February 2007 proposing sub-classifying CKD stage 3 (now stage 1) into two groups: 3A (1A) and 3B (1B), where 3A (1A) defines a lower risk group with eGFR of 45–59 ml/m/1.73m² and 3B (1b) defines a higher risk group with eGFR of 30–44 ml/m/1.73m², and a further stratification by applying the suffix *p* if proteinuria is present, to all stages (exception of kidney failure), to reflect the risk of progressive kidney disease in patients who have proteinuria (Table 1)[24]. This

Table 1

CKD stratification proposal (for a national CKD screening policy, combining values of eGFR ‹60 ml/m/1.73m² and proteinuria)

Category	Description	eGFR (ml/m/1.73 m²)	Proteinuria (› 300 mg/day)
1	1A – moderate impairment in lower risk group	45-59	p
	1B – moderate impairment in higher risk group	30-44	p
2	severe impairment	15-29	p
3	kidney failure	‹15	–

proposal shares some common points with the nomenclature and classification used by KDIGO on the last published guidelines for the evaluation and management of CKD[25]. On these recent outstanding guidelines, authors recommend that CKD prognosis should be classified in risk stratification (low, moderate, high and very high) for outcomes, based on eGFR and albuminuria categories[25]

As stated before, in Portugal we need a screening programme for CKD to control the "epidemic" of the disease. This is not an easy task, as it depends on the critical review of current concepts and risk stratification. We have to decide who will benefit from this work (targeted screening), how tests and clinical evaluation should be done at primary care and, finally, whom to treat in partnership with tertiary centres. In the meantime, to accomplish our main goal, decreasing the burden of ESRD in this country and its high related mortality rate, we must avoid CKD overdiagnosis or pseudodiagnosis. Since contemporary societies go to a lot of trouble to find the resources to treat true chronic diseases, they certainly do not need to invest in treating mild equivocal problems which neglect the survey and the early treatment of those who actually are sick.

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Correspondence to:
Prof. Helena Oliveira Sá
Nephrology Department,
Centro Hospitalar e Universitário de Coimbra
Praceta Prof. Mota Pinto
3000-075, Coimbra
Portugal
E- mail: helena.oliveirasa@sapo.pt