Chronic kidney disease prevalence in the general population: heterogeneity and concerns

Luca De Nicola¹ and Carmine Zoccali²

¹Nephrology, School of Medicine, Second University of Naples, Caserta, Italy and ²CNR-IFC, Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension, Ospedali Riuniti, Reggio Calabria, Italy

Correspondence and offprint requests to: Luca De Nicola; E-mail: luca.denicola@unina2.it

Chronic kidney disease (CKD) is now recognized as a public health priority worldwide [1, 2]. According to the 2010 Global Burden of Disease study [2] that ranked the causes of death worldwide in 1990 and 2010, CKD climbed the list from 27th to 18th position over two decades. The surge of the CKD epidemic over these decades produced an 82% increase in years of life lost related to CKD, a disease toll of the same magnitude of that attributable to diabetes. Premature mortality is only part of the problem because some CKD survivors progress to end-stage renal disease, a condition entailing disability, poor quality of life and substantial social and financial costs. Although varying considerably across countries, the annual

Received for publication: 12.10.2015; Accepted in revised form: 12.10.2015
The public health relevance of the early CKD stages cannot be overemphasized [6, 7]. To optimize preventive strategies and care of CKD, it is indeed essential not only to understand the incidence and prevalence of this disease in global terms but also to gain separate estimates of the early proteinuric stages of disease (CKD stages G1–2) and moderate stages (CKD G3a and b), that are potentially reversible by therapy. Furthermore, precise estimates of the more advanced stages (Stages G4–5) are fundamental for timely health care and RRT planning.

Health examination surveys represent a valuable source of data on the burden of non-communicable diseases. Well-designed analyses in randomized samples of the general population provide an unbiased estimate of the diseases being considered and may form a valid basis for monitoring the health status of the population over time. The periodic National Health and Nutrition Examination Surveys (NHANES) provide detailed information on health status in the USA over the last 50 years, and health status assessments are being performed in the most economically developed countries. These surveillance programmes represent affordable and fruitful opportunities for gathering information on CKD in surveys gathering extensive records on risk factor exposure and concomitant diseases.

Surveys including information on CKD date back to the late 1990s, i.e. prior to implementation of creatinine-based GFR equations. In 2002–03, the third NHANES and the Australian Diabetes, Obesity and Lifestyle (AusDiab) study showed a remarkably high prevalence of CKD in the USA and Australia, 16 and 14%, respectively [8, 9]. Even though the GFR was estimated by imprecise formulas in these population surveys, they also adopted proteinuria as an indicator of kidney damage to identify the early CKD stages. These studies have been a formidable instrument to raise awareness of the problem worldwide, and have initiated an unrelenting effort by the nephrology community to develop the proper appreciation in patients, professionals and health authorities alike for the serious health implications of the ‘CKD epidemic’. Subsequent surveys in European countries, China and Canada have shown prevalence rates of ~7% when limited to Stages G3 and 4, and above 10% for all stages [4, 10–18]. Reassessment of the prevalence in Australia and the USA by the MDRD formula based on calibrated creatinine and the CKD-EPI formula confirmed the high prevalence of CKD in these countries (11.5 and 13.1%, respectively) [19, 20]. The most recent NHANES (2005–10) shows that 14% of all US residents have kidney damage (albuminuria) and/or dysfunction (GFR <60 mL/min/1.73 m² by the CKD-EPI equation) [21].

In this issue of the NDT, Zdrowejski et al. present the results of the 2011 NATPOL survey [22] assessing the prevalence of albuminuria and renal dysfunction (GFR estimated by the CKD-EPI and MDRD equations) in a representative sample of the adult Polish population. This survey documents that the prevalence of CKD in this country (5.8% by CKD-EPI and 6.2% by MDRD) is the lowest registered in economically developed countries. In Table 1, we summarize the main CKD surveys in the last two decades [12–26]. To facilitate reading, countries are arbitrarily divided into three categories (low, intermediate and high CKD prevalence). Prevalence is very heterogeneous and ranges from 5.8% in Poland to more than twice that rate, 13.1%, in the USA. When comparing countries at low and high CKD prevalence, the difference is even more pronounced for advanced stages (GFR <60 mL/min/1.73 m²) with a quadrupling in the prevalence of Stages G3–4 in the USA (8.1%) when compared with Poland (1.9%). CKD is associated with age, obesity, hypertension, diabetes and background cardiovascular (CV) disease according to a survey in a random sample of the Italian population [24]. On the other hand, a marked difference in CKD prevalence was noted in a survey comparing a random population sample of a region in northeastern Italy (CKD stages G1–5: 12.3%) with a well-matched sample extracted from the NHANES database (CKD stages G1–5: 20.7%), and this difference was attributed to the higher frequency of diabetes, obesity and metabolic syndrome in the USA [27].

Variability in the estimates of the prevalence of CKD may depend on various factors including representativeness of the population sample (e.g. data collected in single town or a specific area of a given country), demographic characteristics of the population including ethnicity, participation rate, differences in the cut-off values to classify albuminuria or proteinuria, as well as the type of equation used to estimate GFR and income [28]. In Europe, important inter-country variability in CKD prevalence was also registered in studies based on calibrated creatinine and adopting the CKD-EPI consortium equation [5]. Aging per se is associated with GFR decline and increased prevalence of hypertension and diabetes, i.e. two powerful determinants of CKD [1]. However, in Table 1, the four countries with lower CKD prevalence are characterized by a wide age range, and considering Italy and India as the countries with the oldest and the youngest populations, respectively, a remarkably similar CKD prevalence was displayed (7.1 and 7.5%, respectively). In the two surveys in Western countries based on random population samples and with a quite large participation rate, NHANES in the USA [19] and the CARDiovascular risk profile in Renal...
patients of the Italian Health Examination Survey (CARHES) in Italy [24], the mean age was ~10 years higher in the Italian survey whereas CKD prevalence in the USA was almost double that registered in the Italian survey. Thus, the NATPOL survey [22], where the average age (51 years) was also higher than that in the NHANES survey (46 years), extends to a North European country the previously noted discrepancy in CKD prevalence between a Southern European country, such as Italy, and the USA [24, 27]. In this issue of NDT, we also publish another study by Okparavero et al. [29] enhancing information on CKD in the elderly in the European scenario. This study is a survey in a well-characterized sample of 3173 people older than 67 years from the AGES-Reykjavik cohort where the GFR was estimated by the creatinine–cystatin C equation. State-of-the-art eGFR measurements in elderly Icelanders, one of the populations showing the highest prevalence of CKD in elderly females in the EUGLOREH report [4], as much as 10 elderly individuals out of 25 have a reduced GFR (<60 mL/min/1.73 m²) and 10 out of 22 have a reduced GFR or albuminuria. Of note, in this survey, the prevalence of hyperparathyroidism, anaemia, hypoalbuminaemia and acidosis, all typical complications of CKD, is substantially higher among subjects with CKD when compared with those without, supporting the view that CKD in the elderly should not be seen as an innocent alteration [30]. Going back to the age-dependent atherogenic risk factors in Table 1, it has to be noted that the four countries with lower CKD prevalence (6.8% overall) [22–25] had a higher (rather than lower) prevalence of hypertension and diabetes (on average +34 and +75%, respectively) than the four countries showing higher CKD prevalence (12.2% overall) [16, 18–20]. The magnitude of this discrepancy clearly indicates that still undefined risk factors may modify the risk for CKD portended by diabetes and hypertension.

The seven country study in the general population showed that, at similar levels of serum cholesterol and blood pressure, mortality for coronary heart disease is more than 3-fold higher in American men than in southern European men [31, 32]. These observations go hand in hand with the comment we made regarding the Table 1 data, i.e. that hypertension and diabetes per se largely fail to explain the lower prevalence of CKD in Italy when compared with the USA. Genetic factors [33] and environmental risk factors such as herbs, aristolochic acid, HIV and water scarcity, which are relevant in some areas of the world [1], and dietary habits at the country level deserve attention to explain the local prevalence of CKD. Emerging evidence suggests that the Mediterranean-style diet may be beneficial not only for the prevention of CV disease [34] but also for the prevention of CKD [35, 36], the two effects being possibly attributable to the amelioration of endothelial dysfunction and inflammation [37]. Recently, a large population-based study

### Table 1. Worldwide CKD prevalence, overall and by stage, in the general adult population

<table>
<thead>
<tr>
<th>Country [Ref], [city or area]</th>
<th>Period (year)</th>
<th>N</th>
<th>PR (%)</th>
<th>Mean age (years)</th>
<th>Obesity (%)</th>
<th>DM (%)</th>
<th>HTN (%)</th>
<th>eGFR equation</th>
<th>CKD (%)</th>
<th>CKD by stage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poland [22]</td>
<td>2011</td>
<td>2413</td>
<td>67</td>
<td>51</td>
<td>NR</td>
<td>6.7</td>
<td>31.9</td>
<td>CKD-EPI</td>
<td>5.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Tanzania [23] [Moshi area]</td>
<td>2014</td>
<td>481</td>
<td>70</td>
<td>45</td>
<td>NR</td>
<td>12.7</td>
<td>28.0</td>
<td>MDRD</td>
<td>7.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Italy [24]</td>
<td>2008–12</td>
<td>7552</td>
<td>84</td>
<td>57</td>
<td>26.4</td>
<td>11.8</td>
<td>50.1</td>
<td>CKD-EPI</td>
<td>7.1</td>
<td>4.2</td>
</tr>
<tr>
<td>India [25] [Delhi, Chennai]</td>
<td>2010–11</td>
<td>9797</td>
<td>76</td>
<td>43</td>
<td>17.8</td>
<td>19.0</td>
<td>32.5</td>
<td>CKD-EPI</td>
<td>7.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Malaysia [26] [Western area]</td>
<td>2011</td>
<td>876</td>
<td>76</td>
<td>43</td>
<td>NR</td>
<td>19.6</td>
<td>38.4</td>
<td>CKD-EPI</td>
<td>9.1</td>
<td>6.2</td>
</tr>
<tr>
<td>Switzerland [15] [Lausanne]</td>
<td>2003–06</td>
<td>6317</td>
<td>67</td>
<td>52</td>
<td>15.7</td>
<td>3.4</td>
<td>37.0</td>
<td>CKD-EPI</td>
<td>10.0</td>
<td>5.5</td>
</tr>
<tr>
<td>Norway [13] [Trøndelag]</td>
<td>1995–97</td>
<td>65181</td>
<td>70</td>
<td>50</td>
<td>15.9</td>
<td>3.4</td>
<td>44.8</td>
<td>MDRD</td>
<td>10.3</td>
<td>5.9</td>
</tr>
<tr>
<td>Netherlands [12] [Groningen]</td>
<td>1997–98</td>
<td>2489</td>
<td>29</td>
<td>49</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>MDRD</td>
<td>10.4</td>
<td>5.1</td>
</tr>
<tr>
<td>China [17]</td>
<td>2007–10</td>
<td>47204</td>
<td>93</td>
<td>50</td>
<td>NR</td>
<td>7.4</td>
<td>35.4</td>
<td>MDRD modified</td>
<td>10.8</td>
<td>9.1</td>
</tr>
<tr>
<td>Australia [20]</td>
<td>1999–2000</td>
<td>10949</td>
<td>54</td>
<td>51</td>
<td>21.2</td>
<td>8.5</td>
<td>29.0</td>
<td>CKD-EPI</td>
<td>11.5</td>
<td>5.7</td>
</tr>
<tr>
<td>England [16]</td>
<td>2009–10</td>
<td>5799</td>
<td>67</td>
<td>50</td>
<td>24.7</td>
<td>7.4</td>
<td>34.1</td>
<td>CKD-EPI</td>
<td>11.9</td>
<td>6.7</td>
</tr>
<tr>
<td>Canada [18]</td>
<td>2007–09</td>
<td>3689</td>
<td>45</td>
<td>52</td>
<td>23.0</td>
<td>6.3</td>
<td>16.3</td>
<td>CKD-EPI</td>
<td>12.5</td>
<td>9.4</td>
</tr>
<tr>
<td>USA [19]</td>
<td>1999–2004</td>
<td>13233</td>
<td>78</td>
<td>46</td>
<td>30.8</td>
<td>6.8</td>
<td>27.1</td>
<td>MDRD</td>
<td>13.1</td>
<td>5.0</td>
</tr>
</tbody>
</table>

PR, participation rate, that is, percentage of individuals completing screening out of the planned sample; DM, diabetes mellitus; HTN, hypertension; NR, not reported.

aData are from national surveys (or, if not available, from local areas) providing information on a whole spectrum of CKD. Countries are grouped by ranking CKD prevalence in low (white area), intermediate (light grey) and high (dark grey) prevalence.
in patients with Type 2 diabetes showed that, independent of the severity of diabetes, the higher the adherence to a Mediterranean diet the greater the reduction in both total and CV mortality [38]. This finding supports the hypothesis that diet can be an important modifier of the relationship between traditional risk factors and the incidence of CV disease. Future studies should specifically address the question of whether healthy diets can mitigate the risk for CKD by diabetes and hypertension. Given the unquestionable role of these risk factors in the worldwide epidemic of CKD [1], this issue has to be seen as a research priority.

**CONFLICT OF INTEREST STATEMENT**

None declared.


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The Mesoamerican nephropathy: a regional epidemic of chronic kidney disease?

Vito M. Campese

Division of Nephrology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Correspondence and offprint requests to: Vito M. Campese; E-mail: campese@usc.edu

In the history of humanity, the struggle for survival has been an ongoing issue as human beings face epidemics from different sources, environmental adversities and exposure to toxins.

The kidneys receive approximately one fifth of blood volume per unit time and, given their secretory and excretory functions, they are commonly victimized by environmental toxins or drugs ingested for therapeutic or recreational reasons. In recent years, there has been a substantial rise in kidney diseases caused by drugs, such as heroin, cocaine and amphetamines, and a surge in kidney diseases induced by medications (non-steroidal anti-inflammatory agents, antibiotics, lithium, platinum, immunosuppressive agents, to mention a few) or diagnostic agents (such as, contrast agents).

On occasion, epidemic or endemic forms of kidney diseases caused by environmental toxins have been described. A typical example is the so-called Balkan nephropathy. This is an endemic form of tubule-interstitial nephropathy identified among persons living in rural areas of the Danube River in Serbia, Bulgaria, Croatia, Romania and Bosnia [1]. After approximately 50 years of epidemiologic and clinical studies, it was determined that aristolochic acid, a contaminant of the wheat flour, was the likely cause of this nephropathy. This toxin is also the cause of Chinese herb nephropathy, first described in a cluster of cases in Belgium. Chronic kidney disease (CKD) caused by aristolochic acid has been described in multiple regions of the world, particularly in Asia, in association with ingestion of contaminated food products, beverages and herbal remedies containing aristolochic acid [2].

More recently, several epidemiological studies have described an excess of CKD among younger adult males in the geographic region that includes Southeastern Mexico, Guatemala, Belize, El Salvador, Honduras, Nicaragua, Costa Rica and Panama. This condition is now known as Mesoamerican Nephropathy (MeN).

This form of CKD affects primarily young male agricultural workers, exposed to very hot conditions especially in the sugar-cane fields. Clinically, they usually present with normal or mildly elevated blood pressure, reduction in estimated glomerular filtration rate (eGFR), non-nephrotic proteinuria, hyperuricemia and hypokalemia. Kidney biopsies show a chronic tubulo-interstitial disease with associated glomerulosclerosis [3].

A large population-based cross-sectional study involving approximately 3000 individuals was conducted by Lebov et al. [4] in León, Nicaragua, to evaluate the association between previously investigated risk factors and CKD. CKD prevalence was 13.8% for males and 5.8% for females. Male gender, older age, living in a rural zone, lower education level, self-reported high blood pressure, more years of agricultural work and lija (unregulated alcohol) consumption, were significantly associated with CKD.

In another study, dialysis enrollment rates were evaluated in the The National Center for Chronic Kidney Disease Treatment (Unidad Nacional de Atención al Enfermo Renal Crónico), the largest provider of dialysis in Guatemala. The incidence of CKD appeared to be higher in the high temperature and sugar cane growing regions [5].