Normal reference values for glomerular filtration rate: what do we really know?

Pierre Delanaye1, Elke Schaeffner2, Natalie Ebert2, Etienne Cavalier3, Christophe Mariat4, Jean-Marie Krzesinski1 and Olivier Moranne3

1Department of Nephrology-Dialysis-Transplantation, University of Liège, CHU Sart Tilman, Liège, Belgium, 2Division of Nephrology, Charité University Medicine, Campus Virchow, Berlin, Germany, 3Department of Clinical Chemistry, University of Liège, CHU Sart Tilman, Liège, Belgium, 4Department of Nephrology and Renal Transplantation, University Jean Monnet, PRES University of Lyon, CHU Hôpital Nord, Saint-Etienne, France and 5Department of Nephrology and Public Health, University of Nice, CHU de Nice, Nice, France

Correspondence and offprint requests to: Pierre Delanaye; E-mail: pierre_delanaye@yahoo.fr

Abstract

In nephrology, chronic kidney disease is defined by both proteinuria and measurement of glomerular filtration rate (GFR). This article focuses on GFR and different ways to define its normal reference values. In this context, we compare two perspectives: first the reference values defined by measuring GFR in normal individuals (the ‘classical way’) and secondly a fixed cut-off value at 60 mL/min/1.73 m² according to the associated mortality risk (the ‘prognostic way’). Following the classical way, we can assert that normal GFR values are largely over 60 mL/min/1.73 m² in healthy subjects, at least before the age of 70 years. However, we know that GFR physiologically decreases with age, and in adults older than 70 years, values below 60 mL/min/1.73 m² could be considered normal. Following the ‘prognostic way’, the fixed cut-off of 60 mL/min/1.73 m² has been retained in the K-DiGO guidelines. However, we challenge this concept and the fact that the variable ‘age’ is poorly taken into account in these data. There is an obvious discrepancy between the reference values defined either by the ‘classical way’ or by the ‘prognostic way’ which we think could be largely reduced, if age was better taken into consideration in these definitions.

Keywords: glomerular filtration rate; reference values

Introduction

In Nephrology, as generally in Medicine, making the diagnosis of a disease necessarily implies that we know what the healthy, physiological state is. Because chronic kidney disease (CKD) is most often asymptomatic, it is very important to accurately diagnose CKD as early as possible. At the same time, over-diagnosis of CKD has the potential to cause anxiety or lead to unnecessary clinical evaluation and treatments. Nowadays, the diagnosis of CKD is based on the measurement of two main biological variables: the presence of proteinuria and the decreased glomerular filtration rate (GFR) for at least 3 months. This article will focus on GFR and the difficulty of defining a ‘normal’ GFR value. In this context, a main issue will be the physiological decrease in GFR with ageing [1–3]. Indeed, there is debate in the recent literature regarding the actual criteria published for CKD definition based on estimated GFR (eGFR) or measured GFR (mGFR) [4, 5]. The choice of a fixed value (60 mL/min/1.73 m²) as a cut-off between healthy and CKD status has been criticized. Healthy elderly subjects could be considered as having CKD based on their age-related decline in GFR, although they are actually ‘physiologically’ safe according to their age [4, 6]. This decline in GFR with age is neither absolute nor predictable but is a phenomenon which encompasses senescence and may not necessarily be considered pathological. In this context, a better understanding of the ‘normal’ GFR values will help in this scientific debate. Our goal in this article is to review data from the literature, thus allowing a more precise definition of the normal range of GFR.

Preliminary methodological comments

Two methodological concerns must be addressed beforehand. The first concern is the way GFR is evaluated. Estimating GFR with creatinine-based equations such as the MDRD (for Modification of Diet in Renal Disease) [7] or the CKD-EPI (for Chronic Kidney Disease Epidemiology) [8] study equation can substantially underestimate GFR in a healthy population [9–11]. Even if less bias has been demonstrated for the new CKD-EPI equation in healthy subjects, errors in staging and poor precision still remain [10]. For example, in a series of 583 potential kidney donors with an eGFR of 45–60 mL/min/1.73 m², the corresponding mGFR was 16 or 25% higher (for the CKD-EPI and the MDRD equations, respectively). Moreover, the bias between eGFR and mGFR varies with age [10]. One major drawback
is the relationship between serum creatinine and muscular mass which may be misleading in the interpretation of eGFR, especially in the elderly. Samples in the MDRD and CKD-EPI studies were largely limited to patients under 70 years [8, 12]. Therefore, we have to confess that we do not really know how creatinine-based equations perform in older adults [7, 8]. There is however some reason to think that the performance is worse in elderly than in the young people [10, 13]. Moreover, the performance of the CKD-EPI equation in the elderly may probably not be better than the MDRD equation [6, 10]. Therefore, we focus our review on mGFR whenever data are available.

Our second methodological concern is the way ‘normality’ of a value can be determined. We will first discuss the available data in the literature which define the normal GFR values from ‘the classical way’, i.e. measuring GFR in a healthy population and calculating mean and SD (with stratification according to age) or calculating percentiles. This strategy, for example, has been followed for determining normal reference values of height and weight in paediatrics. However, from other specialties in Medicine, we know that this way to establish reference values is not the only possible one. Another method to define reference values is based on the risk of morbidity or mortality due to a pathological state. We call this strategy ‘the prognostic way’. The classical example is the reference values assigned to total cholesterol values. In this example, the ‘normal’ upper concentrations are 268 mg/dL for men and 252 mg/dL for women if the definition is based on the mean concentration observed in a healthy population [14]. The upper normal reference range can move to only 175 mg/dL (if other cardiovascular risk) or 190 mg/dL (without cardiovascular risk) if the definition is based on the lowest concentration associated with a non-significant risk of cardiovascular mortality [15]. This type of definition is only possible if large population-based studies and intention-to-treat trials are available. Recently, such an approach was proposed for CKD. The fixed cut-off at 60 mL/min/1.73 m² has been justified by those arguments, i.e. the relationship between mortality risk and level of eGFR [5]. Nevertheless, this assertion can be challenged and the interaction of age on this relationship between GFR and mortality is discussed.

Lastly, it should be pointed out that our classification into a ‘classical’ and a ‘prognostic’ way means far more than just two similar approaches but in fact two wholly different entities with different statistical displays. Whereas the classical method aims to compare an individual kidney function to a mean reference value of comparable persons (displayed by means, SDs and percentiles), the prognostic method creates a reference GFR value that predicts an outcome (displayed by relative risks or population attributable risks and risk differences). In the first (classical) case, the reference value might be useful for determining drug dosage or screening metabolic complications [16]. In the second (prognostic) case, it can help to develop a treatment policy for people at a certain risk of developing that outcome. In this context, it should be noted that ‘normal’ values in the classical sense may in fact overlap with ‘increased’ risk values in the prognostic sense.

Distribution of GFR in healthy subjects: ‘the classical way’

The ‘ideal’ study to define ‘normal’ GFR values would be a study with the following characteristics: the sample must be of sufficient size and representative of the general population (according to age, gender and ethnicity), the healthy status of the sample must be unquestionable, and the statistical assessment must be adequate. From a statistical point of view, the distribution of GFR in the population should be described by location parameters such as median, percentiles and the 5th percentile to define the lower normal value [3]. The most important studies on this topic are summarized in Table 1. We focus our review on articles including at least 30 healthy subjects and mGFR by a reference method. We use the Pubmed database and the classical textbooks of Nephrology. The two most cited works are historical and have been published in the famous textbooks published by Smith [17] and Wesson [18] in 1951 and 1969, respectively [17, 18]. These studies are not based on original data because the authors included only few of their own subjects. In fact, they compiled data from different studies published earlier. Most of them included only small sample and subjects included were very heterogeneous. Also, the definition of healthy status is either poorly defined or even inaccurate (hypertensive subjects are often included), the range for age is not sufficient (there were only few individuals above the age of 70 and all derived from the same study [2], see below), the results are often restricted to Caucasians and women are mostly underrepresented [17, 18]. However, because of the large overall sample size and GFR measurement by inulin (the gold standard for GFR measurement), the results are nowadays still considered valid. In summary, Smith [17] found a mean mGFR of 127 mL/min/1.73 m² and 118 mL/min/1.73 m² for men and women, respectively. For Wesson [18], the values were 130 mL/min/1.73 m² and 120 mL/min/1.73 m² for men and women, respectively, which can be considered equivalent. Even if the authors do not discuss this fact [19], Smith [17] and Wesson [18] observed a difference according to gender. However, such a difference was not confirmed by the vast majority of the authors publishing on this topic thereafter [19–26]. Only Poggio et al. [3], in 2009, found a statistical difference between women and men but the authors underlined that this difference (only 3%) was not relevant from a clinical point of view. Interestingly, they hypothesized that this difference ‘could be due to the differences in physiological demand for GFR that is inadequately modeled by body surface area (BSA)’ [3, 27]. Also, more recently published studies presented lower GFR values as normal, i.e. at 100–110 mL/min/1.73 m² [3, 19, 21, 22, 24–26, 28–32] compared with prior studies published in the 1950s or before [2, 17, 18, 33–36]. The first explanation for such a discrepancy could be the BSA adjustment. Indeed, as it was elegantly demonstrated by Poggio et al. in their own cohort, weight, body mass index and thus BSA have increased during the
last three decades, inducing a slight but significant decrease in adjusted GFR. Such a decrease was not observed when non-adjusted GFRs were considered [3]. A second reason could be the differences in GFR measurements. In most recent studies, iothalamate, iohekol, $^{51}$Cr-EDTA and $^{99m}$Tc-DTPA are preferentially used instead of insulin, and slight differences could occur between reference markers [37]. Even when using the same marker, small differences in the proposed reference values can be observed [21, 22], which can at least partly be explained by the difference in methodology used to measure GFR [37]. Also, we have to keep in mind the biological variability of GFR which is estimated between 4% and 10% in healthy subjects [38, 39].

At this point of the discussion, we still have not addressed the potential effect of ethnicity and age on normal GFR ranges. Regarding ethnicity, preliminary data in African-American (AA) subjects published by Shock [36] in 1946 suggested no significant difference between AA and Caucasians. These data have been confirmed by Poggio et al. [3] in a larger cohort, including both Caucasians and AA, showing no significant difference in mgFR according to ethnicity. In the Asian population, normal GFR values could be somewhat lower than for Caucasians as it has been suggested by studies in India, China and, to a lower extent, in Pakistan [20, 24, 40]. This lower value could either be due to differences in diet (most of Indian people are vegetarian) or the use of $^{99m}$Tc-DTPA plasma clearance as a reference method [20, 24]. Additional studies seem still necessary, especially one study including both Caucasians and Asians in the same analysis [41].

Regarding the effect of ageing, it has been suggested for a long time that GFR physiologically decreases with age [42]. Most of the studies confirmed this hypothesis [2, 3, 17–19, 21–25, 28, 30, 32, 36, 43–45]; nevertheless, we still have to explore the following: what are the normal GFR values in the elderly (over 70 years of age) and what is the physiological decline in GFR according to age? The main study on this topic is doubtless the study by Davies and Shock in The Journal of Clinical Investigation in 1950 [2]. The authors included 70 subjects aged 24–89 years. A number of 9–12 subjects were analysed for each decade. They demonstrated a continuous decrease in GFR values (from 123 ± 16 mL/min/1.73 m$^2$ at 20–29 years to 65 ± 20 mL/min/1.73 m$^2$ at 80–89 years). For the authors, the decrease in GFR was evaluated as 10 mL/min per 10 years. Despite the fact that exclusively men were studied and participants’ health status was not sufficiently defined, this study is still frequently cited [2]. Moreover, it must be underlined that other authors showed some discrepant results with a decrease in GFR ranging from 6 [45] to 12 mL/min/1.73 m$^2$ per decade [28] (see Table 1 for details). All these studies are cross-sectional however, and there are no longitudinal studies in the elderly with follow-up data on mGFR. Only one longitudinal study using creatinine clearance has been published where the authors showed a decrease of 7.5 mL/min/1.73 m$^2$ per 10 years [1]. Still further studies are necessary to better understand the natural decline in GFR with age. There is also some doubt about the possible onset of GFR decline. Some authors showed that the decrease in GFR is continuous from the age of 20 years [25, 26, 32], some demonstrated that it begins at the age of 40 or 50 years [2, 17, 18, 21, 28, 30] and others point out that it starts continuously but accelerates (and doubles) from the fourth or fifth decade on [3, 19, 24]. Furthermore, we want to emphasize that in 2012, it is still not possible to predict normal GFR values for subjects older than 70 years with sufficient accuracy. Several studies show some trends but the samples are very limited and/or little representative [2, 19, 24, 25, 28, 32, 36, 43].

From our point of view, the study, performed in 2009 by Poggio et al. [3], is until now the best work about ‘GFR reference values’. The sample was of impressive size ($n = 1057$) and representative (including 11% of AA). GFR was measured by the reference method iothalamate, and results were presented as percentiles. However, also in this study, data are scarce above 60 years of age. Nevertheless, we want to point out some interesting results. The lower reference value (5th percentile) at 60 years was 64 and 60 mL/min/1.73 m$^2$ for men and women, respectively. Moreover, the decrease in GFR was shown to be 8 mL/min/1.73 m$^2$ per 10 years. From these two results, it may reasonably be expected (but not proven) that the value of the 5th percentile in healthy subjects older than 70 years could be below 60 mL/min/1.73 m$^2$.

**Normal GFR with a definition based on CKD-related mortality/morbidity risk: ‘the prognostic way’**

When we focus on studies analysing the mortality risk of CKD according to mGFR levels, a thorough conclusion is not possible because such studies do not exist. Therefore, we have to use data on eGFR which is, by itself, a limitation regarding the poor precision of creatinine-based equations around the value of 60 mL/min/1.73 m$^2$ [9, 10, 46]. The overall mortality (and especially cardiovascular mortality) associated with CKD has been illustrated by numerous studies [47–53]. However, recent data proposed by the Chronic Kidney Disease Prognosis Consortium are the most impressive in terms of sample size (more than 1 000 000 participants). The consortium included data from 21 trials studying mortality risk in the general population where results on proteinuria and eGFR (by the MDRD study equation) were available [54]. In the context of our review, we will focus on the variable ‘age’. Indeed, there is debate in the literature about the interaction [54, 55] (or not [51, 56, 57]) of age on the relationship between mortality and GFR level.

The impact of proteinuria on the cardiovascular and mortality risk has been largely confirmed by data from the consortium trial. The higher ‘power’ of the proteinuria parameter compared with the power of the eGFR in the mortality risk assessment is also evident, especially at higher eGFR levels [54, 58, 59]. Considering the general population, the overall mortality risk significantly increased when the cut-off for eGFR was set at 60 mL/min/1.73 m$^2$, leading the authors to justify this threshold for the definition of CKD [54]. The hazard ratio (HR) for
<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>Age range</th>
<th>Population and GFR methods</th>
<th>Results expressed as mean ± SD (in mL/min/1.73 m² or mL/min if ^a)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldring et al. [34]</td>
<td>11 women 54 men</td>
<td>22–51 18–68</td>
<td>Convalescent patients without renal disease Inulin (continuous infusion) 4 clearances of 10–14 min with urinary catheter</td>
<td>119 ± 18 130 ± 22</td>
<td>GFR in elderly is 60% of GFR observed in young subjects</td>
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<tr>
<td>Hogeman [35]</td>
<td>36 men 20 women</td>
<td>20–30</td>
<td>Healthy (no details) Inulin (no details)</td>
<td>122 ± 13a 124 ± 13a 119 ± 13a</td>
<td>No difference according to gender</td>
</tr>
<tr>
<td>Davies and Shock [2]</td>
<td>70 men (9–12 subjects per 10 decade)</td>
<td>24–89</td>
<td>Convalescent patients without renal disease Inulin 4 clearances of 10–14 min with urinary catheter</td>
<td>20–29 years: 123 ± 16 30–39 years: 115 ± 11 40–49 years: 121 ± 23 50–59 years: 99 ± 15 60–69 years: 96 ± 26 70–79 years: 89 ± 20 80–89 years: 65 ± 20</td>
<td>No women Two subjects with hypertension (more than 160 mmHg of systolic) Decreasing of 1 mL/min/year</td>
</tr>
<tr>
<td>Smith [17]</td>
<td>258 men 118 women</td>
<td>16–55</td>
<td>Compilation of 16 studies for men (including 67 from Smith) and 11 for women (including 37 from Smith) Inulin (continuous infusion and single injection)</td>
<td>Men: 127</td>
<td>Difference according to gender but not unquestionable following the author’s assertion</td>
</tr>
<tr>
<td>Bucht [33]</td>
<td>27 men 23 women</td>
<td>20–45</td>
<td>Convalescent, minor surgical complaints or students Inulin (single injection) 3 clearances of 20 min with urinary catheter</td>
<td>Men: 118 ± 19 Women: 122 ± 24</td>
<td>Some hospitalized subjects and inclusion of women who suffered from toxaemia in the past No difference according to gender</td>
</tr>
<tr>
<td>Wesson [18]</td>
<td>347 men 141 women</td>
<td>1–89 but reference calculated for range of 20–40</td>
<td>Healthy subject but healthy status not confirmed Compilation of 27 (including [2, 33, 34] and including 34 from Smith and 38 from Wesson) Inulin</td>
<td>Men: 130 (sigma: 18%) Women: 120 (sigma: 14%)</td>
<td>Less than 20 subjects per study (except [2, 33, 34])</td>
</tr>
<tr>
<td>Berglund et al. [63]</td>
<td>78 men</td>
<td>50</td>
<td>Non-hypertensive subjects ⁵¹Cr-EDTA (single injection) Plasma clearance according to BM [64]</td>
<td>100 ± 12</td>
<td>Hypertension defined as BP over 175/115 mmHg</td>
</tr>
<tr>
<td>Reference</td>
<td>Sample</td>
<td>Age range</td>
<td>Population and GFR methods</td>
<td>Results expressed as mean ± SD (in mL/min/1.73 m² or mL/min if a)</td>
<td>Comments</td>
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</table>
| Slack and Wilson [26]           | 79 men 62 women   | 20–59 (only 5 less than 20 years and 1 more than 60 years) | Living kidney donors with normal urography and renal arteriography, healthy status confirmed  
Inulin (continuous infusion)  
3 clearances of 45 min | Median (percentile 5 and 95)  
20 years: 118 (90–99)  
30 years: 112 (86–93)  
40 years: 106 (82–88)  
50 years: 101 (78–85)  
60 years: 96 (73–82)  
| No difference according to gender  
Decrease of 4 mL/min per decade from 20 years |
| Landahl et al. [23]            | 70 years: 27 men,  
19 women  
75 years: 16 men,  
17 women | 70 and 75 | No hypertension, prostatism, lithiasis, diabetes, cardiac decompensation  
51Cr-EDTA (single injection)  
Plasma clearance according to BM [64] | 70 years: 75 ± 14  
75 years: 72 ± 11  
| No difference according to gender  
No difference between two ages |
| Granerus and Aurell [19]        | 358 men 145 women | 17–75 | Data from different studies (including [23, 26, 33, 63, 65])  
51Cr-EDTA and inulin | 26–33 years: 105 ± 26  
46–50 years: 98 ± 23  
60–75 years: 78 ± 24  
| No difference according to gender  
Decrease of 4 mL/min per decade before 50 years and of 10 mL/min per decade after 50 years  
Different GFR methods  
Different BSA methods |
| Back et al. [28]               | 67                | 21–77    | Healthy volunteer, healthy status confirmed  
Iohexol (single injection)  
Plasma clearance according to BM [64] | 20–50 years: 100 ± 22  
51–65 years: 83 ± 25  
66–80 years: 72 ± 20  
| Decrease of 12 mL/min per decade after 50 years |
| Fliser et al. [44]             | Young: 13 men,  
11 women  
Elderly: 13 men,  
16 women | 26 ± 3  
68 ± 7 | Non-hypertensive subjects  
Inulin (continuous infusion)  
Plasma clearance | 121 ± 11  
103 ± 11  
| Healthy status not confirmed |
| Hamilton et al. [22]           | 103 men 49 women  | 21–60    | Saudi Arabian subjects, living kidney donors, healthy status confirmed  
51Cr-EDTA (single injection)  
Plasma clearance according to BM [64] | 21–30 years: 108 ± 15  
31–40 years: 108 ± 15  
41–50 years: 109 ± 15  
51–60 years: 104 ± 13  
| No difference according to gender  
No difference between two ages  
Only 8 patients aged of more than 50 years |
| Vervoort et al. [31]           | 23 men 23 women   | 28 ± 6   | Healthy volunteer, healthy status confirmed  
Inulin (continuous infusion)  
4 clearances | 107 ± 11  
| |
| Hoang et al. [30]              | 94 men 65 women   | 18–88    | Healthy volunteer, healthy status confirmed  
Inulin (continuous infusion)  
4 clearances | >40 years: 104 ± 15  
<55 years: 81 ± 17  
| Decrease in GFR after 55 years |
| Fehran-Ekholm and Skeppholm [43]| 32 men 20 women   | 71–110   | Elderly, active subjects  
Iohexol (single injection)  
Plasma clearance | 68 ± 11  
| Healthy status not confirmed  
Decrease of 1.05 mL/min/year |
| Rule et al. [25]               | 160 men 205 women | 18–71    | 80% of Caucasians  
1.4% of African-American  
11.8% of unknown Living kidney donors, healthy status confirmed  
Iothalamate (single injection), one urinary clearance | Mean (percentile 5 and 95)  
20 years: 111 (91–136)  
30 years: 107 (86–131)  
40 years: 102 (81–126)  
50 years: 97 (76–121)  
60 years: 92 (71–116)  
70 years: 87 (66–111)  
| Decrease of 5 mL/min per decade (not different if slope analysed before and after 50 years)  
No difference according to gender  
Very few subjects aged more than 60 years |
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Number</th>
<th>Age Range</th>
<th>Study Details</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Grewal and Blake [21]</td>
<td>208 men 216 women</td>
<td>19–72</td>
<td>Living kidney donors, healthy status confirmed ⁵¹Cr-EDTA (single injection) Plasma clearance according to BM [64]</td>
<td>&gt;40 years: 103 ± 16 No difference according to gender Few subjects aged more than 60 years Decrease of 9 mL/min per decade from 40 years</td>
</tr>
<tr>
<td>Barai et al. [20]</td>
<td>250 men 360 women</td>
<td>20–45</td>
<td>Indian Living kidney donors, healthy status confirmed ⁹⁹Tc-DTPA (single injection) Plasma clearance according to Russell and Dubovský [66]</td>
<td>81 ± 19 No difference according to gender Differences according to gender in the range of 40–45 years Differences according to age</td>
</tr>
<tr>
<td>Hallan et al. [29]</td>
<td>1040 NASubjects from 4 other studies [2, 21, 22, 25]</td>
<td></td>
<td></td>
<td>Median (percentile 2.5) 20 years: 113 (83) 80 years: 79 (56)</td>
</tr>
<tr>
<td>Berg [32]</td>
<td>60 men 62 women</td>
<td>22–67</td>
<td>Living kidney donors, healthy status confirmed Inulin (continuous infusion) 4 clearances of 30 min</td>
<td>105 ± 13 20–30 years: 111 ± 16 30–40 years: 107 ± 12 40–50 years: 103 ± 11 +50 years: 190 ± 10 No difference according to gender Only 6 subjects aged over 50 years Decrease of 5 mL/min per decade</td>
</tr>
<tr>
<td>Poggio et al. [3]</td>
<td>461 men 596 women</td>
<td>39 ± 10</td>
<td>11.1% of African-American Living kidney donors, healthy status confirmed ¹²⁵I-Iothalamic (single injection), two urinary clearances</td>
<td>Median (percentile 5 and 95) Men: 20 years: 116 (89–144) 30 years: 113 (85–140) 40 years: 109 (81–136) 50 years: 101 (74–129) 60 years: 91 (64–119) Women: 20 years: 113 (86–141) 30 years: 109 (82–137) 40 years: 105 (78–133) 50 years: 98 (71–126) 60 years: 88 (60–116) Difference according to gender (109 ± 1 for women and 106 ± 16 for men) Decrease of 4 mL/min per decade up to 45 years and of 8 mL/min per decade after 45 years No difference between African-Americans and Caucasians No data after 60 years</td>
</tr>
<tr>
<td>Ma et al. [24]</td>
<td>130 men 171 women</td>
<td>42 ± 16 46 ± 15</td>
<td>Chinese Healthy status confirmed ⁹⁹Tc-DTPA (single injection) Plasma clearance according to Russell and Dubovský [66]</td>
<td>Men: 99 ± 20 Women: 98 ± 22 Men &lt;50 years: 104 (95% CI: 71–137) Women &lt;50 years: 110 (95% CI 75–145) Over 60 years: 76 (95% CI 46–107) No difference according to gender (except in the 18–29 years range) Decrease of 12 mL/min per decade after 50 years Sample over 60 years is not known</td>
</tr>
<tr>
<td>Jafar et al. [40]</td>
<td>99 men 85 women</td>
<td>48 ± 9</td>
<td>South-Asian, no hypertension, no diabetes, healthy status not confirmed Inulin (continuous infusion) 2 clearances of 30 min</td>
<td>94 ± 28 No difference according to gender Decrease of 0.8 mL/min per year No data about proteinuria</td>
</tr>
</tbody>
</table>

BM, Brochner-Mortensen correction; BSA, body surface area; Cr-EDTA, chrome ethylenediaminetetra-acetic acid; GFR, glomerular filtration rate; NA, not available; Tc-DTPA, technetium diethylenetriaminepenta-acetic acid.
all-cause mortality was statistically significant at 1.18 (95% CI 1.05–1.32). The results for an eGFR cut-off set at 45 mL/min/1.73 m² were more impressive with an HR of 1.57 (95% CI 1.39–1.78). Still, the data regarding cardiovascular mortality were still more favourable for the cut-off at 60 mL/min/1.73 m². When comparing the results by age category (above and below 65 years), the HRs for overall mortality differ. The authors give the example of the eGFR cut-off at 45 (not at 60) mL/min/1.73 m² [for subjects under 65 years: HR 2.14 (95% CI 1.56–2.92); for subjects above 65 years: HR 1.6 (95% CI 1.46–1.75)]. Even if the overall relationship between eGFR and all-cause mortality is similar in the two age categories, the proportion of subjects aged 70 years and above is small. Also, ‘age’ has been analysed in a dichotomous way and only few data are available for applying a continuous analysis. Under the assumption of a constant GFR decline with increasing age, a continuous analysis may be useful. Moreover, for younger adults, a median follow-up of 7.9 years could be considered as too short for endpoints like mortality, inducing an underestimation of the true effect. Let us imagine a 30-year-old man with a mGFR of 65 mL/min/1.73 m²: is it really reasonable to consider this patient as free from renal disease (although his GFR value is, by far, under the 5th percentile of normal mGFR), only because his relative risk to die within 10 years is not different from the population with normal GFR?

In elderly subjects, the relative risk of mortality could also be overestimated because the risk is related to an eGFR cut-off at 95 mL/min/1.73 m² which is probably too high for elderly individuals. The Nijmegen cohort proposed normal eGFR values (percentiles) in the general population by the MDRD study equation [6, 60]. This MDRD value of 95 mL/min/1.73 m² is clearly above the 95th percentile of normal eGFR for individuals above the age of 70 years. Having said that, elderly individuals with a high eGFR could also have a higher mortality risk due to confounding by muscle wasting. This potential contradiction makes a definitive conclusion difficult regarding the link between CKD and mortality in elderly subjects when eGFR is considered. Interestingly, the higher mortality linked to higher eGFR (above 105 mL/min/1.73 m²) was not found when a different renal biomarker like cystatin C was studied [61, 62]. Lastly, it should be remembered that all creatinine-based equations used to estimate GFR contain the variable ‘age’. This could confound the relationship between eGFR and prognosis because age is the major risk factor for death.

Conclusions

The K-DIGO recommendations define GFR below 60 mL/min/1.73 m² as a disease, regardless of age. This recommendation is based on eGFR and on the higher risk of mortality associated with eGFR below 60 mL/min/1.73 m² [5]. We, and others, have already underlined the lack of precision and the systematic underestimation of GFR around 60 mL/min/1.73 m² by the MDRD study equation [9, 10, 46]. Even if the bias was less important with the new CKD-EPI equation, the precision however remains suboptimal [10]. Moreover, the performance of these equations is unknown in the elderly population. Regarding the mortality risk associated with lower eGFR (once again defined by the fixed knot at 60 mL/min/1.73 m²), we feel that this link is not so obvious, and probably overestimated in elderly subjects, although this risk could be underestimated in young individuals.

Regarding the ‘classical way’, we do have sufficient data to assert that we know what normal mGFRs means in healthy individuals younger than 70 years [3]. On the contrary, for subjects over 70 years, it is obvious that we do not know which mGFR values can be considered ‘normal’, even if we can assert that normal values are probably lower than in younger subjects and potentially lower than 60 mL/min/1.73 m² for subjects above 70 years [2, 3, 36].

There is thus a gap (we could say a guilt) between the classically measured normal GFR values and those proposed as normal by the K-DIGO following the ‘prognostic way’. This gap is frequently observed when results applicable to a population level are translated to the patient level. Compared with the Poggio and Rule GFR values [3], the fixed knot at 60 mL/min/1.73 m² could actually be too low for young and too high for elderly people. We think that this gap can only be bridged if the parameter ‘age’ (senescence) is better taken into consideration. We are aware that differences in results may persist between the two definitions after adjustment for age. However, there is no doubt that this difference will be largely reduced.

Conflict of interest statement. None declared.

References


Received for publication: 14.3.2012; Accepted in revised form: 30.4.2012