To the Editor:

Traditionally, glomerular filtration rate (GFR) has been identified as the best marker of global renal function, calculated by using substance clearance techniques such as inulin or creatinine aided with cimetidine1

Chronic kidney disease (CKD) is a syndrome which derives from a progressive and generalized deterioration of renal function secondary to nephronal mass destruction, and renal functional evaluation is very important for doing its diagnosis and follow up2,3. However, since all clearance techniques have some degree of difficulty, an easier way of determining GFR, equations to estimate glomerular filtration have been developed. In the present review article we analyzed which was the evolution of these renal functional equations, and which is their role in CKD patients.

In order to have an easier way of determining GFR, equations to estimate glomerular filtration have been developed, most of them mainly based on serum creatinine (Table 1).

Kampmann et al.4, Cockcroft and Gault5 and Rowe et al.6 described renal function formulas for estimating GFR in the clinical practice. Cockcroft and Gault's formula (1976) is the most frequently used, although it has been questioned due to the fact that it exaggerates the decline in GFR, at least in people older than 804-7. However, Nicoll et al. found a good correlation in 18 individuals of ages between 66 and 82 using eGFR calculated according to Cockcroft and Gault's formula and the one obtained with 99Tc-DTPA7.

One of the problems that appeared when interpreting such studies was that they did not use individuals who represented the population well. Rowe et al. examined healthy old people in the community, while Kampmann et al.4 used hospital population excluding those patients with high levels of creatinine in blood in comparison with healthy adults. Cockcroft and Gault5 used hospitalized patients for their study, without excluding anyone regardless of their renal function3-5.

In 1987 Keller8 pointed out that the simplest formula to estimate GFR for people between 25 and 100, with normal creatinine values, is: [130-age (in years) ml/min]. In the last 20 years other formulas have been developed to predict glomerular filtration using indirect calculations and serum creatinine as a starting point, such as Nankivell's9, and Baracskay's10 (Table 1).
In 1999, with the aim of being more precise regarding glomerular filtration, the MDRD group (The Modification of Diet in Renal Disease) published a new equation to estimate GFR based on creatinine clearance and the concentration of serum creatinine taking into account the demographic and clinical characteristics in patients previously diagnosed with CKD. However, this equation has not been proven in people without renal disease, people with type 1 and 2 diabetes in treatment with insulin, people younger than 18, old people (older than 70), pregnant women, patients with comorbidities and transplant recipients.

In 2001 Lewis et al. recalculated the formula, adding renal transplanted and Afro-American patients with nephrosclerosis. However, neither of the formulas were applied to subgroups: healthy, diabetic and people older than 70. Therefore, such equations are not valid for the general population. Despite all these findings, patients who have a moderate GFR reduction between 30 and 59 ml/min/1.73 m², are still considered in the CKD threshold. If we take into consideration this criteria for diagnosing CKD, by eGFR < 60 ml/min/1.73 m², it would incorrectly indicate that approximately 17% of people older than 60 would suffer from CKD.

In 2009 the CKD-EPI formula was created with the aim of obtaining more reliability for the calculation of eGFR based on the levels of creatinine in blood, but despite the fact that it is more reliable and accurate than MDRD, it appears to have important limitations regarding the representation of the population and, particularly, since it does not have a significant sample of people older than 70 years.

As we can appreciate in Table 2, there are significant differences in a GFR value when it is obtained using creatinine clearance, Cr51-EDTA and the MDRD formula. It can be identified, at the end of the table, that two 80 year old males with the same serum creatinine have substantially different glomerular filtration rates depending on the method used. As both men are the same age and have the same serum creatinine, they have the same GFR value calculated with the MDRD (98.8 ml/min/1.73m²) formula. If we use creatinine clearance instead of MDRD, one of them has a GFR of 99 ml/min/1.73m², while the other only reaches a value of 56.3 ml/min/1.73m².

It is worth noting that the difference between these two healthy old men is in the elimination of urinary creatinine: 120 mg/dL in one and 65 mg/dl in the other. This phenomenon could be explained by creatinine backfiltration phenomenon already described.
in aged people. It is also interesting to observe that both of them have a comparable GFR value (76 and 60 ml/min/1.73 m²) when Cr51-EDTA is used. As a result the same person may be considered as affected with CKD or not depending on the method used to estimate GFR.

There are many difficulties regarding the recommendation of basing CKD diagnosis just on a eGFR critical value, not taking into account other variables such as age, gender, race, renal disease etiology, and associated pathologies. For instance, in stage 3 - CKD (GFR between 30-60 ml/min/1.73 m²), even though a diagnosis has been established by documenting eGFR < 60 ml/min/1.73 m² during a period longer than three months, it should be pointed out that this criteria does not necessarily apply to elderly people since GFR reduction can present as a consequence of normal ageing.

Similarly, a petit vegetarian woman with eGFR < 60 ml/min/1.73 m², who has a very positive renal reserve (> 100 %), and is not suffering from any of the classically associated complications to CKD such as uremic symptoms, anemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperparathyroidism, altered urinalysis, and/or abnormal renal ultrasound, should not be considered a CKD patient.

Even more, some authors do not support the idea of a eGFR < 60 ml/min/1.73 m² “critical value” as an independent risk factor to develop CKD in the future. Firstly, according to what was published by Go et al., independent mortality factors do not increase with eGFR values between 45 and 59 ml/min/1.73 m² when chronic damage has been established from serial measurements of serum creatinine. Secondly, a decrease in mortality risk in people older than 45 has been demonstrated, with a GFR between 50 to 59 ml/min/1.73 m² when chronic damage is established in a period of 3 to 6 months. Thirdly, the PREVEND study shows that approximately two thirds of the patients in stage 3 - CKD do not present albuminuria and their risk of cardiovascular complications, according to the tables adjusted by age and gender, were similar to those people who did not present renal disease.

Another problem related with performing CKD diagnosis based on eGFR is that the obtained CKD prevalence data is exceedingly variable depending on the applied formula. In this sense, the EPIRCE study (2010) found a global prevalence of CKD in stages 3 to 5 (according to the NKF-K/DOQI recommendations with eGFR < 60 ml/min/1.73 m²) of 6.8%, increasing this number to 21.4% in people older than 64. In the EROCAP study (2007), the prevalence of CKD was studied with the same criteria of eGFR < 60 ml/min/1.73 m² obtained in 9233 patients older than 18 who attended a primary health care consultation. According to its results, global prevalence varied depending on the eGFR formula used, between 21.3% and 22.7% while in the population older than 70 it reached 33.7%.

---

**Table 2: Comparison of creatinine clearance using different methods on young and old individuals.**

<table>
<thead>
<tr>
<th>AGE</th>
<th>Gender</th>
<th>Serum Creatinine</th>
<th>Urine Creatinine</th>
<th>Ccr</th>
<th>Cr51-EDTA</th>
<th>MDRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>V</td>
<td>0.8</td>
<td>70</td>
<td>152.7</td>
<td>102.48</td>
<td>140.83</td>
</tr>
<tr>
<td>23</td>
<td>V</td>
<td>0.9</td>
<td>55</td>
<td>70.51</td>
<td>114.73</td>
<td>109.28</td>
</tr>
<tr>
<td>27</td>
<td>V</td>
<td>0.8</td>
<td>305</td>
<td>102.27</td>
<td>100.34</td>
<td>123.25</td>
</tr>
<tr>
<td>32</td>
<td>V</td>
<td>1</td>
<td>175</td>
<td>125.42</td>
<td>95.03</td>
<td>92.04</td>
</tr>
<tr>
<td>36</td>
<td>V</td>
<td>0.8</td>
<td>45</td>
<td>128.7</td>
<td>81.83</td>
<td>114.99</td>
</tr>
<tr>
<td>42</td>
<td>H</td>
<td>0.7</td>
<td>40</td>
<td>121.53</td>
<td>99.19</td>
<td>97.53</td>
</tr>
<tr>
<td>46</td>
<td>V</td>
<td>0.8</td>
<td>138</td>
<td>115.66</td>
<td>88.53</td>
<td>110.81</td>
</tr>
<tr>
<td>48</td>
<td>V</td>
<td>0.8</td>
<td>90</td>
<td>132.53</td>
<td>129.45</td>
<td>105.66</td>
</tr>
<tr>
<td>52</td>
<td>V</td>
<td>0.8</td>
<td>185</td>
<td>165.27</td>
<td>98.72</td>
<td>107.89</td>
</tr>
<tr>
<td>66</td>
<td>V</td>
<td>0.8</td>
<td>110</td>
<td>105.94</td>
<td>63.51</td>
<td>89.19</td>
</tr>
<tr>
<td>71</td>
<td>H</td>
<td>0.8</td>
<td>72</td>
<td>84.39</td>
<td>85.38</td>
<td>75.15</td>
</tr>
<tr>
<td>72</td>
<td>V</td>
<td>1</td>
<td>55</td>
<td>75.14</td>
<td>89.04</td>
<td>76.07</td>
</tr>
<tr>
<td>73</td>
<td>H</td>
<td>0.7</td>
<td>70</td>
<td>83.12</td>
<td>75.90</td>
<td>87.18</td>
</tr>
<tr>
<td>73</td>
<td>V</td>
<td>0.8</td>
<td>120</td>
<td>69.64</td>
<td>95.42</td>
<td>100.71</td>
</tr>
<tr>
<td>73</td>
<td>H</td>
<td>1</td>
<td>70</td>
<td>79.07</td>
<td>75.90</td>
<td>57.76</td>
</tr>
<tr>
<td>74</td>
<td>V</td>
<td>0.8</td>
<td>50</td>
<td>142.32</td>
<td>78.54</td>
<td>87.61</td>
</tr>
<tr>
<td>76</td>
<td>V</td>
<td>1</td>
<td>85</td>
<td>83.96</td>
<td>69.71</td>
<td>76.81</td>
</tr>
<tr>
<td>79</td>
<td>V</td>
<td>0.9</td>
<td>112</td>
<td>89.18</td>
<td>85.61</td>
<td>88.52</td>
</tr>
<tr>
<td>80</td>
<td>V</td>
<td>0.8</td>
<td>120</td>
<td>99.4</td>
<td>79.65</td>
<td>90.66</td>
</tr>
<tr>
<td>80</td>
<td>V</td>
<td>0.8</td>
<td>65</td>
<td>66.82</td>
<td>60.66</td>
<td>98.86</td>
</tr>
</tbody>
</table>

**Legend:** AGE: in years, V: male, H: female; Serum creatinine normal value: 0.9 ± 2 mg/dl, Ccr: creatinine clearance (ml/min/1.73 m²)
In 2008 Zhang and Rothenbacher conducted a systematic review of 26 studies on the prevalence of CKD in different geographical areas of the world. Respecting the same estimation criteria as glomerular filtration, the CKD diagnosis and values which were < 60 ml/min/1.73 m², resulting in a global media prevalence in the adult population older than 30 of 7.2% while in people 64 or older it varied between 23.4% and 35.8%. Then, it seems that eGFR formulas are much more helpful in CKD staging and follow up, than in its diagnosis.

In order to avoid diagnostic errors like the above mentioned one, a new formula has been developed for diagnosing CKD: HUGE formula. It does not take into account patient’s eGFR for diagnosing CKD but two biochemical variables, and a clinical one: hematocrit, uremia, and gender. This formula is as follows

\[
\text{HUGE} = 2.505485 - (0.264418 \times \text{Hematocrit}) + (0.118100 \times \text{Urea}) + 1.383960 \text{ if male}, \text{ where a value > 0 diagnoses CKD.}
\]

HUGE formula allows for the discrimination between a healthy old person (HUGE<0) and a CKD patient (HUGE>0), both with similar eGFR, with high sensitivity and specificity, especially in people older than 70.

In conclusion, according to the aforementioned considerations, we should state that glomerular filtration estimations, in particular those obtained with the MDRD formula or the CKD-EPI formula are, undoubtedly, valid to stage and follow up the progress of patients already diagnosed with CKD. However, the use of eGFR lower than 60 ml/min/1.73 m² to follow up on patients without a known diagnosis is not only controversial but also perhaps not recommended.

On the other hand, to establish an incorrect diagnosis of CKD using estimations of GFR which are lower than 60 ml/min/1.73 m² obtained through routine lab tests could be considered arbitrary, insufficient and especially inadequate in the old population (older than 70).

Conflict of interests: The authors declare not to have conflict of interests in this study

REFERENCES


13.- Levey AS, Greene T, Kusek JW, et al. A simplified equation to predict glomerular filtration rate from serum


18.- Xie P, Huang JM, Lin HY, Wu WJ, Pan LP. CDK-EPI equation may be the most proper formula based on creatinine in determining glomerular filtration rate in Chinese patients with chronic kidney disease. Int Urol Nephrol. 2012 Nov 8. [Epub ahead of print]


CORRESPONDENCE:
Dr. Carlos Musso PhD.
Hospital Italiano de Buenos Aires
Perón 4190.
Buenos Aires. Argentina
E-mail address: carlos.musso @ hospitalitaliano.org.ar

Received: July 7, 2013.
Published: July 16, 2013