Predictors of accelerated renal function decline in the general population
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CHAPTER 2

SCREENING FOR EARLY CHRONIC KIDNEY DISEASE WHAT METHOD FITS BEST?

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INTRODUCTION
Much attention is presently focused on the detection of early chronic kidney disease (CKD). This interest is related to the fact that it is becoming more and more accepted that an impaired kidney function and elevated albuminuria are associated with progressive cardiovascular disease. It is thus important that easy to apply and reliable techniques be available to properly define the presence of renal damage. In this comment, we will describe what methods are available to define the presence of CKD, and we will discuss how these methods should be used in daily practice.

CHANGING CLINICAL NEPHROLOGY PRACTICE OVER THE DECADES
Nephrology practice has dramatically changed since the early sixties of the previous century. In the early years of nephrology, most attention was directed towards setting up dialysis and transplant programmes. In those years, little attention was paid to the prevention of progressive renal function loss. In the nineties, practice started to change, as it became clear that progressive CKD in subjects with known renal disease (and thus under the attention of the nephrologists) could be slowed down by strict blood pressure control and lowering of proteinuria with Angiotensin Converting Enzyme (ACE) inhibitors or angiotensin II receptor blockers [1]. Though in the optimal implementation of such renoprotective regimens much can still be gained, there are indications that the number of patients with end-stage renal disease (ESRD) due to classical renal diseases is diminishing. This favourable sign is, however, overruled by the fact that the number of patients with ESRD due to type 2 diabetes mellitus, hypertension and generalized atherosclerosis is constantly growing, not only in the elderly but also in those under 60 years of age [2]. Unfortunately, these subjects are often brought to the attention of the nephrologists only at a time when they are close to the need for dialysis, that is at a time when treatment opportunity to prevent a further renal function decline is already limited. As such treatments are well available, these patients should be detected earlier in the course of their progressive CKD.

HOW CAN WE DETECT PATIENTS NOT KNOWN WITH A SPECIFIC RENAL DISEASE, BUT AT RISK FOR PROGRESSIVE CKD?
As patients with renal failure due to type 2 diabetes, hypertension or generalized vascular disease have in most cases never experienced acute symptoms indicative of renal disease, such as haematuria, severe hypertension or oedema (as patients with glomerular or interstitial diseases), programmes have to be designed to detect them at an earlier phase.

Table 1. The five stages of CKD, according to the level of GFR and the presence of an elevated albuminuria. Given are the percentages as found in the PREVEND study in Groningen, The Netherlands (de Zeeuw) and the NHANES study in the USA (Coresh)

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR</th>
<th>Elevated albuminuria</th>
<th>PREVEND (%)</th>
<th>NHANES (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>&gt;90</td>
<td>yes</td>
<td>1.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Stage 2</td>
<td>60–89</td>
<td>yes</td>
<td>3.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Stage 3</td>
<td>30–59</td>
<td>yes/no</td>
<td>5.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Stage 4</td>
<td>15–29</td>
<td>yes/no</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Stage 5</td>
<td>&lt;15</td>
<td>yes/no</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>
The KDOQI guidelines defined the five stages of CKD, dependent on the level of glomerular filtration rate (GFR) and the presence of an elevated urinary albumin excretion, defined as microalbuminuria (30–300 mg albumin/24 h) or macroalbuminuria (>300 mg albumin/24 h) (Table 1) [3]. The publication of these definitions facilitated the ideas of approaching early CKD. We could detect subjects at risk for progressive CKD and cardiovascular disease by screening for albuminuria. With this approach, we would be able to detect subjects with stages 1 and 2 CKD, who cannot be detected by screening only for GFR. Various review papers recently described the laboratory methods to measure albuminuria, the way urine samples could be collected, the definitions for an abnormally elevated albuminuria, and the way in which a population screening on albuminuria might be organized [4–6].

It is beyond the scope of this editorial to discuss the pros and cons of these aspects. The second option is screening for GFR, as patients with stages 3 and 4 CKD may have an impaired GFR also without having micro- or macroalbuminuria. It is clear that accurate GFR measurements using inulin or iothalamate infusions cannot be applied in large-scale screening programmes. Accurate 24 h collections necessary for the calculation of a creatinine clearance are also difficult to apply in such programmes. That is the reason why in the last decade, much attention was focused on the optimal formula to estimate GFR from just one single plasma creatinine measurement and some indices of creatinine production. As the latter is determined by muscle mass of the subject, most formulas use age (the elderly produce less creatinine), sex (women produce less creatinine), race (whites produce less creatinine), and weight or height (leaner and smaller subjects produce less creatinine). The most widely used are the Cockcroft–Gault [7] and the Modification of Diet in Renal Disease (MDRD) [8] formula (Table 2).

### Limitations of estimated GFR measurements

Although GFR estimates are easy to apply, the Cockcroft–Gault and MDRD formula as well all the other published formulas have their limitations. It is only if one is aware of these limitations that a good use of the formulas can be expected.

### The creatinine measurement

A major point of concern that affects both formulas is the accuracy of the creatinine assay itself. Calibration of the assay is needed, not only to compare individual laboratory results with each other, but also to standardize the results of an individual over time [9]. Calibration greatly reduces the bias that is found between estimated GFR and true GFR in many studies. Even after calibration, however, still more than half of the results differ more than 15% from true GFR, and more than one-third differ by more than 30% from the correct value [10].

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**Table 2. The Cockcroft–Gault formula and the simplified MDRD formula to estimate glomerular filtration rate**

<table>
<thead>
<tr>
<th>Formula</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft–Gault formula</td>
<td>[(140-age)×weight]/72×(serum creatinine)×(0.85 if female)</td>
</tr>
<tr>
<td>Simplified MDRD formula</td>
<td>186×(serum creatinine)×(age)×(0.742 if female)×(1.210 if black)</td>
</tr>
</tbody>
</table>

Age is included in years, weight in kilogram and serum creatinine in milligram per decilitre.
Second, serum creatinine is not only dependent on endogenous muscle mass, but also on dietary intake of meat, which thus incorrectly may result in a higher serum creatinine value.

**THE CALCULATION OF ESTIMATED GFR**

There are fundamental differences between the Cockcroft–Gault and the MDRD formula to estimate GFR. First, the Cockcroft–Gault formula has originally been validated against creatinine clearance as the gold standard, whereas the MDRD formula was developed against iothalamate-measured GFR. As creatinine, but not iothalamate, is excreted not only by filtration but also by secretion, creatinine clearance always exceeds iothalamate clearance. Consequently, the Cockcroft–Gault-based GFR estimates tend to exceed MDRD-based GFR estimates in most subjects. Second, the Cockcroft–Gault formula (which includes weight in the formula) is expressed in millilitres per minute, while the MDRD formula (which does not include weight in the formula) is expressed in millilitres per minute per 1.73 m². This difference makes a direct comparison between the two difficult. In general, clinicians are not used to expressing GFR normalized for standard body surface area.

**THE BIAS INTRODUCED BY THE ESTIMATES**

It has been shown in various studies that MDRD GFR in general underestimates true GFR [11–13], especially in patients with normal GFR, whereas Cockcroft–Gault GFR overestimates true GFR, especially in patients with impaired kidney function [11]. The biases of the two formulas may be quite different in selected populations, defined by age, sex, body mass index and also level of GFR [14]. In epidemiological studies, the impact of not just age [15] but also of sex, body weight, blood pressure and glucose on renal function will generally result in different conclusions when using an indirect instead of a direct measure of GFR [16].

**THE USE OF FIXED CUT-OFF LEVELS FOR CKD DEFINITIONS**

One should realize that the KDOQI guidelines make their discrimination on stages of GFR based upon fixed cut-off levels, that is a GFR 30–59 (stage 3), or 15–29 ml/min/1.73 m² (stage 4). It is, however, well-known that GFR decreases with advancing age by about 0.8 ml/min/year; it is to be expected that we, by using fixed cut-off levels, will diagnose more elderly subjects to have the worse CKD stages. This may result in unnecessary diagnostics and treatment of the elderly. It will also, and even more unwanted, result in missing this diagnosis in the young and male subjects. This problem could be overcome by making age-specific cut-off values for an impaired GFR. In a recent study in more than 2 million subjects from the Veterans Affairs Health Care System, it was shown that the association of eGFR with mortality was much steeper in younger compared with older subjects. This led the authors to conclude that to properly evaluate the impact of an impaired GFR on mortality, different cut-off values should be used for young compared with older subjects [17].

**AN IMPAIRED GFR OR PROGRESSIVE RENAL FUNCTION IMPAIRMENT?**

Subjects that reach CKD stage 5 will at some point in time have passed KDOQI stages 3 and 4. Screening for estimated GFR therefore seems logical. However, a point of concern is that diagnosing someone with a GFR below a certain cut-off level, does not necessarily mean that this subject will have a progressive loss of renal function. It may well be that he or she has few nephrons and consequently, a low GFR, that however has been and will be stable for many years. Indeed, a population survey showed that in patients with an increased serum creatinine who were not being treated by renal services, only a minority showed progressive renal function decline during 31 months of follow-up [18]. We recently showed over 4.2
years of follow-up that the loss of GFR in subjects, selected because of an impaired GFR, was not higher than in the background population (with a normal GFR), while the fall in GFR in subjects with macroalbuminuria, even those with a better preserved GFR, was much more rapid than the background population. Interestingly, cardiovascular prognosis was similarly unfavourable in the subjects with impaired GFR and in the subjects with macroproteinuria [19]. Thus, it may well be that screening for GFR is not the ideal method to detect patients at risk for progressive renal failure. From a renal perspective, it may be more effective to adopt a screening strategy that is based on the identification of subjects that have the combination of an elevated albuminuria, a decreased GFR and any of the known modifiable progression risk factors, such as hypertension, diabetes, smoking and hyperlipidaemia. This would imply that in analogy to the Framingham risk score for cardiovascular disease, a risk score predicting progressive renal function decline should be applied. Such a renal risk score is however, yet to be developed.

**WHAT IS THE ROLE FOR THE NEPHROLOGIST?**

As it has been shown that 5–6% of the population has stages 1 and 2 CKD, and another 5% has a stage 3 CKD [20,21], the workload required to detect and especially to follow these subjects is tremendous. This will not be feasible for nephrologists, and also not advisable, since many of these subjects will not develop stage 5 CKD. The main risk that threatens such subjects is cardiovascular disease. Screening for early CKD thus requires a combined approach by the (cardiovascular) internist, general practitioner, nurse and technician. The nephrologist should take the initiative. The type of health care system in the individual country will dictate the optimal design of the screening programme. The components to consider include: who will do the testing, who will take care of the individual with an abnormal test result, where will the screening take place (e.g. clinic, health fair), and how it will be financially supported.
Chapter 2

REFERENCES


