Defining risk factors associated with renal and cognitive dysfunction

Joosten, Johanna Maria Helena

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CHAPTER 3

eGFR and creatinine clearance in relation to metabolic changes in an unselected patient population

Drion I, Joosten H, Dikkeschei LD, Groenier KH, Bilo HJ

Abstract

**Background and objectives** It is widely assumed that moderate to severe renal failure (creatinine clearance <60 ml/min; or an MDRD (Modification of Diet in Renal Disease Equation) <60 ml/min/1.73 m²) is associated with metabolic changes, often needing further assessment and treatment. We investigated whether such abnormalities are already present at earlier stages of kidney disease, as assessed by 24-hour urine sampling and MDRD calculation.

**Methods** A select, retrospective cohort study was conducted. Creatinine clearance was measured by collecting 24-hour urines. The individual eGFRs were calculated with the MDRD formula and patients were then divided by renal function category (<15, 15-30, 30-45, 45-60, 60-90, >90 ml/min/1.73 m²)). Per clearance category the number of people with anaemia, hypokalaemia, uraemia and hyperphosphataemia was evaluated.

**Results** The median creatinine clearance rate was 67.3 ml/min (quartiles: 42.9-95.8) versus a median MDRD of 51.6 ml/min/1.73 m² (35.8-67.7). Anaemia, hyperkalaemia, hypocalcaemia, and uraemia were found to be present at higher levels of creatinine clearance rate and eGFR than previously reported (p<0.01). This increased prevalence was more pronounced in elderly subjects, particularly with respect to anaemia (OR 2.71 and 2.02 for MDRD and creatinine clearance respectively, p<0.01). The same holds for the proportion with uraemia (OR 1.85, p<0.01) and hypocalcaemia (OR 1.97, p=0.011) for MDRD.

**Conclusion** Metabolic changes in an in- and outpatient hospital population are present at earlier stages than was stated in recent guidelines, especially when creatinine clearance levels are used as indicators. This might have implications for testing and treatment of patients with suspected kidney disease and/or loss of renal function.
Introduction

Patients with chronic kidney disease (CKD) often experience a gradual decline in renal function which initially is asymptomatic. The K-DOQI (Kidney Disease Outcomes Quality Initiative) guidelines define CKD as an estimated GFR (eGFR) of less than 60 ml/min per 1.73 m² for a period of three or more months, with or without the presence of kidney damage.¹ Earlier studies have shown that chronic renal disease is associated with poor outcomes, impaired renal function, and eventual renal failure.² Patients who have an eGFR of less than 60 ml/min/1.73 m² appear to be at an increased risk for cardiovascular disease and premature death.³ Adverse outcomes may be prevented or delayed by the early detection and treatment of both the declining renal function as well as the haematological and biochemical abnormalities. Moreover, survival rates for dialysis dependent CKD patients improve when optimal treatment is delivered early in the course of their CKD.⁴

In patients with renal disease and a normal or mildly decreased renal function (K-DOQI stage 1 or 2, respectively eGFR >90 ml/min/1.73 m² and eGFR 60-90 ml/min/1.73 m²), homeostatic mechanisms in the renal tubules are able to keep the concentrations of sodium, potassium, calcium, urea, phosphate, and total body water within the normal range. The kidneys of these patients also provide adequate support for the production of erythrocytes through the release of erythropoietin. A further decline in renal function (<60 ml/min/1.73 m²), is considered to be associated with a variety of haematological and biochemical abnormalities (anaemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia, and uraemia), which, in turn, are related to a decreased quality of life, increased morbidity, and premature mortality.

Anticipatory treatment during the earlier stages of chronic kidney disease can significantly reduce the morbidity and mortality caused by renal failure. These efforts should concentrate not only on the preservation of renal function, but also on the correction of the earlier mentioned haematological and biochemical abnormalities. The K-DOQI guidelines therefore recommend that all people with an eGFR of less than 60 ml/min/1.73 m² undergo evaluation for anaemia, biochemical abnormalities, and metabolic bone disease. This recommendation implies that significant abnormalities are not readily found when the eGFR is higher than 60 ml/min/1.73 m². The validity of applying this assumption to hospital patients in general is uncertain.

The purpose of this cross-sectional retrospective cohort study was to assess the prevalence of biochemical abnormalities at different stages of renal function using two methods. The first method uses the Modification of Diet in Renal Disease equation (MDRD formula), as recommended in the K-DOQI guidelines. With the second method, 24 hour urine samples from a random selection of inpatients and outpatients were used to calculate the creatinine clearance.
Materials and Methods

Data Source
In this retrospective cohort study, data were collected from the laboratory facilities of the Isala Clinics in Zwolle, the Netherlands. These facilities provide both primary and secondary health care services for a region with a population of approximately 375,000 inhabitants. Data were obtained from EriDanos, the computerized medical record system used in the Isala Clinics. EriDanos contains patient data, including laboratory measurements; diagnostic information; patient history; and information on the hospital-based care for all outpatient and inpatient patient contacts.

Population
The data for 2,012 adult patients were extracted from the database. Creatinine clearance, based on 24 hour urine samples, was measured for these patients at the Isala Clinics during the years 2005 and 2006. These results, as well as all other available laboratory results on record for these patients, were extracted from the database and imported into an Excel spreadsheet. No personal information was included to protect the anonymity of the patients. The resulting Excel spreadsheet contained all of the data used for the present study and was the only source of data concerning these patients available to the investigators. We did not know anything about specific medical indications leading up to the creatinine clearance rate measurements, nor did we know anything about individual diagnoses, medical histories, or treatment plans.

Patients younger than 18 years were excluded from this study, as were patients for whom then current plasma creatinine levels were unavailable. Neither creatinine clearance nor the MDRD eGFR can be reliably calculated without known plasma levels. Data for 1216 patients were used for this study and subjected to statistical analysis.

Details concerning medication, comorbidity, BMI, and ethnicity were not available due to the nature of our data collection methods. When assessing the known population data in the Zwolle region, it can be safely assumed that the majority of this cohort is of the Caucasian race.

No permission was required from the Medical Ethics Committee as our data only included laboratory result information, which had been obtained from a laboratory database. Moreover, no personal patient information was included.

Data collection
Screening data were collected on available demographic characteristics and laboratory parameters of the participants. All laboratory variables were obtained within one year of the index creatinine clearance rate, except for plasma creatinine values which were obtained within two weeks of the index 24 hour urine sample. To improve the accuracy of the abstracted data, all data were extracted from EriDanos twice, introduced in two different files and afterwards compared to achieve an optimally accurate database. Additional
laboratory measurements were available to a varying extent (74% to 100%). The reference values used by the Isala Clinics laboratory are shown in Table 1. The Jaffé technique, using a Modular PA, was used to measure plasma creatinine. Values between 70 and 110 μmol/L for males and between 55 and 90 μmol/L for females were considered to be in the normal range. Further laboratory measurements were performed using standard laboratory techniques on a Modular PE. Haemoglobin was assessed through a colorimetric SLS-HB method on a Sysmex XE2100-1.

<table>
<thead>
<tr>
<th>Table 1 Reference values at the Isala clinics.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Values considered abnormal (mmol/L)</strong></td>
</tr>
<tr>
<td>Potassium</td>
</tr>
<tr>
<td>Urea</td>
</tr>
<tr>
<td>Phosphate</td>
</tr>
<tr>
<td>Haemoglobin</td>
</tr>
<tr>
<td>Calcium</td>
</tr>
</tbody>
</table>

Renal function measurements

Renal function was assessed by calculating the 24 hour creatinine clearance rate (U×V/P), as well as eGFR calculation, using the MDRD: [MDRD = 186.3 * (serumcreatinine (mmol/L)/88.4)^-1.154 * age (years)^-0.203 x factor] as a measure of glomerular clearance (factor = 1 for men; 0.742 for women; 1.212 for Afro-Americans).

Statistical analysis

Statistical analysis was conducted using SPSS 11.5. Differences between categorical variables were tested using the Fisher's Exact test. In the case of continuous variables the student t-test was used for normally distributed variables, while non-parametric tests were used for skewed variables. Subjects were divided by renal function category and eGFR category (< 15, 15-30, 30-45, 45-60, 60-90, >90 ml/min/(1.73 m²)). Per clearance category the percentage of patients with anaemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia and uraemia was evaluated, plotted and tested with a Chi square test for trend, as well as the degree of these disturbances which were tested with the Jonckheere-Terpstra test. We used binary logistic regression (using repeated contrasts, in which each category is compared with the preceding category) to study whether biochemical and haematological disturbances were additionally more prevalent in elderly patients (older than 65 years) in comparison to younger patients (<65 years) and to identify any gender related differences.
Table 2a  Study population characteristics and overview of haematological and biochemical abnormalities (median and quartiles).

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>median [quartiles]</td>
<td></td>
<td>N</td>
<td>median [quartiles]</td>
</tr>
<tr>
<td>Age (years)</td>
<td>571</td>
<td>58.6 [47.4-71.2]</td>
<td></td>
<td>645</td>
<td>60.4 [50.6-72.1]</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>571</td>
<td>62.2 [41.4-85.5]</td>
<td></td>
<td>645</td>
<td>75.3 [44.1-107.2]</td>
</tr>
<tr>
<td>MDRD*</td>
<td>571</td>
<td>51.5 [35.7-68.8]</td>
<td></td>
<td>645</td>
<td>51.7 [36.0-70.9]</td>
</tr>
<tr>
<td>Measured serum levels of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>571</td>
<td>102.0 [84.0-137.0]</td>
<td></td>
<td>645</td>
<td>130.0 [102.0-174.0]</td>
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<tr>
<td>Haemoglobin (mmol/L)</td>
<td>174</td>
<td>6.9 [6.4-7.2]</td>
<td></td>
<td>269</td>
<td>7.6 [6.9-8.1]</td>
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<tr>
<td>(♀&lt; 7.5; ♂&lt; 8.5)</td>
<td></td>
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<td></td>
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<tr>
<td>Potassium (mmol/L) (&gt; 5)</td>
<td>37</td>
<td>5.2 [5.1-5.4]</td>
<td></td>
<td>83</td>
<td>5.3 [5.2-5.6]</td>
</tr>
<tr>
<td>Urea (mmol/) (&gt; 10)</td>
<td>136</td>
<td>15.4 [12.0-21.0]</td>
<td></td>
<td>212</td>
<td>15.4 [11.9-20.8]</td>
</tr>
<tr>
<td>Phosphate (mmol/L) (&gt; 1.5)</td>
<td>34</td>
<td>1.7 [1.6-1.9]</td>
<td></td>
<td>49</td>
<td>1.7 [1.6-1.9]</td>
</tr>
<tr>
<td>Calcium (mmol/L) (&lt; 2.2)</td>
<td>39</td>
<td>2.1 [2.0-2.2]</td>
<td></td>
<td>52</td>
<td>2.1 [2.0-2.2]</td>
</tr>
</tbody>
</table>

* MDRD: modification of diet in renal disease formula.

Table 2b  Renal function assessment.

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Number of subjects with:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl* rate (ml/min)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&gt; 90 ml/min</td>
<td>117</td>
<td>20.5%</td>
<td></td>
<td>235</td>
<td>36.4%</td>
</tr>
<tr>
<td>60-90 ml/min</td>
<td>180</td>
<td>31.5%</td>
<td></td>
<td>164</td>
<td>25.4%</td>
</tr>
<tr>
<td>45-60 ml/min</td>
<td>114</td>
<td>20.0%</td>
<td></td>
<td>79</td>
<td>12.2%</td>
</tr>
<tr>
<td>30-45 ml/min</td>
<td>65</td>
<td>11.4%</td>
<td></td>
<td>71</td>
<td>11.0%</td>
</tr>
<tr>
<td>15-30 ml/min</td>
<td>61</td>
<td>10.7%</td>
<td></td>
<td>71</td>
<td>11.0%</td>
</tr>
<tr>
<td>&lt; 15 ml/min</td>
<td>34</td>
<td>6.0%</td>
<td></td>
<td>25</td>
<td>3.9%</td>
</tr>
<tr>
<td>eGFR by MDRD# (ml/min/1.73 m2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 90 ml/min</td>
<td>16</td>
<td>2.8%</td>
<td></td>
<td>32</td>
<td>5.0%</td>
</tr>
<tr>
<td>60-90 ml/min</td>
<td>177</td>
<td>31.0%</td>
<td></td>
<td>218</td>
<td>33.8%</td>
</tr>
<tr>
<td>45-60 ml/min</td>
<td>156</td>
<td>27.3%</td>
<td></td>
<td>138</td>
<td>21.4%</td>
</tr>
<tr>
<td>30-45 ml/min</td>
<td>128</td>
<td>22.4%</td>
<td></td>
<td>146</td>
<td>22.6%</td>
</tr>
<tr>
<td>15-30 ml/min</td>
<td>60</td>
<td>10.5%</td>
<td></td>
<td>74</td>
<td>11.5%</td>
</tr>
<tr>
<td>&lt; 15 ml/min</td>
<td>34</td>
<td>6.0%</td>
<td></td>
<td>37</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

* CrCl: Creatinine Clearance
# eGFR by MDRD: estimated glomerular filtration rate by modification of diet in renal disease formula

Results

The data of 1216 patients were examined during the study. Table 2a shows the number and distribution of participants according to demographic and clinical characteristics. Haemoglobin, potassium, calcium, phosphate and urea were measured in 91.3%, 94.5%, 83.3%, 74.4% and 81.3% of patients respectively.

The median creatinine clearance was 67.3 ml/min (quartiles: 42.9-95.8), and the median MDRD was 51.6 ml/min/1.73 m² (35.8-67.7) (Table 2b). The majority of patients (57.2%; n=696) had a creatinine clearance >60 ml/min, whereas the MDRD was >60 ml/min/1.73 m².
Figure 1a Prevalence (%) of anaemia by CrCl / MDRD intervals.

Figure 1b Median values of haemoglobin (mmol/L) by CrCl / MDRD interval in the group of patients with anaemia.

Figure 2a Prevalence (%) of hyperkalaemia by CrCl / MDRD intervals.

Figure 2b Median values of potassium (mmol/L) by CrCl / MDRD interval in the group of patients with hyperkalaemia.

Figure 3a Prevalence (%) of hyperphosphataemia by CrCl / MDRD interval.

Figure 3b Median values of phosphate (mmol/L) by CrCl / MDRD interval in the group of patients with hyperphosphataemia.
in 36.4% of patients (443). Men had a significantly higher mean creatinine clearance than women (78.5 versus 64.5 ml/min; p< 0.001, Mann-Whitney U test). However, eGFR as measured using the MDRD was 53.2 ml/min/1.73 m² for men and 50.91 for women (p=0.205, Mann-Whitney U test). The mean overall difference between the creatinine clearance and the MDRD was 25.3 ml/min/1.73 m² for men (p<0.001, Wilcoxon signed ranks test) and 13.59 ml/min for women (p<0.001 Wilcoxon signed ranks test). The mean age for the men was only slightly higher than that for the women (60.4 versus 58.6 years; p<0.05, Student t-test).

The prevalence of hyperphosphataemia and hypocalcaemia was higher particularly when the creatinine clearance rate was less than 45 ml/min. Figures 1a, 2a, 3a, 4a, and 5a show a progressive prevalence of disturbances in respectively haemoglobin, potassium (>5.0...
mmol/L), phosphate, calcium, and urea, as the creatinine clearance rate or eGFR declines (p<0.001, Chi-square test for trend). In the figures 1b, 2b, 3b, 4b, and 5b the median values of the measured laboratory parameters show the same pattern over the spectrum of creatinine clearance rate and eGFR intervals (p<0.001, Jonckheere-Terpstra test).

Anaemia is often seen in the early stages of renal insufficiency. In the group of patients with mild renal failure (K/DOQI stage 2), 25% already showed an abnormally low haemoglobin level. The observed prevalence of anaemia progressively increases with decreasing renal function. In the early stages of renal failure, low haemoglobin was not the only abnormal laboratory finding. Hyperkalaemia is present in only 5% of patients with mild renal insufficiency, but this number rapidly increases when creatinine clearance rates fall below 60 ml/min. Increased serum phosphate and decreased serum calcium levels are mainly seen in patients with clearances <30-45 ml/min. Urea levels >10 mmol/L are observed in almost 14.4 percent of the patients with mild renal dysfunction.

Almost 60% of patients was 65 years or younger. People in this age group had a significantly higher (p<0.001, Mann-Whitney U test) median creatinine clearance and MDRD (85.5 ml/min and 61.2 ml/min/1.73 m², respectively) compared to patients older than 65 years (50.0 ml/min and 41.3 ml/min/1.73 m², respectively). Binary logistic regression showed that the proportion of elderly subjects (>65 years) with anaemia was significantly higher compared with subjects ≤65 years (Odds Ratio (OR) 2.71 and 2.02 for MDRD and creatinine clearance, respectively, P<0.001). The same trend is only seen with uraemia when eGFR results are examined (OR 1.85, p<0.01). The number of elderly patients with hypocalcaemia for MDRD was also higher than in the population of patients who were 65 years or younger (OR 1.97, p=0.01). For hyperkalaemia and hyperphosphataemia no significant differences in prevalence were found between the two age groups.

With decreasing renal function, all patients showed greater disturbances in laboratory parameters. As could be expected, more abnormal values were seen when using creatinine clearance rates to portray renal function compared to the MDRD method.

Discussion

As renal function decreases, renal dysfunction-associated biochemical abnormalities will become more evident. The K-DOQI guidelines recommend testing for biochemical abnormalities in all patients with an eGFR <60 ml/min/1.73 m². Indeed, in accordance with earlier studies, the severity of anaemia, hyperkalaemia, hypocalcaemia, and uraemia increases with declining GFR.

However, in contrast to earlier reports, we found anaemia, hyperkalaemia, hypocalcaemia and uraemia at higher eGFRs than is suggested by the K-DOQI guidelines,
and with higher creatinine clearance rates than are usually expected or have been previously reported, albeit in a variable percentage. This increased prevalence of abnormalities in earlier stages of renal function decline was more pronounced in elderly subjects.

**Interpretation of results in light of previous research**

With an eGFR of <60 ml/min/1.73 m$^2$, decreased kidney function is strongly associated with a higher prevalence of anaemia among the US adult population. Moreover, anaemia in subjects with chronic renal disease is associated with a decreased quality of life, lower exercise tolerance, and an increased risk for cardiovascular morbidity and mortality. Furthermore, an independent association between elevated serum phosphate levels and the risk of mortality and myocardial infarction was described in a cohort of patients with CKD. Increases in serum potassium levels were apparent in people with mild to moderate renal insufficiency, albeit to a lesser degree.

Since such haematological and biochemical abnormalities can be corrected, guidelines have been developed regarding cut-off points and treatment indications. The K-DOQI guidelines state that patients with a GFR of less than 60 ml/min/1.73 m$^2$ are considered to be at high risk for cardiovascular morbidity, mortality, and end stage renal disease. According to these guidelines this population should undergo further testing and, when indicated, treatment should be initiated. The K-DOQI guidelines recommend calcium, phosphorus and parathyroid hormone (PTH) concentrations to be measured once a year in all CKD patients with an eGFR of 30-60 ml/min. They also state that serum phosphate levels tend to remain within normal limits until relatively late in the course of CKD. This is probably due to an increase in PTH secretion, leading to increased renal phosphate clearance.

The guidelines used by the Dutch Association of Internists (NIV) state that the serum phosphate concentration is not expected to increase until a GFR of ≤30 ml/min/1.73 m$^2$. Levin et al state that serum phosphate will not rise before the eGFR falls below 30 ml/min. In our cohort however, both the prevalence and the severity of hyperphosphataemia were seen to increase when creatinine clearance rates were still between 45 and 60 ml/min. The NIV guidelines furthermore state that serum potassium values are hardly affected until a GFR of <5 ml/min or oliguria is reached. In our study, we found abnormal potassium levels at much higher glomerular filtration rates. The prevalence of hyperkalaemia increased substantially as soon as the creatinine clearance rate dropped below 60 ml/min.

Since an increasing number of people seem to have diminished renal function, screening for laboratory abnormalities might have to be considered in earlier phases of renal function loss, not only when renal function is assessed by MDRD, but particularly when assessed by creatinine clearance rate. As previously mentioned, the MDRD gives an underestimation of the real creatinine clearance, this being most prominent at higher levels of renal function. In the group of patients with a creatinine clearance <60 ml/min the mean MDRD and
creatinine clearance rate are 34.1 versus 36.6, respectively. In the group of patients with a creatinine clearance rate over 60 ml/min the mean MDRD and creatinine clearance rate are 65.5 en 98.4 ml/min, respectively. This implies that a patient with anaemia and hyperkalemia at an MDRD of 55.0 ml/min/1.73 m² (K-DOQI stage 3) in fact has these biochemical disturbances at a higher creatinine clearance (K-DOQI stage 2). Therefore, biochemical disturbances may already be evident in patients with only mild renal failure, which is earlier than stated in most guidelines.

**Strengths and limitations**

In this cohort, we saw a large variety in creatinine clearance levels, MDRD, and age (range 18-95 years), which allowed an overview of the prevalence of laboratory disturbances at all stages of kidney function and at many different ages in a regional population of inpatients and outpatients.

One of the limitations of this study was that we missed a number of laboratory measurements. For example, data on 1.25(OH)2-vitamin D and PTH, PaO₂, pH and iron deficiencies were insufficient. The inclusion of such data would have allowed the analysis to be more complete. Additionally, other laboratory test results were not available for all participants, and, when they were available, there was usually only one test performed per subject. The absence of these numbers did not influence the results of this study, however, as it primarily affected the population of patients without renal failure (clearance >90 ml/min), and our interest was in the patients with renal failure (clearance <90 ml/min). For all patients, only one 24-hour urine sample was collected. Reliability of our results would be higher if at least two samples were collected to take into account inaccuracies and inconsistencies in collection methods.

For estimating renal function, both the MDRD equation and the creatinine clearance were used. The MDRD formula is an estimation of 125I-Iothalamate renal clearance-based GFR measurements in 1628 patients (<70 years) with previously diagnosed CKD. Healthy subjects were not included in the study used to develop the equation. The MDRD calculation method is independent of body weight, which is an advantage. We should mention that the performance of the MDRD is different for different patient groups. It has not been validated for children, elderly subjects (>70 years), patients with acute renal failure or cardiac myopathy. The MDRD method has only been validated for Caucasian and African American subjects. Although the MDRD is quite accurate in patients with moderate to severe renal failure (eGFR <60 ml/min/1.73 m²), it loses accuracy, particularly at the higher eGFR values, leading to a systematic underestimation of renal function. This inaccuracy is further aggravated because the MDRD uses a correction factor to standardize body surface area.

The new MDRD equation is based on enzymatic methods. However, this has not resolved the aforementioned problems. Despite the disadvantages of the MDRD equation, it is currently widely used in daily practice. We should, therefore, keep its limitations in mind.
Another limitation of this study is its cross-sectional design. Only subjects with abnormal biochemistry were considered in the analysis, even though the indication for performing the tests may have been something other than renal disease. This may have resulted in a small selection bias.

Finally, some of the biochemical abnormalities are caused by treatment. E.g. potassium levels may rise as a result of the use of RAAS-inhibitors, including Spironolactone. The cause of the abnormal level is not relevant: each has to be assessed and treated on an individual basis. Accordingly, the statements outlined in the guidelines must be valid for all subjects, not only those who are drug naïve. Virtually everybody with decreasing renal function will need treatment for one or more conditions and abnormalities. Although abnormalities resulting from loss of renal function may develop at a different pace, a holistic approach is indicated in all cases. We have to include that, within a single patient, biochemical and haematological abnormalities may occur at a much earlier stage of declining renal function than previously reported in the literature.

Conclusion

The number of patients with mild renal insufficiency showing haematological and biochemical disturbances is relatively small, ranging from nine (11%) with hyperphosphataemia to 129 (29%) with anaemia in subjects with an eGFR of 60-90 ml/min/1.73 m² as measured with the MDRD method. As these patients represent a significant proportion of the total population of patients with mild renal failure, these numbers should be taken into account in daily practice. Adverse outcomes may be prevented or delayed with the early detection and treatment of declining renal function as well as the resulting haematological and biochemical abnormalities. Special attention should be paid to anaemia and hypocalcaemia in elderly patients with diminishing renal function, since the prevalence of these disorders is notably higher in this group. In subjects with a creatinine clearance of 60-90 ml/min, anaemia was present in 11.0% of subjects <65 years and in 30.2% of subjects >65 years. At a creatinine clearance <45 ml/min, hypocalcaemia was present in 4.9% of <65 year old subjects versus 5.3% in subjects over 65 years of age. When assessing renal function with the MDRD method, these abnormalities are apparent even earlier and to a greater extent.

Based on our results, we would like to propose a change in the presently available guidelines, particularly with respect to the elderly population. We found that anaemia, hyperkalaemia, hypocalcaemia, and uraemia may already be present with only a mild reduction in renal function, independent of the method used to measure creatinine clearance. However, serum phosphate does not increase until a clearance <45 ml/min is reached. It may therefore be important to test patients for serum abnormalities at an earlier stage of their kidney disease so that clinically relevant abnormalities may be treated early.
References

PART 3
THE BRAIN