Sir,

We thank Dr Di Iorio et al. for their comments and interest in our work. We agree with them about a relevant role of comorbidities as predictors of sleep disorders in dialysed patients, as recently reported by De Santo et al. [1] and Mucsi et al. [2]. In our study [3], we considered only a few clinical conditions associated with uraemia, but our questionnaire included a specific question regarding general medical history that was correctly completed by nephrologists. Taking advantage of Di Iorio et al.’s letter, we decided to evaluate in our sample the role of comorbidities as risk factors for sleep complaints, using the Charlson Comorbidity Index (CCI). Our dialytic patients with and without sleep disturbances showed a significantly different CCI score (3.13 ± 1.45 vs 2.59 ± 0.99, P < 0.001, respectively). Multivariate logistic regression confirmed that the CCI score was a significant and independent predictor of sleep disorders in dialysed patients (OR for one unit increment in CCI score, 1.44; 95% CI 1.20–1.73; P < 0.001). In patients with end-stage renal disease undergoing dialysis, comorbidities can affect the patients’ outcome per se [4] and increase the risk of sleep disturbances. Thus according to Di Iorio et al., we suggest an attentive assessment of clinical conditions associated with uraemia.

In our study, sleep disorders were related to age, while we did not observe differences regarding the use of any type of drugs, including anti-hypertensive [3]. In the general population, the relationship between hypertension and sleep disorders, particularly insomnia, is known [5]. Recently, De Santo et al. [1] reported a significant independent association between the use of anti-hypertensive drugs and sleep disorders in dialysed patients, but the mean arterial pressure did not differ in subjects with and without sleep complaints. In our opinion, further studies are necessary to evaluate a possible relation between hypertension and disturbances during sleep in uraemic subjects.

The effect of dialysis shift in the morning on insomnia is known [1,3] and, if possible, it should be treated by nephrologists. Even if psychological problems have been suggested to explain symptoms of insomnia on the morning shift, other mechanisms could be implicated (i.e. abnormal circadian rhythms).

Sleep in patients with chronic kidney disease not yet treated with dialysis is disturbed [6], causing insomnia symptoms [7]. In renal failure, several conditions can compromise quality of sleep determining insomnia (i.e. psychological factors, metabolic abnormalities or specific sleep complaints). The largest studies evaluating patients in chronic kidney disease not treated with dialysis did not consider the effect of peculiar disturbances during sleep, such as restless legs syndrome (RLS) or sleep apnoea [6,7]. Only Parker et al. [8] compared sleep variables in patients with chronic kidney disease and those on haemodialysis using polysomnography. They reported a higher respiratory disturbance index and periodic limb-movement index in dialysed patients, but these differences were not significant. Moreover, Parker’s sample was too small to consider their results as conclusive. We think that an adequate treatment of sleep complaints in chronic kidney disease and an accurate knowledge of pathophysiology of sleep disturbances associated with renal failure (i.e. RLS and sleep apnoea) depend on the answer to the question: ‘Do sleep disorders differ in dialysed patients and in those with early chronic kidney disease?’.

Further studies should investigate this issue.

Conflict of interest statement. None declared.


doi:10.1093/ndt/gfl149

Advance Access publication 12 April 2006

Is the diagnosis of chronic kidney disease missed in diabetic women?

Sir,

Middleton et al. [1] have pointed out the high prevalence of chronic kidney disease (CKD) in diabetes: 27.5% of their 7596 diabetic patients had an estimated (MDRD equation) glomerular filtration rate (GFR) below 60 ml/min/1.73 m², and most of them were unrecognized using the recommended determination of serum creatinine and albumin excretion rate. Interestingly, the MDRD-based diagnosis of CKD was twice as frequent in women in this study. This prompted us to test whether the underestimation of normal GFR by the MDRD equation that we have noted in diabetic subjects [2], was more pronounced in women.

In 81 diabetic patients (51 men, 29 type 1, age: 58 ± 15 years) with a measured GFR (5ICr-EDTA clearance) above 60 ml/min/1.73 m², we compared the MDRD estimation (four-variable version, as described by Middleton et al. [1]) with the measured GFR, before (paired t-test) and after categorizing the subjects according to gender (ANOVA and unpaired t-tests). Results are presented as mean ± SD.

The mean measured GFR was 90.4 ± 27.1 ml/min/1.73 m² (60.4–160). The mean MDRD was 71.4 ± 21.6 (P < 0.0001 vs measured). Twenty-seven (33%) of the 81 patients had an
MDRD estimation below 60. Fourteen (52%) were women, whereas 16 women (29.6%) had an MDRD estimation over 60 ($P < 0.05$ by chi square). The comparison between men and women is shown in the Table 1.

Although populations may differ, diabetic nephropathy is usually reported as more prevalent among men than women [3,4]. The more marked underestimation by the MDRD in women as we found, probably contributed to the gender difference reported by Middleton et al. [1]. The reason why the MDRD underestimates normal GFR to a larger extent in women is unclear, however, it should be borne in mind that the MDRD equation has been established by a multiple regression procedure, from the results of renal insufficient patients, including only 6% diabetic subjects [5]. It is more accurate than the widely used Cockcroft-Gault formula to diagnose and stratify CKD in diabetics [2], but in our opinion the underestimation of high GFR makes it an inappropriate tool for screening diabetic patients for nephropathy. In patients with normal renal function, the MDRD equation should be used with caution, which may lead to the wrong conclusions, as noted by epidemiological studies on the relation between renal function and cardiovascular risk factors [6].

Acknowledgements. We would like to thank Dr S. Jarman for the revision of the English manuscript.

Conflict of interest statement. None declared.

Table 1. Measured and MDRD-estimated GFR (ml/min/1.73 ms) in diabetic men and women, compared by ANOVA and unpaired t-tests

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured GFR</td>
<td>89.8 ± 27.7</td>
<td>90.8 ± 26.9</td>
<td>NS</td>
</tr>
<tr>
<td>MDRD estimation</td>
<td>63.7 ± 17.4</td>
<td>75.9 ± 22.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Difference</td>
<td>26.1 ± 25.8</td>
<td>14.9 ± 20.9</td>
<td>0.03</td>
</tr>
</tbody>
</table>

NS, not significant.


doi:10.1093/ndt/gfl180

Advance Access publication 12 April 2006

Reply

Sir,

We would like to thank Rigalleau et al. for their comments and interest in our study [1]. They have compared the four-variable MDRD-GFR with isotope-GFR (51Cr-EDTA) in 81 subjects with diabetes and normal mildly impaired renal function and found that the MDRD formula underestimated GFR. This has previously been noted in patients with normal/mildly impaired renal function [2], but they found the difference to be greater in the 30 female subjects studied. The authors do not comment on the method of creatinine analysis or on whether this was calibrated to the Cleveland laboratory where the MDRD formula was first derived from creatinine measures, and so it is difficult to confirm whether there is a true gender bias in the MDRD formula.

Whilst the authors find a significant underestimation of GFR using the MDRD formula compared with isotope GFR measurements, we do not believe this necessarily supports the conclusion that ‘underestimation of high GFR makes it an inappropriate tool for screening diabetic subjects for nephropathy’. An essential requirement of a screening tool is that it is cheap and widely available. Hence, it is inappropriate to compare MDRD-GFR with isotope-GFR, which is both expensive and inappropriate for routine use, and which in addition exposes patients to a significant radiation risk.

We do agree with Rigalleau et al.’s conclusion, that the MDRD equation should be used with caution in patients with normal renal function’. The main limitation of the MDRD formula in routine practice is the well-documented imprecision of the formula at normal renal function. In addition, even in subjects with impaired renal function, difficulties in accurate interpretation exist due to issues regarding calibration of creatinine assays. For example, serum creatinine levels were 20.3 μmol/l higher in the White Sands laboratory for the National Health and Nutrition Examination Survey (NHANES) III study when compared with the Cleveland laboratory which undertook the MDRD study [3]. Methodological problems with serum creatinine assays have their greatest impact within or close to the reference range for creatinine, with wide confidence intervals for an individual GFR, and this should be taken into consideration by clinicians when interpreting results.

In the future, superior markers of renal function in the normal or mildly impaired range, such as cystatin C, may supersede creatinine and GFR estimations. Calibration of individual laboratory’s assays to the Cleveland laboratory will help with issues around accuracy in the short term. In the medium term, it is hoped that serum creatinine assays will be calibrated using an internationally agreed standard.

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