

## COMMENTARY

# Chronic kidney disease, 24-h blood pressure burden and their effects on silent cerebral injury and cognitive impairment: might age serve as a modulator?

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Vascular diseases of the brain are a major cause of death and disability.<sup>1</sup> Magnetic resonance imaging has revealed that white matter lesions (WML) are common in the elderly<sup>2</sup> and are associated with stroke.<sup>3</sup>

Given the enigmatic nature of WML, it is important to find novel risk factors that clarify their pathophysiology and serve as targets for risk reduction. Hypertension is a major risk factor for WML,<sup>4</sup> and ambulatory blood pressure is more closely correlated with WML than is casual blood pressure.<sup>5</sup>

Chronic kidney disease (CKD) has emerged as another independent risk factor for stroke.<sup>6</sup> WML is prevalent in patients with end-stage renal disease.<sup>7</sup> In the Northern Manhattan Study, moderate to severe CKD was associated with increased WML volume, indicating the importance of CKD as a possible marker of cerebral microangiopathy.<sup>8</sup>

In this month's issue, Yamamoto *et al.*<sup>9</sup> report their investigation of the relationships among kidney function, ambulatory blood pressure measures, silent cerebral injury and cognitive function in 224 patients with symptomatic lacunar infarction. Non-dipper, riser, estimated glomerular filtration rate (eGFR) <60 and moderate to severe WML are independently and significantly associated with cognitive impairment. Advanced age and eGFR <60 are significantly associated with severe WML. Therefore, CKD seems to have a causal link with cognitive impairment via WML. Although we recognized that CKD

has significant relationships with WML and cognitive impairment in this study population, we wondered whether these relationships would hold true in other populations.

Several points should be considered when interpreting the results of Yamamoto *et al.*<sup>9</sup> study. First, in the Modification of Diet in Renal Disease (MDRD) equation, age, gender and serum creatinine levels were included in the formula.<sup>10</sup> Because creatinine was lowered due to muscle loss, the elderly lean subjects tended to have decreased eGFR. With the current staging system, people who are older than 70 years dominate the category of moderate renal impairment (GFR from 30–59 ml min<sup>-1</sup> per 1.73 m<sup>2</sup>; stage 3).<sup>11</sup> Age might therefore serve as a potential modifying factor, specifically for the relationship among CKD, WML and cognitive impairment in this study.

Second, the mean eGFR in the population ranged from 49.5–64.5 ml/min per 1.73 m<sup>2</sup>. This result should be cautiously interpreted, because the significant association between CKD and cognitive impairment was shown only in the elderly subjects with relatively decreased eGFR. What is the relationship in the general population? The current MDRD equation was inaccurate for mildly decreased eGFR (60–90 ml min<sup>-1</sup> per 1.73 m<sup>2</sup> ranges: stage 2), which is called the 'creatinine-blind' range. Although mildly decreased GFR may be considered a 'preclinical' disease, there is little evidence that they are associated with poorer clinical outcomes.<sup>12</sup>

Recently, several low molecular weight endogenous proteins have been evaluated as alternative markers to creatinine. Cystatin C (CysC), which is rarely affected by muscle loss, has received the most attention.<sup>6</sup> In the

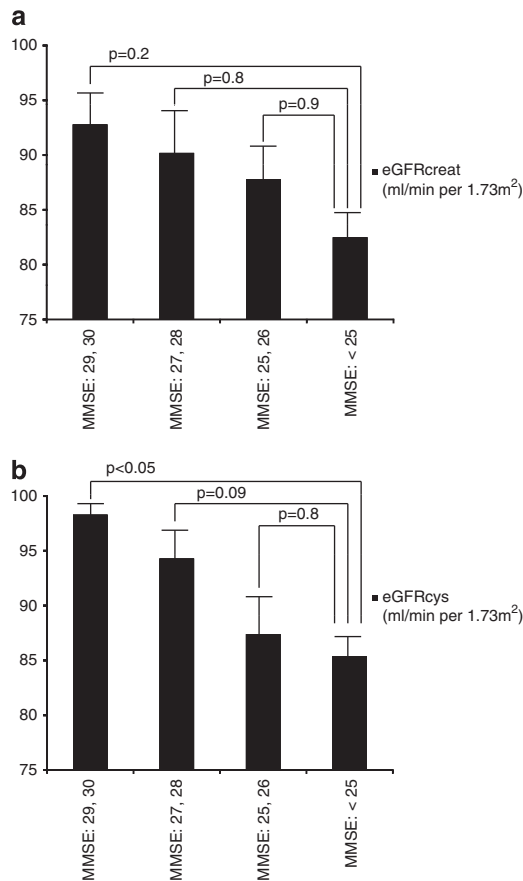
Hiroshima–Shobara–Soryo COhort (3SCO) study, we investigated the relationship between kidney function and cognitive function among the 201 high-risk elderly at cardiovascular disease (79.9 ± 6.4 years old; female, 75%; anti-hypertensive medication use, 71%). Kidney function was estimated on the basis of serum creatinine (eGFR<sub>creat</sub>), using the MDRD equation,<sup>10</sup> and eGFR was estimated on the basis of CysC (eGFR<sub>cys</sub>), using Hoek's equation: eGFR<sub>cys</sub> = -4.32 + 80.35 × 1/CysC.<sup>13</sup>

The mean eGFR<sub>creat</sub> and eGFR<sub>cys</sub> were 88.9 and 92.4 ml min<sup>-1</sup> per 1.73 m<sup>2</sup>, respectively. In the analysis of variance among groups according to the quartile of the Mini Mental State Examination (MMSE) score, eGFR<sub>creat</sub> was not significantly different between the groups ( $P=0.26$ ; Figure 1a). However, eGFR<sub>cys</sub> was significantly different between the groups ( $P<0.05$ ; Figure 1b). Subjects in the lowest quartile of MMSE score had significantly lower eGFR<sub>cys</sub> than those in the highest quartile ( $P<0.05$ ; Figure 1b). However, this relationship was attenuated after adjusting for age ( $P=0.18$ ).

In the high-risk elderly subjects, eGFR<sub>cys</sub> was more closely associated with cognitive function than eGFR<sub>creat</sub>. Earlier studies have shown that serum CysC may be a sensitive indicator in identifying mild reductions in kidney function than serum creatinine.<sup>14</sup> Therefore, lowered cognitive function might be observed in elderly patients with mildly decreased GFR. In addition, age might serve as a moderator for this relationship.

Based on the results of this and previous studies, decreased kidney function might be an indicator for the cognitive impairment in subjects with moderate-to-severe CKD and

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**Figure 1** Mean value of estimated glomerular filtration rate (eGFR). Mean eGFR was presented according to the quartile of mini mental state examination (MMSE) score. Analysis of variance was used to determine differences in serum creatinine (eGFRcreat) (a) and CysC (eGFRcys) (b) among four groups. Although eGFRcreat was not significantly different between the groups ( $P=0.26$ ), eGFRcys was significantly different between groups ( $P<0.05$ ).

in those with mildly decreased GFR. Until now, there have been few reports assessing the relationship among CKD, WML and cognitive impairment. Therefore, the data presented by Yamamoto *et al.*<sup>9</sup> make an important contribution, if they are considered within the context of the study's limitations.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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