The reversible part of cognitive impairment in chronic kidney disease: can mice help men break the TEMPOLimit?

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Discussing the non-adherence to diet or medication with chronic haemodialysis patients can be an utterly frustrating experience, especially if one does this thrice a week. It is also a reflection of the fact that for more than half a century, nephrologists have been focusing on cardiovascular morbidity and mortality in chronic kidney disease (CKD) patients. Over the last decade, however, burgeoning evidence has accumulated to show that CKD also affects the patient’s brain. CKD is accompanied by severe cognitive impairment as recently reviewed by Elias et al. [1]. Kurella et al. [2] could show that decreased estimated glomerular filtration rate (GFR) in postmenopausal women is significantly associated with impairment in global cognition, executive function, language and memory. A community-based cross-sectional study found that global performance and specific cognitive functions are negatively affected early in CKD [3]. Interestingly, not only decreases in GFR but also elevated urinary albumin/creatinine ratios are independently associated with faster decline in cognitive function [4]. In a 5-year longitudinal community-based study, change in renal functioning over time was related to change observed in global cognitive ability, verbal episodic memory and abstract reasoning [5]. Moreover, moderate renal impairment has been shown to be associated with an excess risk of incident dementia among individuals in good to excellent health [6]. Naturally, cognitive impairment cannot be revealed during the discussions about phosphate binders and anti-hypertensives. The backbone for detection of cognitive impairment are psychometric tests, first introduced in 1944 by the US Army in the Army Individual Test Battery—Manual of Directions and Scoring. Part of this test battery was the trail making test (TMT), a neuropsychological test of visual attention and task switching. It consists of two parts in which the subject is instructed to connect a set of 25 dots as fast as possible while still maintaining accuracy (TMT A) [7]. It can provide information about visual search speed, scanning, speed of processing, mental flexibility as well as executive functioning that are evaluated in the TMT B [7]. It is more sensitive to detecting decline in cognitive function in different stages of CKD than the Modified Mini-Mental State Examination (3MS) [8]. The severity of cognitive impairment is best epitomized by the fact that a high school educated 50-year-old person is able to finish the TMT B in ~1 min, whereas ~20% of dialysis patients in the same age group are not able to finish the TMT B in 5 min [9].

The pathophysiological mechanisms leading to cognitive impairment in CKD are still not clearly understood. They may range from effects of urea to the endogenous NOS inhibitor asymmetric dimethylarginine (ADMA [10, 11]). Of note, there is an irreversible and a reversible component of cognitive impairment in CKD (Figure 1).

The underlying diseases causing CKD, mostly arterial hypertension and diabetes, go along with structural cerebral changes. This is best epitomized by the facts that CKD5D patients have a 6-fold age-adjusted relative risk of stroke when compared with the general population [12]. Also, the prevalence of asymptomatic silent cerebral infarction is four to five times higher in dialysis patients than in age- and sex-matched controls [13]. A recent systematic review of structural neuroimaging findings in CKD came to the conclusion that cerebral atrophy and cerebral density changes in patients with CKD are frequently seen along with cerebral vascular disease, including deep white matter hyperintensities, white matter lesions, cerebral microbleeds, silent cerebral infarction and cortical infarction [14], both known to be associated with cognitive impairment and depression [15].

Aside from general risk factors for dementia, like hyperglycemia [16], there are those related to uraemia. The first
shown the relentless loss of weight and the mental deterioration of patients led to a situation in which cognitive impairment is reversible. They stated that the intensity of dialysis in the first two chronic haemodialysis patients led to a situation in which neither patient has yet shown the relentless loss of weight and the mental deterioration which has been encountered in the past [17]. Indeed, in a report of severe uraemia (creatinine 2443 µmol/L), a day-to-day improvement in neuro-cognitive function by dialysis using a state-of-the-art test battery could be shown [18]. Especially executive functions, which are assumed to be working memory performance in CKD mice. In parallel to the (partial) correction of cognitive decline in severe uraemia, experiments with animals may represent an indispensable tool. In this issue of NDT, Fujisaki et al. [22] choose a preclinical approach to this problem. They subjected male C75Bl/J6 mice to 5/6 nephrectomy and studied them for a period of 4 and 8 weeks. Deng et al. [23] showed already more than a decade ago that 5/6 nephrectomy in rats resulted in oxidative stress and increased tyrosine nitration in the cerebral cortex. The novelty in the study of Fujisaki is that they performed functional tests, i.e. working memory tested by radial arm water maze. While there was no difference after 4 weeks, 8 weeks after CKD induction, vehicle-treated mice made significantly more errors than sham-operated control mice. Tempol (TMP) improved working memory performance in CKD mice. In parallel to the working memory tests, 5/6 nephrectomy for 8 weeks was associated with accumulation of 8-hydroxy-2′-deoxyguanosine in the hippocampal neuronal cells, but not so in the TMP-treated CKD mice. Increased numbers of pyknotic neuronal cells were observed in the hippocampus of CKD mice at 8 weeks, but pyknotic neuronal cell numbers were decreased under the influence of TMP in uraemic mice. Interestingly, a previous report indicated that antioxidant therapy and angiotensin-converting enzyme inhibition alleviated the oxidative stress and mitigated tyrosine nitration in the brain of uraemic rats [23]. Fujisaki et al. also explain the beneficial effect of TMP on disrupted behaviour as well as on the reduction of neuronal damage in uraemic rodents by its antioxidative action. Uraemia-induced oxidative stress is known to overactivate glutamatergic N-methyl-D-aspartate receptors and to increase nitric oxide synthesis, which leads to the formation of peroxinitrite and to protein nitration. These cell pathological alterations may indeed significantly contribute to cognitive impairment [24]. So, why not try TMP in patients, all the more as TMP (4-Hydroxy-TEMPO) is a well-characterized superoxide scavenger that displays neuroprotective, anti-inflammatory and analgesic effects, which was ranked 10th out of 8508 ‘compound’ concepts (top 0.12%) in BioGraph’s knowledge? Nota bene—TMP is ranked 10th in a list of ideas for future treatment of renal failure, but not of treatment practised in humans. As far as we know, TMP has not yet been administered to human subjects (except as a topical agent to prevent radiation-induced alopecia [25]). Remarkably, TMP has recently been demonstrated to prevent carboxylation and covalent dimerization of human superoxide dismutase (SOD) 1, events which lead to structural modification and functional impairment of SODs [26], thus giving hope for being active in the defence of free radicals in humans, too. And so, should we now use TMP or other antioxidants in our CKD patients to slow down the decline in cognitive function or even reverse it like Fujisaki et al. did in mice? In real life, the antioxidant defence system is more complex and consists of hundreds of enzymes and endogenous and dietary antioxidant molecules which are not interchangeable and work in concert to maintain redox balance. Excessive exogenous amounts of antioxidants can even worsen oxidative stress as shown for TMP in an animal model of glomerulonephritis where it increased production of hydrogen peroxide and triggered inflammation and tissue damage via activation of NfκB [27]. Also, in men, the data from antioxidant use in larger patient population failed to show an improvement in cognitive function. In the 2824 participants of the Women’s Antioxidant Cardiovascular Study, antioxidant supplementation did not slow cognitive change among women with preexisting cardiovascular disease or cardiovascular disease during the 5.4-year study period. A limitation of big studies is the fact that insensitive cognitive tests, sometimes performed via telephone, are used [28]. But also a recent Cochrane analysis that could not find an effect of therapy with antioxidants in CKD patients neither in general nor on cerebrovascular disease (cognitive impairment was not specifically tested) curb our enthusiasm [29]. For now, we should start screening our patients for cognitive impairment ideally before we have the third discussion about diet and non-adherence of the week.

**FIGURE 1:** Examples for irreversible, reversible and potentially reversible components of cognitive impairment in CKD.
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CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Fujisaki et al. Cerebral oxidative stress induces spatial working memory dysfunction in uremic mice: neuroprotective effect of tempol. Nephrol Dial Transplant 2014; 29: 529–538.)

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