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Kidney disease and aging: A reciprocal relation

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ABSTRACT

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are overrepresented in elderly patients. This provides specific challenges for the treatment, as the start of dialysis in vulnerable elderly patients may be associated with a rapid decline in functional performance. However, prognosis in elderly patients with ESRD is quite variable and related to the presence of comorbidity and geriatric impairments. The decision to start dialysis in elderly patients should always be based on shared decision making, which may be aided by the use of prediction models which should however not be used to withhold dialysis treatment. The treatment of ESRD in elderly patients should be based on a multidimensional treatment plan with a role for active rehabilitation.

Moreover, there also appears to be a reciprocal relationship between aging and CKD, as the presence of geriatric complications is also high in younger patients with ESRD. This has led to the hypothesis of a premature aging process associated with CKD, resulting in different phenotypes such as premature vascular aging, muscle wasting, bone disease, cognitive dysfunction and frailty. Prevention and treatment of this phenotype is based on optimal treatment of CKD, associated comorbidities, and lifestyle factors by established treatments. For the future, interventions, which are developed to combat the aging process in general, might also have relevance for the treatment of patients with CKD, but their role should always be investigated in adequately powered clinical trials, as results obtained in experimental trials may not be directly translatable to the clinical situation of elderly patients. In the meantime, physical exercise is a very important intervention, by improving both physical capacity and functional performance, as well as by a direct effect on the aging process.

1. Introduction

Chronic kidney disease (CKD) is a very important non-communicable disease that affects millions of people worldwide these days (Couser et al., 2011). This is of great importance, given the fact that CKD is associated with a significant increase in morbidity and mortality and a decrease in health related quality of life. The severity of these complications is generally proportional to the decline in renal function and by far most pronounced in patients with end-stage renal disease (ESRD) (Abdel-Kader et al., 2009; Perlman et al., 2005; Matsushita et al., 2010). Next to this, CKD has significant economic consequences. This is exampled by the fact that Medicare in 2009 spent 29 billion dollars for ESRD treatment (U.S. Renal Data System).

The risk of CKD increases with age and elderly patients are overrepresented in the dialysis population (Nitta et al., 2013). Moreover, there appears to be a reciprocal relation between CKD and aging, since it also may contribute to premature biological aging of different organ systems (Kooman et al., 2014; Stenvinkel and Larsson, 2013). This may result in the occurrence of "geriatric" complications in relatively young patients with ESRD (Johansen et al., 2007).

The aim of this review is firstly to provide a global overview on the reciprocal relation between CKD and aging, and secondly, to discuss the specific challenges of treating ESRD in the elderly.

1.1. Prevalence of CKD in the elderly

According to convention, CKD is subdivided into 5 different stages, of which CKD 3 (estimated glomerular filtration rate [eGFR] 30–60 ml/min/1.73 m^2) is the most common, and CKD 5 (eGFR below 15 ml/min/1.73 m^2) is classified as ESRD. The prevalence of all stages of CKD combined was between 9.2 and 12.5% in the general population according to different European cohort studies, with a large overrepresentation of early stages of CKD (de Jong et al., 2008). Although many younger patients are affected by CKD due to congenital disorders, glomerulonephritis and type I diabetes, CKD is overrepresented in the elderly. Firstly, this is due to the age-related decrease in kidney function due to glomerular, tubular and vascular changes, and secondly to the fact that age-related diseases such as type II diabetes and generalized atherosclerosis often affect the kidney (Nitta et al., 2013). Also, due to its reduced functional reserve, the aging kidney is more susceptible to nephrotoxic agents and drugs (Abdel-Kader and Palevsky, 2009). In

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the NHANES study, the risk for CKD was increased more than 8 times in patients above 60 years of age (http://www.usrds.org/2014/download/V1_Ch_01_GenPop_14.pdf), although there is discussion whether stage 3a CKD (eGFR 30–45 ml/min/1.73 m^2) without other signs of renal damage can really be classified as a "disease" in the elderly given the generalized age related decline in renal function (Delanaye et al., 2015). Moreover, it should be noted that there is still limited validation of the most commonly used formulas to estimate renal function, such as the CKD-EPI formula, in elderly subjects. However, there is no consistent evidence for larger misclassification errors in the elderly as compared to younger persons with the use of a prediction formula for estimated glomerular filtration rate (Kilbride et al., 2013).

Most elderly patients with CKD do not progress to ESRD or die from causes other than renal failure (Hemmelgarn et al., 2006; O'Hare et al., 2007). Nevertheless, their mortality risk, mainly from cardiovascular (CV) causes is increased as compared to elderly without CKD (O'Hare et al., 2007).

Despite the fact that most elderly patients with CKD do not experience a rapid decline in renal function, due to the aging of the general population also the use of dialysis treatment in the elderly is globally rising (Canaud et al., 2011). As will be discussed later, this may impose treatment challenges given the generally limited prognosis of ESRD in the elderly and the possible adverse effect on functional status (Kurella Tamura et al., 2009).

1.2. ESRD treatment in elderly

When reaching ESRD, patients are usually prepared for renal replacement therapy. There are three main forms of renal replacement therapy. Although no absolute chronological age limit for renal transplantation can be identified, most elderly patients are either treated with intermittent hemodialysis (HD) or peritoneal dialysis (PD). During intermittent HD, patients are generally treated 3 times weekly during 4 h and are connected to a dialysis module. During HD, blood is recirculated through an artificial membrane and is cleansed by diffusion with a purified solution (dialysate) from which it is separated by an artificial membrane. Excess fluid is removed by a pressure gradient between the blood and the dialysate compartment (ultrafiltration) Dialysis is very efficient in removing uremic toxins and water as well as in correcting electrolyte and acid base disorders, but also increases the risk for homeostatic imbalance due to the rapid changes in the internal. During PD, a sterile dialysis fluid is installed in the peritoneal cavity through a catheter. This fluid is exchanged several times either manually or with the aid of a device.

Whereas dialysis techniques are lifesaving in ESRD, the start of dialysis in an elderly patient with multiple geriatric impairments may have significant consequences on their functional performance. In a study in nursing home patients with a mean age of 73.4 $\pm$ 10.9 years, 58% had died within one year whereas functional status had only been maintained in 13% of patients (Kurella Tamura et al., 2009). However, other cohorts with a less selected elderly population showed a less dramatic view although outcome of elderly patients appeared to be highly variable (Couchoud et al., 2009).

In other cohorts in elderly dialysis patients, survival was significantly higher with dialysis as compared to conservative treatment but a significant part of this increased survival time was occupied by days on which dialysis was performed or when patients were hospitalized (Carson et al., 2009).

1.3. Prediction models in elderly patients with ESRD and their role in shared decision making

Given the varied outcome of elderly patients with CKD, the question therefore is whether outcome on HD can be predicted in order to aid shared decision making whether to start dialysis or not.

In order to address this question several survival scores were developed, based on different parameters such as nutritional factors, comorbidity and functional status. Whereas these scoring systems all had a significant relation to survival, it remains difficult to reliably stratify patients according to the available scoring systems as none of the available models achieved a concordance ("c") statistic above 0.7 [a c-statistic 1.0 means perfect prediction, whereas a c-statistic of 0.5 is equal to the flip of a coin) (Cheung et al., 2014).

The so-called surprise question, by which the health care professional answers the questions whether he/she would be surprised if the patient died during the coming year also carries prognostic significance and adds information to the existing models. In one study, a prognostic model including the surprise question yielded a c-statistic of 0.8 (Cohen et al., 2010). Although these models should in our opinion not be used to withhold dialysis treatment, they may play an important role in shared decision making. At present, the Renal Physicians Association (RPA) guidelines for shared decision making advice considering conservative therapy in elderly patients with a high comorbidity score (Charlson > 8), a markedly impaired functional impairment (Karnovsky < 40), severe malnutrition and a positive "surprise question" (Moss, 2001).

Treatments of elderly ESRD patients with multiple comorbidities and geriatric impairments is challenging, and dialysis treatment should be regarded as one part of a multidimensional treatment plan, with an active role for rehabilitation and psychosocial support (Jassal and Watson, 2010).

1.4. Premature biological aging

CKD is not only a disease of the aged, but also appears to contribute to a premature aging process. This is especially apparent in ESRD, but is likely to originate earlier in the course of renal disease (Kooman et al., 2014; Stenvinkel and Larsson, 2013). In ESRD patients, the mortality rate is increased in all age groups, as compared to the general population, with the largest relative difference in younger subjects (Koopman et al., 2011).

Next to cellular signs of aging such as shortened telomeres, the premature aging syndrome is evident from various phenotypes. One of the most distinct phenotypes is the uremic vascular phenotype, characterized by medial calcifications and increased vascular stiffness, which are both important risk factors for mortality in this population (Briet et al., 2012). Also an increase in vascular stiffness is already observed in early stages of CKD (Hermans et al., 2007) and is generally increased at all age groups as compared to the general population. Interestingly, the relation between CKD and arterial stiffness may be mutually reinforcing, possibly by changes in glomerular hemodynamics due to the increase in pulse pressure (Ford et al., 2010). Vascular calcification and an increase in vascular stiffness are even highly prevalent in young-adult ESRD patients (Goodman et al., 2000).

Also the prevalence of cognitive dysfunction, which may be related to white matter lesions secondary to microvascular dysfunction, is far more prevalent in ESRD as compared to healthy controls, although subclinical abnormalities are also apparent at earlier stages of CKD (Kurella et al., 2005; Bugnicourt et al., 2013).

CKD has important effects on mineral metabolism, both with regard to deficiency of active vitamin D, an increase in serum phosphate and a decrease in calcification inhibitors. Moreover, there is an intricate relation between renal bone disease and vascular abnormalities whereas phosphate itself appears to be an important pro-aging factor (Stenvinkel and Larsson, 2013; Moe et al., 2007; Shanahan, 2013).

In addition, muscle wasting is common in advanced CKD and independently related to outcome (Stenvinkel et al., 2015a). Of concern is the very high prevalence of frailty even in young patients with ESRD. As an example, in a study of 2275 HD patients, 44% of patients under the age of 40 were classified as frail according to the presence of 3 or more criteria according to the modified Fried classification (Johansen et al., 2007). The high prevalence of frailty is of major importance given its adverse relation to outcome and relation to disability (McAdams-DeMarco et al., 2013;