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NEPHROLOGY - REVIEW

Promoting functioning and well-being in older CKD patients: review of recent evidence

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Abstract Osteoporosis, falls, sleep difficulty, cognitive impairment, and depressed mood are major clinical concerns in the geriatric population that are physiologically and psychologically based and are often interrelated. All of these issues have implications for patients' daily functioning and quality of life (QOL). This review synthesizes recent evidence about these prominent issues in geriatric care and related implications for care of older patients with chronic kidney disease (CKD). Recent evidence about pre-dialysis and dialysis treatment strategies that may help to optimize management of older patients is also considered. Although elderly patients often report better psychosocial adjustment to dialysis than do younger patients, physical functioning and cognitive functioning losses challenge the QOL of many elderly persons. Early management of CKD and attention to anemia, consideration of the benefits of peritoneal dialysis compared with hemodialysis, and inclusion of some form of exercise or regular physical activity in routine care provide key opportunities to enhance the functioning and well-being of older patients.

Keywords Anemia management · Chronic kidney disease · Cognitive functioning · Depression · Dialysis modality · Exercise · Osteoporosis · Quality of life · Sleep disorders

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Introduction

The expanding knowledge base in geriatrics and gerontology provides important insights for managing issues that challenge the functioning and well-being of geriatric patients. These insights have important implications for optimal management of older persons with chronic kidney disease (CKD) who require renal replacement therapy. Osteoporosis, falls, sleep difficulty, cognitive impairment, and depressed mood are prominent clinical concerns in the geriatric population that are physiologically and psychologically based and are often interrelated. All of these issues have implications for patients' daily functioning and quality of life (QOL). The purpose of this review is to synthesize recent evidence about management of these prominent issues in geriatric care that in turn have implications for care of older patients with CKD. Recent evidence about pre-dialysis and dialysis treatment strategies that may help to optimize management of older patients is also summarized.

Challenges to functioning and well-being in geriatric patients

Osteoporosis, falls, and fractures

Among the risk factors for osteoporosis in the general population are advancing age, female gender, white race, and low physical activity. Bone strength may be more severely affected during the course of CKD than in the normal aging process because of the additional effects of renal osteodystrophy. When it induces musculoskeletal pain, osteoporosis negatively influences patients' QOL.

Osteoporosis also contributes to increased bone fracture risk. In end-stage renal disease (ESRD) patients, the risk for hip fracture is 3–4 times greater than in the general population. Secondary hyperparathyroidism, adynamic bone disease and osteomalacia, prior use of corticosteroids, and chronic acidosis are factors that may reduce bone mineral density and contribute to increased fracture risk in ESRD patients. Bone biopsy to exclude adynamic bone disease is recommended before beginning treatment with biophosphonates in CKD and dialysis patients [1].

Given an increased risk of bone fracture among renal patients, it is important to consider the factors associated with falls in the geriatric population and in renal patients in particular. Falls are attributable to multifactorial events that have intrinsic components, such as changes in single or multiple physiological systems, as well as extrinsic factors, including medication intake and environmental hazards [2]. These intrinsic and extrinsic factors are relevant for elderly persons generally, and the fall risk associated with some of these factors may be increased for elderly renal patients.

Fall events are important not only because of potential fractures and hospitalization but also because of QOL consequences. Fear of experiencing repeated falls can results in loss of self-confidence and self-restriction of activity, which may in turn contribute to reduced exercise and muscle mass and increased fall risk. Falls are also a leading cause of admission to nursing homes [3].

Roberts et al. [4] found in a study of 78 hemodialysis (HD) patients that a recent fall was much more often reported by patients >65 years old (38%) than by patients who were ≤65 years old (4%). One-quarter of the HD patients studied by Roberts et al. reported experiencing syncope. A high rate of post-dialysis hypotension is known to occur among dialysis patients and may contribute to syncope, which in turn may increase risk of falling. Desmet at al. [3], who studied 308 elderly HD patients in Belgium (median age 70.9 years), found that falls tended to be more common within the first half of the interval between HD treatments. The investigators suggested that this finding might reflect a greater risk for hypovolemia following HD treatment and that it calls for additional caution to prevent falls following HD treatment, as well as for careful continuous adaptation of dry body weight.

The role of impaired strength and balance in older patients should also be considered. Among 162 elderly HD patients (mean age 75 years) studied by Cook and Jassal [5], one-third reported that they had fallen during the past year. Multiple falls were common among these patients [6], and impaired mobility, as assessed by standardized physical performance tests, was prominent [5].

The potential of targeting physical performance remains largely unexplored in elderly dialysis patients. Geriatric research increasingly suggests that walking speed provides a single, sensitive screen for vulnerability to outcomes such as falls, and increased physical activity can help to decrease this vulnerability [7, 8]. Although guidelines are needed, targeting deficits in patients' mobility, strength, and balance would be a valuable addition to nephrology practice [5]. A logical first step would be simple interventions to increase physical activity, such as recommending that patients begin a walking program [9].

Sleep disturbance and cognitive functioning

Sleep disturbance is reported by the majority of older persons. For example, among more than 9,000 community dwellers aged 65+ years who were interviewed for the Established Populations for Epidemiologic Studies of the Elderly (EPESE), only 12% of the participants did not report sleep complaints [10]. The depth and continuity of sleep quality deteriorates with age, and the subjective perception of poor sleep can significantly decrease QOL in older adults [11, 12].

There is considerable evidence underscoring direct and indirect effects of medical illness on sleep in old age [13]. CKD is a condition associated with a high

prevalence of sleep disturbance [14]. In addition, CKD patients are at increased risk for other disorders such as diabetes and cardiovascular conditions which have been shown to have negative effects on sleep quality in later life.

Sleep disorders encompass several conditions, which may have somewhat varying etiologies and may overlap in contributing to sleep difficulty in an individual patient. Insomnia is characterized by difficulty falling asleep, difficulty staying asleep, and/or early morning awakening [15]. We found that almost 60% of patients in a large US cohort of incident dialysis patients reported that they woke up too early, did not fall asleep for a long time, and/or awakened frequently at night [16]. Daytime sleepiness, sleep apnea, periodic limb movements of sleep, and restless legs symptoms are additional conditions known to be associated with impaired nocturnal sleep quality in CKD patients. The prevalence of some type of sleep disorder among CKD patients ranges from approximately 40% to 80%, depending on the assessment method and the type of population studied [14].

The prevalence of specific sleep disorders is not clearly associated with increasing age of patients [14, 16]. Severity of kidney dysfunction in pre-dialysis CKD patients [17] and the type of HD therapy received by dialysis patients [18, 19] have been shown to be associated with sleep quality. Sleep quality improves after kidney transplantation, but allograft recipients still have significantly more sleep disorders than healthy individuals [14]. Underlying kidney disease and uremic toxins may be stronger influences on sleep quality than the patient's chronological age.

Wide agreement exists that sleep disorders in CKD patients are associated with lower perceived QOL [14, 20]. Poor sleep, pain, and depressed mood may form an interrelated complex of symptoms, based on evidence from studies of both older community dwellers [21] and HD patients [22]. In addition, we found in a US sample of incident dialysis patients that patient-reported sleep difficulty, bodily pain, and depressed mood were independently associated with patient-reported impairment in cognitive functioning [16]. The cognitive function measure used was a scale included in the Kidney Disease Quality of Life (KDQOL) instrument [23] that assesses individuals' perceived difficulties with cognitive performance in carrying out daily activities. At a follow-up evaluation 9–12 months post baseline (approximately 60 days post treatment start), cognitive function scores had declined among more than one-third of the cohort, and patients who reported sleep difficulty over the first year of dialysis treatment had the lowest average cognitive function scores [24].

A gender difference may exist in the nature of sleep disturbance among older persons. Polysomnographic data indicate that men may have more objectively disturbed sleep than women [13]. Thus, men may have a higher threshold than women for reporting sleep complaints. A recent study of persons aged 70–89 years showed that men were 1.5 times more likely than women to exhibit memory and other thinking skills that were worse than expected based on age and educational level [25]. It is possible that sleep quality mediates this association. Our analysis of decline in self-reported sleep quality and cognitive function among incident dialysis patients showed an association between chronic insomnia and decreased cognitive function that was independent of depression in men but not in women [24], and a similar finding was reported for community dwellers aged 65+ years in the EPESE [26].

Patients with sleep difficulty are more likely to have sleep-inducing medications prescribed [14, 16, 27]. Medications described as efficacious in treating insomnia may be associated with impairment in daytime cognitive and psychomotor performance [28]. Kurella et al. [29] found an association between benzodiazepine use and lower patient-reported cognitive function among both CKD and prevalent HD patients, and we showed an association between listing of sleep-inducing medications in the patient's medical record and increased risk for lower patient-reported cognitive function [16]. In addition, depressed mood is often associated with sleep difficulty [24, 28], and Gusbeth-Tatomir and colleagues [14] noted that many antidepressants appear to cause restlessness. It has been recommended that behavioral treatments and newer nonbenzodiazepine medications (e.g., zaleplon, zolpidem, eszopiclone) be considered as first lines of treatment for sleep difficulty [28, 30].

Depressed mood

In addition to its probable association with sleep difficulty, pain, and cognitive function as noted

above, depressed mood is often associated with the risk of falls [31, 32] and hip fractures [33]. Data summarized by the American Geriatrics Society suggest that depression confers a higher relative risk for falls than even cognitive impairment or age, which are far less modifiable [31]. Depression in the context of a condition such as hip fracture carries a significant risk of poorer outcomes [34]. More generally, depression affects patients' daily function, their ability to sustain social networks, and their QOL.

All antidepressants have potentially significant side effects for dialysis patients [28, 35]. Nonpharmacologic interventions may be a preferable alternative, although the evidence base is limited [35]. In the general population, use of a collaborative care model has been shown to be a promising approach for management of depression among older adults. In such a model, patients would receive information such as an educational videotape and booklet about late-life depression, with follow-up by a nurse or psychologist trained as a depression clinical specialist. The specialist would obtain a clinical and psychosocial history, review the educational materials, and discuss different treatment options, including brief psychotherapy for depression, with the patient and primary care provider. When compared with patients receiving usual care, a study of patients receiving collaborative care found that patients managed with this model less often rated their health as fair or poor and were more likely to report better physical functioning [36]. Chilcot et al. [35] emphasize the need to undertake trials of treatments for depression that may be suitable for persons on dialysis.

Optimizing pre-dialysis and dialysis care

Management of anemia and other CKD comorbidities

In CKD patients anemia is likely to be present at a glomerular filtration rate (GFR) below 30 ml/min/1.73 m^2 and becomes more severe with decreasing renal function [37], contributing to decreased QOL and survival. Arora and colleagues [38] investigated the care of elderly CKD patients by primary care physicians in a retrospective chart review of male patients referred to a Veterans Affairs (VA) Nephrology Clinic over the period 1999 to 2002. All patients over 65 years of age with serum creatinine $\geq$1.4 mg/dl on two occasions 3 months apart ($n = 377$) were included in the study. Follow-up information was obtained until the start of dialysis, transplantation, loss to follow-up, or study end date. Among patients with hemoglobin <11 g/dl, darbepoietin/epogen was used in only 31%.

In addition, Arora et al. [38] found that angiotensin converting enzyme inhibitors were used in only half of the CKD patients, and there was limited screening for depressive symptoms. Lipid disorders and hemoglobin A1C were monitored in accordance with VA guidelines, but screening for other frequent abnormalities in CKD (anemia, abnormalities of calcium-phosphorus metabolism, malnutrition, and cardiovascular disease) and remedial action as recommended by the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines were not routinely carried out. Although there was a trend towards earlier referral, care that addressed comorbid CKD conditions did not change significantly between 1999 and 2002. The authors concluded that increased education of primary care physicians and nephrologists is needed in order to improve care, and hence QOL, of elderly CKD patients [38].

In a non-VA hospital providing chronic dialysis, Post et al. [39] found that anemia, defined as hemoglobin <11 g/dl, was present in 68% of 102 patients starting HD. Among the 102 patients who were studied, 28.4% were iron deficient, defined as serum ferritin <100 ng/ml and transferrin saturation < 20% as per the NKF K/DOQI criteria for absolute iron deficiency. In addition, partial criteria for iron deficiency were present in 66% of patients. Iron deficiency was found in 29% of the patients who received erythropoietin (EPO) and 26% of patients who did not receive EPO prior to starting HD. In four patients with iron deficiency who had not received EPO, there was a significant rise in hemoglobin levels following administration of intravenous iron gluconate. The investigators recommended that replenishing iron stores in anemic patients with CKD should be considered as an integral part of the therapy for treating anemia in the pre-dialysis population.

Neves et al. [40] investigated the impact of nutritional and inflammatory status on darbepoeitin dose requirements of 71 patients aged $\geq$65 years followed

for 12 months in a pre-dialysis CKD clinic. Patient age ranged from 65 to 96 years (mean 76.2 ± 6.6 years). All patients were receiving iron therapy and 75% needed darbepoeitin to correct anemia. Markers of poor nutritional status (Subjective Global Assessment) and inflammation (Interleukin-6 and tumor necrosis factor-alpha) were found to independently predict use of higher doses of darbepoietin to correct anemia.

Modality selection

Peritoneal dialysis (PD) offers elderly patients several potential advantages over HD, especially hemodyamic stability, steady-state metabolic control, good control of hypertension, and avoidance of repeated vascular access [41]. Early referral increases the likelihood that PD will be considered as the initial modality. Several studies have found little variation in QOL among patients of different ages using PD [42–44].

In the United Kingdom, Harris et al. [45] assessed QOL in 78 elderly patients on PD and 96 elderly patients on HD. All patients were 70 years or older at the start of dialysis and had similar sociodemographic and clinical characteristics. Adjusted analyses showed no association of modality (PD, HD) with hospitalization or mortality rates. After 6 months and after 12 months of dialysis, linear regression analyses showed no statistically significant differences between patients on PD and patients on HD in their responses to Short-Form 36 (SF-36) health status domains and the symptoms/problems scale of the KDQOL instrument. Based on a meta-analysis reported by Cameron et al., however, elderly patients treated by continuous ambulatory peritoneal dialysis reported a greater sense of psychological well-being than patients on in-center HD [46]. Because there is likely to be differential selection of patients for treatment by PD and HD, variation in findings across studies may occur when patient characteristics are not controlled similarly in the analyses.

Pre-dialysis care and early QOL

Loos et al. [47] studied 169 patients aged 70 years and older at the time of their first dialysis and an equal number of non-CKD age- and sex-matched control patients who were hospitalized for chronic conditions. First dialysis was planned in approximately half of the patients starting chronic dialysis treatment. All subjects completed the SF-36 health survey. After adjustment for age, sex, and comorbid conditions, no significant differences in QOL reported on the SF-36 survey were found between patients who started planned dialysis and the non-CKD controls.

On the other hand, patients whose dialysis was unplanned had significantly lower QOL scores on the SF-36 physical function and vitality dimensions compared with patients who started planned dialysis and compared with non-CKD controls. Baseline QOL is a strong predictor of subsequent QOL scores, and patients who started unplanned dialysis were therefore at a distinct QOL disadvantage from the start of their treatment. Importantly, patient-reported physical function and vitality have been shown to be closely linked with frailty in both the general population [48] and in dialysis patients [49]. Frailty, a nonspecific state of increasing risk reflecting multisystem physiological change [50], predicts an increased risk of hospitalization and mortality [48, 49].

Physical activity/exercise

In addition to improving physical parameters such as strength, balance, and mobility and thereby potentially lowering risk of falls [50], exercise programs may also improve important dimensions of older persons' QOL and functioning. For example, among older persons in the general population, there is evidence that exercise can improve sleep quality [51]. The ongoing Mayo Clinic Study of Aging in over 800 persons aged 70–89 years indicates that those individuals who engaged in moderate exercise when they were aged 50–65 years had reduced risk of developing mild cognitive impairment at later ages [52]. Similar associations may exist among CKD patients.

In a study of 50 in-hospital HD patients in Canada aged 65 years and older, Logan et al. [53] found that fatigue ranked high as a patient-reported source of stress. Kontos et al. [54] found that both fatigue and depression were cited by older patients as impediments to exercising, but both fatigue and depression can be improved by exercise. Improvement in the psychosocial functioning of HD patients after exercise participation has been shown in randomized clinical trials [55].

Studies of patients on HD have provided evidence to support an increase in hemoglobin concentration and

hematocrit levels and reduced need for antihypertensive medications in association with participation in exercise interventions [9, 56]. Improvements in physical functioning associated with increased physical activity/exercise have been found using both objective measures of physical fitness and subjectively reported physical functioning and energy [9, 57]. Patients on all renal replacement therapies have been shown to benefit from physical activity/exercise.

Conclusion

Geriatrics has been termed the new frontier of medicine. Gerontologists and geriatricians have developed valuable tools for assessing patient care needs, such as Multidimensional Geriatric Assessment [58]. Insights from geriatric care are doubly relevant for CKD patients because the average CKD patient in the USA is 63 years old at the time of initiating renal replacement therapy [59] and because CKD patients on dialysis in many ways provide a model of early aging [49].

At the same time, elderly patients gain added lifetime on dialysis that is satisfying [60], and elderly patients as a group frequently report better psychosocial adjustment to dialysis than do younger patients [61]. The evidence supporting this conclusion is generally consistent across countries and among patients using different types of renal replacement therapy [61]. Decline in physical and cognitive functioning and associated depressive symptoms and sleep disorders are the major issues that challenge QOL in elderly persons, including elderly patients on dialysis. Early CKD management, application of best practices from the fields of gerontology and geriatrics, and inclusion of some form of exercise or increased physical activity in routine care, provide growing opportunities to enhance the functioning and well-being of older patients.

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