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Sleep and pain management are key components of patient care in ESRD†

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The care for patients with end-stage renal disease (ESRD) has focused on easily measurable processes of care outcomes such as Kt/V, hemoglobin and serum phosphorus levels. It has been thought that these metrics reflect the quality of care. Furthermore, improving these measurements would favorably influence the quality of life and survival on dialysis. However, an observational study of over 11 000 hemodialysis patients demonstrated no substantial improvement in health-related quality of life (HRQOL), despite secular changes in Kt/V, hemoglobin and serum phosphorus [1]. In addition, randomized trials testing whether increasing Kt/V or hemoglobin reduces mortality and improves the quality of life had demonstrated no substantial increase in quality or length of life [2–4]. As it turns out, these measures may not be adequate proxies for patient well-being and attention to them may not substantially increase survival. The present study by Kimmel and colleagues [5] is noteworthy because of its examination of potential associations between pain, sleep, quality of life and survival. The work of this group supports the position that patient-reported outcomes may present an important tool to improve the quality of life and the survival duration of patients with ESRD.

The report measured self-reported pain and sleep in 128 patients with ESRD in two dialysis units in Washington, DC, between 2001 and 2003 with follow-up of the cohort for survival through 2005. The study population had a mean age of 57, 60% male, 91% African-American and had a mean duration of dialysis of 40 months. There was a high rate of other chronic health conditions since 48% were diabetic, 10% had HIV and the average Karnofsky score was 75. One of the strengths of this investigation is the early use of the McGill Pain questionnaire and the Pittsburgh Sleep Quality Index (PSQI). These now widely used tools provide reliable and valid measures of pain and sleep quality. In order to assess whether pain differs between the time on dialysis and non-dialysis, the investigators modified the McGill Pain questionnaire to examine the nature, location, intensity, duration and frequency of pain on and off dialysis. Dialysis pain intentionally was measured by asking the patient to disregard discomfort associated with the use of vascular access. The investigators found that a substantial proportion of ESRD patients reported pain during off-dialysis (44%) time and poor sleep (45% have a PSQI score of >5). The measures of pain and sleep quality were later analyzed in relation to survival. After controlling for age, diabetes, serum albumin and HIV, non-dialysis pain was significantly associated with an increased risk of death.

While this report demonstrates a high prevalence of pain and poor sleep in patients with ESRD, there are a number of limitations which should be considered when comparing these findings to other studies. First, this was a small study with limited power to demonstrate clinically meaningful associations with survival. Only 32 deaths were reported during the study and observation periods. This lack of power may explain the non-significant association between sleep quality and survival. Other larger studies have demonstrated a significant relationship between self-reported sleep quality and survival in ESRD [6, 7]. Second, this report modified the McGill Pain questionnaire to determine whether there was a difference in the experiences of patient on and off dialysis. One wonders if patients can reliably report differences in pain on versus off dialysis. Furthermore, it is questionable whether patients can reliably attribute and exclude pain to the access site from other sources of pain during dialysis. Also, this is a single measure of pain and we expect that pain would be changing during the course of the study with new condition or medications. This is admittedly not a longitudinal study, and it does not provide data to explore these variables. Third, it would be of tremendous interest to understand the relationship between sleep, pain and depression. To what extent are poor sleep and pain causes or consequences of depression in ESRD? Lastly, the causal pathway between pain and survival remains uncertain. As noted by the investigators, there is exciting work relating inflammation to the symptom complex of pain, sleep and depression. However, this report does not examine such relationships. It would be possible for pain to reflect an unmeasured chronic health condition or the severity of a reported condition such as diabetes.

It would be wonderful if more adequate attention and management of pain could prolong survival. For this reason alone, the study findings are worth remembering, although they reflect a very preliminary exploration. For example, we do not know anything about the etiology of the pain and whether it is somatic, neuropathic, generalized or localized or the extent of analgesic treatment. The investigators' clever attempt at distinguishing between pain that occurs during dialysis sessions and at other times is unusual, and it is important to note that they found only the latter pain to be significantly associated with lowered survival. The non-dialysis pain was more intense, more frequent and of greater duration. Was this because of the difficult-to-define benefits that are present for many patients who attend hemodialysis clinics: the three times/week attention they receive with the chance to speak with interested staff and fellow patients, the excursion from home to a safe and stimulating place, and possibly the opportunity to be removed from family conflicts or demands? The association with survival is fascinating and bears further investigation. It takes place at a time when many medical societies are requiring additional training for all physicians in the area of modern pain management.

These findings extend previous work showing that sleep quality has been related to functional outcomes and mortality in both the general adult population and ESRD. Many older adults have reported difficulty initiating sleep, feel tired during the day, have difficulty maintaining sleep and wake up too early in the morning [8, 9]. Among older adults, those reporting poor sleep quality use more health services [10], more hypnotic drugs [11] and report reduced functional capabilities and lower health-related quality of life (HRQOL) [12]. Poor sleep quality has been linked to disability days, health-care utilization, vitality, quality of life and mortality [7, 13]. However, the objective measures of sleep quality are only weakly correlated with self-reported measures of sleep quality in middle-aged [14] and older adults [15] as well as those with chronic kidney disease [16]. Hence, it is important to recognize that self-reported sleep quality has been strongly associated with patient outcomes, despite a lack of correlation with polysomnogram (PSG) findings.

It is particularly important to measure self-reported sleep quality in patients with ESRD. There are a number of key relationships supporting the measure of sleep quality in this population. First, sleep and fatigue have been reported to be key determinants of whether ESRD patients will be willing to undergo more frequent hemodialysis. Second, self-reported sleep quality has been associated with hypertension and non-dipping blood pressure (BP) [17, 18] in observational studies, suggesting that sleep may be an important factor in the high rate of cardiovascular outcomes observed in this population. Third, sleep quality and fatigue may influence adherence in chronic health conditions [19, 20]. Fourth, medications used in the care of patients with ESRD may increase sleepiness. For example, small studies have shown that β-blockers such as metoprolol (but not nebivolol) may lead to worsening global PSQI score [21] and atenolol may decrease total sleep time and rapid eye movement (REM) sleep [22, 23]. Short and fragmented sleep has been associated with daytime symptoms, decreased psychomotor vigilance, poor driving performance, diminished memory, increased risk of cardiovascular disease events [24] and premature death [25–27] and may predict higher BP and adverse changes in BP over time [28]. Recurrent sympathetic excitation, hemodynamic instability and nighttime BP surges associated with recurrent arousals [29] and possibly increased coronary calcification associated with shorter sleep [30] may partly explain the increased morbidity and mortality in those with poor sleep quality. In observational studies, African-American race has been associated with lighter sleep and African-American women were shown to have decrements in self-reported sleep quality and sleep duration measured by PSG compared with white women [31, 32]. These differences in sleep by race underscore the authors' call for larger multicenter studies which may provide a more ethnically diverse sample of patients with ESRD.

Sleep quality and pain are common and important to the chronic dialysis population and may have day-to-day or diurnal variation related to dialysis treatment that can be measured using ecological momentary assessment (EMA). EMA is a technique for assessing symptoms prospectively, repeatedly and in the participants' natural environment. EMA provides an important measuring tool to measure subjective sleep quality and fatigue repeatedly, reliably and with limited burden while avoiding recall bias [33]. Often, study participants complete questionnaires or items several times per day during the course of usual activities, thereby permitting the assessment of diurnal and day-to-day variation in symptoms [34]. EMA has been shown to be less susceptible to recall bias and has been used in a wide range of investigations such as studies of pain, sleepiness and fatigue in breast cancer patients, addiction, coping and optimal experience [33–36]. EMA studies have shown completion rates of greater than 90% and time validity with diverse study populations including adolescents, addicts, the elderly and those with chronic medical illness [33]. The investigators modified the McGill to test whether pain changes during the day for patients undergoing dialysis—other approaches such as using EMA may provide further insight into the experiences of patients with ESRD.

This report by Kimmel and colleagues is prescient in its use of patient-reported outcomes and demonstrates that these have a relationship to survival. It may well be that attention to symptoms and patient well-being improves survival. A recent study in advanced lung cancer has suggested that early palliative care improves patient survival [37]. However, addressing human suffering is a key component of patient care and should be recognized as important in its own right for patients with ESRD.

Conflict of Interest statement. None declared.

(See related article by Harris *et al.* Pain, sleep disturbance and survival in hemodialysis patients. *Nephrol Dial Transplant* 2012; 27: 758–765.)

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