Fatigue in advanced kidney disease

Micol Artom[1], Rona Moss-Morris[1], Fergus Caskey[2] and Joseph Chilcot[1]

[1]Health Psychology Section, Psychology Department, Institute of Psychiatry, King's College London, London, UK and [2]The Richard Bright Renal Unit, North Bristol NHS Trust and The School of Clinical Sciences, University of Bristol, Bristol, UK

Fatigue is commonly experienced in patients with advanced kidney disease and associated with poor outcomes. The prevalence of fatigue ranges from 42% to as high as 89% according to treatment modality and the measurement instruments used. This paper reviews studies examining sociodemographic, biological, and psychological factors associated with fatigue in advanced kidney disease. The association between fatigue and psychological factors, such as depression and anxiety, behavioral factors, such as sleep and nutrition, and cytokines, such as IL-6 and CRP corroborates the view of fatigue as a multidimensional and multifactorial problem. Although depression and fatigue are related, the relationship is typically moderate in size, thus fatigue should not simply be seen as a symptom of distress. Accordingly, it is important for treatment plans to address the complex etiology of fatigue through pharmacological and nonpharmacological interventions. To date, results of nonpharmacological interventions are promising, with physical exercise and cognitive-behavioral therapy showing beneficial results. Work conducted in other patient populations highlights the importance of cognitions and behaviors in the prediction and maintenance of fatigue. Such work could be applied to advanced kidney disease allowing a model of fatigue to be developed from which to base suitable interventions in this setting.

Kidney International (2014) **86,** 497–505; doi:10.1038/ki.2014.86; published online 2 April 2014

KEYWORDS: chronic kidney disease; end-stage renal disease; fatigue; symptoms; transplantation; treatment

Correspondence: *Joseph Chilcot, Health Psychology Section, Psychology Department, Institute of Psychiatry, King's College London, 5th floor Bermondsey Wing, Guy's Hospital Campus, London Bridge, London SE1 9RT, UK. E-mail: joseph.chilcot@kcl.ac.uk*

Received 14 October 2013; revised 10 December 2013; accepted 9 January 2014; published online 2 April 2014

Fatigue is a common symptom in patients with advanced kidney disease, with implications for quality of life (QoL) and clinical outcomes. Fatigue is a complex, multidimensional, and multifactorial phenomenon, which has been defined as 'extreme and persistent tiredness, weakness or exhaustion-mental, physical or both'.[1,2] Common symptoms also include reduced motivation and physical activity, in addition to general lethargy. Renal patients adjust the timing and intensity of their daily activities in order to accommodate their fatigue.[3,4] For example, some dialysis patients who suffer from post-treatment fatigue require more than 3 h of rest after each session to recover,[5] which is a considerable burden on top of the treatment regimen. Accordingly, the management of fatigue is an important clinical priority for enhancing the patients' QoL.[6]

In addition to recognizing fatigue and its severity, it is important to consider the sociodemographic, physiological, and psychological correlates of fatigue in chronic kidney disease (CKD), end-stage renal disease, and transplantation[7] in order to develop and test treatment models specific to these settings.[8] The purpose of this review is to discuss the assessment methods, prevalence, correlates, and the main outcomes associated with fatigue in patients with kidney disease. This review also examines possible interventions to improve fatigue and concludes by defining some future research directions.

ASSESSMENT OF FATIGUE IN CKD

Fatigue assessment tools are generally self-report measures, which are either evaluative, assessing the severity of fatigue, or discriminative, which have the purpose of differentiating fatigued from nonfatigued individuals.[9] Discriminative tools use cutoffs, which are used to indicate fatigue 'caseness'. Several fatigue measures have been shown to hold good psychometric properties in patients with chronic illness.[10] When choosing a fatigue instrument it is important to consider the particular aspect of fatigue intended for study (i.e. unidimensional/multidimensional measure), the psychometric properties of the measure, and the population in which the scale has been used previously.[10] Many of the widely used scales are not specific for kidney patients but have been applied to a variety of other conditions. Although most fatigue instruments measure the overall experience of fatigue during a period of weeks or months, dialysis patients also experience day-to-day and diurnal variation in fatigue.

Ecological momentary assessment procedures have been used to measure fatigue in patients receiving intensive cancer therapy[11] and could be used in the dialysis population to improve our understanding of fatigue and its variation over time, particularly over the interdialytic period. Listed below are some of the most frequently used scales for measuring fatigue in renal patients. For a more detailed review on the assessment of fatigue in chronic illness, see Dittner *et al.*[12]

SF-36 vitality subscale

The four-item SF-36 vitality subscale is often used as a measure of fatigue. Scores range from 0 to 100, with higher scores reflecting higher energy levels.[13,14] The concept of vitality is considered to be at the opposite pole to fatigue on a fatigue–vitality continuum.[15] However, the vitality construct captures the reduction in energy level but fails to reflect other aspects of fatigue such as lack of motivation and weakness.[7]

Fatigue severity scale

The fatigue severity scale is a nine-item unidimensional questionnaire[16] scored on a seven-point Likert scale, with high sum scores indicating greater fatigue. The scale's psychometric properties have been corroborated by studies in multiple diseases, including fibromyalgia,[17] multiple sclerosis,[18,19] chronic hepatitis,[20] and Parkinson's disease.[21,22] Overall, the fatigue severity scale has been shown to have a good test-retest reliability and a high internal consistency.[12]

Visual analog scale to evaluate fatigue severity

The visual analog scale is a unidimensional scale in which a 100-mm line is anchored at either end: by 'no tiredness at all' at the left end and 'complete exhaustion' at the other. The intensity of fatigue is measured in millimeters from the low (left) end of the scale with, again, a higher score indicating an increased level of fatigue. Studies have suggested that the descriptiveness of the visual analog scale to evaluate fatigue severity is considerably lower compared with other measures.[23] Furthermore, the scale might fail to differentiate between sleepiness and fatigue.[24]

Multidimensional fatigue inventory

The multidimensional fatigue inventory[25] contains 20 statements that are organized into five dimensions of fatigue (general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation). A global fatigue score combining results from the five dimensions ranges from 20 to 100, with higher scores indicating higher levels of fatigue. However, the hemodialysis (HD) population has shown difficulty in understanding the instrument.[26]

Although the above scales have generally shown adequate psychometric properties, future work needs to evaluate their performance in patients with kidney disease. Currently there are no robust data specific for CKD to recommend a particular measure. For use in routine clinical practice, a simple visual analog scale may provide a useful and quick assessment. Although not widely used in the renal literature, the Chalder fatigue scale[27] measures both mental and physical fatigue, thus evaluation of this measure in CKD would be of interest.

PREVALENCE OF FATIGUE IN RENAL PATIENTS

Fatigue is one of the most frequently reported symptoms in renal disease patients.[28–30] Compared with the general population,[31,32] dialysis patients report far higher fatigue levels.[33–38] A significant proportion of patients with renal disease report problematic levels of fatigue (Figure 1),[28,29,37–45] at rates comparable to other physical conditions.[46] However, the exact prevalence remains contentious as most of the research has focused on the HD population, neglecting transplant and peritoneal dialysis (PD) patients. The estimated prevalence of fatigue ranges between 42 and 89% according to treatment modality and the instruments used to measure the presence of fatigue. A recent investigation using visual analog scale reported that 81.5% of HD patients experienced fatigue.[29] A similarly high prevalence of fatigue in the HD population (77.9%) is reported elsewhere,[43] although lower rates are seen when using the SF-36 vitality subscale (41.9%, Figure 1).[39]

CORRELATES OF FATIGUE IN CKD

Sociodemographic factors

CKD fatigue has a complex multifactorial etiology (Figure 2). Studies indicate that women report significantly higher levels of fatigue than men,[29,35,37,38,47–49] although others report no gender association.[34,39,47,50] Gender differences could reflect greater symptom reporting in females compared with males.[51–54] Age is also fairly consistently associated with higher fatigue levels in renal patients[35,37–39,42,48,55–59] with those over 60 years of age reporting higher levels of fatigue.[55] The age–fatigue relationship might be explained by differences in dialysis vintage, physical activity, malnutrition

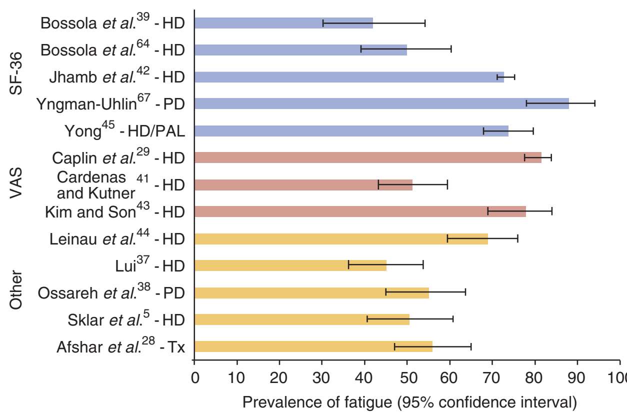

Figure 1 | Prevalence estimates of fatigue in advanced kidney disease (%). HD, hemodialysis; PAL, palliative care; PD, peritoneal dialysis; SF-36, Medical Outcome Study SF-36; Tx, transplant recipients; VAS, visual analogue scale - Fatigue.

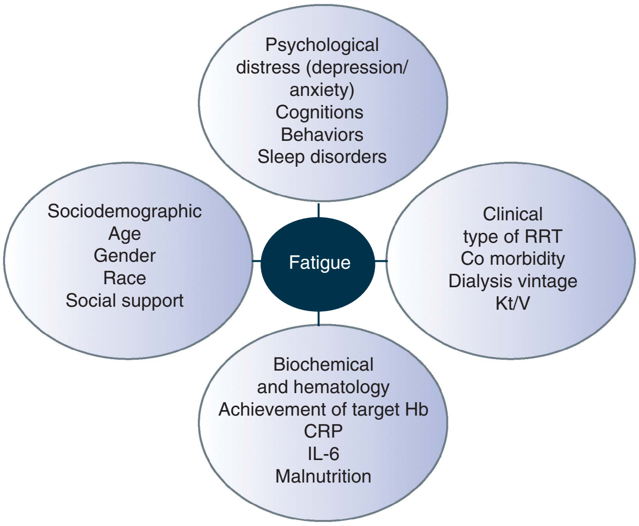

Figure 2 | Correlates of fatigue in end-stage renal disease (ESRD). CRP, C-reactive protein; Hb, hemoglobin; IL-6, interleukin-6; Kt/V, dialysis adequacy; RRT, renal replacement therapy.

and inflammation, and greater age-related multi-morbidity[60] resulting in higher reports of fatigue in the elderly. It has also been suggested that with age there may be a shift in patients' report of fatigue, owing to some level of accommodation for or acceptance of reduced activity levels.[61] There is some indication that fatigue is less prevalent in black and Asian patients,[42,62,63] although data are conflicting[34] and warrant further enquiry.

Social and situational factors including education, and marital and employment status have also been explored in relation to fatigue. Karadag *et al.*[47] found that education was associated with fatigue severity: those who were graduates had higher fatigue scores than other groups. Four recent studies have linked unemployment to fatigue,[37,42,48,58] which could be related to lower mood- and greater illness-related disability. Finally, marital status can have an impact on fatigue, with single patients generally reporting feeling more energetic compared with married patients,[35,55,59] although marriage could also be a reflection of older age, a confounding factor. Nonetheless, this association has not been supported by other researchers,[47,50] hence the underlying mechanisms of the link between fatigue and these sociodemographic factors should be explored further.

Clinical factors

Multiple studies have shown that extra renal multi-morbidity is significantly higher for fatigued than for nonfatigued HD patients.[39,42,64] Multi-morbidity leads to greater burden and stress, more time spent in hospital accompanied by the need for additional therapies, all factors which may contribute to heightened fatigue.[39] Furthermore, a relationship exists between fatigue and poor physical functioning,[48,50] although causality remains an issue. In patients with end-stage renal disease, side effects related to renal replacement therapy and worsening morbidity combine to discourage physical activity (for a detailed review on physical exercise in patients with CKD, see Kosmadakis *et al.*[60]). Studies have consistently reported that there is a bidirectional relationship between physical inactivity and fatigue in patients undergoing dialysis.[35,41,51]

Nutrition and sleep have also been explored by a number of studies. A recent study showed that anorexia and fatigue are strongly related, with the frequency of fatigue being significantly higher in anorexic than in nonanorexic patients. The presence of both anorexia and fatigue in HD patients was also associated with significantly higher levels of interleukin-6 (IL-6) and C-reactive protein (CRP).[64] Joshwa *et al.*[36] reported an association between daytime sleepiness, poor night-time sleep, and fatigue; results that were supported in both HD[50,65] and PD patients.[66,67] In addition, Sanner *et al.*[15] found that the severity of sleep-related breathing disorders was associated with levels of vitality.

Treatment modality and fatigue

Dialysis is associated with a number of side effects, including fatigue.[68] Approximately 86% of patients experience post-dialysis fatigue ranging from mild-to-severe.[69] Feelings of fatigue peek at the end of a dialysis session and are at their lowest during the interdialytic period.[70] Fatigue is moderately associated with dialysis recovery time,[70] with approximately a quarter of patients returning back to their baseline within a few minutes of ending dialysis, around a third recovering by the time they reached home, and almost a quarter only recovering by the following morning.[29] Longer dialysis recovery time is associated with mortality,[71] possibly as a result of higher inflammation.[72] Post-dialysis fatigue is influenced by several factors including osmotic disequilibrium, blood membrane interactions, ultrafiltration, diffusion, and greater tumor necrosis factor.[5,73,74] Recovery time from dialysis and post-dialysis fatigue has been shown to improve significantly with more frequent dialysis regimens.[75,76]

Type and duration of renal replacement therapy have also been investigated in relation to fatigue. Transplant recipients report lower levels of fatigue compared with HD, PD, and CKD patients.[34] A more recent study revealed that PD patients were the most fatigued and least active, whereas transplant recipients engaged in most activities, even when fatigue was high.[35] The data on duration of dialysis are mixed and contradictory. Karadag *et al.*[47] reported higher fatigue scores for patients who had started dialysis more recently, supporting findings from the HEMO study.[42] It may be that over time patients also begin to accept and adapt to the treatment regimen, which may positively impact fatigue.[77] In contrast, Letchmi *et al.*[78] found a significant relationship between fatigue and dialysis vintage, with patients who had undergone treatment for more than 2 years experiencing high levels of fatigue. An explanation for the latter findings may be that, although with time patients become accustomed to the dialysis routine, their coping mechanisms in response to symptoms may remain unchanged.[78] However, others[34,44,50,51] report no relationship between the duration of renal replacement therapy and fatigue levels experienced by patients. Regarding dialysis adequacy (Kt/V), PD Kt/V has been associated with fatigue,[79] although others report no association between HD Kt/V or dialysis vintage and fatigue levels.[37] The mixed findings regarding Kt/V are likely the result of homogeneity observed within the respective studies.[40] The state of current knowledge concerning the differences between generalized fatigue and dialysis treatment–related fatigue is still unclear, therefore further research is needed to discern the mechanisms involved in these two processes.[68,70]

Biochemistry and hematology factors

Biochemistry and hematology factors have also been investigated with regard to fatigue in renal patients and include factors such as anemia, inflammatory cytokines, hemoglobin (Hb), and serum albumin. The majority of patients with CKD are anemic[80] owing to multiple factors, including the inability to produce erythropoietin. The relationship between anemia and fatigue has been studied extensively and there is little question that severe anemia can cause fatigue. Indeed, anemia affects normal physiological functioning and also leads people to experience increased tiredness and reduced ability to undertake daily activities. In a retrospective study,[38] Hb levels were consistently significantly lower in PD patients with fatigue—results that have been supported across the spectrum of advanced kidney disease.[58,81–84] However, a number of studies report no correlation between Hb levels and fatigue.[34,37,44,50,51,59,78,79] The connection between the two has been further explored by studies that have administered erythropoietin-stimulating agents (ESA) to improve anemia. Bonner *et al.*[33] found a significant improvement in fatigue levels after 12 months of ESA. Finally, a recent systematic review of the impact of ESA in dialysis patients[85] found that a partial correction of anemia with ESA showed the largest improvements in fatigue for patients with baseline Hb levels <10 g/dl.

Chronic inflammation has recently been suggested to have a significant role in the onset of fatigue in renal patients. Inflammatory cytokines may result in fatigue directly through the central nervous system, pituitary gland, hypothalamus, and adrenal glands or indirectly through sleep and psychological disorders. For a detailed review of the role of cytokines in HD see Pertosa *et al.*[86] Significantly higher IL-6 and CRP levels have been observed in fatigued dialysis patients compared with nonfatigued patients.[34,61] A recent study reports a significant, albeit small, positive correlation between fatigue (Chalder fatigue scale) and IL-6, although no association was observed between CRP and fatigue.[87] Jhamb *et al.*[62] report that poor vitality was significantly related to both IL-6 and CRP. Other studies[39,82,88,89] have found that serum albumin and creatinine levels were significantly lower in patients with fatigue and depression, respectively. In addition, serum creatinine is predictive of decreasing vitality over time.[62] However, most have failed to demonstrate associations between fatigue and creatinine[7,37] and fatigue and serum albumin levels.[37,49,50,79] Calcium and phosphate levels have been associated with fatigue in renal patients,[58,79] although data are conflicting.[7,37,39,44,49,50]

In summary, the variability in reported fatigue levels is only partially explained by biochemistry and hematological factors. It should also be noted that some studies fail to suitably control for comorbidity and other potentially confounding factors that may have an impact upon fatigue levels. This highlights the importance of understanding other factors, particularly psychological, that may help to further explain fatigue levels in advanced kidney disease.

Psychosocial factors

There are a number of psychosocial factors that have been related to fatigue in renal patients, including depression, health-related QoL, anxiety, loneliness, social support, and suicide risk. Although the direction of these associations cannot be inferred, it appears that the relationship between fatigue with physiological and psychological factors, is reciprocal.[50] Of the psychological factors, depression has been the most extensively studied. Fatigue and depression are interrelated, and depression may manifest as feelings of lack of energy and tiredness.[7] Multiple studies on dialysis patients[5,36,37,39,41,43,44,50,56,58,65,90,91] have found significant correlations between fatigue and depression in them, although effect sizes have tended to be moderate. Cardenas and Kutner[41] showed that patients who reported being fatigued upon arising had significantly higher average depression scores than their counterparts who felt mediocre or better upon arising. In addition, Chen *et al.*[90] found that not only depression but also suicide risk correlated with fatigue in HD patients. Studies also show a significant association between fatigue and anxiety in HD patients.[39,50,90] However, others[78] have found no significant relationship between fatigue and depression and between fatigue and anxiety. Differential findings could be justified by the measurement scale used in the study, that is, the Depression Anxiety Stress Scale as opposed to the Beck Depression Inventory that was used in the majority of the studies above. Indeed, the Depression Anxiety Stress Scale and the Beck Depression Inventory have been found to be only moderately correlated, and the Depression Anxiety Stress Scale does not include several items, which are not uniquely related to depression, including weight loss, loss of libido, irritability, loss of appetite, and somatic preoccupation.[92] Moreover, the studies above were all conducted on dialysis patients and did not include transplant patients. As successful transplantation has been associated with reduced levels of anxiety and depression compared with those experienced by dialysis patients,[93] further studies regarding the relationship between depression, anxiety, and fatigue in transplant patients should therefore be considered, particularly in relation to graft function and rejection episodes.

Akin *et al.*[55] described a relationship between fatigue, loneliness, and self-care: as levels of loneliness and fatigue increased, the self-care ability of HD patients decreased, which could help explain poor clinical outcomes associated with fatigue. Bolstering social support may therefore be an important factor to improve fatigue symptoms and self-care behavior in dialysis patients.[94] Indeed, Karadag *et al.*[47] found that patients with severe fatigue perceived lower social support from family and friends. Although similar results have been reported in other disease groups, some renal studies have failed to find a relationship between fatigue and social support.[43,83]

ASSOCIATED OUTCOMES

Fatigue symptoms are associated with all cause and cardiac-related mortality in HD patients.[42,62] Koyama *et al.*[57] showed that highly fatigued HD patients exhibited a significantly greater risk for cardiovascular events, but not mortality. The relationship was independent of the well-known risk factors, including age, diabetes, cardiovascular disease history, inflammation, and malnutrition markers.

There are a number of ways through which fatigue may be associated with poor outcomes. Chaudhary[95] suggested that fatigue is one of the causes of treatment dropout in PD patients. As withdrawal from dialysis has been found to be the most common cause of death after CVD,[96] fatigue may affect mortality through dialysis non-adherence. Poor nutrition could also have a role in mortality as it is well established that serum albumin predicts survival in dialysis patients.[97] Fatigue is also associated with and is a feature of depression, which is well recognized to predict mortality in end-stage renal disease patients.[98,99] Whether fatigue is an independent predictor of outcome, above and beyond the effects of depression, still requires further evaluation.

Multiple studies have found that fatigue is significantly associated with lower QoL in renal patients.[42,62,100] A longitudinal study found that fatigue was strongly negatively correlated with physical and mental health over time, with higher fatigue levels leading to lower health-related QoL 12 months later.[33] As health-related QoL is strongly associated with higher risk of mortality and hospitalization in dialysis patients,[101] more research is required to assess whether interventions to improve fatigue and QoL could improve clinical outcomes.

NONPHARMACOLOGICAL TREATMENT OF FATIGUE IN RENAL PATIENTS

As the etiology of fatigue in renal patients is still largely unknown, no consistent treatment model exists. Studies that have examined therapeutic strategies are few, heterogeneous, and generally have methodological limitations. Treatment of fatigue can be divided into pharmacological and non-pharmacological interventions. Pharmacological interventions include: l-carnitine, growth hormone, nandrolone decanoate, and vitamin c supplementation (for a review see Bossola *et al.*[40]). For the purpose of this review we will focus on nonpharmacological interventions for the treatment of fatigue.

Much evidence supports the positive effects of regular physical activity on fatigue.[102] In dialysis patients, both aerobic and resistance exercises are associated with improvements in muscle structure and function, cardiac function, blood pressure, psychological adaptation, and QoL.[60,103,104] A recent randomized controlled trial[105] revealed how performing a leg ergometry exercise within the first hour of HD session can significantly improve fatigue and activity levels at 8 weeks after intervention. In addition, van Vilsteren *et al.*[106] reported improved vitality levels following a low–medium intensity exercise program. Partial data from a study in pediatric patients showed decrease in perceived fatigue after an exercise program, although adherence to the program was low.[107] Indeed, when exercise therapy is available in routine practice, uptake by dialysis patients is low. A likely contributor to poor uptake and adherence may be the fact that exercise protocols have been developed primarily for research purposes and hence may be unsuitable for patients with poorer health and multi-morbidities due to the frequency and vigor of particular regimens.[60] Furthermore, patients' illness and treatment perceptions have been shown to predict adherence in dialysis patients,[108,109] thus may also help explain uptake and adherence to exercise interventions. Moreover, evidence of plausible mechanisms regarding the benefits of physical activity upon fatigue levels remains unclear.[102] It is well established that exercise interventions improve physical QoL in both clinical and healthy populations[110] and can lead to reductions in pro-inflammatory cytokines,[111] which could have an impact upon fatigue levels. In HD patients, physical inactivity is associated with greater post-dialysis fatigue.[69] Although data are inconclusive,[112] small studies in dialysis patients have indicated reductions in CRP following both stationary dialysis cycling[113,114] and high-intensity, progressive resistance training.[115] Other studies have shown that exercise regimens are associated with improvements in nutritional parameters and QoL in CKD,[104,116] mood,[117] and sleep quality.[114] However, given that many of these studies suffer from small sample sizes, or other methodological concerns, further longitudinal studies are required to understand the mechanism through which exercise may lead to improved fatigue levels in dialysis patients.

Cognitive-behavioral therapy (CBT) for sleep disturbances in dialysis patients has shown promising effects on fatigue, with modest but significant reductions in fatigue scores after intervention.[118,119] A very small individual sleep intervention study by Yngman-Uhlin *et al.*[66] also revealed similar results, with four out of nine patients reporting reductions in fatigue. Although these findings corroborate the association between sleep problems and fatigue, larger investigations are needed to support these data. A small number of studies have been conducted on alternative therapies for fatigue in renal patients. These encompass: acupressure, reflexology, and yoga. Tsay[65] conducted an randomized controlled trial on the effect of acupressure and found that patients in the acupressure group, not only had significantly lower levels of fatigue but also had significantly better sleep quality compared with patients in the control group. A recent study by Ozdemir *et al.*[89] evaluated the effect of foot reflexology on fatigue on HD patients and reported significant differences in fatigue levels between the experimental and the control group. Finally, an randomized controlled trial in HD patients found significant effects of yoga on fatigue, with a 55% reduction of fatigue following treatment compared with the control group.[120] Although these results look promising, the studies used small samples and no follow-up data were included, hence the generalizability and long-term outcomes of these interventions on fatigue are yet to be defined. Indeed, a recent meta-analysis on the effects of yoga interventions in different chronic illnesses was not able to demonstrate effects of yoga on fatigue levels.[121]

As fatigue is a multifactorial problem, a multidisciplinary approach to treatment may be the most appropriate approach to treatment, with the need to consider treatment models adopted in other long-term medical conditions (Figure 3). For example, tackling unhelpful cognitions and behaviors thought to perpetuate fatigue would be an important target of fatigue intervention in dialysis patients (i.e., increasing perceptions of control over symptoms, increase understanding, seeing fatigue as time-limited and as having less serious consequences). Owing to the large prevalence of fatigue among renal patients, it is important for all renal providers to receive training on the identification and treatment of fatigue. Anemia and inflammation appear to be the primary physiological correlates of fatigue in renal patients, albeit with small–moderate effect sizes, and remain targets for treatment of fatigue in advanced kidney disease. However, acknowledging the growing evidence that supports the links between fatigue and psychosocial factors, clinicians should address these aspects in order to comprehensively address fatigue. Moreover, given the bidirectional relationship between fatigue and physical inactivity, it could be useful to incorporate physical rehabilitation as part of the kidney patients' care.[60] Similarly, following guidelines from the UK National Institute for Health and Clinical Excellence,[122] patients with CKD should be encouraged to exercise by providing them with information on the benefits of exercise on fatigue. Sleep and nutrition should also be factors to consider when developing nonpharmacological interventions. Finally, the different fatigue levels in relation to dialysis duration and frequency and rates of ultrafiltration suggest that clinicians may wish to regard these as potentially modifiable factors to improve fatigue in dialysis patients.

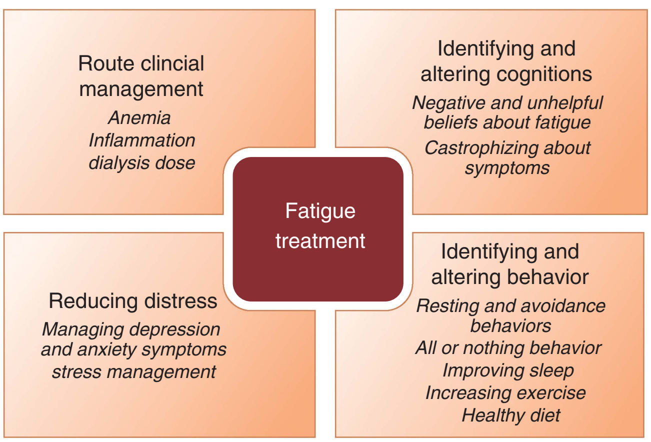

Figure 3 | Proposed modifiable factors for the treatment of fatigue in advanced kidney disease. Behavior factors (e.g., resting and avoidance, and all or nothing behaviors) and cognitive factors (e.g., castrophizing) are hypothesized to predict fatigue in advanced kidney disease patients and are targets of fatigue interventions in other long-term medical conditions.

CONCLUSIONS AND FUTURE DIRECTIONS

Fatigue is a common phenomenon among patients with kidney disease, yet it is often unrecognized and undertreated. The lack of a comprehensive definition and a relatively poor understanding of its pathogenesis and measurement issues combine to make treatment development challenging across the spectrum of advanced kidney disease. Studies that address fatigue have found that fatigue is more prevalent among older, white women. Behavioral factors such as: physical inactivity, sleep, and nutrition appear to have a significant impact on fatigue. The type of renal replacement therapy may also have an effect on fatigue, with transplant patients displaying significantly less fatigue than patients on dialysis. However, there is conflicting evidence on how the duration of dialysis affects fatigue in renal patients. There is a need to conduct large-scale longitudinal studies in order to determine how these factors are associated with fatigue over time. Interesting findings have been made from the investigation of fatigue and biochemistry and hematology factors, with studies reporting significant correlations between fatigue and hemoglobin levels, inflammatory and nutrition markers, and dialysis adequacy markers. However, results are not always consistent and further insights into how behavioral and disease-related factors interact with each other to cause fatigue would deepen our understanding of the pathology and treatment of fatigue. Research regarding the relationship between fatigue and psychosocial factors is not extensive and most findings are focused on depression and anxiety. Nevertheless, the different etiologies and clinical outcomes of depression and fatigue indicate two correlated but distinct phenomena, which require specific interventions. It has been shown in cancer patients that depression and fatigue share no structural relationship over time.[123] Further studies are therefore needed to address other potential correlates, including cognitive and behavioral factors, where research is limited in this patient population. Indeed, research from the multiple sclerosis literature[124] shows that changes in beliefs about fatigue have a crucial role in CBT for multiple sclerosis fatigue. Having more positive views about fatigue (i.e., having more control over it, having a better understanding of it, seeing it as time-limited and as having less serious consequences) is associated with a reduction in fatigue severity. Furthermore, as illness perceptions have been shown to have a role in survival[125] and depression[126,127] in HD patients, exploring the relationship between illness perceptions and fatigue could be a logical next step in fatigue research. The recognition of the importance of the sociodemographic, physiological, and psychological correlates of fatigue can help researchers and clinicians gain further understanding of fatigue and aid in the development of more targeted interventions. Addressing factors associated with fatigue through nonpharmacological as well as pharmacological treatment methods, may help improve QoL and have an impact on mortality. To date, data on interventions on renal patients are sparse and definitive conclusions cannot be drawn due to the limited number of studies and their lack of generalizability to the wider population. However, more comprehensive results have been found by large-scale RCTs addressing fatigue in other chronic illnesses including graded exercise therapy and CBT in chronic fatigue syndrome,[128,129] CBT in multiple sclerosis,[130,131] and CBT in patients with cancer.[132] These treatment protocols have been based on multifactorial models of understanding fatigue in these populations, which include an interaction between biological, psychological, and social factors.[133–136] Drawing from theories and research in other clinical populations can provide us with a better appreciation of the way different factors contribute to fatigue in general, and illuminate appropriate areas for future research and interventions in patients with advanced kidney disease.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Pawlikowska T, Chalder T, Hirsch SR *et al.* Population based study of fatigue and psychological distress. *BMJ* 1994; **308**: 763–766.
2. David A, Pelosi A, McDonald E *et al.* Tired, weak, or in need of rest: fatigue among general practice attenders. *BMJ* 1990; **301**: 1199–1202.
3. Heiwe S, Clyne N, Dahlgren MA. Living with chronic renal failure: patients' experiences of their physical and functional capacity. *Physiother Res Int* 2003; **8**: 167–177.
4. Horigan AE, Schneider SM, Docherty S *et al.* The experience and self-management of fatigue in patients on hemodialysis. *Nephrol Nurs J* 2013; **40**: 113–122.
5. Sklar AH, Riesenberg LA, Silber AK *et al.* Postdialysis fatigue. *Am J Kidney Dis* 1996; **28**: 732–736.
6. Lee BO, Lin CC, Chaboyer W *et al.* The fatigue experience of haemodialysis patients in Taiwan. *J Clin Nurs* 2007; **16**: 407–413.
7. Jhamb M, Weisbord SD, Steel JL *et al.* Fatigue in patients receiving maintenance dialysis: a review of definitions, measures, and contributing factors. *Am J Kidney Dis* 2008; **52**: 353–365.
8. Horigan AE. Fatigue in hemodialysis patients: a review of current knowledge. *J Pain Symptom Manage* 2012; **44**: 715–724.
9. Taylor RR, Jason LA, Torres A. Fatigue rating scales: an empirical comparison. *Psychol Med* 2000; **30**: 849–856.
10. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. *J Pain Symptom Manage* 2009; **37**: 107–128.
11. Hacker ED, Ferrans CE. Ecological momentary assessment of fatigue in patients receiving intensive cancer therapy. *J Pain Symptom Manage* 2007; **33**: 267–275.
12. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004; **56**: 157–170.
13. Ware JE, Snow KK, Kosinski M *et al.* SF-32 Health Survey. *Manual and Interpretation Guide*. Nimrod Press: Boston, Massachusetts, 1993.
14. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1992; **30**: 473–483.
15. Sanner BM, Tepel M, Esser M *et al.* Sleep-related breathing disorders impair quality of life in haemodialysis recipients. *Nephrol Dial Transplant* 2002; **17**: 1260–1265.
16. Krupp LB, LaRocca NG, Muir-Nash J *et al.* The Fatigue Severity Scale. *Arch Neurol* 1989; **46**: 1121–1123.
17. Gencay-Can A, Can SS. Validation of the Turkish version of the fatigue severity scale in patients with fibromyalgia. *Rheumatol Int* 2012; **32**: 27–31.
18. Armutlu K, Korkmaz NC, Keser I *et al.* The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients. *Int J Rehabil Res* 2007; **30**: 81–85.
19. Learmonth YC, Dlugonski D, Pilutti LA *et al.* Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. *J Neurol Sci* 2013; **331**: 102–107.
20. Kleinman L, Zodet M, Hakim Z *et al.* Psychometric evaluation of the fatigue severity scale for use in chronic hepatitis C. *Qual Life Res* 2000; **9**: 499–508.
21. Valderramas S, Feres AC, Melo A. Reliability and validity study of a Brazilian-Portuguese version of the fatigue severity scale in Parkinson's disease patients. *Arq Neuro-Psiquiatr* 2012; **70**: 497–500.
22. Elbers RG, Rietberg MB, van Wegen EE *et al.* Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. *Qual Life Res* 2012; **21**: 925–944.
23. Vasconcelos OM Jr, Prokhorenko OA, Kelley KF *et al.* A comparison of fatigue scales in postpoliomyelitis syndrome. *Arch Phys Med Rehabil* 2006; **87**: 1213–1217.
24. LaChapelle DL, Finlayson MA. An evaluation of subjective and objective measures of fatigue in patients with brain injury and healthy controls. *Brain injury* 1998; **12**: 649–659.
25. Smets EM, Garssen B, Schuster-Uitterhoeve AL *et al.* Fatigue in cancer patients. *Br J Cancer* 1993; **68**: 220–224.
26. Strömgren AS, Goldschmidt D, Groenvold M *et al.* Self-assessment in cancer patients referred to palliative care. *Cancer* 2002; **94**: 512–520.
27. Chalder T, Berelowitz G, Pawlikowska T *et al.* Development of a fatigue scale. *J Psychosom Res* 1993; **37**: 147–153.
28. Afshar M, Rebollo-Mesa I, Murphy E *et al.* Symptom burden and associated factors in renal transplant patients in the U.K. *J Pain Symptom Manage* 2012; **44**: 229–238.
29. Caplin B, Kumar S, Davenport A. Patients' perspective of haemodialysis-associated symptoms. *Nephrol Dial Transplant* 2011; **26**: 2656–2663.
30. Curtin RB, Bultman DC, Thomas-Hawkins C *et al.* Hemodialysis patients' symptom experiences: effects on physical and mental functioning. *Nephrol Nurs J* 2002; **29**: 567–574.
31. Lerdal A, Wahl AK, Rustoen T *et al.* Fatigue in the general population: a translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. *Scand J Public Health* 2005; **33**: 123–130.
32. Cauch-Dudek K, Abbey S, Stewart DE *et al.* Fatigue in primary biliary cirrhosis. *Gut* 1998; **43**: 705–710.
33. Bonner A, Caltabiano M, Berlund L. Quality of life, fatigue, and activity in Australians with chronic kidney disease: A longitudinal study. *Nurs Health Sci* 2013; **15**: 360–367.
34. Bonner A, Wellard S, Caltabiano M. Levels of fatigue in people with ESRD living in far North Queensland. *J Clin Nurs* 2008; **17**: 90–98.
35. Bonner A, Wellard S, Caltabiano M. The impact of fatigue on daily activity in people with chronic kidney disease. *J Clin Nurs* 2010; **19**: 3006–3015.
36. Joshwa B, Khakha DC, Mahajan S. Fatigue and depression and sleep problems among hemodialysis patients in a tertiary care center. *Saudi J Kidney Dis Transpl* 2012; **23**: 729–735.
37. Liu HE. Fatigue and associated factors in hemodialysis patients in Taiwan. *Res Nurs Health* 2006; **29**: 40–50.
38. Ossareh S, Roozbeh J, Krishnan M *et al.* Fatigue in chronic peritoneal dialysis patients. *Int Urol Nephrol* 2003; **35**: 535–541.
39. Bossola M, Luciani G, Tazza L. Fatigue and Its Correlates in Chronic Hemodialysis Patients. *Blood Purification* 2009; **28**: 245–252.
40. Bossola M, Vulpio C, Tazza L. Fatigue in chronic dialysis patients. *Semin Dial* 2011; **24**: 550–555.
41. Cardenas DD, Kutner NG. The problem of fatigue in dialysis patients. *Nephron* 1982; **30**: 336–340.

42. Jhamb M, Pike F, Ramer S *et al.* Impact of fatigue on outcomes in the hemodialysis (HEMO) study. *Am J Nephrol* 2011; **33**: 515–523.
43. Kim HR, Son GR. Fatigue and its related factors in Korean patients on hemodialysis. *Taehan Kanho Hakhoe Chi* 2005; **35**: 701–708.
44. Leinau L, Murphy TE, Bradley E *et al.* Relationship between conditions addressed by hemodialysis guidelines and non-ESRD-specific conditions affecting quality of life. *Clin J Am Soc Nephrol* 2009; **4**: 572–578.
45. Yong DS, Kwok AO, Wong DM *et al.* Symptom burden and quality of life in end-stage renal disease: a study of 179 patients on dialysis and palliative care. *Palliat Med* 2009; **23**: 111–119.
46. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *J Pain Symptom Manage* 2006; **31**: 58–69.
47. Karadag E, Kilic SP, Metin O. Relationship between fatigue and social support in hemodialysis patients. *Nurs Health Sci* 2013; **3**: 12008.
48. O'Sullivan D, McCarthy G. An exploration of the relationship between fatigue and physical functioning in patients with end stage renal disease receiving haemodialysis. *J Clin Nurs* 2007; **16**: 276–284.
49. Morsch CM, Goncalves LF, Barros E. Health-related quality of life among haemodialysis patients–relationship with clinical indicators, morbidity and mortality. *J Clin Nurs* 2006; **15**: 498–504.
50. McCann K, Boore JR. Fatigue in persons with renal failure who require maintenance haemodialysis. *J Adv Nurs* 2000; **32**: 1132–1142.
51. Brunier GM, Graydon J. The influence of physical activity on fatigue in patients with ESRD on hemodialysis. *ANNA J* 1993; **20**: 457–461discussion 462, 521.
52. Curtin RB, Mapes DL. Health care management strategies of long-term dialysis survivors. *Nephrol Nurs J* 2001; **28**: 385.
53. Lindqvist R, Carlsson M, Sjödén P-O. Perceived consequences of being a renal failure patient. *Nephrol Nurs J* 2000; **27**: 291.
54. Van Wijk CM, Kolk AM. Sex differences in physical symptoms: the contribution of symptom perception theory. *Soc Sci Med* 1997; **45**: 231–246.
55. Akin S, Mendi B, Ozturk B *et al.* Assessment of relationship between self-care and fatigue and loneliness in haemodialysis patients. *J Clin Nurs* 2014; **23**: 856–864.
56. Bossola M, Di Stasio E, Antocicco M *et al.* Qualities of fatigue in patients on chronic hemodialysis. *Hemodial Int* 2013; **17**: 32–40.
57. Koyama H, Fukuda S, Shoji T *et al.* Fatigue is a predictor for cardiovascular outcomes in patients undergoing hemodialysis. *Clin J Am Soc Nephrol* 2010; **5**: 659–666.
58. Karakan S, Sezer S, Ozdemir FN. Factors related to fatigue and subgroups of fatigue in patients with end-stage renal disease. *Clin Nephrol* 2011; **76**: 358–364.
59. Cantekin I, Tan M. Determination of sleep quality and fatigue level of patients receiving continuous ambulatory peritoneal dialysis in Turkey. *Scand J Urol Nephrol* 2011; **45**: 452–460.
60. Kosmadakis GC, Bevington A, Smith AC *et al.* Physical exercise in patients with severe kidney disease. *Nephron Clin Pract* 2010; **115**: c7–c16.
61. Schwartz CE, Bode R, Repucci N *et al.* The clinical significance of adaptation to changing health: a meta-analysis of response shift. *Qual Life Res* 2006; **15**: 1533–1550.
62. Jhamb M, Argyropoulos C, Steel JL *et al.* Correlates and outcomes of fatigue among incident dialysis patients. *Clin J Am Soc Nephrol* 2009; **4**: 1779–1786.
63. Kutner NG, Brogan D, Fielding B *et al.* Black/white differences in symptoms and health satisfaction reported by older hemodialysis patients. *Ethn Dis* 2000; **10**: 328–333.
64. Bossola M, Luciani G, Giungi S *et al.* Anorexia, fatigue, and plasma interleukin-6 levels in chronic hemodialysis patients. *Ren Fail* 2010; **32**: 1049–1054.
65. Tsay SL. Acupressure and fatigue in patients with end-stage renal disease-a randomized controlled trial. *Int J Nurs Stud* 2004; **41**: 99–106.
66. Yngman-Uhlin P, Fernstrom A, Borjeson S *et al.* Evaluation of an individual sleep intervention programme in people undergoing peritoneal dialysis treatment. *J Clin Nurs* 2012; **21**: 3402–3417.
67. Yngman-Uhlin P, Johansson A, Fernstrom A *et al.* Fragmented sleep: an unrevealed problem in peritoneal dialysis patients. *Scand J Urol Nephrol* 2011; **45**: 206–215.
68. Sakkas GK, Karatzaferi C. Hemodialysis fatigue: just 'simple' fatigue or a syndrome on its own right? *Front Physiol* 2012; **3**: 31.
69. Gordon PL, Doyle JW, Johansen KL. Postdialysis fatigue is associated with sedentary behavior. *Clin Nephrol* 2011; **75**: 426–433.
70. Lindsay RM, Heidenheim PA, Nesrallah G *et al.* Minutes to recovery after a hemodialysis session: a simple health-related quality of life question that is reliable, valid, and sensitive to change. *Clin J Am Soc Nephrol* 2006; **1**: 952–959.
71. Kutner NG, Brogan D, Fielding B. Physical and psychosocial resource variables related to long-term survival in older dialysis patients. *Geriatr Nephrol Urol* 1997; **7**: 23–28.
72. Aukrust P, Yndestad A, Smith C *et al.* Chemokines in cardiovascular risk prediction. *Thromb Haemost* 2007; **97**: 748–754.
73. Sklar A, Newman N, Scott R *et al.* Identification of factors responsible for postdialysis fatigue. *Am J Kidney Dis* 1999; **34**: 464–470.
74. Dreisbach AW, Hendrickson T, Beezhold D *et al.* Elevated levels of tumor necrosis factor alpha in postdialysis fatigue. *Int J Artif Organs* 1998; **21**: 83–86.
75. Lindsay RM, Kortas C. Daily/Nocturnal Dialysis Study G. Hemeral (daily) hemodialysis. *Adv Ren Replace Ther* 2001; **8**: 236–249.
76. Heidenheim AP, Muirhead N, Moist L *et al.* Patient quality of life on quotidian hemodialysis. *Am J Kidney Dis* 2003; **42**: 36–41.
77. Erek E, Süleymanlar G, Serdengeçti K *et al.* Registry of the nephrologist, dialysis and transplantation in Turkey. Registry 2001. Turkish Society of Nephrology, Istanbul, 2002.
78. Letchmi S, Das S, Halim H *et al.* Fatigue experienced by patients receiving maintenance dialysis in hemodialysis units. *Nurs Health Sci* 2011; **13**: 60–64.
79. Chang WK, Hung KY, Huang JW *et al.* Chronic Fatigue in Long-Term Peritoneal Dialysis Patients. *Am J Nephrol* 2001; **21**: 479–485.
80. Erslev AJ, Besarab A. Erythropoietin in the pathogenesis and treatment of anemia of chronic renal failure. *Kidney Int* 1997; **51**: 622–630.
81. Foley RN, Curtis BM, Parfrey PS. Erythropoietin therapy, hemoglobin targets, and quality of life in healthy hemodialysis patients: a randomized trial. *Clin J Am Soc Nephrol* 2009; **4**: 726–733.
82. Senol V, Sipahioglu MH, Ozturk A *et al.* Important determinants of quality of life in a peritoneal dialysis population in Turkey. *Ren Fail* 2010; **32**: 1196–1201.
83. Williams AG, Crane PB, Kring D. Fatigue in African American women on hemodialysis. *Nephrol Nurs J* 2007; **34**: 610–617.
84. Roumelioti ME, Wentz A, Schneider MF *et al.* Sleep and fatigue symptoms in children and adolescents with CKD: a cross-sectional analysis from the chronic kidney disease in children (CKiD) study. *Am J Kidney Dis* 2010; **55**: 269–280.
85. Johansen KL, Finkelstein FO, Revicki DA *et al.* Systematic review of the impact of erythropoiesis-stimulating agents on fatigue in dialysis patients. *Nephrol Dial Transplant* 2012; **27**: 2418–2425.
86. Pertosa G, Grandaliano G, Gesualdo L *et al.* Clinical relevance of cytokine production in hemodialysis. *Kidney Int Suppl* 2000; **76**: S104–S111.
87. Wang L-J, Wu M-S, Hsu H-J *et al.* The Relationship between Psychological Factors, Inflammation, and Nutrition in Patients with Chronic Renal Failure Undergoing Hemodialysis. *Int J Psychiat Med* 2012; **44**: 105–118.
88. Montinaro V, Iaffaldano GP, Granata S *et al.* Emotional symptoms, quality of life and cytokine profile in hemodialysis patients. *Clin Nephrol* 2010; **73**: 36–43.
89. Ozdemir G, Ovayolu N, Ovayolu O. The effect of reflexology applied on haemodialysis patients with fatigue, pain and cramps. *Int J Nurs Pract* 2013; **19**: 265–273.
90. Chen CK, Tsai YC, Hsu HJ *et al.* Depression and suicide risk in hemodialysis patients with chronic renal failure. *Psychosomatics* 2010; **51**: 528–528.
91. Lin J, Guo Q, Ye X *et al.* The effect of social support and coping style on depression in patients with continuous ambulatory peritoneal dialysis in southern China. *Int Urol Nephrol* 2013; **45**: 527–535.
92. Lovibond PF, Lovibond SH. The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behav Res Ther* 1995; **33**: 335–343.
93. Cameron JI, Whiteside C, Katz J *et al.* Differences in quality of life across renal replacement therapies: a meta-analytic comparison. *Am J Kidney Dis* 2000; **35**: 629–637.
94. Heidarzadeh M, Atashpeikar S, Jalilazar T. Relationship between quality of life and self-care ability in patients receiving hemodialysis. *Iran J Nurs Midwifery Res* 2010; **15**: 71–76.
95. Chaudhary K. Peritoneal Dialysis Drop-out: Causes and Prevention Strategies. *Int J Nephrol* 2011; **2011**: 434608.
96. Birmelé B, François M., Pengloan J *et al.* Death after withdrawal from dialysis: the most common cause of death in a French dialysis population. *Nephrol Dial Transplant* 2004; **19**: 686–691.

97. Owen WF Jr, Lew NL, Liu Y *et al.* The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 1993; **329**: 1001–1006.
98. Chilcot J, Davenport A, Wellsted D *et al.* An association between depressive symptoms and survival in incident dialysis patients. *Nephrol Dial Transplant* 2011; **26**: 1628–1634.
99. Kimmel PL, Peterson RA, Weihs KL *et al.* Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. *Kidney Int* 2000; **57**: 2093–2098.
100. Davison SN, Jhangri GS. Impact of pain and symptom burden on the health-related quality of life of hemodialysis patients. *J Pain Symptom Manage* 2010; **39**: 477–485.
101. Mapes DL, Lopes AA, Satayathum S *et al.* Health-related quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int* 2003; **64**: 339–349.
102. Puetz TW. Physical activity and feelings of energy and fatigue. *Sports Med* 2006; **36**: 767–780.
103. Painter P, Moore G, Carlson L *et al.* Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. *Am J Kidney Dis* 2002; **39**: 257–265.
104. Painter P, Carlson L, Carey S *et al.* Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. *Am J Kidney Dis* 2000; **35**: 482–492.
105. Chang Y, Cheng SY, Lin M *et al.* The effectiveness of intradialytic leg ergometry exercise for improving sedentary life style and fatigue among patients with chronic kidney disease: a randomized clinical trial. *Int J Nurs Stud* 2010; **47**: 1383–1388.
106. van Vilsteren MC, de Greef MH, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. *Nephrol Dial Transplant* 2005; **20**: 141–146.
107. van Bergen M, Takken T, Engelbert R *et al.* Exercise training in pediatric patients with end-stage renal disease. *Pediatr Nephrol* 2009; **24**: 619–622.
108. Chilcot J. The importance of illness perception in end-stage renal disease: associations with psychosocial and clinical outcomes. *Semin Dial* 2012; **25**: 59–64.
109. Chilcot J, Wellsted D, Farrington K. Illness representations are associated with fluid nonadherence among hemodialysis patients. *J Psychosom Res* 2010; **68**: 203–212.
110. Gillison FB, Skevington SM, Sato A *et al.* The effects of exercise interventions on quality of life in clinical and healthy populations; a meta-analysis. *Soc Sci Med* 2009; **68**: 1700–1710.
111. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J Am Coll Cardiol* 2005; **45**: 1563–1569.
112. Dungey M, Hull KL, Smith AC *et al.* Inflammatory factors and exercise in chronic kidney disease. *Int J Endocrinol* 2013; **2013**: 569831.
113. Zaluska A, Zaluska WT, Bednarek-Skublewska A *et al.* Nutrition and hydration status improve with exercise training using stationary cycling during hemodialysis (HD) in patients with end-stage renal disease (ESRD). *Ann Univ Mariae Curie-Sklodowska [Med]* 2002; **57**: 342–346.
114. Afshar R, Emany A, Saremi A *et al.* Effects of intradialytic aerobic training on sleep quality in hemodialysis patients. *Iran J Kidney Dis* 2011; **5**: 119–123.
115. Cheema B, Abas H, Smith B *et al.* Progressive exercise for anabolism in kidney disease (PEAK): a randomized, controlled trial of resistance training during hemodialysis. *J Am Soc Nephrol* 2007; **18**: 1594–1601.
116. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney diseas. *Cochrane Database Syst Rev* 2011; **5**: CD003236.
117. Kouidi E, Iacovides A, Iordanidis P *et al.* Exercise renal rehabilitation program: psychosocial effects. *Nephron* 1997; **77**: 152–158.
118. Chen HY, Chiang CK, Wang HH *et al.* Cognitive-behavioral therapy for sleep disturbance in patients undergoing peritoneal dialysis: a pilot randomized controlled trial. *Am J Kidney Dis* 2008; **52**: 314–323.
119. Chen HY, Cheng IC, Pan YJ *et al.* Cognitive-behavioral therapy for sleep disturbance decreases inflammatory cytokines and oxidative stress in hemodialysis patients. *Kidney Int* 2011; **80**: 415–422.
120. Yurtkuran M, Alp A, Dilek K. A modified yoga-based exercise program in hemodialysis patients: a randomized controlled study. *Complement Ther Med* 2007; **15**: 164–171.
121. Boehm K, Ostermann T, Milazzo S *et al.* Effects of yoga interventions on fatigue: a meta-analysis. *Evid Based Complement Alternat Med* 2012; **2012**: 124703.
122. Crowe E, Halpin D, Stevens P. Guidelines: Early Identification and Management of Chronic Kidney Disease: Summary of NICE Guidance. *Brit Med J* 2008; **337**: 812–815.
123. Brown LF, Rand KL, Bigatti SM *et al.* Longitudinal Relationships Between Fatigue and Depression in Cancer Patients With Depression and/or Pain. *Health Psychol* 2012; **27**: 27.
124. Knoop H, van Kessel K, Moss-Morris R. Which cognitions and behaviours mediate the positive effect of cognitive behavioural therapy on fatigue in patients with multiple sclerosis? *Psychol Med* 2012; **42**: 205–213.
125. Chilcot J, Wellsted D, Farrington K. Illness perceptions predict survival in haemodialysis patients. *Am J Nephrol* 2011; **33**: 358–363.
126. Chilcot J, Wellsted D, Davenport A *et al.* Illness representations and concurrent depression symptoms in haemodialysis patients. *J Health Psychol* 2011; **16**: 1127–1137.
127. Chilcot J, Norton S, Wellsted D *et al.* Distinct depression symptom trajectories over the first year of dialysis: associations with illness perceptions. *Ann Behav Med* 2013; **45**: 78–88.
128. Moss-Morris R, Sharon C, Tobin R *et al.* A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. *J Health Psychol* 2005; **10**: 245–259.
129. Castell BD, Kazantzis N, Moss-Morris RE. Cognitive Behavioral Therapy and Graded Exercise for Chronic Fatigue Syndrome: A Meta-Analysis. *Clin Psychol Sci Pr* 2011; **18**: 311–324.
130. Mohr DC, Hart SL, Goldberg A. Effects of treatment for depression on fatigue in multiple sclerosis. *Psychosom Med* 2003; **65**: 542–547.
131. van Kessel K, Moss-Morris R, Willoughby E *et al.* A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosom Med* 2008; **70**: 205–213.
132. Given C, Given B, Rahbar M *et al.* Effect of a cognitive behavioral intervention on reducing symptom severity during chemotherapy. *J Clin Oncol* 2004; **22**: 507–516.
133. Van Kessel K, Moss-Morris R. Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. *J Psychosom Res* 2006; **61**: 583–585.
134. Moss-Morris R, Deary V, Castell B. Chronic Fatigue Syndrome. In: Barnes M, Good D (eds) *Neurological Rehabilitation: Handbook of Clinical Neurology*. Vol. 110, Elsevier: London, 2013. pp 303.
135. Mitchell SA. Cancer-Related Fatigue: State of the Science. *PM&R* 2010; **2**: 364–383.
136. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychol Bull* 2008; **134**: 700–741.