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Fatigue in Individuals with End Stage Renal Disease

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Abstract

Fatigue is a subjective overwhelming feeling of tiredness at rest, exhaustion with activity, lack of energy that impedes daily tasks, lack of endurance, or a loss of vigor. Individuals with end stage renal disease (ESRD) experience a high rate and severity of fatigue. Symptom management of fatigue in this population is critical, since fatigue has been linked with lower quality of life and higher mortality rates. In this article, we present a definition and overview of fatigue, a review of factors contributing to fatigue, and ways to manage fatigue in individuals with ESRD.

Keywords

End stage renal disease; fatigue; symptom management

Fatigue is defined as a subjective overwhelming feeling of tiredness at rest, exhaustion with activity, lack of energy that impedes daily tasks, lack of endurance, or as loss of vigor that can be unpleasant, distressing, and can interfere with physical and social activity (Finsterer & Mahjoub, 2013; Schipper & Abma, 2011). In general, fatigue is associated with chronic conditions, depression, poor sleep quality, stress, and extended periods of energy expenditure. In addition, susceptibility to fatigue may be influenced by genetic factors (Ali

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& Taha, 2017; Bossola, Luciani, & Tazza, 2009; Bossola, Di Stasio, Giungi, Rosa, & Tazza, 2015; Flythe et al., 2015; Liu, 2006; Wang, Yin, Miller, & Xiao, 2017; Williams, Crane, & Kring, 2007). Untreated fatigue can impact quality of life, leading to weakness, increased dependence on others, decreased physical and mental energy, social withdrawal, and depression (O'Sullivan & McCarthy, 2009).

Methods

A narrative review approach was selected to synthesize the current evidence due to the immense amount of literature regarding fatigue in individuals with ESRD. A thorough literature search was conducted of PubMed/Medline, Web of Science, and Cochrane Database of Systematic Reviews. Articles and reference lists from December 2001 to June 2018 were referred. This timeframe was chosen based on the state of the science. The search strategy included terms for end stage renal disease, kidney failure, fatigue, genetic, interventions, symptom management, and treatment. Hand searches were conducted of reference lists of all included articles and pertinent systematic reviews. Abstracts were screened for relevance.

Fatigue Prevalence and Impact in ESRD

Fatigue affects 60% to 97% of individuals with ESRD undergoing hemodialysis (HD) (Jhamb et al., 2013). The severity of fatigue in individuals with ESRD undergoing HD treatment is one of the highest among individuals with a chronic condition, including patients with cancer who are undergoing chemotherapy treatment, patients with depression, and patients with Systemic Lupus Erythematosus (Zyga et al., 2015). The impact of fatigue in individuals with ESRD is so profound that 94% of patients on HD reported they would be willing to receive more frequent HD if it would increase energy levels; however, only 19% would agree to more frequent treatments for a three-year increase in survival (Jhamb et al., 2009). Fatigue was one of the four symptoms associated with worse quality of life, with the other three being pain, shortness of breath, and lack of well-being (Davison & Jhangri, 2010). Fatigue affects many aspects of life for individuals with ERSD undergoing dialysis. It is linked with lower quality of life, negatively impacts daily living and activity, increases risk for cardiovascular events, and is associated with higher mortality rates (Bonner, Wellard, & Caltabiano, 2007; Bossola, DiStasio, Antocicco, Panico et al., 2015; Flythe et al, 2015; Jhamb et al., 2009; Koyama et al., 2010; Letchmi et al., 2011; O'Sullivan & McCarthy, 2009; Wang et al., 2017; Zyga et al., 2015).

Factors Contributing to Fatigue

The causes of fatigue in individuals with ESRD remain poorly understood. Fatigue can be experienced regardless of race, gender, and age. Table 1 depicts recent studies that have examined the association of demographic factors with fatigue and the fatigue measure utilized, design, strengths, and weaknesses of these studies. Based on examined studies, there is inconclusive evidence regarding difference in prevalence among race, gender, or age for those living with ESRD.

Clinical Laboratory Values Associated with Fatigue

Experimental studies are also inconclusive about the relationship between fatigue and renal-specific laboratory parameters, which include Kt/V (quantifies dialysis treatment adequacy), parathyroid hormone level, anemia, and albumin (Bossola et al., 2009; Bossola, Di Stasio, Antocicco, & Tazza, 2013; Jhamb et al., 2009; Liu, 2006; Williams et al., 2007). Severe anemia is related to fatigue in general and several factors affect this relationship. Individuals with chronic kidney disease have a target maintenance hemoglobin level of 10 to 11.5 g/dL (Mimura, Tanaka, & Nangaku, 2015). The lower target hemoglobin level in this patient population may confound this correlation with fatigue. Bossola and colleagues (2009) and Jhamb and colleagues (2009) suggest that markers of systemic inflammation, C-reactive protein, and IL-6, and decreased levels of albumin are associated with fatigue in individuals with ESRD who are receiving dialysis. While Bossola and colleagues (2013) did not show statistical significance between IL-6 levels and fatigue, serum IL-6 levels did increase with fatigue. The lack of statistical significance could be attributed to small sample size. Table 2 depicts recent studies that have examined the association of clinical laboratory values with fatigue and the fatigue measure utilized, design, strengths, and weaknesses of these studies.

Limitations of these studies include cross-sectional designs, limited sample sizes, and varied fatigue measures. The cross-sectional nature of these studies decreases the ability to recognize the dynamic nature of fatigue experienced in this patient population. Small sample sizes undermine the validity of the studies and may mask a potential significant relationship. Lack of a gold-standard measure of fatigue in this patient population decreases the ability to compare and generalize results across studies and populations.

Factors Associated with Fatigue

Table 3 depicts recent studies that have examined the association of different factors with fatigue and the fatigue measure utilized, design, strengths, and weaknesses of these studies. Based on examined studies, there is strong evidence regarding correlations between the following and fatigue: increased body mass index (BMI), number of co-morbidities, decreased physical activity, and depression. Severity of fatigue is associated with increasing BMI and number of co-morbidities in several key studies (Bossola et al., 2009, 2013; Chilcot et al., 2015; Jhamb et al., 2009; Picariello, Moss-Morris, Macdougall, & Chilcot, 2017). Many individuals with ESRD have multiple co-morbidities, such as diabetes and hypertension which have contributed to the development of ESRD. It should be noted that a study by Bai, Lai, Lee, Chang, and Chiou (2015) showed no association between the number of co-morbidities and fatigue. This may be attributed to study exclusion criteria of certain co-morbidities, including clinical depression, cancer, and dementia (Bai et al., 2015). Decreased physical activity is often found in this patient population (Bossola, Vulpio, & Tazza, 2011). Though much research demonstrates that fatigue is associated with decreased physical activity it is unclear whether fatigue may cause physical inactivity or physical inactivity may contribute to fatigue (Bossola et al., 2011). Further investigation is warranted to better understand this important relationship. Fatigue and depression are related in the general population and research suggests that the association remains for individuals with ESRD (Bai et al, 2015; Bossola et al., 2009, 2013; Liu, 2006). High levels of social support have been associated with decreased fatigue severity in two studies, but limited research has examined this association (Bai et al., 2015; Karadag, Kilic, & Metin, 2013). One large study (n = 105) found fatigue scores were positively correlated with problems of sleep latency (Ali & Taha, 2017). Mixed results regarding the association between fatigue and education level remain (Ali & Taha, 2017; Liu, 2006; Wang et al., 2016; Zyga et al., 2015). Education level warrants further investigation to provide insights to providers on potential patients at higher risk of fatigue.

Limitations of these studies include mostly cross-sectional designs, limited sample sizes, few studies, and bidirectional nature of variables associate with fatigue. Use of correlational analysis to determine the relationship between fatigue and physical activity, fatigue and depression, and fatigue and social support can depict effects that may be bidirectional. Therefore, causality cannot be determined without further investigation.

Assessment of Fatigue in the Clinical Setting

It is important to recognize indicators associated with fatigue in order to assess fatigue effectively in this patient population. Figure 1 represents risk factors associated with ESRD, fatigue, and mutual risk factors between the two (Hsu Iribarren, McCullough, Darbinian, & Go, 2009). Health care providers play a critical role in assessment and management of fatigue in this patient population. Fatigue is important to assess because it is one of the most burdensome symptoms encountered by patients with ESRD affecting not only quality of life, but increasing their risk for cardiovascular events and contributing to higher mortality rates (Bonner et al., 2007; Bossola, DiStasio, Antocicco, Panico et al., 2015; Flythe et al, 2015; Jablonski, 2007; Jhamb et al., 2009; Koyama et al., 2010; Letchmi et al., 2011; O'Sullivan & McCarthy, 2009; Wang et al., 2017; Zyga et al., 2015). Regardless, fatigue remains under-recognized and difficult to manage (Ju et al., 2018). Various measures exist to assess the level of fatigue experienced. Unfortunately, there is no gold-standard measure of fatigue in this patient population (see Table 1).

Based on study findings, Chao, Huang, and Chiang (2016) suggested that the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) demonstrated independent and significant correlations with key outcomes in patients with ESRD, which include age, serum albumin, creatinine, and frailty severity. This study had a sample size of 46, and only seven fatigue instruments were examined. Ju and colleagues (2018) suggested, based on study findings, that a core outcome measure for fatigue should incorporate a balance between generalizability and sensitivity, with items phrased to accurately measure the concept of fatigue in individuals undergoing dialysis. Furthermore, to gain a more comprehensive understanding regarding experience of fatigue, health care providers should directly ask patients how they are feeling and about the patient's preferences in addressing and managing their fatigue (Ju et al., 2018). Assessment of fatigue should occur repeatedly, perhaps at follow-up appointments or weekly at dialysis treatment. Time of assessment of fatigue is essential to keep in mind as fatigue is often increased directly after dialysis, but can resolve as time passes (Ju et al., 2018). It should also be noted that fatigue can be a manifestation of depression, which is also common among individuals with ESRD (Horigan, Schneider, Docherty, & Barroso, 2013).

Clinical Management of Fatigue

Fatigue in this patient population is unique due to the multidimensional nature of dialysis, and in turn, is difficult to manage. Effective treatment of fatigue is further complicated in this patient population because we do not understand the cause(s) of fatigue. Currently, there is nominal research examining genetic associations with fatigue. Some research has examined potential medical treatment options for fatigue, such as the correction of anemia and physical activity to improve clinical outcomes with varying success (Bossola et al., 2011; Horigan et al., 2013; Liu, 2006; Williams et al., 2007; Yurtkuran, Alp, Yurtkuran, & Dilek, 2007). Many of the research studies examining interventions to prevent or mitigate fatigue in individuals with ESRD are limited by small sample sizes and a lack of randomization (Bossola et al., 2011). Interventions to prevent and mitigate fatigue include pharmacological and non-pharmacological strategies (see Table 4). Pharmacological interventions to mitigate fatigue include vitamin C and L-carnitine (Brass et al., 2001; Fukuda et al., 2015; Singer, 2011). Nonpharmacological interventions to mitigate fatigue include exercise, acupressure, trans cutaneous electrical acupoint simulation (TEAS), psychological interventions, and correction of anemia (Chang, Cheng, Lin, Gau, & Choa, 2010; Cho & Sohng, 2014; Cho & Tsay, 2004; Hadadian et al., 2016; Johansen et al. 2012; Keown et al., 2010; Kim et al., 2016; Sabouhi, Kalani, Valiani, Mortazavi, & Bemanian, 2013; Yurtkuran et al., 2007). Table 4 depicts the most recent and sentinel studies addressing pharmacological and non-pharmacological interventions for fatigue in individuals with ESRD.

Generally, exercise involving resistance training and/or aerobic activity, as well as yoga, are safe and positive for patients on dialysis, especially individuals with low baseline physical functioning self-opinions (Bossola et al., 2011). Several studies suggest acupressure and TEAS interventions are favorable, though a systematic review by Kim and colleagues (2016) noted there is a very low quality of evidence of short-term effects of acupressure as an intervention for fatigue in this patient population. Furthermore, none of the studies specified the occurrence of severe adverse events nor assessed pain outcomes related to the intervention (Kim et al., 2016). Research examining the efficacy of counselling to reduce fatigue and improve the quality of life among patients on dialysis is ongoing (van der Borg, Schipper, & Abma, 2016). This study should conclude in 2019 and results should be available shortly thereafter. This is the first protocol to utilize mixed methods, including a randomized control trial, to examine a psychosocial intervention for reducing fatigue and improving quality of life in individuals with ESRD (van der Borg et al., 2016). A systematic review by Johansen and colleagues (2012), examining 15 articles, concluded that partial correction of anemia with erythropoiesis-stimulating agents (ESAs) leads to improvement of fatigue especially in individuals with a baseline hemoglobin level of less than 10 g/dL.

It is essential to note there is no standardization of interventions nor gold-standard measure of fatigue utilized. The lack of a standardized intervention limits our ability to determine which intervention is most impactful. Sabouhi and colleagues (2013) and Cho and Tsay (2004) demonstrated an acupressure intervention had positive effects on fatigue, but we are unable to determine which of the two methods is more effective due to lack of a standardized measure of fatigue. In the future, it will be helpful to determine a gold standard measure for fatigue in this patient population to compare effectiveness of interventions to mitigate fatigue. Additionally, future research studies need to include large randomized samples to increase generalizability of findings.

Key Findings

Research on fatigue in patients with ESRD has demonstrated that fatigue is a serious issue that needs to be addressed to improve quality of life and poor health outcomes. In this article, we presented a definition and overview of fatigue, factors contributing to fatigue, assessment of fatigue in the clinical setting, and clinical management of fatigue.

There are several key limitations regarding research examining fatigue in individuals with ESRD. A majority of the studies had a limited sample size and cross-sectional study design. Utilization of a cross-sectional design hinders the ability to capture the dynamic nature of fatigue experienced in this patient population. Lack of a gold standard measure of fatigue in this patient population is concerning. Future research must examine the best measure of fatigue in this patient population to determine a gold standard measure and increase the ability to compare and generalize results. Possible bidirectional nature of variables (physical activity, depression, and social support) associated with fatigue demonstrates that causality cannot be determined without further investigation.

Conclusion

There is much to learn regarding fatigue in this patient population, including causes, a gold standard measure for assessment, and effective management of fatigue. To address the unique and multifaceted nature of fatigue in this patient population related to dialysis, we think assessment with a standardized validated measure and interventions aimed to address the various dimensions of fatigue will produce the best results to mitigate the detrimental symptom of fatigue.

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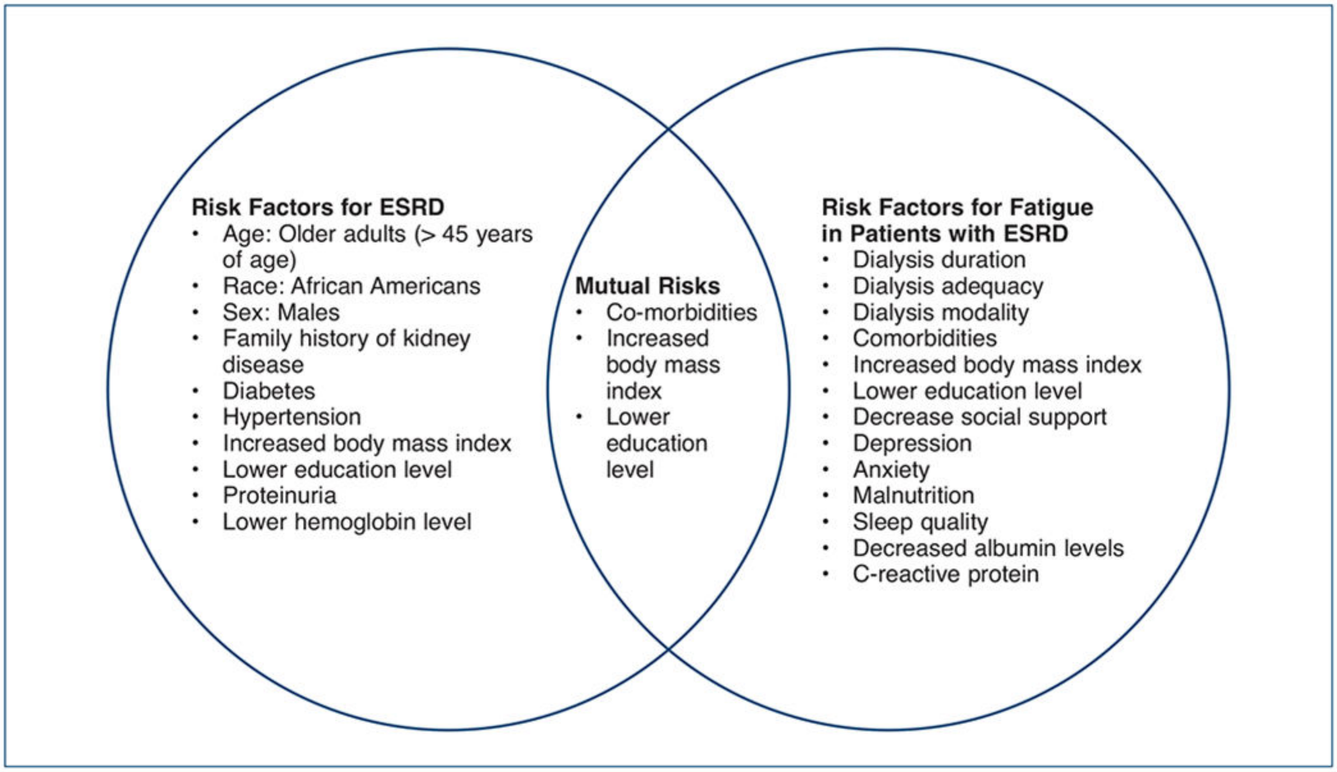

Figure 1.

Risk Factors Associated with ESRD and Fatigue in Patients with ESRD

Table 1

Demographic Factors Attributing to Fatigue

Author/Year	Number of Participants	Race	Gender	Age	Design	Fatigue Measure	Strengths	Weaknesses
Bai et al., 2015	193	N/A	No	Yes (older – ↑ fatigue)	Descriptive Correlational	Fatigue Scale for patients on HD	Participants recruited from six HD centers	Cross-sectional
Bonner, Wellard, & Caltabiano, 2007	92	No	No	No	Cross-sectional Descriptive	Fatigue Severity	Included patients on HD, PD, and who had received a kidney transplant	Included pre-dialysis patients Limited sample size Cross-sectional
Bossola, Luciani, & Tazza, 2009	62	N/A	No	Yes (older – ↑ fatigue)	Cross-sectional	Scale SF-36	Comparison of fatigue and non-fatigued participants on HD	Limited sample size Cross-sectional
Bossola, Stasio, Antocicco, & Tazza, 2013	68	N/A	No	Yes (older – ↑ fatigue)	Cross-sectional	Six Yes or Noquestions based on Hardy and Studenski model	Described study sample of individuals on HD and limitations in detail	Dichotomous fatigue measure Limited sample size Cross-sectional
Chilcot et al., 2015	174	Yes Caucasian – ↑ fatigue for fatigue severity only	No	No	Cross-sectional	Chalder Fatigue Questionnaire (primary outcome) The Work and Social Adjustment Scale (secondary outcome)	Measured fatigue severity and fatigue related functional impairment in individuals on HD	Cross-sectional
Jhamb et al., 2009	917 (705 included in adjusted models)	Yes Caucasian – ↑ fatigue	No	No	Longitudinal	SF-36 Vitality Scale	Large sample size Included individuals on HD and PD Longitudinal	Fatigue was only measured at baseline and one year on dialysis through vitality scores
Liu, 2006	119	N/A	Yes (female – ↑ fatigue)	Yes older – ↑ fatigue)	Cross-sectional Correlational	Fatigue Assess Scale	Large sample size Individuals on HD	Gender differences may have been attributed to Taiwan culture. Men are taught to avoid emotional expression Cross-sectional
O'Sullivan & McCarthy, 2007	46	N/A	Yes (female – ↑ fatigue)	No	Cross-sectional Correlational Exploratory	Multidimensional Fatigue Inventory	The sample was representative for gender	Limited sample size Cross-sectional Average length of time patients receiving HD was minimal (2 years)
Wang et al., 2016	345	N/A	No	Yes (older – ↑ fatigue)	Cross-sectional Descriptive Correlational	FACIT-Fatigue	Participants recruited from two HD centers Large sample size	Cross-sectional Only examined a few potential variables for fatigue

Notes: N/A = not available, ↑ = increased.

Table 2

Clinical Laboratory Values Associated with Fatigue

Author/Yea	Number of Participants	Kt/V	Serum Creatinine	Parathyroid Hormone	Anemia	Albumin	Markers of Inflammation	Design	Fatigue Measure	Strengths	Weaknesses
Bossola, Luciani, & Tazza, 2009	62	N/A	Yes (↓)	No	N/A	Yes (↓)	Yes: IL-6 (↑)	Cross-sectional	SF-36	Comparison of fatigue and non-fatigued participants on HD	Limited sample size Cross-sectional
Bossola, Stasio, Antocicco, & Tazza, 2013	68	No	No	No	N/A	No	No	Cross-sectional	Six Yes or No questions based on the Hardy and Studenski model	All patients on HD received erythropoietin to maintain hemoglobin levels between 11- 12 g/L and treated to target PTH and albumin levels and Kt/V according to the guidelines	Dichotomous fatigue measure Limited sample size Cross-sectional
Jhamb, et al., 2009	917 (705 included in adjusted models)	No	Yes (↓)	N/A	No	Yes (↓)	Yes: C-reactive protein (↑) and IL-6 (↑)	Longitudinal	SF-36 vitality scale	Large sample size Included patients on HD and PD Longitudinal	Fatigue was only measured at baseline and one year on dialysis through vitality scores
Liu, 2006	119	No	N/A	N/A	No	No	N/A	Cross-sectional Correlational	Fatigue Assess Scale	Large sample size of individuals on HD	Cross-sectional
Wang et al., 2016	345	Yes Kt/V < 1.2	Yes(↓)	N/A	No	No	N/A	Cross-sectional	FACIT-Fatigue	Participants recruited from two HD centers Large sample size	Cross-sectional Only examined a few potential variables for fatigue
Williams, Crane, & Kring, 2007	36	N/A	N/A	N/A	No	No	N/A	Cross-sectional Descriptive Correlational	Fatigue Visual Analog Scale	Homogenous sample of only African American women on HD.	Limited sample size Analyzed only African American women.

Notes: N/A = not available, ↑ = increased, ↓ = decreased.

Table 3

Factors Associated with Fatigue

Author/Year	Number of Participants	Body Mass Index	Co-morbidities	Physical Activity	Depression	Social Support	Sleep	Education Level	Design	Fatigue Measure	Strengths	Weaknesses
Ali & Taha, 2017	105	N/A	N/A	N/A	No	N/A	Yes (sleep latency – ↑ fatigue)	No	Descriptive Cross-sectional	Fatigue Severity Scale	Large sample size of patients on HD	Cross-sectional
Bai et al., 2015	193	N/A	No	Yes – (↓)	Depression – (↑)	Yes (No spouse – ↑ fatigue)	N/A	N/A	Descriptive Correlational	Fatigue Scale for hemodialysis patients	Participants recruited from six HD centers	Cross-sectional
Bossola, Luciani, & Tazza, 2009	62	N/A	Yes – (↑)	N/A	Depression – (↑)	N/A	N/A	N/A	Cross-sectional	SF-36	Comparison of fatigue and non-fatigued participants on HD	Limited sample size Cross-sectional
Bossola, Stasio, Antocicco, & Tazza, 2013	68	Yes – (↓)	Yes – (↓)	N/A	Depression – (↓)	N/A	N/A	N/A	Cross-sectional	Six Yes or No questions based Hardy and Studenski model	None of the patients on HD were on antidepressants	Dichotomous fatigue measure Limited sample size Cross-sectional
Chilcot et al., 2015	174	Yes – (↑)	Yes – (↑)	Yes – (↓)	N/A	No (marital status does not impact fatigue)	N/A	N/A	Cross-sectional	Chalder Fatigue Questionnaire (primary outcome) The Work and Social Adjustment Scale (secondary outcome)	Measured fatigue severity and fatigue related functional impairment in individuals on HD	Cross-sectional
Jhamb et al., 2009	917 (705 included in adjusted models)	Yes – (↑)	Yes – (↑)	Yes – (↓)	N/A	N/A	Yes (↓)	N/A	Longitudinal	SF-36 vitality scale	Large sample size Included patients on HD and PD Longitudinal	Fatigue was only measured at baseline and 1 year on dialysis through vitality scores
Karadag,Kilic, & Metin, 2013	73	N/A	N/A	N/A	N/A	Social support – ↓ fatigue	N/A	N/A	Descriptive Cross-sectional	Fatigue Severity Scale	Compared association of fatigue in individuals on HD with	Cross-sectional Correlational analysis determined relationship

Author/Year	Number of Participants	Body Mass Index	Co-morbidities	Physical Activity	Depression	Social Support	Sleep	Education Level	Design	Fatigue Measure	Strengths	Weaknesses
											support from family, friends, special person, and overall	between fatigue, effects may be bidirectional
Liu, 2006	119	N/A	N/A	N/A	Depression – (↓)	N/A	N/A	No	Cross-sectional Correlational	Fatigue Assess Scale	Large sample size of individuals on HD	All patients were married Cross-sectional
Wang et al., 2016	345	No	Yes	Yes – (↑)	N/A	No	N/A	No	Cross-sectional	FACIT-Fatigue	Participants recruited from two HD centers Large sample size	Cross-sectional Only examined a few potential variables for fatigue
Zyga et al., 2015	129	N/A	N/A	N/A	N/A	N/A	N/A	Yes – education	Cross-sectional	Fatigue Assessment Scale	Participants recruited from two HD centers Large sample size	Cross-sectional Physicians, nurses, and other health care providers were present during survey administration

Table 4

Fatigue Interventions: Pharmacological and Non-Pharmacological

	Author/Year	Intervention and Type of Dialysis	Participants	Result
Pharmacological Interventions	Singer, 2011	Vitamin C 250 mg, 3 times per week (oral) Individuals on HD or PD	48 intervention 48 placebo	No improvement in fatigue.
	Fukuda et al., 2015	500 mg carnitine within a nutritional drink, 3 times per week for 12 weeks (oral) Individuals on HD	87 intervention 86 placebo	No improvement in fatigue.
	Brass et al., 2001	Study A: IV 20 mg/kg L-carnitine after each dialysis session for 20 weeks. Study B: IV 10 mg/kg, 20 mg/kg, or 40 mg/kg L-carnitine after each dialysis session for 20 weeks.	Study A: 28 placebo 28 (20 mg/kg) Study B: 33 placebo 32 (10 mg/kg) 30 (20 mg/kg) 32 (40 mg/kg)	Study A: Deceased level of fatigue for intervention group. Study B: Decreased level of fatigue for intervention group, no difference in level of fatigue between intervention groups.
Non-Pharmacological Interventions	Chang et al., 2010	Individuals on HD Physical activity: leg ergometry exercise within the first hour of each HD session for 30 min for 8 weeks. Individuals on HD	35 control 36 experimental	Leg erometry exercise decreased fatigue in active and sedentary HD patients.
	Yurtkuran et al., 2007	Group yoga exercise, 30 minutes per day, twice a week for 3 months. Individuals on HD	18 control 19 experimental	Group yoga exercise decreased fatigue levels by 55%.
	Cho & Sohng, 2014	Virtual reality exercise program (Nintendo Wii Fit Plus) for 40 minutes, 3 times per week for 8 weeks. Individuals on HD	23 control 23 experimental	Level of fatigue decreased in the exercise group.
	Sabouhi et al., 2013	Experimental and placebo groups received acupressure intervention during HD on six acupoints with massage for 20 minutes, 3 days per week for 4 weeks. Placebo group-intervention performed, but 1cm away from intervention site. Individuals on HD	32 control 32 placebo 32 experimental	Experimental group experienced less fatigue severity compared to placebo and control.
	Cho & Tsay, 2004	Experimental group received acupoint massage for 12 minutes per day, 3 times per week, for 4 weeks.	30 control 28 experimental	Experimental group demonstrated greater improvement in fatigue compared to control group.
	Hadadian et al., 2016	Individuals on HD Trans Cutaneous Electrical Acupoint Simulation (TEAS) for 5 minutes, 2-3 times per week, for 5 weeks.	28 control 28 experimental	Experimental group had a better recovery rate of fatigue compared to the control group.
	Keown et al., 2010	Individuals on HD Epoetin alfa intravenously 3 times per week to attain a hemoglobin of 9.5–11.0 g/dL (low-target group, n=40), or 11.5–13.0 g/dL (high-target group, n=38) for 6 months.	40 control 78 experimental	Experimental group had improvement in fatigue compared to control group.