Published in final edited form as:
Am J Nephrol. 2022 ; 53(4): 253–263. doi:10.1159/000523714.

Fatigability and the Role of Neuromuscular Impairments in Chronic Kidney Disease

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Abstract

Background: The combination of neuromuscular impairments plus psychosocial aspects of chronic kidney disease (CKD) may predispose these patients to greater risk for experiencing increased levels of fatigability. There has been extensive clinical and scientific interest in the problem of fatigue in CKD and end-stage kidney disease (ESKD) patients, whereas less attention has been directed to understanding fatigability. Accordingly, the primary purposes of this review are to (1) discuss fatigue and fatigability and their potential interactions in patients with CKD and ESKD, (2) provide evidence for increased fatigability in CKD and ESKD patients, (3) examine how commonly experienced neuromuscular impairments in CKD and ESKD patients may contribute to the severity of performance fatigability, and (4) highlight preliminary evidence on the effects of exercise as a potential clinical treatment for targeting fatigability in this population.

Summary: Fatigue is broadly defined as a multidimensional construct encompassing a subjective lack of physical and/or mental energy that is perceived by the individual to interfere with usual or desired activities. In contrast, fatigability is conceptualized within the context of physical activity

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Author Contributions

Conceptualization: J.M.G., M.R.B., S.S.P., and M.O.H.-L.; writing: J.M.G., M.R.B., S.S.P., M.O.H.-L., and S.D.C. visualization: J.M.G; project administration: J.M.G.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

and is quantified as the interactions between reductions in objective measures of performance (i.e., performance fatigability) and perceptual adjustments regulating activity performance (i.e., perceived fatigability). We propose herein a conceptual model to extend current understandings of fatigability by considering the interactions among fatigue, perceived fatigability, and performance fatigability. Neuromuscular impairments reported in patients with CKD and ESKD, including reductions in force capacity, skeletal muscle atrophy, mitochondrial dysfunction, abnormal skeletal muscle excitability, and neurological complications, may each contribute to the greater performance fatigability observed in these patients.

Key Messages: Considering the interactions among fatigue, perceived fatigability, and performance fatigability provides a novel conceptual framework to advance the understanding of fatigability in CKD and ESKD patients. Measures of fatigability may provide valuable clinical insights into the overall health status of CKD and ESKD patients. Existing data suggest that CKD and ESKD patients are at greater risk of experiencing increased fatigability, partly due to neuromuscular impairments associated with reduced kidney function. Further investigations are warranted to determine the potential clinical role fatigability measures can play in monitoring the health of CKD and ESKD patients, and in identifying potential treatments targeting fatigability in this patient population.

Keywords

Fatigue; Fatigability weakness; Depression; Functional impairment; Renal failure

Introduction

Chronic kidney disease (CKD) is a debilitating condition affecting approximately 10%–15% of the global population [1]. Fatigue is one of the most common symptoms in patients with CKD not on dialysis, and in those with end-stage kidney disease (ESKD) [2–7]. Fatigue is broadly defined as a multidimensional construct encompassing a subjective lack of physical and/or mental energy that is perceived by the individual to interfere with usual or desired activities [8–10]. Patients with CKD who experience greater fatigue are at an increased risk of adverse cardiovascular events, decreased quality of life, and mortality [3, 11].

Fatigability, in contrast to fatigue, is conceptualized within the context of physical activity and is quantified as the interactions between reductions in objective measures of performance (i.e., performance fatigability) and perceptual changes regulating activity performance (i.e., perceived fatigability) [12]. While the symptom of fatigue can be chronic in nature, fatigability is reversible with rest [13, 14]. The predominant factors that affect fatigability are strongly influenced by the activity being performed [12, 15–17]. For example, during tasks isolating a specific muscle or muscle group(s), the primary mechanisms contributing to fatigability are directly related to the active muscles involved in performing the task [16, 18]. In comparison, during whole-body activities such as walking, there is an increase in the amount of active muscle mass and required support from other physiological systems to sustain muscle function [18]. This increases the potential involvement of psychobehavioral and central nervous system (CNS) factors contributing to fatigability [14, 19, 20]. In clinical populations, additional factors such as fatigue,

lack of motivation, anxiety, depression, disease/injury severity, and physical inactivity may contribute more importantly to fatigability and must also be considered [12, 14, 21].

The combination of neuromuscular impairments plus psychosocial aspects of CKD may predispose these patients to greater risk for experiencing increased fatigability [22–24]. There has been extensive clinical and scientific interest in the problem of fatigue in CKD and ESKD patients, whereas less attention has been directed to understanding fatigability. Although fatigue is a major challenge to everyday life, fatigue is not synonymous with fatigability [8, 12, 13, 25–31]. Accordingly, the primary purposes of this review are to (1) discuss fatigue and fatigability and their potential interactions in patients with CKD and ESKD, (2) provide evidence for increased fatigability in CKD and ESKD patients, (3) examine how commonly experienced neuromuscular impairments in CKD and ESKD patients may contribute to the severity of performance fatigability, and (4) highlight preliminary evidence of the effects of exercise as a potential clinical treatment for targeting fatigability in this population.

Fatigue and Fatigability and Their Potential Interactions in Patients with CKD and ESKD

Fatigue is often reported as a symptom of disease reflecting a formed representation of the specific condition [10, 32]. For example, fatigue has been proposed as a state of feeling in which there is a lack of motivation to deploy resources and engage in high effort performance to cope with a situation [10]. In this context, fatigue in CKD patients may occur as an adaptive process resulting from declines in kidney function that allow for mobilization of critical resources while preserving energy necessary for the maintenance of homeostasis so as to ensure survival [33–35]. Factors associated with fatigue in non-dialysis CKD patients include unemployment, comorbidities, antidepressant medication use, and anemia [36]. In a multivariable regression analysis, Jhamb et al. [37] observed that cardiovascular disease, low serum albumin, depressive symptoms, poor subjective sleep quality, excessive daytime sleepiness, and restless leg syndrome were independently associated with greater fatigue in CKD and ESKD patients. The findings of these studies highlight the multitude of factors associated with fatigue in non-dialysis CKD and ESKD patients, and their potential differences based on the severity of disease.

Complicating the understanding of fatigue in patients with ESKD is the phenomenon of post-dialysis fatigue. Such patients often report feelings of physical and mental fatigue immediately following dialysis treatment [38]. Symptoms of physical fatigue include feeling a lack of strength, worn out, drained, or exhausted. Regarding symptoms of mental fatigue following dialysis treatment, patients reported the inability to remember conversations, name recall challenges, and forgetfulness of where they were driving in their cars [38]. The time to recover from dialysis sessions varies among individuals and ranges from minutes to days but is typically resolved within 4 h [2, 39]. Importantly, the time to recover from dialysis is significantly related to fatigue status [40]. The type and duration of kidney replacement therapy, osmotic dis-equilibrium, blood membrane interactions, isolated ultrafiltration and

diffusion, and serum cytokine concentrations all influence the level of fatigue experienced after completing a dialysis session [2, 3, 41].

Psychological disorders and cognitive impairment are common in patients with CKD. Depression occurs in up to 20%, and anxiety in 10%–50%, of CKD patients [42–47]. Patients with depression and anxiety disorders are more likely to score higher on self-reported fatigue scales [41]. Cognitive impairment is associated with the severity of kidney disease and is thought to result from an accumulation of uremic neurotoxins that interact with neural progenitor cells, brain vasculature, the lymphatic system, and monoaminergic neurons [48–51]. Impaired kidney function has also been associated with reductions in cerebral gray matter volume and cortical thickness [52]. The high prevalence of depression, anxiety, and cognitive impairment is particularly salient when assessing fatigue and fatigability of CKD patients. While depression, anxiety, and fatigue constitute separate psychological states, their interrelationship has the potential to impact a person's willingness to engage in physical activity or exert oneself (i.e., perceived fatigability) [10, 20, 53]. This may help explain the observation that fatigue and low energy levels are the most common perceived barriers to exercise in patients with CKD and ESKD [54].

From a bioenergetic perspective, dysregulation of energy use (i.e., adenosine triphosphate, ATP) is a principal mechanism responsible for performance fatigability [55]. Augmented breakdown of ATP increases circulating and tissue concentrations of metabolic byproducts (hydrogen ions and inorganic phosphate) and decreases calcium sensitivity, resulting in impaired skeletal muscle cross-bridge function during high-intensity physical activity [15, 16, 56, 57]. In comparison, fatigability experienced during moderate-intensity activity is thought to result from reductions in substrate availability and muscle activation [14, 58–62]. Sensory feedback from receptors located in skeletal muscle is sent to the CNS via myelinated (group III) and unmyelinated (group IV) nerve fibers [58, 59]. The afferent information received by the CNS from the group III/IV nerve fibers during skeletal muscle contraction exerts inhibitory influences on the central motor drive and muscle activation [58, 59]. Reductions in physiologic capacity and/or increases in energetic cost of muscle contraction with aging place greater strain on bioenergetic systems, accelerating the accumulation of metabolic by-products and the increased sense of effort required to perform a given activity [20, 56, 63, 64].

Recent efforts have been made to further clarify distinctions between fatigue and fatigability [8, 12, 25–31]. These efforts are influenced, in part, by the lack of significant associations between measures of fatigue and performance fatigability in the medical literature, suggesting potential differences in biological underpinnings [25, 65–72]. Perceived fatigablity has been shown to be significantly associated with heightened perceived effort and reduced affect, but not performance fatigability, when assessed during knee extensor contractions [73]. The transient changes in an individual's psychophysiological state influence the decision or desire to continue with activity performance [20, 53]. In ESKD patients, this is reflected in how individuals adjust the timing and intensity of their activities to accommodate their level of fatigue [38]. Fatigability thus emerges as the interactions among fatigue, perceived fatigability, and performance fatigability[12]. Such a model also allows possible underlying determinants of fatigue, perceived fatigability, and performance

fatigability to be identified, and to be used in combination to inform the clinical decision-making process. Furthermore, simultaneous monitoring of each domain may provide a more comprehensive understanding of how fatigue and fatigability respond to specific interventions [74].

Evidence of Elevated Fatigability in Patients with CKD and ESKD

Evidence from several cross-sectional studies suggests that such individuals are more susceptible to greater levels of fatigability than are their age-matched healthy counterparts (Table 1) [75–79]. For example, Johansen et al. [75] observed greater performance fatigability of the ankle dorsiflexors during maximum voluntary isometric contractions in dialysis patients versus control subjects. Similarly, performance fatigability, as determined during thirty maximal isokinetic contractions at 180°/s, was estimated to be 1.6-fold higher in kidney transplant and hemodialysis (HD) patients than in control subjects [76]. During rhythmic hand-grip exercise, HD patients exhibited greater fatigability than did transplant recipients or control subjects [79]. Macdonald et al. [77] noted that patients with CKD stages 3b and 4 reported greater ratings of perceived exertion than did control subjects when engaging in exercise intensities representative of various activities of daily living.

To our knowledge, few longitudinal studies have been reported examining changes in measures of fatigability in patients with CKD. In one 2-year longitudinal study in patients with non-dialysis-dependent CKD, whole-body performance fatigability increased, as measured by reductions in peak oxygen consumption [80]. However, in the same study, knee extensor performance fatigability remained unchanged, despite reductions in creatinine clearance and isokinetic strength [80]. More and larger longitudinal studies are warranted to determine the extent to which fatigability levels change over time in CKD and ESKD patients [80].

Neuromuscular Impairments Influencing Fatigability in Patients with CKD and ESKD

The remainder of this review is focused on commonly observed neuromuscular impairments that are likely to exacerbate performance fatigability in CKD and ESKD patients (shown in Fig. 1). This represents just one example of how consequences associated with CKD and ESKD could exacerbate fatigability. Moreover, the influences of performance fatigability resulting from neuromuscular impairments on fatigue and perceived fatigability have yet to be thoroughly investigated. Importantly, factors other than neuromuscular impairments are likely to contribute to fatigability in CKD and ESKD patients and should also be considered [7, 81].

Force Capacity

Skeletal muscle weakness is commonly associated with CKD and ESKD [82–84]. Although there is some overlap between the mechanisms contributing to muscle weakness and performance fatigability, these two phenomena are not synonymous [85]. For example, after the termination of activity, performance fatigability is mitigated with rest while muscle

weakness is evident even in a fully rested state [14]. The reductions in force capacity experienced with CKD may promote greater fatigability through decreases in physiologic reserve [86]. Moreover, this may have a direct impact on functional capabilities, as weaker individuals require a greater percentage of their physiologic capacity to perform a given amount of work. During exercise at lower relative intensities, more rapid depletion of phosphocreatine and increased intracellular acidosis occur in HD patients compared with transplant recipients and control subjects [79]. In comparison, isokinetic knee extensor strength is directly associated with whole-body exercise endurance in patients with CKD and ESKD, suggesting that level of strength positively influences whole-body performance fatigability [80, 87].

Skeletal Muscle Atrophy

Declines in force capacity are, in part, explained by the loss of skeletal muscle mass in individuals with CKD and ESKD [88–90]. Skeletal muscle atrophy has also been associated with declines in certain measures of physical function [88, 89, 91–93]. Individuals with compromised kidney function are predisposed to accelerated skeletal muscle loss via upregulation of protein degradation and downregulation of protein synthesis [94]. Johansen et al. [95] reported decreased amounts of contractile tissue in the anterior compartment of the lower leg in dialysis patients compared to control subjects. Using a subjective clinical assessment for skeletal muscle atrophy, Carrero et al. [96] found that 30% of patients initiating HD and 39% of prevalent HD patients exhibited signs of muscle atrophy. Skeletal muscle cross-sectional area of the mid-thigh, determined via computed tomography, declined 4.3% over a 2-year period in stage 4 CKD and HD patients [88]. Atrophy of type II muscle fibers may, in part, explain the reductions in muscle force capacity observed in this population [84]. Additional mechanisms involved in the promotion of skeletal muscle atrophy may also contribute to increased fatigability, such as alterations in mitochondrial function, which have been identified as a primary cause of skeletal muscle atrophy in aging, physical inactivity, and various diseases, including CKD [97, 98].

Mitochondrial Dysfunction

Skeletal muscle mitochondrial dysfunction is directly associated with disease severity in patients with CKD [99–104]. Mitochondrial dysfunction promotes skeletal muscle atrophy and impairs bioenergetic processes [103–106]. Thome et al. [104] reported significant impairments in oxidative phosphorylation in skeletal muscle of mice with adenine-induced CKD. In other rodent models of CKD (i.e., C57BL/6N), uremic metabolites contribute to decreased energy transfer, impaired complex III and IV enzyme activity, and elevated oxidant production within mitochondria [103]. Similarly, accumulation of the uremic metabolite indoxyl sulfate in skeletal muscle tissue upregulates glycolysis with concomitant downregulation of oxidative metabolism [107]. Indoxyl sulfate also decreases the expression of peroxisome proliferator-activated receptor-gamma coactivator-1 alpha, a principal regulator of mitochondrial biogenesis [105]. Human vastus lateralis skeletal muscle in patients on maintenance HD exhibits reduced enzymatic activity of succinate dehydrogenase, an enzyme involved in oxidative metabolism, compared to that in control subjects [108]. Similarly, in calf muscle of HD patients, energy production via oxidative metabolism was impaired and compensated for by an increase in anaerobic glycolysis [109].

Therefore, in addition to promoting skeletal muscle loss, mitochondrial dysfunction and altered oxidative metabolism may serve as contributing factors to excess fatigability in CKD and ESKD patients.

Skeletal Muscle Excitability

Disturbances in skeletal muscle potassium (K^+), sodium (Na^+), chloride (Cl^-), and Na^+-K^+ pump activity have been implicated in promoting fatigability [110–113]. In particular, elevations in skeletal muscle K^+ concentrations [K^+] depolarize the sarcolemma and inactivate voltage-gated Na^+ channels, decreasing membrane excitability [111, 113]. During intense muscular activity, ionic shifts can exert profound effects on skeletal muscle contractile function [111]. For example, the rate of interstitial [K^+] accumulation is likely to hasten the onset of activity termination by preventing calcium (Ca^{2+}) release [111, 114]. This concept is supported by the finding that a more rapid accumulation of skeletal muscle interstitial [K^+] induced by prior arm exercise was associated with a reduced time to exhaustion during subsequent leg exercise [115, 116]. However, interstitial [K^+] does not seem to act independently during the fatigability process, but in combination with intracellular [K^+], [Na^+], and [Cl^-] and Na^+-K^+ pump activity [111].

Abnormal K^+ regulation is frequently reported in patients with CKD and may explain, in part, findings of greater fatigability in this population [76, 117–119]. Friedland & Paterson described the potential impact of elevated K^+ on performance fatigability during exhaustive cycle ergometry exercise in ESKD patients on maintenance HD [120]. These authors observed arterial plasma $[K]^+$ of about 7 mmol/L at the end of exercise and suggested that this increase in [K^+] was sufficient to impair membrane excitability, thereby decreasing muscle contractility [120]. The resting transmembrane potential of myocytes in uremic patients decreases progressively with declining kidney function and assumes a linear relationship with creatinine clearance values below 6.3 mL/min per 1.73 m^2 [121]. Of note, maximal Na^+-K^+ pump activity of the vastus lateralis is reduced by approximately 30% in HD patients and kidney transplantation recipients, and dialysis transiently normalizes sarcolemmal membrane potential, but not t-tubule function [76, 122].

Neurological Impairments

CNS contributions to the suppression of motoneuron excitability can occur via multiple processes, resulting in elevated fatigability [14, 58, 59, 123]. Neurological complications accompany CKD and become more pronounced in those with ESKD [23, 24, 124, 125]. Isaacs observed considerable dropout of motor unit activity during isometric fatigability testing of the abductor pollicis brevis in patients with CKD and clinical neuropathy [126]. Subsequent studies demonstrated that the nerves of uremic patients exhibit a chronically depolarized state before dialysis, with improvement and normalization of nerve resting membrane potential 1 h after a standard 5 h HD session [127]. The magnitude of depolarization was directly related to the serum $[K]^+$, suggesting that depolarization due to chronic elevations in $[K]^+$ plays an important role in the development of nerve dysfunction and performance fatigability in patients with ESKD [24, 127].

The exercise pressor reflex is a pathophysiological mechanism that elicits increased sympathetic nerve activity in the heart, blood vessels, and adrenal medulla, and decreased parasympathetic activity in the heart, so as to ensure matching the circulatory and metabolic demands of muscle contraction [128, 129]. Both mechanical (mechanoreflex) and metabolic (metaboreflex) stimuli produced by contracting skeletal muscle trigger autonomic activation during physical activity [129]. In patients with ESKD, exaggerated increases in the exercise pressor reflex may contribute to fatigability [130]. In this context, ESKD patients exhibit decreased muscle oxygenation at rest and an impaired ability of skeletal muscle to oppose sympathetically mediated vasoconstriction during exercise (functional sympatholysis) [131]. Moreover, reduced flow-mediated dilation has been significantly associated with a higher slope-of-rise in systolic blood pressure during exercise, and poorer exercise capacity, in CKD patients [132]. The aforementioned factors all contribute to greater peripheral resistance, increased myocardial work-load, and diminished blood flow.

Effects of Exercise on Fatigability in Patients with CKD and ESKD

Improvements in energy and strength are the two most desired benefits from exercise in those with ESKD [133]. Exercise interventions exert beneficial effects on fatigue, anxiety, depression, and quality of life in patients with ESKD, and both resistance exercise and aerobic exercise improve neuromuscular and functional outcomes in people with CKD and ESKD [134–139]. In comparison, the effects of exercise on fatigability in CKD and ESKD patients are not as clear, due to the relatively limited number of studies to date. In this regard, in one study, 6 weeks of cycling exercise performed for 30-min a day 3 days/week during the first hour of dialysis treatment increased whole-body performance fatigability [78]. However, in the latter study, knee extensor performance fatigability index did not change significantly despite improvements in absolute and relative peak torque [78]. Similarly, in a recent pilot study, 12 weeks of flywheel resistance exercise in adults with CKD not on dialysis elicited no change in a maximal isometric or isokinetic knee extensor performance fatigability index despite increases in torque capacity [140].

The force-fatigability relationship suggests that, in general, the degree to which fatigability is expressed is related to the amount of force produced, so that greater force elicits greater fatigability [141]. Therefore, patients with CKD and ESKD are seemingly more resistant to activity-induced fatigability following exercise, given that fatigability level was unchanged despite increased force generation [78, 140]. Further investigations are warranted to identify the most effective exercise interventions for reducing fatigability in patients with CKD and ESKD and to determine how various exercise paradigms alter neuromuscular factors implicated in fatigability.

Conclusion

Fatigability reflects activity-induced declines in performance (performance fatigability) and changes in perceptions regulating activity performance (perceived fatigability). Herein, we extend the understanding of fatigability by presenting a conceptual framework that considers fatigability as the interactions among fatigue, perceived fatigability, and performance fatigability and discuss how neuromuscular impairments reported in CKD

and ESKD patients may provide a treatment target to diminish performance fatigability. Limited preliminary evidence in CKD and ESKD patients supports the notion that exercise interventions may beneficially affect elevated fatigability. It remains unclear as to whether treatment of secondary sequelae of CKD and ESKD, such as anemia, secondary hyperparathyroidism, and metabolic acidosis, will improve fatigability status. Further investigations are warranted to determine the potential clinical utility fatigability measures might play in monitoring the health of CKD and ESKD patients, and in identifying potential treatments targeting fatigability in this patient population.

Funding Sources

This work was completed as part of a Career Development Award (CDA-2; 1IK2RX003423-01A1) funded by the Rehabilitation Research & Development Service at the VA's Office of Research & Development (J.M. Gollie). The views expressed here are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

Data Availability Statement

All data used to support the findings of this study were obtained from studies included in this article's reference list.

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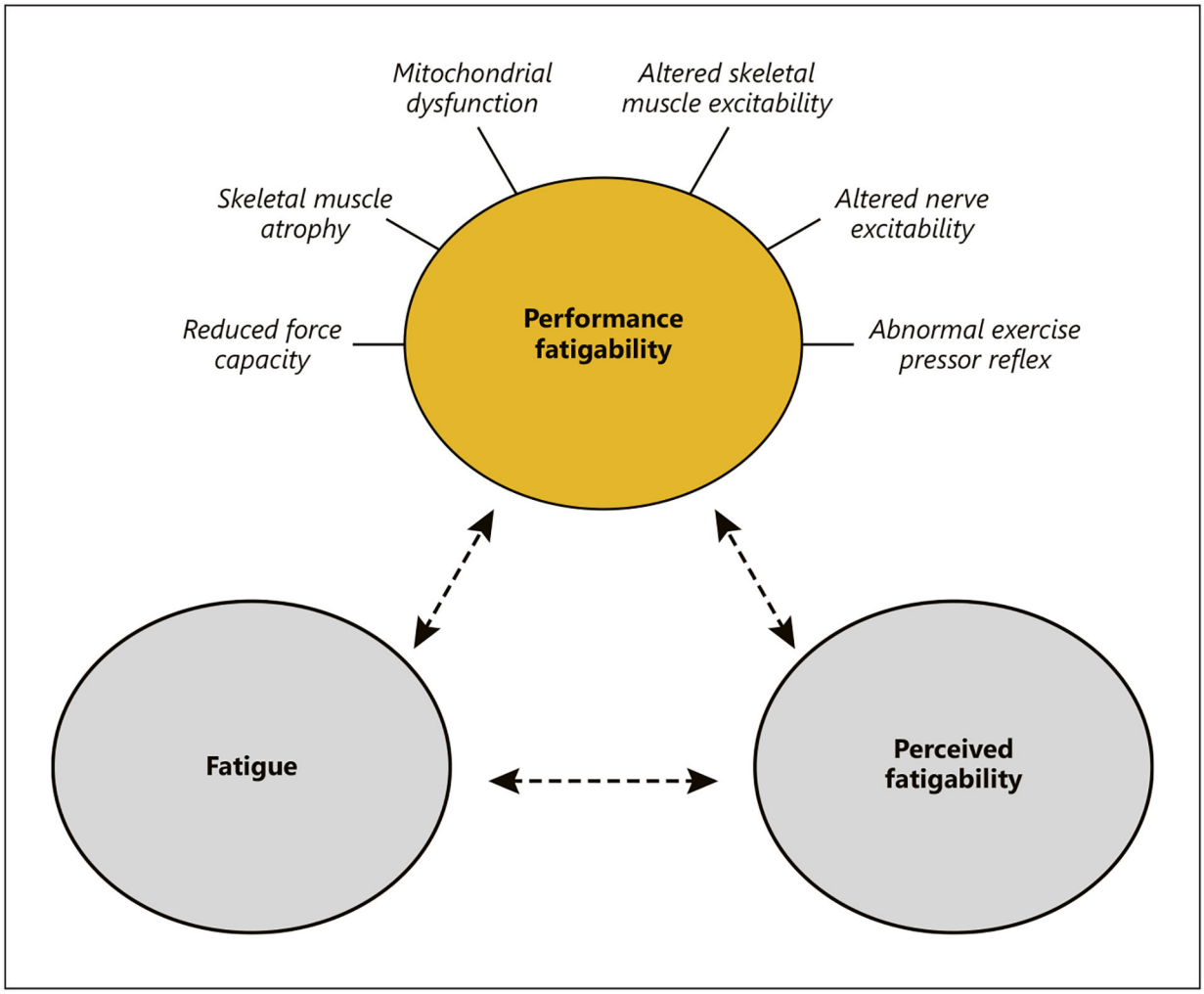

Fig. 1.

Depicts neuromuscular impairments potentially contributing to performance fatigability in patients with CKD (yellow circle). Fatigue and perceived fatigability may act to further exacerbate performance fatigability (gray circles and dashed lines). Performance fatigability is defined as declines in objective measures of performance and perceived fatigability as the perceptual adjustments regulating activity performance. Fatigue represents a self-reported symptom defined as a subjective lack of physical and/or mental energy that is perceived by the individual to interfere with usual or desired activities.

Table 1.

Studies examining fatigability in CKD and ESKD patients

Author(s), year	Sample size, *n*	Fatigability measurement	Outcome: Performance fatigability	Outcome: Perceived fatigability
Johansen et al. [76], 2005	Dialysis subjects: *n* = 33 Control subjects: *n* = 12	Performance fatigability = began at 10% MVC of the ankle dorsiflexors and increased by 10% every 2 min for 14 min Performance FI (%) = ([MVC preexercise − MVC postexercise]/MVC preexercise) × 100	All controls completed the performance fatigability protocol whereas only 18 dialysis subjects were able to complete the protocol Performance FI (%) Dialysis subjects = 37.1±15.9 Control subjects = 12.6±13.5	NA
Petersen et al. [77], 2012	Kidney transplant subjects: *n = 9* HD subjects: *n* = 10 Control subjects: *n* = 10	Performance fatigability = 30 maximal isokinetic knee extensor contractions at 180°s^{-1} Performance FI (%) = ([starting peak torque-final peak torque]/starting peak torque) × 100, where starting peak torque is the average of the highest 3 of the first 5 repetitions and final peak torque is the highest of the 3 of the last 5 repetitions	Performance FI was significantly higher in the kidney transplant subjects (24%) and HD subjects (25%) compared to the control subjects (15%), with no differences between kidney transplant and HD subjects	NA
Macdonald et al. [78], 2012	CKD subjects (stages 3b–4): *n* = 13 Control subjects: *n* = 13	Perceived fatigability = RPE (6–20) were recorded in the last 30 s at each intensity during submaximal cycle ergometry exercise	NA	RPE was significantly greater in CKD subjects compared to control subjects at each exercise intensity assessed (1.8 METs, 2.4 METs, 3.1 METs)
Petersen et al. [79], 2009	HD subjects: *n* = 8 Control subjects: *n* = 6	Performance fatigability = 30 maximal isokinetic knee extensor contractions at 180°s^{-1} Performance FI (%) = ([starting peak torque-final peak torque]/starting peak torque) × 100, where starting peak torque is the average of the highest 3 of the first 5 repetitions and final peak torque is the highest of the 3 of the last 5 repetitions	Performance FI data were excluded on one subject due to highly variable and unreliable results Performance FI was higher in HD subjects at baseline (27±2%, $p < 0.001$), pretraining (26±4%, $p < 0.005$), and post-training (27±9%, $p < 0.001$) compared to control subjects (13±3%) Performance FI was unchanged in HD subjects (baseline, 27±2%; pretraining, 26±4%; and post-training, 27±9%) following 30 min of aerobic exercise performed on a cycle ergometer 3 times per week for 6 weeks at intensities corresponding to 50–80.5% pretraining peak oxygen consumption	NA
Moore et al. [80], 1993	Chronic HD subjects: *n* = 11 kidney transplant recipients: *n* = 11 Control subjects: *n = 9*	Performance fatigability consisted of handgrip MVCs. Subjects were asked to perform 1-s isometric contractions followed by a 9-s relaxation period and instructed to attempt to equal their MVC with each repetition Performance FI was defined as the inability to maintain a percentage of the maximal voluntary contraction	Chronic HD subjects experienced greater fatigability (71±2%) than kidney transplant recipients (78±1%) and control subjects (81±1%)	NA

n, sample size; FI, fatigability index; RPE, rating of perceived exertion; HD, hemodialysis; CKD, chronic kidney disease; ESKD, end-stage kidney disease; MVC, maximal voluntary contraction.