ARTICLES

Morphological, Electrophysiological, and Metabolic Characteristics of Skeletal Muscle in People with End-Stage Renal Disease: A Critical Review

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ABSTRACT

Purpose: Fatigue is one of the most frequent debilitating symptoms reported by people with end-stage renal disease (ESRD) on haemodialysis (HD) therapy. A wide range of underlying abnormalities, including skeletal muscle weakness, have been implicated as causes of this fatigue. Skeletal muscle weakness is well established in this population, and such muscle weakness is amenable to physical therapy treatment. The purpose of this review was to identify morphological, electrophysiological, and metabolic characteristics of skeletal muscles in people with ESRD/HD that may cause skeletal muscle weakness. *Method:* Electronic databases were searched for relevant literature from inception to March 2010. Inclusion criteria were English language; adult subjects with ESRD/HD; and the use of muscle biopsy, electromyography, and nuclear magnetic spectroscopy (^{31}P-NMRS) techniques to evaluate muscle characteristics. *Results:* In total, 38 studies were included. All studies of morphological characteristics reported type II fibre atrophy. Electrophysiological characteristics included both neuropathic and myopathic skeletal muscle changes. Studies of metabolic characteristics revealed higher cytosolic inorganic phosphate levels and reduced effective muscle mass. *Conclusion:* The results indicate an array of changes in the morphological, electrophysiological, and metabolic characteristics of skeletal muscle structure in people with ESRD/HD that may lead to muscle weakness.

Key Words: electromyography, end-stage renal disease (ESRD), metabolism, muscle weakness, skeletal muscle

RÉSUMÉ

Objectif : La fatigue est l'un des symptômes débilitants signalés chez les personnes aux prises avec une insuffisance rénale chronique au stade ultime avec l'hémodialyse (IRSU/HD). Un large éventail d'anomalies sous-jacentes, y compris de la faiblesse du muscle squelettique, ont été mises en cause dans cette fatigue. La faiblesse du muscle squelettique est courante au sein de cette population; une telle faiblesse musculaire peut faire l'objet de traitements en physiothérapie. L'objectif de cette analyse était d'identifier les caractéristiques morphologiques, électrophysiologiques et métaboliques des muscles squelettiques qui pourraient susciter une faiblesse du muscle squelettique chez les personnes avec IRSU/HD. *Méthode :* Une recherche a été réalisée dans les bases de données électroniques de leur création à mars 2010 afin de répertorier la documentation pertinente. Les critères d'inclusion étaient que ces documents soient en anglais, qu'ils concernent des adultes avec IRSU/HD et que des techniques de biopsie musculaire, d'électromyographie et de spectroscopie magnétique nucléaire (^{31}P-NMRS) avaient été utilisées pour évaluer les caractéristiques des muscles concernés. *Résultats :* Au total, 38 documents ont été répertoriés et utilisés. Toutes les études des caractéristiques morphologiques faisaient état d'atrophie des fibres de type II. Les caractéristiques électrophysiologiques incluaient à la fois les changements névropathiques et myopathiques. Les études des caractéristiques métaboliques ont révélé des niveaux de phosphate inorganique cytosolique plus élevés et ont réduit la masse musculaire effective. *Conclusion :* Les résultats font état d'une gamme de changements dans les caractéristiques morphologiques, électrophysiologiques et métaboliques de la structure du muscle squelettique chez les personnes avec IRSU/HD susceptibles de provoquer une faiblesse musculaire.

Mots clés : électromyographie, faiblesse musculaire, insuffisance rénale chronique au stade ultime (IRSU), métabolisme, muscle squelettique

The authors have no conflicts of interest to declare.

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INTRODUCTION

The incidence of chronic renal disease, defined as progressive loss of renal function over a period of months or years, has increased in the last decade. According to a report published by the Canadian Organ Replacement Register (CORR), the rate of incident renal replacement therapy has increased by 19% in Canada since 1999.[1] At the end of 2008, more than 36,638 Canadians registered with CORR (an increase of 57% since 1999) were either on renal replacement therapy (21,754) or living with a kidney transplant (14,884).[1] Renal disease affects multiple organ systems, resulting in a constellation of symptoms related to anaemia, impaired cardiac function, changes in skeletal muscle strength, and reduced aerobic capacity.[2] In the end stages of renal disease (ESRD), renal replacement therapies such as haemodialysis (HD), peritoneal dialysis (PD), or kidney transplant are required to prevent death. A successful kidney transplant provides a better quality of life because it allows greater freedom and is often associated with increased energy levels and a less restricted diet.[3]

Haemodialysis is considered to have more pronounced deleterious effects on skeletal muscle than PD.[4] The two types of dialysis differ in both technique and function. One difference is fluctuation in toxin levels: people on PD dialyze every four hours or daily, whereas HD is typically conducted three times per week, and toxin levels therefore range from very low immediately after dialysis to very high before dialysis.[4] The permeability of the dialyzer used for HD may also contribute to the catabolic effect on muscle mass.[5] This review focuses only on people with chronic ESRD receiving HD.

Fatigue is one of the most common debilitating symptoms reported by people with ESRD/HD: the prevalence of fatigue in this population ranges from 60% to 97%.[6] Various factors—including (a) physiological (decreased aerobic capacity and muscle strength); (b) psychological and behavioural (anxiety, stress, depression, sleep disorders); (c) dialysis-related (dialysis-related fatigue, frequency of dialysis, associated changes in lifestyle leading to physical limitations); and (d) sociodemographic (employment status, social support)—have been implicated as causative mechanisms associated with this fatigue.[6] Some of these underlying mechanisms of fatigue, such as skeletal muscle weakness, can be treated by physiotherapists working regularly with this population.[7–9]

Several reviews have confirmed the presence of muscle weakness and reduced physical function in this population.[2,10–12] A similar report of reductions in physical function in a Canadian ESRD/HD sample was reported by Overend et al.;[13] mean scores of the physical function measures were in the tenth percentile of established normative values for community-dwelling residents between 65 and 85 years of age.[14]

Observations of progressive proximal muscle weakness in people with ESRD/HD by Floyd et al.,[15] Lazaro and Kirshner,[16] and others were ascribed to myopathy (skeletal muscle damage). However, other factors related to ESRD/HD, such as sensorimotor neuropathy from uremia and defects of the neuromuscular junction, have also been considered as possible causes of muscle weakness in people with ESRD/HD.[17] Myopathy is characterized by structural changes in skeletal muscle that modify its morphological features and its electrophysiological and metabolic responses to exercise. For example, accumulation of metabolic by-products such as inorganic phosphate (Pi) inhibits force generation in the first dorsal interosseous muscle of both healthy people and those with myophosphorylase deficiency.[18] Knowledge of underlying mechanisms underpins the rationale of safe exercise administration;[19] this may be particularly important in people with ESRD/HD who have documented evidence of muscle weakness and progressive deterioration of strength. For example, exercise administration in people with neurological disorders is targeted at improving neural plasticity[20] and strength,[21] whereas for people with myopathic disorders, exercise interventions require careful monitoring to avoid muscle damage.[22] According to Phillips and Mastaglia,[23] further research is required to determine optimum training protocols for people with various types of myopathies. There is no current review of changes intrinsic to skeletal muscle at rest or during activity in people with ESRD/HD. The aim of our review, therefore, was to identify the underlying morphological, electrophysiological, and metabolic changes in skeletal muscle that may cause skeletal muscle weakness in people with ESRD/HD and to discuss the clinical relevance of these findings.

METHODS

Literature Search

Electronic databases (AMED, CINAHL, EMBASE, Medline, PubMed, and SCOPUS) were searched from their inception until March 2010, using different strategies reflecting the heterogeneity of the causes of skeletal muscle weakness and/or endurance. The following keywords were searched as MeSH or "mapped terms" and as text-words:

- [*Chronic kidney failure* OR *chronic renal failure* OR *haemodialysis*] AND *skeletal muscle* AND *biopsy*
- [*Chronic kidney failure* OR *chronic renal failure* OR *haemodialysis*] AND *skeletal muscle* AND *electromyography*
- [*Chronic kidney failure* OR *chronic renal failure* OR *haemodialysis*] AND *skeletal muscle* AND *energy metabolism*

Reference lists in retrieved articles were hand-searched to identify citations not captured by the primary search strategy.

Inclusion Criteria

The inclusion criteria were as follows: (a) paper was published in English; (b) study participants were adults (>18 years of age) receiving haemodialysis; and (c) studies used skeletal muscle biopsy, electromyography (EMG), or magnetic resonance spectroscopy (^{31}P-NMRS) as tools to identify structural, electrophysiological, and metabolic changes in skeletal muscle (these tools have been identified for evaluation of changes associated with muscle damage[17]).

Exclusion Criteria

The exclusion criteria were the following: (a) ESRD was a complication of an underlying disease mechanism other than renal disease, such as systemic lupus erythematosus or Wegener's disease; (b) study participants received haemodialysis following acute renal failure (the aim of our review was to identify changes in skeletal muscle as a sequel to maintenance haemodialysis for ESRD); (c) the paper described an animal study; or (d) energy metabolism was studied using techniques other than ^{31}P-NMRS.

Methodological Quality

To identify the relationship between muscle weakness and changes in skeletal muscle, case-control studies in which people with ESRD were compared to people without the disease were considered appropriate.[24] Internal and external validity were assessed according to criteria recommended by Elwood for critical appraisal of case-control studies.[24] As statistical criteria, sample size, and power need to be considered for establishing possible type I or type II errors, these were included in the critical appraisal. Case series were also included in this review, as case-control studies have been considered a progression of case series.[24] However, case-series studies were not critically appraised, since a case study or case series, by definition, consists of a description of one or several people with the outcome of interest and documents one or more unusual conditions.[25]

RESULTS

The primary search retrieved a total of 490 citations. After removal of duplicates, the remaining citations were subjected to sequential title, abstract, and full-text screens for final inclusion in the review. The reference sections of articles that met the inclusion criteria were hand-searched for citations missed during the electronic searches. Finally, 38 studies that met the inclusion criteria were included in the study (see Figure 1). All studies included in this review were either case-control (cross-sectional) studies ($n = 26$) or case series (including one single case report) ($n = 12$).

Methodological Quality

Description of the participants obtained from 10 case-control studies[26–35] provided adequate evidence of equal opportunity of inclusion in the study to demonstrate absence of selection bias. Of the remaining case-control studies, seven[15,36–41] included participants with chronic renal disease not on HD and with comorbidities (clinical evidence of polyneuropathy, varying degrees of paresis, myopathy, renal bone disease, cerebrovascular accident, diabetes mellitus, peripheral vascular disease, etc.); four included male participants only;[42–45] and five[46–50] did not provide adequate description of the participants included in the study. Inclusion of participants with clinical evidence of neuromuscular involvement, wide age ranges, and comorbidities that could contribute to neuromuscular impairment suggested possible selection bias that could confound the outcomes of these studies.[24]

None of the studies blinded outcome assessors, a protocol that has been recommended for credibility of study results of muscle biopsy.[51] Although the outcomes included for this review appear to be objective measures, interpretation of outcomes such as interference patterns obtained during EMG[52] and interpretation of skeletal muscle biopsy with prior knowledge of diagnosis have been considered subjective.[51] In order to minimize potential subjectivity associated with lack of blinding to participant diagnosis, however, computerized detection and quantification of outcomes in accordance with standardized criteria were employed in studies using muscle biopsy and EMG. None of the studies reported power analyses or sample-size calculations justifying an adequate number of participants to guard against type II error, although studies that demonstrated statistical significance had sufficient power, by convention, to protect against type I error.

Muscle Biopsy Studies

Table 1 summarizes the data from the 16 studies that used muscle biopsy as a tool to evaluate morphological characteristics of skeletal muscle in people with ESRD/HD. Atrophy of type II fibres was a common finding in all studies. Five studies[9,27,34,37,53] objectively measured muscle strength using laboratory measures such as isokinetic muscle dynamometry,[27] maximum voluntary contraction (MVC) with strain gauge/dynamometry,[9,34,37,53] or functional strength measures.[37] Two of these studies[27,37] reported statistically significant reductions in muscle strength in all participants with ESRD/HD. Of these, one[27] suggested an association of muscle weakness with mixed (neuropathic and myopathic) changes; the biopsy findings from the second study[37] were comparable between participants with ESRD/HD and control subjects. The remaining three studies[9,34,53] reported lower or reduced values of muscle strength in people on HD.

Search Strategy	PubMed	Embase	MEDLINE	CINAHL	AMED	Scopus
[chronic kidney failure OR haemodialysis] + skeletal muscle + biopsy	123	0	28	6	0	112
[chronic kidney failure OR haemodialysis] + skeletal muscle + electromyography	21	4	18	0	0	23
[chronic kidney failure OR haemodialysis]+ skeletal muscle + energy metabolism	42	10	35	4	0	64
Total	186	14	81	10	0	199

Total = 490

Duplicates removed

Total = 283

Initial title/abstract

Total = 71

Full text screened, references hand-searched
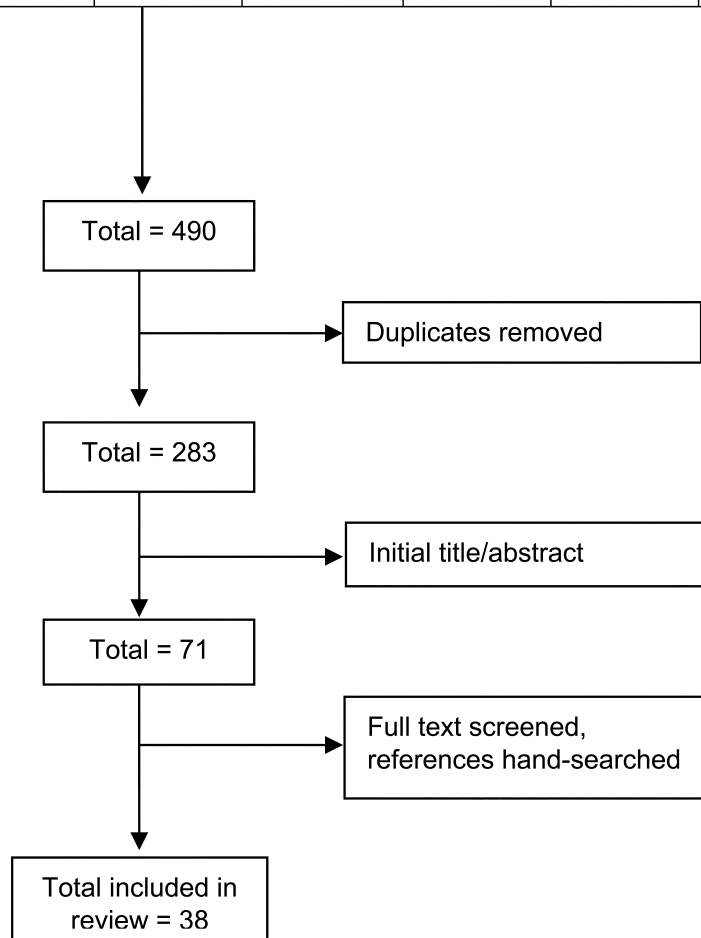
Total included in review = 38

Figure 1   Search and selection process for included studies

Table 1 Muscle Biopsy Studies in People with End-Stage Kidney Disease on Haemodialysis

Author (Date)	Study Design	Muscle; Biopsy Type	Measure of Muscle Strength	Sample (n)	Results: Type I Fibres	Type II Fibres	Other Microscopic Changes	Comments
Adeniyi (2004)[55]	Single case report	Quadriceps; type of biopsy not indicated	Clinical assessment of muscle strength (measures not reported); report of difficulty rising from the chair	HD = 1	Scattered atrophic fibres	Scattered atrophic fibres	Type I and II fibres equally involved, consistent with neuropathic myopathy	Reports do not support myopathy as a primary cause of weakness.
Ahonen (1980)[36]	Case-control	Gastrocnemius (medial head); open muscle biopsy	Implicit suggestions of muscle weakness based on prior published reports of myopathy in people with ESRD/HD	HD = 11 Con = 9	• Diameter of type I fibres slightly larger than reference group (type I hypertrophy) ($p > 0.01$)	• Type II fibre diameter smaller than reference group (type I hypertrophy) ($p > 0.01$) • Type II fibre distribution more frequent ($p > 0.01$)	• Myopathic changes of fibre size variation (18%), central nuclei (9%), necrotic and phagocytic fibres (36%), and moth-eaten and whorled fibres (73%) in 3/11 biopsies • Typical neurogenic changes were angulated atrophic fibres • Neurogenic changes in 7/11 biopsies • Mixed neuropathic and myopathic changes in 1/11 biopsies	• Results suggest presence of myopathic changes in distal muscles. • Mixed results indicating effect of uremia on the different components of motor-unit complex
Bautista (1983)[56]	Case series	Deltoid; method of biopsy not indicated	Clinical evaluation demonstrated proximal muscle weakness (measures not reported)	HD = 10	• Occasional atrophy of type I fibres • Negative hypertrophy factor	• Type II atrophic fibres • Infrequent angulated, rounded, or polygonal atrophic fibres • Negative hypertrophy factor	• No predominance of either type of fibres • Electron microscopy (n = 9)—all biopsies showed abnormal amount of subcutaneous lipofuscin located beneath cell membrane • One case showed loss and derangement of myofilaments • One case showed sub-sarcolemmal aggregates of normal mitochondria	Myofibrillar changes suggestive of myopathic factors contributing to muscular weakness

(Continued)

Table 1 (continued)

Author (Date)	Study Design	Muscle; Biopsy Type	Measure of Muscle Strength	Sample (n)	Results Type I Fibres	Type II Fibres	Other Microscopic Changes	Comments
Crowe (2007)[26]	Case-control	Quadriceps femoris (lateral); percutaneous needle biopsy	Implicit suggestions of muscle weakness based on prior published reports of limited exercise capacity contributing to poor quality of life	HD = 10 Con = 10	Fibre diameter reduced by 15% ($p = 0.04$)	Fibre diameter reduced by 20% ($p = 0.03$)	No difference in proportion of type I and II fibres compared to Con ($p = 0.9$)	• Change in fibre size was unrelated to oxidative stress. • Relative atrophy (change in fibre size) of type 1 fibres suggestive of myopathies • Type II fibre atrophy— non-specific • Results support changes in the muscle causing muscular weakness.
Diesel (1993)[27]	Case-control	Vastus lateralis; open muscle biopsy	• Isokinetic muscle strength using Cybex II • HD = Isokinetic strength ($p < 0.05$)	HD = 8 Athl = 7 Con = 5	Hypertrophy of type I fibres ($n = 2$)	• Atrophied type II fibres ($n = 8$) from 6%—62%, $n = 2$ significant type II fibre atrophy • Predominance of type II fibres ($n = 2$)	• Electron microscopy revealed mitochondrial changes, Z-band degeneration, and loss of myofilaments ($n = 8$) • Changes suggestive of progressive muscle involvement, with some cells more affected than others	• Selective hypertrophy of type I fibres and type II predominance in $n = 2$ supports neuropathic factors affecting muscular strength. • Myofibrilar changes and atrophy of type I fibres supports myopathic causes of weakness. • Results suggest neuro/myopathy causing muscular weakness.
Fahal (1997)[37]	Case-control	Quadriceps femoris (lateral); percutaneous conchotome biopsy	• MVC using strain-gauge measurements recorded using rapid-response oscillograph • HD = Reduced MVC ($p < 0.01$) • Objective functional measures • HD = most to all results abnormal	HD = 12 Con = 10	• Low prevalence of type I fibres ($n = 5$) • High prevalence of type I fibres ($n = 1$) • Mean prevalence of type I fibres similar in both groups ($p = 0.1$)	• High prevalence of type II fibres ($n = 1$) • Difference of prevalence of type II fibres in the two groups not significant ($p = 0.5$)	• Fibre areas slightly smaller in participants on HD • Mean difference of fibre areas similar in both groups	• Atrophy and high prevalence of type I fibres suggestive of myopathic changes • High prevalence of type II fibres in $n = 1$ suggestive of neuropathic changes • Results reflect heterogeneity of neuro/myopathic changes in muscles of HD group causing muscular weakness.

(Continued)

Table 1 (continued)

Author (Date)	Study Design	Muscle; Biopsy Type	Measure of Muscle Strength	Sample (n)	Results — Type I Fibres	Type II Fibres	Other Microscopic Changes	Comments
Floyd (1974)[15]	Case-control	Quadriceps or biceps; open muscle biopsy	Clinical assessment of strength (measures not reported)	HD = 10 Non-dialyzed = 4	Variation in muscle fibre size was outside normal limits in the majority of the cases	Type II fibre atrophy in each case	• Some fibres were rounded, and a few contained internal nuclei • Type I fibres contained excessive amounts of glycogen in the region of subsarcolemmal aggregates	Results support myopathic changes associated with renal failure as possible cause of muscular weakness.
Giovenali (1994)[53]	Case series	Vastus lateralis; open muscle biopsy	• MVC—using objective methodology described by Edwards et al. (1977) • HD—all results below normal values	HD = 26	Atrophy of type I fibres	Atrophy of type II fibres	N/A	The main objective of the study was to assess the effect of L-carnitine on muscle strength. The baseline data were included.
Kouidi (1998)[9]	Case series	Vastus lateralis; open muscle biopsy	MVC using dynamometer	HD = 7	Changes in HD: • Reduced mean fibre area • Atrophy of type I fibres • Random variation in fibre size • Predominance of type I fibres	• Type II fibre size almost equal to type I fibre size • Atrophy of type II > type I fibres	• Glycogen deposition in most muscle fibres • Non-specific degenerative changes in muscle fibres, mitochondria, and capillaries • External lamina of fibres' sarcolemma and basal lamina of capillaries remained after their necrosis • Central nuclei with invaginations • Disorganization of sarcomeres with Z-disk streaming and loss of A & I bands in many fibres	• Atrophy and high prevalence of type I fibres, changes in the myofibrils, mitochondrial changes, and central nuclei suggestive of myopathic changes • Glycogen deposition associated with carnitine deficiency • Supports neuro/ myopathy causing muscular weakness, as suggested by fibre atrophy grouping and small-group atrophy in most patients.
Lazaro (1980)[16]	Case series	Quadriceps femoris; open muscle biopsy	Clinical assessment of strength (measures not reported), participant reports of gait abnormalities such as waddling gait or difficulty walking, difficulty rising from chair	HD = 4	No comment on changes in type I fibres	• 90% atrophic fibres (n = 1) • Comprised 80% and 85% of the small fibres (n = 2)	• No evidence of phagocytosis, necrosis, or regeneration • Few moth-eaten fibres were seen (n = 4)	• Type II fibre atrophy— non-specific • Results indicate possible myopathic changes associated with muscular weakness in people with renal disease.

(Continued)

Table 1 (continued)

Author (Date)	Study Design	Muscle; Biopsy Type	Measure of Muscle Strength	Sample (n)	Results: Type I Fibres	Results: Type II Fibres	Other Microscopic Changes	Comments
Moore (1993)[57]	Case series	Rectus femoris; percutaneous needle biopsy	Implicit suggestions of muscle weakness based on prior published reports of uremic myopathy	HD = 11	Numerous atrophic type I fibres	Numerous atrophic type II fibres	Variability in type I and type II fibres was large	Peripheral factors contributing to skeletal muscle weakness
Molsted (2007)[31]	Case-control	Vastus lateralis; open muscle biopsy	• Implicit suggestions of muscle weakness based on prior published reports of uremic myopathy • Researchers tested aerobic capacity, but results not reported in context to Con population	HD = 14 Con = 12	Several patients on HD had <15% type I fibres $p < 0.001$	More of type IIx fibres	N/A	• Uremia affected composition rather than size of muscle fibres; increase of type IIx fibres was considered compensatory for loss of type I fibres. • Atrophy of type I fibres usually associated with myopathic changes • Results support myopathy causing muscular weakness.
Sakkas (2003)[58]	Case series	Medial head of gastrocnemius; percutaneous muscle biopsy using conchotome technique	Implicit suggestions of muscle weakness based on prior published reports of reduced exercise capacity in people on HD	HD = 12	Dominance of type I fibres	Type IIa fibres dominant in the distribution of type II fibres	Proportion of fibres with central nuclei within the normal range	• Atrophy of type IIb fibres has been associated with painless myopathies associated with chronic alcohol- or steroid-related neuro/myopathy. • Results support myopathy as a possible cause of skeletal muscle weakness.
Sakkas (2004)[4]	Case series	Medial head of gastrocnemius; percutaneous muscle biopsy using conchotome technique	Implicit suggestions of muscle weakness based on prior published reports of uremic myopathy	HD = 12	No data	No significant difference between mean CSA of type IIa and IIx fibres	No data	• Suggestive of type II fibre atrophy • Primary objective was to examine differences in morphology of muscles of patients on CAPD and HD. Data on participants on HD were included in this review.

(Continued)

Table 1 *(continued)*

Author (Date)	Study Design	Muscle; Biopsy Type	Measure of Muscle Strength	Sample (n)	Results		Other Microscopic Changes	Comments
					Type I Fibres	Type II Fibres		
Shah (1983)[49]	Case-control	Quadriceps; method of biopsy not indicated	Complaints of proximal muscle weakness in all participants	HD = 10 Con = 8	Atrophy of type I fibres	Preferential atrophy of type II fibres	Abundant lipid droplets in type I and II fibres	• Findings attributed to myopathic changes • Possible relation to effects of HD on muscle metabolism
van den Ham (2007)[34]	Case-control	Vastus lateralis; needle biopsy techniques	MVC using dynamometry HD = Reduced MVC	HD = 14 Con = 18	Similar to that of Con group	Similar to Con group	N/A	Physical inactivity in people on HD contributes to muscle weakness.

Athl = athletes; CAPD = continuous ambulatory peritoneal dialysis; Con = control group; CSA = cross-sectional area; HD = haemodialysis; MVC = maximim voluntary contraction; N/A = not applicable

One of these studies[9] suggested that muscle weakness was associated with mixed (neuropathic and myopathic) changes. Giovenali et al.[53] observed atrophy of Type I and II fibres (changes similar to those following myopathy and/or disuse atrophy[54]) but did not attribute these to myopathic or neuropathic changes, as their primary objective was to evaluate changes in muscle morphometry following L-carnitine intervention. Biopsy findings from the final study[34] were comparable between participants with ESRD/HD and controls. All five studies investigated the same muscle (quadriceps), so the variation in results may reflect the differences in the techniques used to analyze the biopsy results or the influence of ESRD/HD on different components of the motor-unit complex, as suggested by Griggs et al.[17]

Five studies[15,16,49,55,56] reported the presence of muscle weakness based on clinical assessment or subjective reports of muscle weakness in the participants on HD. Based on the pattern of atrophy observed, two studies[16,55] suggested neuropathic changes preceding myopathic changes; in the remaining three studies,[15,49,56] myopathic changes were observed.

Six studies[4,26,31,36,57,58] suggested, based on previous literature, that muscle weakness exists in people with ESRD/HD. Five of these studies[4,26,31,57,58] observed myopathic changes on biopsy, and the remaining study[36] observed myopathic changes in three participants, neuropathic changes in seven participants, and mixed neuropathic and myopathic changes in one participant.

A review of changes detectable via electron microscopy was beyond the scope of this review. However, findings of streaming and degenerating Z-bands in two studies[9,27] on electron microscopy by two studies included in this review were considered notable, as these changes indicate muscle damage.

Electrophysiological Characteristics

Table 2 summarizes the findings of the 15 studies that assessed electrophysiological associations of muscle weakness with varying electrophysiological protocols using surface or needle electrodes. Various electrophysiological techniques—(1) motor-unit recruitment pattern or interference pattern; (2) compound muscle action potential (CMAP), a measure of summed electrical activity in the muscle; (3) total muscle power analysis using computer techniques; and (4) single-fibre EMG—were used to detect motor-unit characteristics in the studies included in this review.

Three studies measured muscle strength objectively, using dynamometry and functional measures of strength.[37,38,59] Two of these studies[37,38] found statistically significant reductions in muscle strength in participants with ESRD/HD. However, Johansen et al.[38] suggested neural mechanisms contributing to muscle weakness, while Fahal et al.[37] identified causes intrinsic

to the muscle. The variation in results may be related to the differences in the electrophysiological techniques used by these studies: Johansen et al.[38] used CMAP, whereas Fahal et al.[37] used EMG (interferential pattern). The third study,[59] a case series, reported the presence of myopathic changes. The functional measures of strength reported in this study implicitly suggested muscle weakness, since the performance of the ESRD/HD group (age 54.5 ± 2.6 years) on the 30-second chair-stand test (12 ± 0.8 reps) was comparable to that of women between 75 and 79 years of age.[60]

Of the four studies[15,16,55,56] that reported muscle weakness based on clinical assessments (measures not reported), two[15,55] suggested neuropathic changes preceding myopathic changes, based on the motor-unit recruitment pattern; one case series[16] observed myopathic changes; and the final study[56] observed EMG changes comparable to those observed in the control group.

Blank et al.[61] observed both myopathic and neuropathic changes, one sub-group demonstrating myopathic changes and a second showing neuropathic changes. While no objective measure of participants' muscle strength was reported by Blank et al.,[61] association of muscle weakness with these electrophysiological changes is a possibility, as people with ESRD/HD commonly complain of muscle weakness. Neuropathic changes found in one sub-group by Blank et al.[61] are supported by three studies[30,35,62] that have suggested possible muscle weakness based on the presence of polyneuropathy in people with ESRD/HD and one study[63] reporting muscle weakness based on subjective reports of muscle weakness and functional limitations observed in the study participants. The finding of myopathic changes in another sub-group by Blank et al.[61] is supported by similar findings in two studies[46,48] that did not suggest (implicitly or otherwise) the presence of muscle weakness in their participants.

Energy Metabolism: *In Vivo* Studies

Table 3 summarizes the findings of the 13 case-control studies that investigated energy metabolism using ^{31}P-NMRS at rest and during sub-maximal exercise protocols at varying intensities. All studies that used sub-maximal exercise protocols reported reduced exercise durations in all participants with ESRD/HD. Eight studies[33,39–42,44,45,50] reported increased cytosolic inorganic phosphates (Pi) at rest in people with ESRD/HD, while four[28,38,43,47] reported similar Pi values for the experimental and control groups. One case-control study[32] observed lower Pi values in the ESRD/HD group than in the control group, and another[33] did not clearly indicate whether the absolute cytosolic Pi values were lower or higher for the ESRD/HD group.

Of the four studies that reported similar Pi values for the experimental and control groups,[28,38,43,47] one

Table 2 Electrophysiological Studies of People with End-Stage Renal Disease on Haemodialysis

Author (Date)	Study Design	Muscle; Type of Investigation	Measure of Muscle Strength	Sample (n)	Results	Comments
Adeniyi (2004)[55]	Single case report	Iliopsoas, quadriceps, and TA; EMG recordings (type of electrode used not clearly indicated)	Clinical assessment of muscle strength (measures not reported); participant report of difficulty rising from chair	HD = 1	Brief, small, abundant polyphasic potentials characteristic of myopathy	EMG studies suggestive of neuropathic and myopathic changes
Albertazzi (1980)[46]	Case-control	• TA and EDB; EMG using co-axial needle electrode • amplitude, duration, and phases of MUAPs, EMG of MVC, were recorded and analyzed using FFT	Unclear	HD = 20 Con = 20	• 4 patients showed myopathic EMG pattern with low voltage peaks • Low muscle contraction to reach a full interference pattern	Results support myopathy as a possible cause of muscular weakness.
Bautista (1983)[56]	Case series	Deltoid; type of electrodes used not indicated	Clinical evaluation demonstrated proximal muscle weakness (measures not reported)	HD = 8	Normal interference pattern	Normal EMG changes
Blank (1986)[61]	Case series	BB; EMG using needle electrode	Implicit suggestions of muscle weakness based on prior published reports of common complaints of muscle weakness in people on haemodialysis	HD = 9	• Increased frequency of spikes was seen in 6/9 participants with peripheral neuropathy during progressive muscle contraction • Average maximal amplitude and average duration increased in the same 4 participants and decreased in 5 participants • Total voltage area increased in 5 participants and decreased in 4 participants; 4 participants exhibited pattern similar to myopathic or healthy muscles, and 5 participants demonstrated neuropathic pattern	Observations suggest neuropathic origin in 4 participants and myopathic origin in 5 participants.
Fahal (1997)[37]	Case-control	• Quadriceps; tetanic electrical stimulation at 100 Hz contraction up to 60% MVC • Stimulations were applied at frequency range of 1, 10, 20, 50, and 100 Hz, each for 1s, except 10 Hz was applied for 2s • E–C coupling—20:50 Hz stimulation	• MVC using strain-gauge measurements recorded using rapid-response oscillograph: HD = Reduced MVC (p < 0.01) • Objective functional measures: HD = most-to-all results abnormal	HD = 19 Con = 27	• Muscle strength—male and female HD patients were significantly weaker than the Con group (p < 0.001) • E–C coupling—the force/ frequency curve was similar in the HD and Con groups	• Observations of this study support the hypothesis that muscle weakness contributes to fatigue and that these changes are perhaps intrinsic to the muscle. • Altered Ca+ release

(Continued)

Table 2 *(continued)*

Author (Date)	Study Design	Muscle; Type of Investigation	Measure of Muscle Strength	Sample (n)	Results	Comments
Floyd (1974)[15]	Case-control	Quadriceps and deltoid; EMG recordings using needle electrode	Clinical assessment of strength (measures not reported)	HD = 10 Con = 7	• Average MAPD in the quadriceps and deltoid significantly shorter than Con group ($p < 0.01$) • MAPA differed significantly between groups ($p < 0.05$) • Increased polyphasic potentials in participants on HD ($p < 0.002$)	Results suggest skeletal muscle weakness of neuropathic and myopathic origin.
Gambaro (1987)[29]	Case-control	ABD and EDB (authors have not clearly indicated the muscles explored); EMG using needle electrode to study motor unit action potential following stimulation of ulnar and CPN	Symptoms of peripheral nervous system involvement, including muscle weakness, present in 55% of participants on HD (measures not reported)	HD = 31 Con = 30	• Values of MUAP on stimulation of CPN were significantly lower in HD group than in Con group • Values of MUAP on stimulation of ulnar nerve were similar to Con values	• EMG findings suggestive of neuropathic ("dying-back degeneration") changes affecting LEs > UEs • Results support neuropathy as leading to muscle weakness.
Harrison (2006)[59]	Case series	1st dorsal interosseous and vastus lateralis; EMG recordings using surface electrode	30-second chair-stand test (12 ± 0.8); no comparison with Con	HD = 25	EMG frequency recorded prior to HD was generally low and abnormal.	• Results support possible disorder of the muscle causing muscle weakness. • Primary objective of the study was to compare pre- vs. post-HD changes using EMG.
Isaacs (1969)[63]	Case series	• APB and deltoid; EMG using needle electrode • Deltoid muscle was explored for presence of polyphasic potentials. • Fatigue test—isometric contraction against 2 lb weight maintained until 7 min or inability to hold the muscle contraction	Participant complaints of muscle weakness by the participants on HD associated with functional limitations (measures not reported)	HD = 15	• Focal areas of denervation in all participants; recruitment of the motor unit activity was abnormal and in most severe cases only isolated functioning motor units were present. • Polyphasic counts were on the high side and ranged between 6% and 15% of total activity. • Fatigue test—12 cases with clinical evidence of neuropathy showed considerable fallout of motor-unit activity, and the motor-unit amplitude fell when the tension could no longer be maintained.	• Demonstrates involvement of the distal muscle • Results indicative of neuropathic involvement affecting muscular strength
Johansen (2005)[38]	Case-control	TA; CMAP before and after exercise protocol: start @ 10% MVC and ↑ 10% every 2 min. End-of-exercise MVC and CMAP obtained	MVC using dynamometry ($p = 0.04$)	HD = 33 Con = 12	CMAP was lower at baseline and did not change significantly after the exercise ($p = 0.003$).	• Fatigue was neural in nature, with reduced central activation ratio and poor metabolic response. • Findings support neural causes of fatigue.

(Continued)

Table 2 *(continued)*

Author (Date)	Study Design	Muscle; Type of Investigation	Measure of Muscle Strength	Sample (n)	Results	Comments
Konishi (1981)[30]	Case-control	EDC; SFEMG using needle electrode to obtain fibre-density and jitter values	Implicit suggestions of muscle weakness based on presence of peripheral neuropathy in people on HD as per prior published reports	HD = 19 Con = 20	• 8 participants showed abnormal jitter recordings. • Mean fibre-density value was similar to Con group.	• Abnormal jitter values indicate either impaired neuromuscular junction or variability of conduction time in each nerve twig. • Results support possible neuropathic involvement affecting muscle function.
Lazaro (1980)[16]	Case series	Variable proximal muscles	Clinical assessment of strength (measures not reported), participant reports of gait abnormalities such as waddling gait or difficulty walking, difficulty rising from the chair	HD = 4	Bizarre high-frequency discharges in one participant; all participants demonstrated short-amplitude and short-duration polyphasic potentials in all muscles examined.	Changes attributed to uremic myopathy
Rochhi (1986)[48]	Case-control	• TA; EMG recordings using surface and needle electrode • Total power obtained using FFT analysis	Possible presence of weakness based on presence of myopathy and neuropathy as per prior published reports	HD = 20 Comparison with normal values for the laboratory	8 HD participants showed significant shift of the peak frequency of the spectral array toward values higher than Con group.	• The shift in the spectral power frequency to higher values has been reported in people with myopathic disorders and is related to presence of polyphasic potentials. Results support myopathy as cause of muscle weakness.
Sobh (1992)[62]	Case series	BB representative of proximal muscle, and APB representative of distal muscle; EMG study including duration of MUAP amplitude, and interference pattern	Possible presence of weakness based on presence of neuropathy as per prior published reports	HD = 6	• Clinical neuropathy (n = 2) • Incomplete interference pattern on EMG of the APB (n = 3)	Results indicate distal involvement and neuropathic pattern.
Tilki (2009)[25]	Case-control	• BB and TA; QEMG • NCS median, ulnar, and sural nerves	Possible presence of weakness based on presence of neuropathy as per prior published reports	HD = 30 Comparison with normal values for the laboratory	• Clinical neuropathy present in most the participants • Evidence of axonal and/or demylinating polyneuropathy in all patients on HD	• The primary objective of the study was to determine the most common abnormality of electrophysiologic changes among participants on HD and CAPD. • Clinical evidence of polyneuropathy was presented for the whole group. Differences in clinical presentations of participants on HD and CAPD cannot be determined from the data.

APB = abductor pollicis brevis; ABD = abductor digiti minimi; BB = biceps brachii; Con = control group; CPN = common peroneal nerve; CMAP = compound muscle action potential; CRF = chronic renal failure; EDB = extensor digitorum brevis; EDC = extensor digitorum communis; EMG = electromyography; E-C coupling = excitation–contraction coupling; FFT = fast Fourier transform; HD = haemodialysis group; Hz = hertz; MAPD = mean action-potential duration; MAPA = mean action-potential amplitude; MUAP = motor-unit action potential; MVC = maximum voluntary contraction; NCS = nerve-conduction studies; QEMG = quantitative electromyography; SFEMG = single-fibre electromyography; TA = tibialis anterior; UE = upper extremity

Table 3 ^{31}P-NMR Spectroscopy Studies of Skeletal Muscle in People with End-Stage Renal Disease on Haemodialysis

Author (Date)	Study Design	Muscle	Exercise Protocol	Sample (n)	Resting Muscle	End Exercise	Recovery	Comments
Durozard (1992)[28]	Case-control	Calf— dominant side	Pedal against 98.1N @ 2 Hz (Isotonic) until exhaustion	HD = 6 Con = 6	pH, PCr, Pi, PCr/Pi, ATP were not statistically different (p-value unavailable)	• Rate of PCr depletion was similar in both groups. • Intracellular pH declined rapidly in the HD group ($p < 0.001$).	• Workload required to produce exhaustion in Con group 7.4 times greater ($p < 0.05$). • Muscle ATP concentration diminished at end of exercise in HD group ($p < 0.05$) • Half-time recovery of PCr increased in the HD group ($p < 0.05$) • pH recovery slower in HD group	• Impaired oxidative phosphorylation • Recovery of PCr comparable to those with heart failure and mitochondrial myopathy
Johansen (2005)[38]	Case-control	Dorsiflexors	10%MVC ↑10%MVC every 2 min to fatigue	HD = 18 Con = 11	At-rest Pi, PCr, Pi/PCr, H_2PO_4, and pH similar between the two groups	• Participants on HD unable to complete fatigue protocol; stopped at 6 and 13.5 min due to exhaustion • All metabolic parameters significantly perturbed in HD group (end exercise Pi and PCR: $p = 0.006$; Pi/PCr: $p = 0.01$; H_2PO_4: $p = 0.01$; pH: $p = 0.01$) • Combined model of change in CAR and oxidative potential explained 56% of variation in fatigue ($p = 0.006$) • Muscle fatigue excessive following statistical adjustment for activity level ($p = 0.003$)	Delayed recovery of MVC returning to ~85% of pre-exercise MVC after 10 min of rest; Con group recovered fully within same duration ($p = 0.006$)	Excess fatigue attributed to poor oxidative metabolism and greater accumulation of metabolic by-products in people on HD affecting CAR
Kemp (1995)[42]	Case-control	FDS	Finger flexion @40/min @ 0.75 kg resist for 5 min, ↑by 0.25 kg / 1.25	HD = 6 Con = 10	• Cell Pi increased in HD compared to reference range • Values of cell PCr, pH, and ADP similar in both groups	• Mean exercise duration in HD group reduced by 50 ± 10% ($p = 0.0001$) • Total work decreased to 70 ± 10% in HD group • Average rate of change in PCr ($p = 0.01$) and pH ($p = 0.02$) during exercise increased 3×–4× in HD group	• Rate of PCr recovery slower in HD group ($p = 0.02$) • Q_{MAX}, mitochondrial capacity significantly lower in HD group ($p = 0.04$)	Reduced effective muscle mass of FDS by 30% of normal in HD group based on metabolic data

(Continued)

Table 3   (continued)

Author (Date)	Study Design	Muscle	Exercise Protocol	Sample (n)	Resting Muscle	End Exercise	Recovery	Comments
Kemp (2004)[43]	Case-control	Lateral gastrocnemius	3–5 min voluntary 0.5 Hz, isometric plantar flexion at 50% MVC and 75% of MVC each, 5 min recovery	HD = 23 Con = 15	pH, PCr/γATP, and Pi/γATP similar in both groups	HD group exerted less force ($p = 0.04$).	• Slow recovery of PCr ($p = 0.0001$) • Exercise duration shorter by $30 \pm 11\%$ in HD group ($p < 0.0001$)	• Contractile efficiency normal (force/CSA/ATP turnover) • Impaired mitochondrial efficiency
Moore (1993)[47]	Case-control	FDS	• Static exercise protocol—5 min of isometric hand grip starting @ 40% MVC • Rhythmic exercise protocol—1 s isometric handgrip alternating with 9s of relaxation for 10 min	HD = 11 Con = 9	Data presented in the graphs suggest no differences in pH, [PCr]/[PCr + Pi] at rest	• Rapid depletion of PCR in HD group during rhythmic exercise ($p < 0.01$) • HD group had greater intracellular acidosis at lower relative exercise intensity.	• No differences observed in recovery curves of pH or PCr/[PCr + Pi] during recovery from static or rhythmic exercise • HD group experienced more fatigue and maintained only 71% of MVC ($p < 0.01$).	• Subnormal oxidative metabolism in skeletal muscles of HD group • Similarities with McArdle's disease
Nishida (1991)[44]	Case-control	Biceps femoris, dominant side	• Aerobic exercise—flexion/extension of leg once every 2 s for 5 min • Anaerobic exercise—following recovery from aerobic exercise, same exercise repeated under ischemic exercise with occlusion of femoral artery using inflated cuff	HD = 8 Con = 6	• At-rest PCr and ATP concentrations lower in people on HD than in Con ($p < 0.05$) • Intracellular Pi concentrations higher in HD group ($p < 0.01$)	• pH decreased rapidly during exercise in HD group and remained constant in Con group ($p < 0.05$). • Rapid decrease in PCr and increase in Pi • End-exercise PCr/[PCr + Pi] ratios, pH lower in HD group ($p < 0.05$) • During anaerobic exercise, changes in pH similar in both groups	• Slower recovery of pH & PCr ($p < 0.01$) • All participants on HD completed exercise protocol.	• Participants on HD recruited type II fibres at a very low level of exercise. • Impaired aerobic energy production with dependence on anaerobic metabolism at low levels of workload
Táborsky (1993)[50]	Case-control	Gastrocnemius	Data collected with muscle at rest	HD = 21 Con = 24	PCr/Pi and PCr/ATP ratios higher than Con group ($p < 0.01$)	Examination at rest only—no data	Examination at rest only—no data	Authors suggest possible effect of the impaired metabolism and uremic myopathy. The increase in resting PCr/Pi levels reflects the subjective complaints of muscle weakness.
Thompson (1993)[45]	Case-control	FDS	Finger flexion @ 40/min against 0.75 kg resistance for 5 min and then ↑ by 0.25 kg every 1.25 min	HD = 5 Con = 6	• Pi/ATP elevated in HD group ($p = 0.01$) • Muscle pH, PCr/ATP, and ADP similar in both groups	• End-exercise pH and [PCr]/[PCr + Pi] similar in both groups • Increased rate of PCr depletion ($p = 0.03$)	• Longer half-time PCr recovery in HD group ($p = 0.04$) Duration of exercise significantly shorter in HD group ($p = 0.006$)	• Impaired oxidative ATP synthesis and reduced effective muscle mass

(Continued)

Table 3 (continued)

Author (Date)	Study Design	Muscle	Exercise Protocol	Sample (n)	Resting Muscle	End Exercise	Recovery	Comments
Thompson (1994)[39]	Case-control	Calf	PF of R ankle 30×/min @ 10% of LBM ↑ 2% of LBM after every 1 min, to fatigue	Uremics + HD = 9 Con = 18	• Increased Pi/ATP in uremic group ($p = 0.01$) • Similar PCr/ATP and pH in both groups	End-exercise pH and [PCR]/[PCr + Pi] similar between two groups	• Q_{MAX} reduced in HD group and not correlated with exercise duration or Pi/ATP • Duration of exercise reduced in uremic group ($p = 0.03$)	• Fatigue possibly related to extent of acidification within muscle cell during exercise • Recovery of PCr comparable to those with heart failure and mitochondrial myopathy
Thompson (1996)[32]	Case-control	FDS	Ramp exercise protocol requiring participants to frequency of 0.5 Hz through a ROM of 70^0 and ↑ 0.13 W/min from 0.50 W until exhaustion	HD = 5 Con = 8	Lower values of Pi/Pcr in the HD group ($p < 0.05$)	• Maximal power attained by HD group was 67% of Con group • pH at end of exercise was lower ($p < 0.05$)	• Prolonged recovery in Pi/PCr observed in HD group ($p < 0.05$) • Initial slope Pi/PCr (phosphorylation potential)–work relationship (correlated with aerobic capacity) was 88% greater in HD group ($p < 0.05$).	Metabolic data suggest possible higher percentage/ predominance of type II fibres, de-conditioning, or impaired aerobic metabolism.
Thompson (1996)[40]	Case control	Calf	PF of R ankle 30×/min @ 10% of LBM ↑ 2% of LBM after every 1 min, to fatigue	HD = 9 Con = 9	• Increased Pi and PCr in HD group ($p < 0.05$) • Reduced pH in HD group ($p < 0.05$)	• Increased PCr depletion and rapid acidification in HD group ($p < 0.05$) • Duration of exercise significantly shorter in HD group ($p < 0.05$)	• PCr and ADP recovery significantly slower in HD group ($p < 0.05$) • Q_{Max} significantly lower in HD group ($p < 0.05$)	• Initial increase in ATP synthesis suggests impaired contractile efficiency or skeletal muscle atrophy. • Reduced oxidative capacity associated with impaired mitochondrial function
Thompson (1997)[41]	Case-control	Calf	PF of R ankle 30×/min @ 10% of LBM ↑ 2% of LBM after every 1 min, to fatigue	PD+HD = 10 Con = 33	• PCr/ATP and Pi/ATP significantly higher in HD group ($p < 0.05$) • pH lower in HD group ($p < 0.05$)	• Increased PCr depletion and rapid acidification in HD group ($p < 0.05$) • Duration of exercise significantly lower in HD group ($p < 0.05$)	• PCr and ADP recovery significantly slower in HD group ($p < 0.05$) • Q_{Max} significantly lower in HD group ($p < 0.05$) • pH recovery similar in both groups	• Initial increase in ATP synthesis suggests impaired contractile efficiency or skeletal muscle atrophy. • Reduced oxidative capacity associated with impaired mitochondrial function

(Continued)

Table 3 *(continued)*

Author (Date)	Study Design	Muscle	Exercise Protocol	Sample (n)	Resting Muscle	End Exercise	Recovery	Comments
Vaux (2004)[33]	Case-control	Calf	PF of R ankle 30×/min @ 10% of LBM ↑ 2% of LBM after every 1 min, to fatigue	HD = 13 Comparison with normal lab values for people without the disease as Con	Decreased mitochondrial capacity	Drop in muscle pH during exercise to below 6.9 mmol.min^{-1} ($p = 0.01$)	Slow proton efflux, reduced exercise duration, slow metabolic recovery, and low Q_{MAX} in HD vs. normal lab values	• Primary objective was to evaluate intervention of L-carnitine. • After 16 weeks of L-carnitine intervention, differences in muscle metabolism were not significant.

ADP = adenosine diphosphate; ATP = adenosine triphosphate; CAR = central activation ratio; Con = control group; FDS = flexor digitorum superficialis; HD = haemodialysis group; LBM = lean body mass; MVC = maximum voluntary contraction; PCr = creatine phosphate; PD = peritoneal dialysis; pH = potential hydrogen (concentration of hydrogen ion); PI = inorganic phosphate; PF = plantarflexion; RCT = randomized controlled trial

investigated the calf muscle,[28] one investigated the dorsiflexors,[38] and two[43,47] investigated the finger flexors. Specific differences among these four studies could not be clearly identified to establish why the cytosolic Pi was comparable to controls; they investigated the same muscles (calf and finger flexors) as the group of studies reporting increased cytosolic Pi, with the exception of the dorsiflexor muscle.[38] Perhaps these findings can be attributed to differences in the techniques used to measure the metabolites at rest, as one study[28] reported using "unique" methods of measuring absolute cytosolic Pi.

Four studies[40–42,45] suggested "reduced effective muscle mass" based on the rate of adenosine triphosphate (ATP) synthesis during incremental sub-maximal exercise. Four studies[39–42] investigated Q_{MAX} (maximum rate of mitochondrial ATP production) in people with ESRD/HD; values ranged from 44% to 77% of control values, indicating impaired ATP production in this population.

Seven studies[28,38,39,42,43,45,47] found resting phosphocreatine (PCr) and ATP concentrations comparable to control-group values, including Johansen et al.,[38] who also documented reduced MVC force in people with ESRD/HD. Higher levels of PCr and ATP concentration were noted by three studies.[40,41,50] According to Nishida et al.,[44] however, muscle weakness may be associated with lower concentrations of resting PCr and ATP values in people with ESRD/HD, since these lowered concentrations are consistent with reduced energy production at rest. Nishida et al.'s[44] suggestion is supported by findings of lowered resting PCr and ATP in one other case-control study.[32] This variability in resting PCr and ATP concentrations may be explained by differences in measurement techniques used, muscles investigated, and/or characteristics of participants included in these studies.

DISCUSSION

Our results indicate an array of changes in the morphological, electrophysiological, and metabolic characteristics of skeletal muscle structure in people with ESRD/HD that, alone or in combination, may lead to muscle weakness. These changes include (1) myopathic, (2) neuropathic, and (3) mixed (neuropathic and myopathic) changes existing independently; (4) initial neuropathic changes leading to myopathic changes; and (5) reduced effective muscle mass. Thus, a single potential mechanism associated with muscle weakness in people with ESRD/HD could not be established, since the studies reviewed here indicated neuropathic and myopathic changes together with morphological and electrophysiological changes related to disuse atrophy. Also, because not all studies measured muscle strength directly, consistent relationships between muscle weakness and changes in morphological and electrophysiological characteristics can only be inferred.

The general observation of type II fibre atrophy in all studies using muscle biopsy suggests the presence of weakness linked to sedentary lifestyle in people with ESRD/HD, since type II fibre atrophy is essentially the result of disuse. According to Henneman's size principle, type II motor units are the last to be recruited in voluntary actions.[64] The poor health status of people with ESRD/HD may thus restrict activities that require large force production, necessitating recruitment of type II motor units. The findings of muscle damage observed on electron microscopy by Diesel et al.[27] and Kouidi et al.[9] are similar to changes observed following muscle damage due to eccentric contraction in people without ESRD/HD.[65] These findings may support suggestions of progression of proximal muscle weakness[15,16] resulting from ongoing muscle damage associated with eccentric contractions of proximal muscles carrying out their postural stabilization role during antigravity activities such as sitting on a chair, standing, or walking.[66]

The observed electrophysiological changes and the morphological changes in muscle characteristics are similar; both indicate myopathic, neuropathic, and mixed (neuropathic and myopathic) changes in skeletal muscle. These findings support the suggestion of a possible effect of ESRD/HD on the different components of the muscle motor-unit complex. Interestingly, Bautista et al.[56] observed morphological characteristics suggestive of myopathy with no changes in electrophysiological characteristics, which implies that these changes could be present independently of each other. This finding may be attributed to the nature of the tools used and the status of the muscle during the test performed, given that EMG reflects muscle characteristics during activity whereas biopsy provides insight into muscle morphology at rest (Bautista et al.[56] did not perform muscle biopsy during exercise). Thus, the difference in these outcomes may be related to measurement methods.

Since the exercises prescribed by physiotherapists for people with neuropathic disorders differ from those for people with myopathic conditions,[19] an EMG examination to differentiate between neuropathy and myopathy could be recommended for patients with ESRD/HD in order to guide treatment. For example, people with inflammatory polyneuropathy (e.g., Guillain-Barré syndrome) require careful exercise prescription to include activities that facilitate recruitment of type II fibres (speed or rapid rises and falls in muscle force production).[67] In the presence of myopathic conditions such as Duchenne's muscular dystrophy, on the other hand, strength training usually begins at a low percentage of the person's one RM (repetition maximum) and requires monitoring for signs and symptoms of overuse, such as myalgias.[22]

Kemp et al.[42] defined "effective muscle mass" as the product of true muscle mass and metabolic efficiency of exercising muscle fibres, basing their calculations of

metabolic efficiency on the initial rate of non-oxidative ATP synthesis during incremental sub-maximal exercise, measured using ^{31}P-NMRS. Observations of exercising muscle metabolism were therefore ascribed to "reduced effective mass," as muscle atrophy alone could not explain the changes in muscle metabolism during incremental sub-maximal exercise in people with ESRD/HD. These observations of reduced effective muscle mass suggest reduced intrinsic contractile efficiency.[68] The findings of increased cytosolic Pi lend further support to the theory of reduced contractile efficiency; according to Cady et al.,[18] high concentrations of Pi within the muscle have been shown to inhibit maximal force in skeletal muscle. However, using isometric exercise at intensities of 50% and 75% of MVC, Kemp et al.[43] showed normal contractile efficiency (measured as force per unit cross-sectional area per unit ATP turnover) of the calf muscle in people with ESRD/HD, and suggested that the reduced oxidative contribution during exercise was due to mitochondrial defects measurable during recovery. The above findings relating to contractile efficiency of skeletal muscle require further exploration, using exercises with various combinations of metabolic demands to establish contractile efficiency of the muscles. Whether such reduced effective muscle mass is also associated with changes in electrophysiological parameters also requires further study; muscle atrophy alone could not account for the lack of correlation between compound muscle action potential (CMAP) and the anterior tibial muscle cross-sectional area observed by Johansen et al.[38]

In their study, Johansen et al.[38] used EMG and spectroscopy techniques suggested by Kent-Braun et al.[69] to provide a thorough understanding of electrophysiological and metabolic characteristics during exercise. They suggested that changes in EMG (expressed as central activation ratio) could be associated with poor oxidative metabolism and greater accumulation of metabolic by-products. The metabolic changes observed in people with ESRD/HD following sub-maximal exercise were comparable to those observed following high-intensity (90% maximal) isometric exercise in people without the disease,[28] which suggests a significant reduction in exercise capacity, changes in the EMG, and high energy demands during activities requiring sub-maximal effort, such as activities of daily living. The high energy demands of sub-maximal activity and reduced effective muscle mass provide a rationale for the difficulty with activities of daily living experienced by people with ESRD/HD and, as such, may be an important cause of their functional limitation.

Implications for Physiotherapy

Exercise interventions to address skeletal muscle weakness are important, as people with ESRD/HD have identified management of complications related to dialysis,

including fatigue, as the second-highest priority for research.[70] The range of changes in the morphological, electrophysiological, and metabolic characteristics associated with muscle weakness in people with ESRD/HD suggest that interventions at an early stage to strengthen the weakened muscles may be beneficial. Kouidi et al.[9] were able to demonstrate muscle-fibre hypertrophy and an increase in proportion of type II fibres following six months of exercise (including low-weight resistance training) in this population. Johansen et al.[38] did not observe any change in the CMAP (an electrophysiological characteristic of skeletal muscle) following a single bout of exercise. The question of whether a prolonged exercise intervention leads to any changes in electrophysiological and metabolic characteristics requires further investigation.

Sub-maximal isometric contractions in the shortened positions of the muscle are known to be more effective than dynamic training in maintaining type II fibres.[71,72] However, this strengthening option has yet to be adequately explored as an intervention strategy in people with ESRD. Although progressive muscle weakness resulting from eccentric muscle contractions has been implicated, research on eccentric muscle damage indicates that practice with eccentric contractions may provide a protective effect for future eccentric contractions. However, the effect of eccentric contractions in muscle demonstrating myopathic changes has not been adequately explored.

The metabolic impairments observed at rest that are suggestive of reduced effective muscle mass or of an anaerobic metabolism may require considerations for appropriate prescription of specific exercise, such as resistance training at lower intensities, for optimal benefits. Several studies have implicated proximal muscle weakness as one of the clinical symptoms of myopathy in people with ESRD/HD. Other studies, however, have demonstrated involvement of the distal muscles as well. This variability in findings is consistent with McElroy et al.'s[73] finding of a variable pattern of muscle weakness in people with ESRD/HD. Physiotherapists working with this patient population should therefore perform a complete strength assessment of both proximal and distal muscles prior to prescribing resistance exercise. The impact of ESRD/HD on multiple organ systems, cardiovascular and nutrition status, and the effect of comorbid conditions should also be assessed to determine an individual's ability and tolerance to participate in resistance exercises.

LIMITATIONS

Only studies published in English were included in our review, and we restricted the review to morphological, electrophysiological, and metabolic characteristics of skeletal muscles. Other factors associated with skeletal

muscle weakness, such as malnutrition, comorbidities associated with ESRD, vitamin D abnormalities, and impaired glycolytic metabolism, have not been explored in the current review.

CONCLUSION

We reviewed the current best evidence to identify possible muscle-characteristic causes of muscle weakness in people with ESRD/HD. Our findings suggest that numerous changes in the muscle (myopathic, neuropathic, mixed neuropathic and myopathic, and impaired contractile efficiency) may be associated with muscle weakness in this population. The presence of skeletal muscle weakness indicates a need for physiotherapists to adequately assess skeletal muscle strength when people with ESRD/HD report fatigue. Assessment should be followed by initiation of low-intensity strength training as appropriate to each individual's overall physiological status.

KEY MESSAGES

What Is Already Known On This Topic

Physiotherapists treat people with ESRD/HD. There is a high incidence of fatigue in this population, which results in significant functional limitation. Several factors contribute to fatigue, including skeletal muscle weakness. Skeletal muscle weakness is amenable to exercise, but the actual causes of such weakness in people with ESRD/HD have not been determined.

What This Study Adds

This study reviews the best available evidence to identify the morphological, electrophysiological, and metabolic characteristics of skeletal muscle in people with ESRD/HD. The results indicate muscle changes associated with these characteristics, including myopathic changes, neuropathic changes, changes resulting from disuse, and reduced effective muscle mass. A comprehensive assessment is recommended prior to initiating strength training to address skeletal muscle weakness in this patient population.

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