

A Systematic Review of the Acute Effects of Hemodialysis on Skeletal Muscle Perfusion, Metabolism, and Function



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Introduction: The underlying mechanisms of skeletal muscle wasting in hemodialysis patients are complex. We performed a systematic review to summarize evidence on whether hemodialysis has acute effects on skeletal muscle perfusion, metabolism, and function.

Methods: The protocol was registered on PROSPERO (Registration number CRD42018103682). A systematic search was performed in MEDLINE, PubMed, Cochrane, Embase, Scopus, and Web of Science. Citation, reference list, and gray literature searches were also performed. Studies were selected in 2 stages: title and abstract review, then full-text review.

Results: A total of 65 full-text articles were reviewed, and 14 studies were eligible for inclusion. No studies were identified that assessed muscle perfusion during dialysis. Two studies used near-infrared spectroscopy to indirectly measure skeletal muscle oxygen consumption, which increased during dialysis in 1 study but only in patients with diabetes in the second. Metabolism was examined in 9 studies. A number of acute metabolic changes were reported (e.g., caspase-3 activity, polyubiquitin, and interleukin-6 protein increased in response to hemodialysis) as was a net negative protein balance over the dialysis session. Three studies examining muscle function did not produce consistent findings.

Conclusion: Gaps remain in understanding the acute effects of hemodialysis on skeletal muscle, particularly for changes in perfusion and function, although there does appear to be an acute effect on muscle metabolism.

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KEYWORDS: end-stage kidney disease; function; hemodialysis; metabolism; perfusion; skeletal muscle; systematic review

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Skeletal muscle wasting (MW) is a common complication of hemodialysis (HD). It is seen in 18% to 80% of patients and is associated with mortality, lower quality of life, reduced activity, and poorer immune function.^{1,2} The underlying mechanisms of MW are complex, with several factors identified to which MW could be attributed. These factors include nutritional deficiency, hormonal abnormalities, chronic inflammation, metabolic acidosis, regular hospitalizations, and gastroparesis. It has also been suggested that the dialysis treatment *per se* is implicated in

MW. Some studies of the metabolic effects of HD have reported that it exerts an acute catabolic effect on whole-body and muscle protein.^{3,4} In parallel, evidence has grown to show that circulatory stress induced by HD causes hypoperfusion in certain vascular beds—specifically, myocardial stunning and cerebral ischemia.^{5,6} Our aim was therefore to perform a systematic review to provide a summary of the best available evidence on the acute effects of hemodialysis treatment on skeletal muscle perfusion, metabolism, and function.

METHODS

A systematic review of the published literature was conducted of the acute effects of hemodialysis on muscle perfusion, metabolism, and function according to the PRISMA checklist statement. The methods were

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Table 1. PICO terms

Acronym	Definition	Description
P	Population	End-stage renal disease patients receiving in-center hemodialysis
I	Intervention	Hemodialysis
C	Comparison	Pre- versus posthemodialysis, or pre- versus intrahemodialysis
O	Outcomes	Skeletal muscle perfusion, metabolism, or function

registered at PROSPERO (registration number CRD42018103682) before study commencement. The research question was formulated according to PICO strategy⁷ (Table 1).

Inclusion criteria for the studies and search strategy restrictions are detailed in [Supplementary File S1](#). The systematic search was carried out from July 13, 2018, to July 27, 2018. The following databases were searched from their inception: MEDLINE, PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Scopus, and Web of Science (core collection). All citations were imported to EndNote X8.0.1 (Clarivate Analytics, Philadelphia, PA) for deduplication, screening, and management. Full-text articles were retrieved by EndNote. If not retrieved, articles were found through online database searches and imported to EndNote as an attachment. The applied search limits in each database along with the date of search can be found in [Supplementary Table S1](#). In addition, using Web of Science, a citation author search was performed to identify earlier and more recent studies from key articles that were identified from the initial database search. Reference lists for the identified studies were systematically searched for potential studies that may have been missed by electronic database searches. Gray literature was searched using ProQuest (Ann Arbor, MI). Free text and subject heading key terms were used to ensure a thorough search. In addition, word synonyms, relevant abbreviations, alternative spellings, and potential spelling mistakes were considered in the search strategy. Boolean line-by-line searches for each database can be found in [Supplementary File S2](#). Selection of studies was performed according to the eligibility criteria. It involved 2 stages: title and abstract review, and full-text review. The title and abstract review was performed by a single author (SJA), whereas the full-text review was performed on all retained articles from stage 1 by 2 authors (SJA and SH) with disagreements resolved by a third reviewer (NMS). The checklist and questions for these stages can be found in [Supplementary File S3](#).

The methodologic quality of included studies was assessed using the Critical Appraisal Skills Programme tool for cohort studies.⁸ The appraisal was conducted by 2 individual reviewers (SJA and SH). Disagreements were resolved by a third reviewer (NMS).

A data extraction form tailored to the review questions was designed by SA and used to extract data from selected studies ([Supplementary File S4](#)). Extraction was performed by 2 authors (SJA and SH) and cross-checked by NMS.

RESULTS

[Figure 1](#) shows a systematic review flow diagram. A total of 1118 articles were screened and 14 studies were eligible for inclusion. Characteristics of included studies are summarized in [Table 2](#),^{2,9–21} and characteristics of patients included in studies in [Table 3](#).^{2,9–21}

Methodologic Assessment

[Table 4](#)^{2,9–21} provides a summary of the methodologic quality of the included studies. All of the included studies had methodologic weaknesses, including risk of selection bias, measurement bias, and confounding ([Table 5](#)^{2,9–21}). Adequacy of study reporting was also variable ([Table 6](#)^{2,9–21}).

Outcome Measures

Measurement techniques varied among studies (detailed in [Table 2](#)). A meta-analysis was deemed inappropriate due to the differences in the methodologies of the studies.

Perfusion Studies

No studies were identified that measured changes in muscle perfusion in response to HD. Two prospective studies examined the acute effects of HD on skeletal muscle oxygenation and microcirculation using near-infrared spectroscopy (NIRS) with a vascular occlusion test (VOT), which measures the percentage of oxyhemoglobin in total hemoglobin for a certain tissue volume (tissue oxygen saturation). Using NIRS with VOT (NIRS-VOT) allows other measures to be derived that indirectly provide information on oxygen consumption (maximum volume of oxygen) and vascular reactivity.

In the study conducted by Pipili *et al.*,⁹ NIRS-VOT was used to assess thenar muscle microcirculation in patients undergoing HD and hemodiafiltration. The only measure that changed significantly after dialysis was the maximum volume of oxygen (24.5% ± 7.5%/min versus 40% ± 17.7%/min after dialysis, $P = 0.03$) but this was only observed in the HD subgroup. There was a nonsignificant trend toward an increase in postdialysis vascular reactivity in the HD group, with no such trend apparent after hemodiafiltration.

De Blasi *et al.*¹⁰ used a different NIRS-VOT device applied to the gastrocnemius muscle. Two equal groups of participants (10 diabetic and 10 nondiabetic patients) were enrolled. The authors did not find any change in

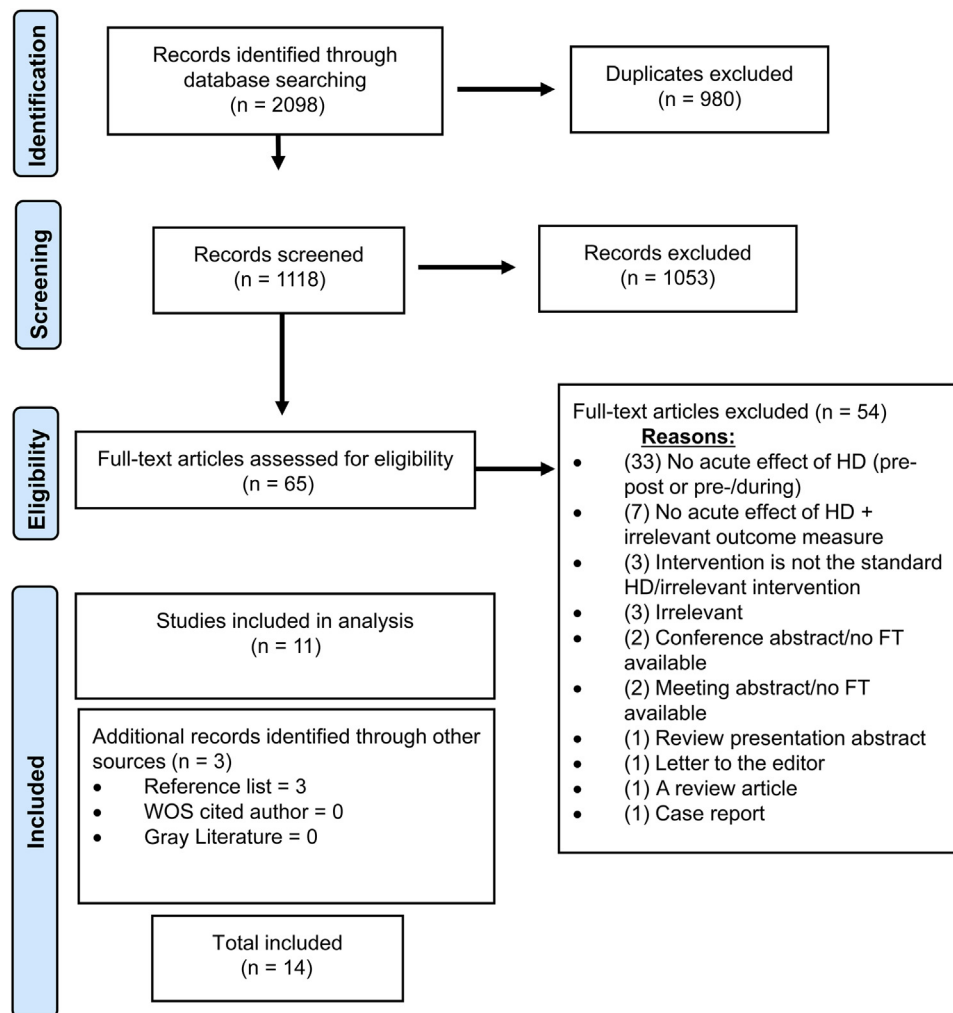


Figure 1. Study selection flow diagram. FT, full-text; HD, hemodialysis; WOS, Web of Science.

tissue oxygen saturation in either group in response to dialysis. The calculated values for maximum volume of oxygen results did differ between the diabetic and nondiabetic groups. In the nondiabetic group, there was no change in maximum volume of oxygen values during dialysis, whereas in the diabetic group, values increased during dialysis from 0.29 ± 0.15 ml/min per 100 ml to 0.72 ± 0.21 ml/min per 100 ml in the third hour and to 0.58 ± 0.20 ml/min per 100 ml in the fourth hour of treatment. In both groups, total hemoglobin increased significantly from baseline during dialysis, reflecting hemoconcentration in response to ultrafiltration. There was also a rapid and significant decrease in microvascular compliance within the first hour of dialysis for both groups. This decrease was more pronounced in the diabetic group and microvascular compliance diminished further throughout the whole dialysis session in both groups.

Functional Studies

Three studies examined the acute effect of HD on skeletal muscle function. The study by Saiki *et al.*²⁰

produced diverse results. Results for quadriceps muscle strength testing showed that muscle strength increased after HD in 6 patients, decreased in 3 patients, and was unchanged in 1 patient. Results for handgrip strength testing showed that muscle strength had increased after HD in 5 patients, decreased in 3 patients, and was unchanged in 2 patients. However, intra-individual repeatability of the testing was not reported. In the study by Harrison *et al.*,²¹ electromyography was used on the hand (second dorsal interosseous) and on the leg (vastus lateralis). For the hand muscle, a comparison between pre-HD and post-HD tests showed a significant overall increase (18 Hz) in signal frequency. In the leg, there was no significant change. Two studies, those by Harrison *et al.*²¹ and Soangra *et al.*,² examined sit-to-stand and sit-to-walk tests, respectively, before and after HD. Harrison *et al.*²¹ reported a small (6%) yet significant increase in the number of stands immediately following HD compared with the pre-HD test. Soangra *et al.*² used a sit-to-walk test and observed a significantly slower rise in patients following the dialysis session.

Table 2. Characteristics of included studies

Author	Publication year	Sample size	Design	Intervention	Outcome measurement tool
Perfusion studies					
Pipili <i>et al.</i> ⁹	2015	20	Prospective	HD + HDF	<ul style="list-style-type: none"> Near-infrared spectroscopy with vascular occlusion test
De Blasi <i>et al.</i> ¹⁰	2009	20	Prospective	HD	<ul style="list-style-type: none"> Near-infrared spectroscopy with vascular occlusion test
Metabolism studies					
Cardoso <i>et al.</i> ¹¹	1988	3	Prospective	Acetate HD	<ul style="list-style-type: none"> ³¹P Magnetic resonance spectroscopy, using 1.5-Tesla magnet and 6-cm surface coil
Lofberg <i>et al.</i> ¹²	1991	8	Prospective	HD	<ul style="list-style-type: none"> Muscle biopsies
Taborsky <i>et al.</i> ¹³	1993	7	Prospective	HD	<ul style="list-style-type: none"> ³¹P Magnetic resonance spectroscopy, using 1.5-Tesla magnet and 8-cm surface coil
Ikizler <i>et al.</i> ¹⁴	2002	11	Prospective	HD	<ul style="list-style-type: none"> Primed constant infusion of stable isotopes tracers: L-[1-¹³C] leucine and L-[ring-²H₆] phenylalanine with AV blood sampling
Raj <i>et al.</i> ¹⁵	2003	12	Prospective	HD	<ul style="list-style-type: none"> Muscle biopsy: mRNA levels of caspase-3, and ubiquitin Plasma levels of cytokines, IL-1, IL-6, and TNF
Raj <i>et al.</i> ¹⁶	2004a	9	Prospective	HD	<ul style="list-style-type: none"> Primed constant infusion of stable isotopes tracer: L-[ring-¹³C₆] phenylalanine with AV blood sampling Blood samples to estimate fractional synthesis rates of albumin (FSR-A), fibrinogen (FSR-F) Muscle biopsies to measure isotopic carbon enrichment Cytokines (IL-1, IL-6, IL-10, C-reactive protein, and TNF-α)
Raj <i>et al.</i> ¹⁷	2004b	6	Prospective	HD	<ul style="list-style-type: none"> Primed constant infusion of stable isotopes tracers: phenylalanine, leucine, lysine, alanine, and glutamine before and during HD with AV blood sampling and muscle biopsies to measure isotopic carbon enrichment Cytokines (IL-1, IL-6, IL-10, and TNF-α) in plasma samples
Raj <i>et al.</i> ¹⁸	2005	17	Prospective	HD	<ul style="list-style-type: none"> Muscle biopsy Femoral AV balance of IL-1, IL-6, IL-10, and TNF-α cytokines were measured using ELISA kit Levels of cytokines quantification in the skeletal muscle
Boivin <i>et al.</i> ¹⁹	2010	8	Prospective	HD	<ul style="list-style-type: none"> Primed constant infusion of stable isotope of L-(ring 13C6) phenylalanine and AV blood sampling Muscle biopsy: aspase-3 enzyme activity; TUNEL assay to detect apoptotic DNA damage Percentage of apoptotic cells was calculated by a pathologist, and IL-6 levels in skeletal muscle extracts were quantified
Function studies					
Saiki <i>et al.</i> ²⁰	1980	10	Prospective	HD	<ul style="list-style-type: none"> Handgrip and quadriceps muscle strength
Harrison <i>et al.</i> ²¹	2006	25	Prospective	HD	<ul style="list-style-type: none"> Surface electromyography Sit-to-stand test
Soangra <i>et al.</i> ²	2013	6	Prospective	HD	<ul style="list-style-type: none"> Sit-to-walk test

³¹P, phosphorus 31; AV, arteriovenous; ELISA, enzyme-linked immunosorbent assay; IL, interleukin; TNF, tumor necrosis factor; TUNEL, terminal deoxynucleotidyl transferase dUTP nick-end labeling.

Metabolism Studies

Protein Turnover

Protein turnover was measured in 4 studies. Ikizler *et al.*¹⁴ studied muscle protein breakdown and synthesis before, during, and after dialysis sessions. Results showed that muscle protein breakdown was significantly increased during dialysis from baseline. Although forearm protein synthesis also increased, the magnitude of increase was less than the increase in protein breakdown. This resulted in an increase in net forearm protein loss by approximately 3-fold during dialysis. In the postdialysis period, forearm protein breakdown was significantly decreased from the dialysis period but remained significantly higher (84% greater) than the baseline. Similarly, forearm protein

synthesis also fell from during dialysis to the post-dialysis period, but not back to baseline levels. However, net forearm protein loss was similar between basal and postdialysis periods. Table 7^{14,16,17,19} shows protein breakdown and synthesis values.

Raj *et al.*¹⁶ estimated the fractional synthesis rates and their findings supported the results of Ikizler *et al.*¹⁴; both muscle protein synthesis and breakdown increased significantly during HD. Again, the increase in muscle breakdown was higher than synthesis during HD, resulting in net muscle protein loss. The arteriovenous balance of amino acids was also measured. Results showed that phenylalanine concentration in the artery decreased from $86.1 \pm 7.7 \mu\text{mol/l}$ to $67.6 \pm 6.4 \mu\text{mol/l}$ ($P < 0.01$) during dialysis, whereas the

Table 3. Patients characteristics

Author (yr)	Sample size	Age (mean ± SD, yr)	Gender M/F (%)	Ethnicity	BMI	ESRD cause	Comorbidity No. (%)
Perfusion studies							
Pipili <i>et al.</i> ⁹ (2015)	HD: 11 HDF: 9	69.5 ± 12.0	Both groups: 75 (25) HD: 82 (18) HDF: 67 (33)	NR	26.0 ± 3.4 kg/m ²	NR	DM: 5 (25) HTN: 14 (70)
De Blasi <i>et al.</i> ¹⁰ (2009)	20: 10 DM, 10 non-DM	DM group: (60.1 ± 10.1) Non-DM group: (57.8 ± 11.5)	DM group: 60 (40) Non-DM group: 70 (30)	NR	NR	10: DN (DM group) non-DM group: lupus nephritis 1, PKD 2, nephrosclerosis 7	NR
Metabolism studies							
Cardoso <i>et al.</i> ¹¹ (1988)	3	NR	NR	NR	NR	NR	NR
Lofberg <i>et al.</i> ¹² (1991)	8	52.1 ± 24.89	50 (50)	NR	Weight (kg): 58.2	6 chronic GN, 1 IgA nephritis, 1 nephrosclerosis and GN	NR
Taborsky <i>et al.</i> ¹³ (1993)	7	48 ± 9	NR	NR	NR	NR	NR
Ikizler <i>et al.</i> ¹⁴ (2002)	11	43.8 ± 3.7	55 (45)	Caucasian/African American 45 (55)	28.3 ± 1.9 kg/m ²	2 (18%) DM 4 (36%) HTN, 2 (18%) GN, 1 (9%) APCKD, 2 (19%) unknown	NR
Raj <i>et al.</i> ¹⁵ (2003)	12	46.1 ± 3.6	92 (8)	NR	Weight (kg): 76.2 ± 14.4	NR	6 (50) diabetes %
Raj <i>et al.</i> ¹⁶ (2004a)	9	43 ± 5.9	83.3 (16.7)	NR	Weight (kg): 74.8 ± 3.4	2GN, 2 HTN, 1 TIN, 2 DM, 2 unknown	Diabetes: 2 (22.2%)
Raj <i>et al.</i> ¹⁷ (2004b)	6	43 ± 5.10	83.3 (16.7)	NR	23.6 ± 1.2	1GN, 2 HTN, 1 TIN, 2 unknown	NR
Raj <i>et al.</i> ¹⁸ (2005)	17	44 ± 5.4	NR	NR	Weight (kg): 75.2 ± 5.5	2 HTN, 6 DN, 3GN, 2 TIN, 4 unknown	35.3% diabetic
Boivin <i>et al.</i> ¹⁹ (2010)	8	43 ± 5.9	NR	NR	Weight (kg): 75.2 ± 3.5	2 GN, 2 HTN, 1 TIN, 3 unknown	NR
Function studies							
Saiki <i>et al.</i> ²⁰ (1980)	10	20–71 range	60 (40)	NR	NR	(i) Chronic GN, HTN, congestive heart failure (ii) NAS (iii) Chronic TIN (iv) DN (v) PKD (vi) Chronic GN (vii) Chronic IN (viii) Chronic GN (ix) SLE nephropathy (x) Hypertensive NAS	NR but myopathies were excluded
Harrison ²¹ (2006)	25	54.5 ± 2.6	64 (36)	NR	Male: 25.8 ± 1.3 kg/m ² Female: 22.4 ± 0.8 kg/m ²	GN (5); NAS (3); PKD (6); renal failure (6); other or unknown (5)	NR, but patients with malignancy; severe heart, lung, or liver disease; type 1 or 2 DM were excluded
Soangra <i>et al.</i> ² (2013)	6	54 ± 4	33 (67)	NR	NR	NR	NR, free of orthopedic injury

APCKD, autosomal polycystic kidney disease; chronic IN, chronic interstitial nephritis; DM, diabetes mellitus; DN, diabetic nephropathy; DM, diabetes mellitus; ESRD, end-stage renal disease; GN, glomerulonephritis; HD, hemodialysis; HDF, hemodiafiltration; HTN, hypertension; NAS, nephroangiosclerosis; NR, not reported; PKD, polycystic kidney disease; SLE, systemic lupus erythematosus; TIN, tubulointerstitial nephropathy.

Table 4. Summary of CASP tool assessment

Question	Author (yr)													
	Saiki <i>et al.</i> ²⁰ (1980)	Cardoso <i>et al.</i> ¹¹ (1988)	Lofberg <i>et al.</i> ¹² (1991)	Taborsky <i>et al.</i> ¹³ (1993)	Ikizler <i>et al.</i> ¹⁴ (2002)	Raj <i>et al.</i> ¹⁵ (2003)	Raj <i>et al.</i> ¹⁶ (2004a)	Raj <i>et al.</i> ¹⁷ (2004b)	Raj <i>et al.</i> ¹⁸ (2005)	Harrison <i>et al.</i> ²¹ (2006)	De Biasi <i>et al.</i> ¹⁰ (2009)	Boivin <i>et al.</i> ¹⁹ (2010)	Soangra <i>et al.</i> ² (2013)	Pipili <i>et al.</i> ⁹ (2015)
Clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acceptable recruitment? (selection bias)	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Exposure and outcome accurately measured? (measurement bias)	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Confounding factors in the design/ analysis were considered (confounding bias)	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Believable results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results can be applied locally?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N	Yes
Results fit with other evidence?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Implications for practice	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Score (yes: 1; no: 0; maximum possible: 8)	4	3	4	3	4	4	4	4	3	4	3	4	3	4
Percentage of yes scores	50	38	50	38	50	50	50	50	38	50%	38	50	38	50

CASP, Critical Appraisal Skills Programme.

The CASP assessment tool contains 12 questions. No scoring system is provided by CASP, but for the purpose of this review, scores were allocated as follows: "1" was awarded for a "yes" answer; "0" was awarded for a "no" answer; and overlapping questions were merged into 1 point (questions 3 and 4, questions 5a and 5b). This resulted in a maximum score of 8 points, with higher scores representing better methodology.

venous concentration did not show significant change ($86.6 \pm 7.4 \mu\text{moersuss}$. $76.2 \pm 6.8 \mu\text{mol/l}$, suggesting intradialytic muscle breakdown.

Another study by Raj *et al.*¹⁷ studied intracellular amino acid transport kinetics and protein turnover using before and during HD results. Arteriovenous balance was also measured. In addition, muscle biopsy specimens were obtained to calculate intracellular amino acid transport and muscle protein synthesis and breakdown. The fractional synthesis rate was estimated by the precursor product approach and increased during HD ($0.0521 \pm 0.0043\%/h$ vs. $0.0772 \pm 0.0055\%/h$, $P < 0.01$). Compartmental modeling showed that both protein synthesis and breakdown increased during HD ($P < 0.01$), with intradialytic protein breakdown greater than synthesis ($P < 0.05$). These results suggest that HD alters amino acid transport kinetics and increases protein turnover with net increase in protein catabolism.

In the study by Boivin *et al.*,¹⁹ skeletal muscle metabolism was measured with tracer labeling. Leg muscle protein synthesis and breakdown increased significantly during HD. However, the increase in muscle breakdown was significantly higher than synthesis during HD, resulting in a net negative protein balance.

Protein Breakdown Markers

Several of the included studies reported that hemodialysis was associated with increases in protein breakdown markers. In particular, skeletal muscle biopsy samples showed increased caspase-3 enzyme level at the end of dialysis in 2 studies: from 0.50 ± 0.01 units

to 0.81 ± 0.04 units,¹⁵ and from 25 ± 40 units to 38 ± 42 units.¹⁹ In addition, polyubiquitin was reported to increase during dialysis.¹⁵ One study also reported a significant increase in the percentage of apoptotic cells in muscle samples obtained after HD (6.9%), as compared with pre-HD samples (4.3%).¹⁹

Inflammatory Markers

Raj *et al.*¹⁵ reported that plasma interleukin-6 (IL-6) concentrations significantly increased from 7.54 ± 2.24 pg/dl before dialysis to 27.86 ± 4.94 pg/dl during dialysis. In a different study, the same authors also reported similar results (IL-6 increased from 11.53 ± 6.73 pg/dl to 27.86 ± 14.83 pg/dl during dialysis).¹⁶ In a third study, Raj *et al.*¹⁸ demonstrated higher concentrations of IL-6 in the femoral vein than in the femoral artery (16.27 ± 2.42 pg/dl vs. 11.29 ± 2.17 pg/dl) during dialysis. In the latter study, 2 patients underwent muscle biopsies for IL-6 before and at the end of dialysis, which showed an intradialytic increase of IL-6 in muscle. IL-6 levels were also measured in the muscle extract in a study conducted by Boivin *et al.*,¹⁹ and again results showed increased IL-6 concentrations at the end of dialysis. Additionally, 1 study reported an increase in plasma IL-10 and C-reactive protein during dialysis. Levels of IL-1 and tumor necrosis factor- α did not change significantly.^{15,16,18}

Muscle Energy Metabolism

Distinct from studies examining protein turnover, studies have also attempted to assess the acute effects of HD on skeletal muscle energy metabolism. Skeletal muscle spectra from phosphorus-31 magnetic resonance spectroscopy show resonances from inorganic

Table 5. Recruitment, measurement, and confounding biases of the selected studies

Study outcome	Study (yr)	Recruitment and selection bias	Confounding factors	Measurement bias	
			Potential confounding factors that were present or not reported	Were full details of measurement method/operator reported?	Other measurement biases
Perfusion studies	Pipili <i>et al.</i> ⁹ (2015)	Small sample size (HD: 11, HDF: 9); age range was not reported	Patients' food intake and exercise history		No
	De Blasi <i>et al.</i> ¹⁰ (2009)		Patients' food intake and exercise history, concomitant medication, dialysis access		No
Metabolism studies	Cardoso <i>et al.</i> ¹¹ (1998)	Small sample size (only 3); patients' gender and age were not reported	Patients' gender, patients' food intake and exercise history, concomitant medication, dialysis membrane and access, comorbidity, and baseline data were not compared with controls	No	Acetate HD was used
	Lofberg <i>et al.</i> ¹² (1991)	Small patient size (8); mean age was 52 yr	Exercise history, dialysis access, comorbidity		No
	Taborsky <i>et al.</i> ¹³ (1993)	Small sample size (only 7 of 21 chronic renal failure patients had pre- and post-HD measurements); mean age was 48 ± 9 yr	Patients' food intake and exercise history; concomitant medication, dialysis membrane and access, comorbidity		No
	Ikizler <i>et al.</i> ¹⁴ (2002)	Small sample size (11); mean age was 43.8 yr	Patients' food intake and exercise history, concomitant medication, comorbidity	No	No samples from muscle intracellular pool were taken to measure protein turnover.
	Raj <i>et al.</i> ¹⁵ (2003)	Small sample size (12), 1 female, 11 males; mean age was 46 yr	Patients' exercise history, dialysis access and vintage		No
	Raj <i>et al.</i> ¹⁶ (2004a)	Small sample size (9), 1 female, 8 males; mean age was 43 yr	Patients' exercise history, dialysis access and vintage		No
	Raj <i>et al.</i> ¹⁷ (2004b)	Small sample size (6), 1 female, 5 males; mean age 43 yr	Patients' exercise history; dialysis access; baseline data were not compared with controls		No
	Raj <i>et al.</i> ¹⁸ (2005)	Small sample size (17); mean age 44 yr	Patients' food intake and exercise history; dialysis access and vintage; gender		Yes
Boivin <i>et al.</i> ¹⁹ (2010)	Small sample size (8); mean age 43 yr	Patients' exercise history, dialysis access and vintage, comorbidity; gender		No	
Function studies	Saiki <i>et al.</i> ²⁰ (1980)	Small sample size (10)	Patients' exercise history; diabetes, as comorbidity, was not identified, in selected patients; baseline data were not compared with controls		Yes
	Harrison <i>et al.</i> ²¹ (2006)		Patients' food intake and exercise history; dialysis membrane and access; baseline data were not compared with controls	No	Intrasubject variability
	Soangra <i>et al.</i> ² (2013)	Small sample size (6), no reporting of age range, more females than males	Patients' food intake and exercise history; dialysis membrane, access, and vintage; baseline data were not compared with controls	No	Intrasubject variability

HD, hemodialysis; HDF, hemodiafiltration.

phosphate, phosphocreatine, and adenosine triphosphate allowing quantification. Additionally, indirect other function-related measures can be retrieved from the phosphorus-31 spectra: adenosine diphosphate and intracellular pH.²² Phosphorus-31 magnetic resonance spectroscopy was used in 2 studies to assess the effect of hemodialysis on skeletal muscle energy metabolism.^{11,13} In both studies, the gastrocnemius muscle was assessed. The aim of the study conducted by Cardoso *et al.*¹¹ was to examine the effect of dialysis with an acetate buffer on the concentration of phosphate-containing metabolites in the muscle. The magnetic resonance spectroscopy spectra were obtained before and during dialysis and it was reported that muscle adenosine triphosphate and adenosine triphosphate concentrations did not change significantly during dialysis, and no significant inorganic

pyrophosphate accumulation was noted. Although the authors concluded that dialysis did not affect the energy status of the gastrocnemius muscle, the study included only 3 patients. In the study by Taborsky *et al.*,¹³ 7 patients had magnetic resonance spectroscopy performed before and after dialysis. Signal intensities showed a slight increase in the phosphocreatine/inorganic phosphate ratio after dialysis.

Ribosome Concentration

In a study by Lofberg *et al.*,¹² muscle biopsies were performed to assess ribosome concentration before and after dialysis. The results showed that total ribosome concentration declined by 22.8 ± 6.7 optical density units/mg of DNA from a basal predialysis value of 71.3 ± 7.4 optical density units/mg of DNA ($P = 0.02$). The relative proportion of polyribosomes also declined by

Table 6. Adequacy of reporting

Author (yr)	Judgment	Description
Pipili <i>et al.</i> ⁹ (2015)	Yes	NIRS variables were fully reported in text/tables with <i>P</i> values.
De Blasi <i>et al.</i> ¹⁰ (2009)	Yes	NIRS variables were fully reported in text/tables with <i>P</i> values.
Cardoso <i>et al.</i> ¹¹ (1998)	No	ADP values were not reported. No <i>P</i> values for ATP and pyrophosphate accumulation, but mean standard error was reported.
Lofberg <i>et al.</i> ¹² (1991)	Yes	Concentration of ribosome content and amino acid is fully reported with <i>P</i> values.
Taborsky <i>et al.</i> ¹³ (1993)	No	No <i>P</i> value for phosphocreatine/ATP ratio of for the pre- and postdialysis values
Ikizler <i>et al.</i> ¹⁴ (2002)	Yes	Fully reported with <i>P</i> values
Raj <i>et al.</i> ¹⁵ (2003)	Yes	Fully reported with <i>P</i> values
Raj <i>et al.</i> ¹⁶ (2004a)	Yes	Fully reported with <i>P</i> values
Raj <i>et al.</i> ¹⁷ (2004b)	Yes	Fully reported with <i>P</i> values
Raj <i>et al.</i> ¹⁸ (2005)	Yes	Fully reported with <i>P</i> values
Boivin <i>et al.</i> ¹⁹ (2010)	Yes	Fully reported with <i>P</i> values
Saiki <i>et al.</i> ²⁰ (1980)	No	<i>P</i> values for the pre- and postdialysis mean values of muscles strengths were not reported; only reported as not significant
Harrison <i>et al.</i> ²¹ (2006)	No	EMG signal peak-to-peak amplitude and signal root mean square data were not reported. EMG frequency pre- and postdialysis are only presented in figure.
Soangra <i>et al.</i> ² (2013)	Yes	Fully reported with <i>P</i> values

ADP, adenosine diphosphate; ATP, adenosine triphosphate; EMG, electromyography; NIRS, near-infrared spectroscopy.

3.2% ± 1.35% of total ribosomes compared with before dialysis (*P* < 0.05), which indicates lower capacity for protein synthesis in patients undergoing dialysis.

DISCUSSION

In this systematic review of 14 prospective studies, we sought to assess the acute effects of HD on skeletal muscle perfusion, metabolism, and function. This is a relatively understudied area, and all of the included studies were of low to medium methodologic quality. Despite these limitations, there were consistent results regarding the effects HD on skeletal muscle metabolism, generally suggesting an acute increase in protein breakdown during dialysis, associated with an inflammatory response. However, studies investigating the effect of dialysis on muscle perfusion and function

have shown diverse findings from which it is not possible to draw definite conclusions.

Skeletal MW is a common complication of HD, occurring in 18% to 80% of patients,¹ and is associated with significant morbidity and mortality rates.^{23,24} Mechanisms leading to MW are complex. Putative causative factors include nutritional deficiency,²⁵ hormonal abnormalities,²⁶ chronic inflammation,²⁷ metabolic acidosis,²⁸ and gastroparesis.²⁹ Over recent years, there has been a recognition that the acute effects of dialysis are implicated in a variety of pathophysiologic processes. For example, HD can result in acute reductions in blood flow to the heart and brain that over time result in ischemic damage and organ dysfunction.^{5,6} Our aim was therefore to review the current literature and assess the current evidence as to whether the dialysis process may contribute to pathologic changes in skeletal muscle. In addition, the observation that dialysis patients often have long recovery times following HD treatments raises the question as to how muscle function may be affected by hemodialysis.^{30–32}

Our review suggests that there is limited evidence as to whether HD results in altered perfusion of skeletal muscle. The studies by Pipili *et al.*⁹ and De Blasi *et al.*¹⁰ did not demonstrate changes in tissue oxygen saturation. Increases in muscle oxygen consumption were reported, suggesting an increase in muscle oxygen utilization during dialysis, although these were not universally observed, and a number of other measures did not change. Some discrepancy between the 2 studies could be due to the different muscle groups studied (thenar muscles versus gastrocnemius) and differences in the NIRS models. Additionally, both studies categorized participants into 2 subgroups, (in 1 study HD and hemodiafiltration groups and in the other diabetic and nondiabetic patients), which made the already modest sample sizes yet smaller. We found no studies that directly studied muscle perfusion, and currently it is not possible to draw any conclusions as to whether HD alters muscle perfusion.

Similarly, we found very limited data on the effect of HD on short-term muscle function. The 3 studies used

Table 7. Protein breakdown and synthesis between studies

Study (yr)	Baseline muscle protein breakdown	Intradialytic muscle protein breakdown	Baseline muscle protein synthesis	Intradialytic muscle protein synthesis	Net muscle protein loss	Postdialysis muscle protein breakdown	Postdialysis muscle protein synthesis	Postdialysis net muscle protein loss
Ikizler <i>et al.</i> ¹⁴ (2002), μg/100 ml per min	77 ± 13	180 ± 17	56 ± 8	123 ± 19	From -22 ± 7 to -58 ± 17	127 ± 19	98 ± 16	-28 ± 12
Raj <i>et al.</i> ¹⁶ (2004a), nmol/min per 100 ml	40.7 ± 2.4	83.1 ± 3.6	39.1 ± 7.3	54.7 ± 4.0	From 1.5 ± 1.9 to 29.1 ± 5.3			
Raj <i>et al.</i> ¹⁷ (2004b), nmol/min per 100 ml leg volume	57.8 ± 13.8	—	28.0 ± 8.5	—	Protein breakdown being greater than synthesis (<i>P</i> < 0.05)			
Boivin <i>et al.</i> ¹⁹ (2015), nmol/min per 100 ml	41.63 ± 2.47	84.61 ± 3.65	41.19 ± 3.03	55.15 ± 4.48	Net negative protein balance			

different methods of assessment, produced conflicting results and were of small sample size. In contrast, much more is known about the change in muscle mass and function over time. It has been shown in several studies that dialysis patients have reduced muscle strength compared with healthy subjects.^{33–37} When compared with controls, dialysis patients are weaker, walk slower, and show slower phosphocreatine recovery after exercise, which results in slower recovery from muscle contraction. The latter implies a functional defect in energy metabolism.^{38,39} Muscle mass and function also deteriorate over time, as reported in a study of peritoneal and hemodialysis patients in which muscle mass and the sit-to-stand test were assessed.⁴⁰ This is particularly true with elderly patients. The incidence of sarcopenia in 131 patients receiving dialysis who underwent testing with bioelectrical impedance analysis and grip strength was 13.7% but was much higher at 33.3% in patients older than 60 years.⁴¹ Also, in a cross-sectional study of 95 elderly ESRD patients, sarcopenia was highly prevalent (37.0% in males and 29.3% in females).⁴²

A relationship to short-term changes during dialysis and longitudinal deterioration in muscle physiology was suggested by the results from the studies examining short-term changes in muscle metabolism during HD. This was an area we examined in 9 of the 14 included studies, and in general their results were broadly consistent. In addition, some of these studies used gold standard techniques such as muscle biopsy and tracer techniques with arteriovenous sampling. The invasive nature and technical complexity of this type of study help in explaining the small sample size of these studies. A number of acute metabolic changes were reported. The gold standard for measuring protein turnover is the fractional synthesis rate and fractional breakdown rate with muscle biopsies to look at incorporation of tracer into muscle protein. This approach was used by Raj *et al.*¹⁶ to measure isotopic carbon enrichment of bound and free phenylalanine in the muscle. Results from this study showed an increase in muscle protein breakdown and net protein loss during dialysis. Although other studies also reported similar results, it should be noted that different methods were used across the studies, thereby making comparisons more difficult. To further support the findings of increased catabolism during dialysis, a number of studies reported acute increases of static muscle protein breakdown markers (caspase-3 activity and polyubiquitin), as well as increases of cytokines, especially IL-6, which has a major role in the balance between protein breakdown and synthesis in inflammatory conditions.^{15,27,28} Although the mechanisms that may cause increased protein breakdown during dialysis are

not fully described, the included studies also reported that these changes occurred in association with increased expression of inflammatory cytokines^{43,44} that may influence the metabolism of muscle protein.

To the best of our knowledge, this is the first systematic review to examine the acute effect of a single HD session on skeletal muscle perfusion, metabolism, and function. There are some limitations, including that this review did not include studies published in languages other than English and that hand searches of journals were not performed. All included studies were of small sample size and of low to medium quality, which limits drawing definitive conclusions.

In conclusion, based on studies included in this systematic review, gaps remain in our understanding of the acute effects of HD on skeletal muscle and further research in this field is warranted. This is particularly true for changes in perfusion and physical functioning, although there does appear to be an acute effect of dialysis on skeletal muscle metabolism, with increased inflammatory signaling and catabolism. A systematic review of available strategies to overcome acute protein-energy catabolic effect of hemodialysis can be of interest for future research.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

File S1. Inclusion criteria for the studies and search strategy restrictions.

Table S1. Databases' applied search limits and date of search.

File S2. Boolean line-by-line searches.

File S3. Title and abstract and full-text review checklist and questions.

File S4. A data extraction form.

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