Original Article

Physiological abnormalities of skeletal muscle in dialysis patients

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Abstract

Background. Muscle weakness is a commom but unexplained feature of dialysis patients. This study investigated the prevalence and causes of muscle weakness in dialysis patients by examining the quadriceps muscle force and contractile properties.

Methods. The quadriceps femoris was studied in terms of force, force–frequency curve, and speed of muscle relaxation in 49 dialysis patients and 27 healthy subjects. In addition nutritional, haematological, biochemical, and histological assessments were performed, and steps of force generation were analysed to reach the possible mechanisms leading to the observed weakness.

Results. Muscle weakness, though invariable as a symptom, was subtle or absent on clinical examination. Quadriceps force measurements, however, revealed unequivocal weakness in most of the patients (71%). The quadriceps muscle was weaker (317 ± 115 versus 460 ± 159 N, $P < 0.01$) compared to healthy individuals, but there was no evidence of impaired excitation–contraction coupling (0.79 ± 0.05 versus 0.76 ± 0.07, $P = 0.1$). Among dialysis patients the older and the malnourished ($n = 23$) were the weaker but there was no relationship to the type or duration of dialysis. The serum albumin was the only biochemical parameter related to the muscle force ($r = 0.6$, $P = 0.01$). The other most prominent abnormality of quadriceps muscle function observed in this study was slowing of relaxation (patients versus controls; $8.7 \pm 1.8\%$ versus $10.8 \pm 1.1\%$ force loss/10 ms, $P < 0.0001$) particularly in the malnourished group (malnourished versus well nourished; 8.3 ± 2.1 versus 9.4 ± 0.95, $P = 0.03$). Muscle histology was investigated ($n = 12$) and revealed that type II fibres were mildly atrophic in 40% of the biopsies in most areas, but predominantly type IIB. Although type IIB fibre areas are slightly smaller in the dialysis patients compared to the controls, this was not statistically significant (3025 ± 578 versus 4406 ± 1582, $P = 0.1$) except in the malnourished group compared to the well-nourished dialysis patients (2092 ± 304 versus 4346 ± 1496, $P = 0.04$), and in the malnourished dialysis patients type IIB fibre area was significantly correlated to the strength ($r = 0.6$, $P = 0.02$).

Conclusions. The only significant predictor of loss of muscle strength and abnormality of relaxation in this study was the nutritional state. A regular assessment of the nutritional state is required to ensure adequate nutrition to prevent the observed abnormalities of the skeletal muscles.

Key words: dialysis patients; nutrition; skeletal muscle; weakness

Introduction

Muscle weakness, a failure to generate force [1] is a well-recognized [2–9] but unexplained, feature of dialysis patients. This weakness is usually attributed to the effects of anaemia [10], water and electrolytes disturbances [11,12], cardiac failure, medications, particularly corticosteroids [13], malnutrition [14], peripheral neuropathy [15,16], ischaemic myopathy [17–19], vitamin D abnormalities [20–23], excessive parathormone production [24–26], carnitine deficiency [27,28], abnormal energy metabolism [29], and the sedentary life-style of the patients [30].

Muscles generate force through a series of events involving a controlling 'chain of command' from the brain to actomyosin cross-bridge [31]. Using well-established physiological techniques [32–35], failure of muscle contraction has been categorized as 'central' where there is volitional or non-volitional failure of neural drive to the muscles, or 'peripheral' where there is failure in force generation by mechanisms at or beyond the neuromuscular junction. Loss of force generation producing weakness is also seen when there is loss of muscle bulk but the mechanisms by which altered renal function may cause this weakness are poorly understood. This study has examined the contractile properties of a large proximal muscle, quadriceps femoris, used in everyday activity. Force, force–frequency curve, and speed of muscle relaxation were measured; the findings were related to the biochemical, nutritional parameters and the muscle histological abnormalities in an attempt to analyse the factors involved in the observed abnormalities.

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Subjects and methods

Nutritional, haematological, biochemical and skeletal muscle function assessment were performed in 49 patients with end-stage renal disease on dialysis therapy. In addition a muscle biopsy specimen was obtained from 12 patients. A group of 27 healthy subjects were also studied as a comparison group. Patients and control groups characteristics are shown in Table 1. A detailed history and examination was taken from each patient and included a careful search for musculoskeletal symptoms (muscle weakness, fatigue, pain, cramps, and stiffness). Standard history and clinical examination form was used for all patients. Muscle pain was differentiated from that arising from bone (renal osteodystrophy) or isch-aemic pain of peripheral vascular disease, both are common in dialysis patients. A systematic examination for myopathy and neuropathy was undertaken. Patients were observed performing everyday tasks such as rising from a low chair without the aid of the hands and sitting up in bed. Vibration sense, a marker of peripheral neuropathy, was assessed by means of a 256 Hz tuning fork applied to the medial aspect of the great toe metatarsophalageal joint and the lateral malleolus on each leg. Foot pulses were assessed by palpation. Results of the neuromuscular examination and other related medical findings are shown in Table 2.

Patients were stabilized on renal replacement therapy for more than 6 months, the CAPD patients were using the Baxter Disconnect system, and exchanging 8 litres of dialysis solution per day. Haemodialysis patients were dialysing for 4 h, three times weekly. None of the patients was on a protein-restricted diet. The aetiology of chronic renal disease in the patients were as follows: glomerulonephritis ($n=14$), hypertension ($n=8$), diabetes mellitus ($n=7$), chronic pyelo-nephritis ($n=5$), polycystic kidneys ($n=3$), unknown aeti-ology ($n=7$) and other causes ($n=5$). All but two patients were receiving antihypertensive therapy; drugs used most commonly were calcium-channel antagonist, beta blockers, and angiotension-converting enzyme inhibitors. The majority of patients were taking aluminium hydroxide as a phosphate binder and 1 alpha calcitriol. None of the patients was on corticosteroids and only 14 were receiving human recombin-ant erythropoietin subcutaneously.

Nutritional assessment

The nutritional status was assessed by the Subjective Global Assessment (SGA) method [36] and visceral protein status. The SGA method involved a careful history and clinical examination. The accuracy, reproducibility, and validity of this method have previously been shown in different groups [37, 38] including dialysis patients [39]. Patients were divided into well-nourished ($n=26$) and malnourished ($n=23$) groups. The well-nourished group corresponded to Baker

Table 1. Clinical characteristics of dialysis patients and controls

	Patient group (Mean ± SD)	Control group (Mean ± SD)
Number	49	27
Sex M (F)	29 (20)	16 (11)
Age (years)	42.1 ± 14.6	36.7 ± 12.1†
Weight (kg)	66.4 ± 8	64.6 ± 7.8†

† = $P > 0.05$.

Table 2. Neuromuscular characteristics and other medical problems of the dialysis patients studied. Some parameters were not tested in all patients. In these cases results are expressed as number of abnormal results/number of tests performed

History of:	
Fatigue	49/49
Weakness	44/49
Muscle pain or cramps	26/49
Muscle stiffness	2/49
Bone pain	3/49
Symptoms worse after dialysis	17/49
Symptoms worse before dialysis	1/49
Weakness	
Sit up in bed unaided:	49/49 (2 with difficulty)
Climb stairs	46/49 (5 with difficulty)
Raise arms above head	49/49 (3 with difficulty)
Rise from chair	47/49 (6 with difficulty)
Squat	41/49 (12 with difficulty)
Wasting	
Upper limb	16/49
Lower limb	26/49 (thighs thinner)
Evidence on examination of:	
Upper limb wasting	23/49
Lower limb wasting	21/49
Upper limb weakness	10/49 (MRC-grade 4)
Lower limb weakness	16/49 (MRC-grade 4)
Other medical problems	
Clinical neuropathy	3/49
Neurophysiological neuropathy	5/30
Myopathy (electromyography)	0/30
Ischaemic heart disease	4/49
Renal bone disease	5/49

et al. [38] class A, and the malnourished group to class B (mild to moderate). The visceral protein, albumin, and transferrin were also used to measure the nutritional status, serum albumin has been observed to be a marker of the nutritional status and a predictor of survival in dialysis patients [40]. It is important to realize that serum transferrin levels fluctuate with the use of erythropoietin and iron status [41].

Haematological and biochemical evaluation

At the time of the muscle function testing a blood sample was obtained for haemoglobin, serum or plasma creatinine, urea, potassium, bicarbonate, albumin, transferrin, creatine kinase, parathyroid hormone, thyroid stimulating hormone, and thyroxine. Table 3 shows the anthropometry, and clin-ical, biochemical, and nutritional parameters of the study population.

Choice of muscle

The quadriceps femoris is a large, proximal muscle of major functional importance; impairment of its function can have serious practical implications for everyday activities. Most of the muscle acts across only one joint (the knee) and it is easily to immobilize the hip while examining the mechanical properties of the muscle. A repeat needle biopsy is feasible and safe due to the large size and lack of major nerves and blood vessels. There is also evidence that the quadriceps

Table 3. Anthropometry, and clinical and nutritional parameters of the study population

	CAPD	HD	MN	WN
Number	30	19	23	26
Males/(females)	16 (14)	13 (6)	14 (9)	16 (10)
Age (years)	41.6 ± 12.8	43 ± 17.8†	48.6 ± 15.9	36.8 ± 11.3‡
Age range (years)	19–60	26–71	28–71	19–60
Height (cm)	165 ± 7	170 ± 7†	166 ± 8	170 ± 7†
Weight (kg)	66.6 ± 8	66 ± 8.3†	65 ± 6.6	67.6 ± 9†
BMI (kg/m2)	25 ± 2.9	23.4 ± 3.8†	23.7 ± 2.9	25 ± 3.2†
Mode of dialysis HD (CAPD)	19 (30)	30 (19)	9 (14)	10 (16)
Months on dialysis	25.4 ± 19	30.9 ± 22†	33.7 ± 18	23 ± 20.8‡
Range on dialysis	9–79	4–78	12–79	4–78
Nutritional status WN (MN)	17 (13) 10 (9)	23	26	
Haemoglobin (g/dl)	9.2 ± 1.4	9.5 ± 2.4†	9.5 ± 2.6	9.3 ± 1.6†
Urea (mmol/l)	26 ± 9	25 ± 7†	26 ± 10	25 ± 6†
Creatinine (mmol/l)	1037 ± 248	990 ± 300†	1020 ± 187	994 ± 346†
Calcium (mmol/l)	2.5 ± 0.3	2.4 ± 0.2†	2.4 ± 0.2	2.5 ± 0.2†
Phosphorus (mmol/l)	1.8 ± 0.5	1.8 ± 0.4†	1.8 ± 0.5	1.8 ± 0.4†
Potassium (mmol/l)	4.8 ± 0.6	4.5 ± 0.7†	4.7 ± 0.6	4.5 ± 0.8†
Bicarbonate (mmol/l)	23 ± 4.7	22 ± 3.1†	22 ± 4	22 ± 3†
Albumin (g/l)	42.5 ± 5.9	37.6 ± 4.1*	38.2 ± 3.8	40 ± 6.3†
Transferrin (g/l)	2.4 ± 0.5	2.3 ± 0.3†	2.2 ± 0.2	2.4 ± 0.4†
PTH (pmol/l)	28.6 ± 19.6	26 ± 28.1†	26 ± 23.8	27.9 ± 26.8†
Aluminium (mmol/l)	1.4 ± 0.6	1.8 ± 0.6†	1.3 ± 0.6	1.8 ± 0.6†
Thyroxine ug/dl	89 ± 17	71 ± 40†	86 ± 31	75 ± 29†
Creatine kinase	98 ± 21	55 ± 25**	64 ± 28	94 ± 29*

CAPD, continuous ambulatory peritoneal dialysis group; HD, haemodialysis group; MN, malnourished group; WN, well-nourished group.
†$P > 0.05$; ‡$P < 0.05$; *$P < 0.01$; **$P < 0.001$.

muscle is selectively weakened in uraemia [2,4–5], making it a suitable model for study.

Assessment of muscle structure

Muscle biopsy was obtained from 12 male dialysis patients and 10 male normal volunteers. Muscle biopsies were taken from the lateral portion of right quadriceps under local anaesthetic using the conchotome biopsy technique [42] on a non-haemodialysis day in the haemodialysis group and any day in the CAPD group. Assessment of the morphology of the muscle was performed by a pathologist with an interest in muscle disease and as described previously by our group [43].

Muscle function tests

Both voluntary and stimulated isometric contractions of quadriceps femoris was assessed with the subject seated in an adjustable, straight-backed chair with the lower leg dependent and the knee flexed to 90 degrees [34] based on that originally described by Tornvall [44]. The pelvis was secured by an adjustable belt. Force was measured with a strap looped around the leg just proximal to the malleoli. The amplified output from the strain gauge was recorded with a rapid response oscillograph. The subject performed a maximal effort knee extension against the strain gauge.

Voluntary strength of the quadriceps

Maximum voluntary contractions (MVC) were maintained until the examiner was satisfied (usually in 2–4 s) that the force (Newton units) produced was no longer increasing. The value of each maximal voluntary contraction was measured as the greatest force held for 1 s. Three MVCs trials were made with each quadriceps. Stimulated twitches of quadriceps (see below) were superimposed on the voluntary contraction and stimulating the muscle at 1 Hz [45]. With this technique of interpolating twitches the force is increased by the stimulated twitches only when voluntary contractions are submaximal.

Electrical stimulation studies

For electrical stimulation of the quadriceps two large, flexible, saline-soaked pad electrodes (approximately 14×12 cm) were closely applied proximally and distally to the anterolateral thigh. Stimulation was with unidirectional, square-wave pulses of 50 ms duration and up to 70 V (maintained between the electrodes). Tetanic electrical stimulation at 100 Hz produced contractions of up to 60% of the quadriceps MVC. Physiological characterization of muscle function to electrical stimulation was assessed by applying a train of impulses from a Devices 3072 stimulator driven by a computer (Apple IIe) over a frequency range 1, 10, 20, 50, 100 Hz, each for 1

s (except that of 10 Hz was given for 2 s to obtain a plateau force) as described previously [34].

Relaxation characteristics of the muscle

The maximum relaxation rate (MRR) of the quadriceps muscle from a 100 Hz electrically stimulated isometric contraction (force = 20–40% of the force of a maximum voluntary contraction) was determined from the differential force record. Both force and MRR were displayed on a UV oscillograph. The maximum relaxation rate was expressed as the percentage of the plateau force lost/10 ms.

Excitation–contraction coupling

Impaired excitation–contraction coupling leads to weakness due to failure of activation of the contractile process despite adequate membrane excitation. Its measure was obtained by using the 20:50 Hz tetanic force ratio (comparing the forces of contraction resulting from stimulation at low frequencies of stimulation '20 Hz' with those obtained at higher frequencies '50 Hz').

Results

Muscle strength

The contractile properties of the quadriceps muscle of all the subjects studied appears in Table 4. Our results indicated that the dialysis patients were weaker compared to the healthy subjects (mean ± SD); 317 ± 115 *versus* 460 ± 159 N, $P < 0.01$ (Figure 1), but there was no difference between the CAPD and the haemodialysis group (309 ± 117 *versus* 330 ± 116, $P = 0.4$). The malnourished dialysis group was weaker than the well-nourished dialysis group; 239 ± 56 *versus* 381 ± 112 N; $P < 0.001$, Figure 2.

Subdividing the dialysis group by gender revealed similar results. Male dialysis patients were significantly weaker than male controls; 365 ± 115 *versus* 530 ± 98 N, $P < 0.001$ and female dialysis patients were significantly weaker than female controls; 238 ± 60 *versus* 360 ± 100 N, $P < 0.001$.

Isometric relaxation rate (MRR) of the quadriceps

The muscle of dialysis patients is slow, the MRR was (mean ± SD) 10.8 ± 1.1% force loss/10 ms in the control
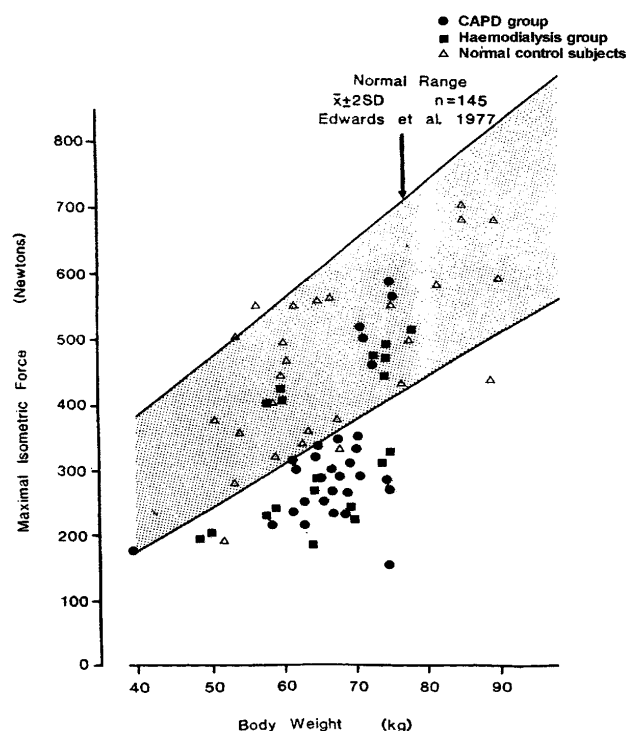

Fig. 1. Force (N) of maximum voluntary isometric contractions of quadriceps in all dialysis patients and controls. Shaded area represents normal range of 84 males (age 6–63 years) and 61 females (age 5–46 years) from Edwards *et al.* [34].

group but was significantly reduced in the dialysis group 8.7 ± 1.8% force loss/10 ms, ($P < 0.0001$).

The MRR was significantly reduced in the malnourished group compared to the well-nourished dialysis group; 8.3 ± 2.1 *versus* 9.4 ± 0.95, $P = 0.03$ (Figure 3), but there was no difference in the MRR between the haemodialysis and CAPD groups; 9.1 ± 1 *versus* 8.9 ± 1.9, $P = 0.4$.

Assessment of excitation-contraction coupling

The force/frequency curve was similar in the dialysis group and the controls. There was no significant difference in the 20:50 Hz force ratio which is a measure of the excitation-contraction coupling between the patient and control groups (0.79 ± 0.05 *versus* 0.76 ± 0.07, $P = 0.1$), the malnourished and the well

Table 4. Contractile properties of the quadriceps muscle in the study population

	CAPD	HD	MN	WN	All patients	Controls
Force (N)	309 ± 117	330 ± 116†	239 ± 56	381 ± 112**	317 ± 115	460 ± 159*
Force N/kg	4.6 ± 1.5	4.95 ± 1.5	3.6 ± 0.8	5.6 ± 1.3	4.7 ± 1.5	7.2 ± 2.6
MRR	8.85 ± 1.9	9.1 ± 1†	8.3 ± 2.1	9.4 ± 0.95‡	8.7 ± 1.8	10.8 ± 1.1**
20:50 ratio	0.81 ± 0.1	0.78 ± 0.1†	0.8 ± 0.05	0.8 ± 0.07†	0.79 ± 0.05	0.76 ± 0.07†

CAPD, continuous ambulatory peritoneal dialysis group; HD, haemodialysis group; MN, malnourished group; WN, well-nourished group; Force (N), absolute force in Newtons; Force (N/kg), specific force in Newtons per kilogram body weight; MRR, maximum relaxation rate expressed as % force loss/10 ms; 20:50 ratio, force at 20 Hz/force at 50 Hz, a measure of excitation contraction failure.
†$P > 0.05$; ‡$P < 0.05$; *$P < 0.01$; **$P < 0.001$.

nourished dialysis groups (0.8 ± 0.05 *versus* 0.8 ± 0.07, *P* = 0.4), and the haemodialysis and CAPD groups (0.78 ± 0.1 *versus* 0.81 ± 0.1, *P* = 0.2).

Correlation with clinical and biochemical parameters

In the dialysis patients there was a significant negative correlation between the MVC and age, $r = -0.5$, $P = 0.01$, and a positive and significant correlation with serum albumin $r = 0.6$, $P = 0.01$ and weight, $r = 0.5$, $P < 0.01$, but no correlation with the haematological or biochemical parameters (haemoglobin, creatinine, urea, potassium, bicarbonate, transferrin, CK, PTH, and aluminium).

There was no significant correlation between the MRR or the 20:50 Hz ratio in the dialysis patients and the age, weight, or the haematological or biochemical parameters.

Morphological abnormalities of the muscle in dialysis patients

Several mild, non-specific abnormalities were present in 78% of dialysis patients biopsies. five (45%) biopsies showed a low prevalence of type I fibres and one (10%) showed a high prevalence of type I fibres for the quadriceps muscle. However, there was no statistically significant difference in the prevalence of type I fibres (mean % type I ± SD) between the dialysis patients and controls (31 ± 10 % *versus* 41 ± 8%; *P* = 0.1). One (10%) biopsy showed a high prevalence of type II fibres for the quadriceps muscle but there was no statistically significant difference between dialysis patients and controls (type IIA, (mean % type IIA ± SD; 39 ± 3.5% *versus* 35 ± 9%; *P* = 0.5), and type IIB, (mean % type IIB ± SD; 30 ± 14% *versus* 24 ± 8%; *P* = 0.5) (Table 5). Type II fibre areas were mildly atrophic in four biopsies (40%) in most areas but predominantly type IIB. Although dialysis patients' type I and II fibre areas were slightly smaller than those of the controls, this was not statistically significant (Table 5). Type IIB fibre area was significantly smaller in the malnourished group compared to the well nourished (Table 6).

Morphological abnormalities in relation to the physiological function of muscle

Physiological contractile properties of quadriceps and muscle histology were obtained from 12 dialysis
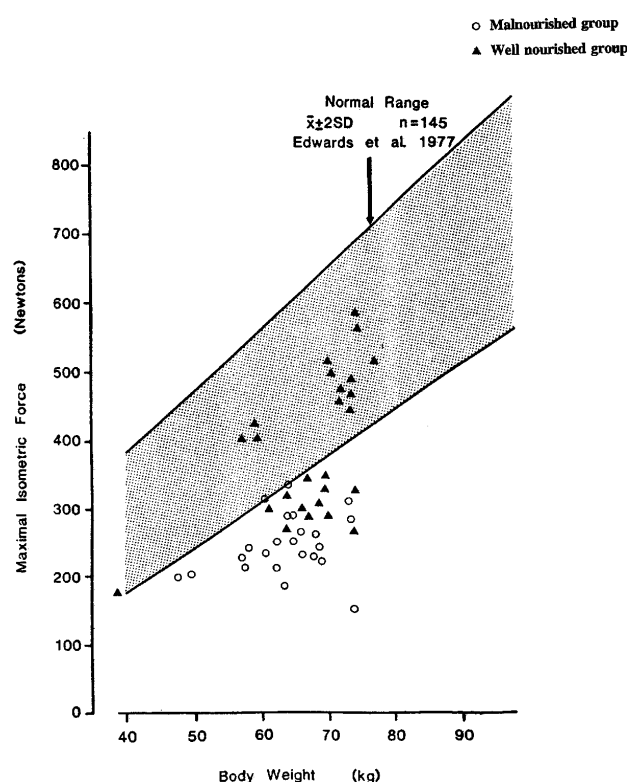

Fig. 2. Force (N) of maximum voluntary isometric contractions of quadriceps in malnourished and well-nourished dialysis patients. Shaded area represents normal range of 84 males (age 6–63 years) and 61 females (age 5–46 years) from Edwards *et al.* [34].

patients. The patients are weaker and their muscle is slow to relax compared with the controls (Table 6). The muscle of the malnourished dialysis patients were weaker and slower than the well-nourished dialysis group. There was no correlation between MVC, MRR or 20:50 ratio and the mean type I, IIA, or IIB fibre areas, but in the malnourished dialysis patients type IIB mean fibre area was significantly correlated to the strength, $r = 0.6$, $P = 0.02$ (Table 6).

Discussion

Apart from the weakness, the most prominent abnormality of quadriceps muscle function observed in this study was slowing of relaxation. These abnormalities

Table 5. Fibre type area and prevalence in dialysis patients and controls

	Patient	Control	*P* value
Fibre prevalence (%)			
Type I	31 ± 10	41 ± 8	0.1
Type IIA	39 ± 3.5	35 ± 9	0.5
Type IIB	30 ± 14	24 ± 8	0.5
Fibre area (mm²)			
Type I	4011 ± 458	4627 ± 1112	0.3
Type IIA	3883 ± 557	5213 ± 1288	0.06
Type IIB	3025 ± 578	4406 ± 1582	0.1

Table 6. Physiological contractile properties and fibre area of quadriceps in malnourished and well-nourished dialysis patients

	Malnourished	Well-nourished	*P* value
Number	5	7	
MVC (N)	239 ± 56	381 ± 112	0.001
Type IIB fibre area (mm²)	2092 ± 304	4346 ± 1496	0.04
Type IIB area *versus* MVC	$r = 0.6, P = 0.02$	NS	

Speed of muscle relaxation in dialysis patients

MN = Malnourished
MW = Well nourished
HC = Healthy controls
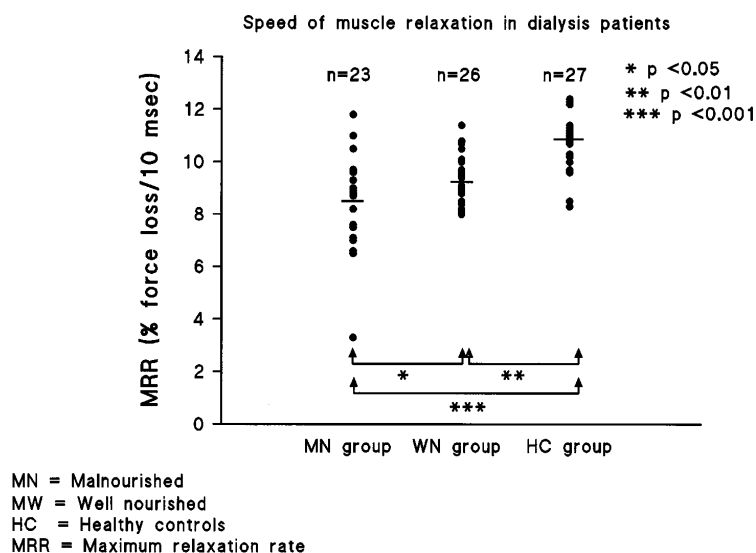MRR = Maximum relaxation rate

Fig. 3. Speed of muscle relaxation in the malnourished and well-nourished dialysis patients compared to controls.

are analysed and related to the biochemical and nutritional parameters to reach their possible mechanisms.

Muscle strength

The possible causes of muscular weakness are considered in three broad categories—defective electromechanical activation (impaired neuromuscular transmission or impaired excitation-contraction coupling), impaired short-term energy supply (reduced short-term energy stores or impaired energy exchange), or inadequate contractile machinery (smaller muscle cells or fewer muscle cells) [46].

Defective electromechanical activation (impaired neuromuscular transmission or impaired excitation-contraction coupling)

A normal electromyogram was obtained for each of the 30 patients on whom it was done. This is in contrast to Floyd *et al.* [5] who studied 11 patients in end-stage renal failure who developed proximal muscle weakness. The muscle weakness in all patients was shown to be myopathic in nature by electromyography, while Isaacs [3] found that three of 15 patients in chronic renal failure and severe muscular weakness had electromyography evidence of myopathy while the others suffered from neuropathy.

From the above discussion, myopathic and/or neuropathic electromyograms have been reported previously in uraemia. Our results indicated a normal records. Perhaps other factors contribute to the myopathic muscles, and with the improvement in dialysis techniques offering adequate dialysis, a better management, or prevention of osteomalacia and hyperparathyroidism, a myopathic process in the muscles can be prevented, as shown by our normal records.

However, neither the literature nor the results of the present study give any indication that a myasthenia-like failure of neuromuscular transmission might be the cause of the weakness of dialysis patients. Evidence for excitation–contraction coupling failure was sought by comparing the forces of contraction resulting from stimulation at low frequencies of stimulation (20 Hz) with those obtained at higher frequencies (50 Hz). This gave no indication of the selective, low-frequency force loss associated with 'uncoupling' of excitation and contraction, ruling out an impaired excitation–contraction coupling as a cause of the observed weakness in dialysis patients.

In contrast to our findings, Brautbar [29] in his review suggested excitation–contraction coupling abnormalities in dialysis patients. He based his suggestion on the work of Heimberg *et al.* [47] and Ritz *et al.* [22] who found a marked reduction in all parameters of calcium ion transport by the sarcoplasmic reticulum reversed upon the administration of $1,25\,(OH)_2D3$. These findings led Brautbar to conclude that excitation–contraction coupling is abnormal in dialysis patients because calcium release from the sarcoplasmic reticulum is of critical importance in the sequence of events leading from excitation to contraction. We have demonstrated a normal excitation–contraction coupling in dialysis patients by transcutaneous stimulation of the quadriceps method based on our group and other investigators previous work [34,48], and measuring the 20:50 Hz tetanic force ratio.

In addition central causes for the weakness, e.g. lack of central drive or motivation, have been eliminated by the twitch interpolation technique [30,49].

Impaired short-term energy supply (reduced short-term energy stores or impaired energy exchange)

Although we were unable to investigate the energy metabolism in our patients, reviewing the literature disclosed that both aerobic [50–52] and anaerobic

[53–55] energy metabolism is abnormal in uraemic muscles.

The cause of these abnormalities is unknown; however, one possibility is that the exchange of metabolites between blood and muscle is limited. This is in agreement with the findings of impaired skeletal muscle blood flow during exercise [56] and an improved peripheral oxygen extraction after exercise training in end-stage renal disease patients [51]. In a more recent work Kemp et al. [57], using a theoretical analysis applied to ^{31}P magnetic resonance spectroscopic studies of dialysed uraemic patients, found that the substantial exercise abnormalities seen by ^{31}P MRS are due mainly to a decrease in effective muscle mass (muscle mass and metabolic efficiency), which outweighs the oxidative defect implied by the abnormal PCr recovery kinetics. On the other hand, Barany et al. [58] have shown that there is an enhanced capacity for ATP production (relative to mitochondrial mass) in anaemic haemodialysis patients; this suggests that mitochondrial respiratory capacity does not limit maximal performance in uraemia; on the contrary there is a metabolic adaptation to the decreased delivery of oxygen.

Reports of ATP production in uraemia have been inconsistent; while some have reported impaired oxidative energy metabolism [51, 52] and low cellular levels of both ATP and phosphocreatine [59], others have reported enhanced production of ATP [58]. Nevertheless it would appear that quadriceps weakness in dialysis patients may be associated with impaired oxidative energy metabolism, but the severity of the weakness may, however, bear no relationship to the muscle's concentration of high-energy phosphate as shown by Young et al., [60]. Further studies of energy metabolism in dialysis patients relating the abnormalities to the muscle strength would contribute to our understanding of the pathophysiology of weakness in these patients.

Inadequate contractile machinery (smaller or fewer muscle cells)

The force produced depends on the cross-sectional area of the muscle; thus it would be expected that any degree of muscle wasting will lead to loss of force. Twenty-six patients reported thigh muscle wasting and in 21 of them significant quadriceps muscle wasting was observed. In dialysis patients numerous factors may lead to malnutrition and muscle wasting, among which are dietary restriction, inadequate dialysis, intercurrent infection, anorexia and vomiting, protein loss in the peritoneal fluid, and drugs, particularly steroids.

In the present study plasma values for creatine kinase activity were normal, in keeping with the absence of any biopsy evidence of destruction of muscle cells. A tendency to a smaller fibre area in the quadriceps muscle, more pronounced in the malnourished group, was demonstrated. A significantly reduced type IIB mean fibre area correlated to the strength was demonstrated in this group.

The relaxation rate of the quadriceps muscle

The muscle was slow in all dialysis patients and was further slowed in the malnourished group. In contrast to our findings, Berkelhammer et al. [61] indicated that MRR is affected by malnutrition but not by azotaemia, as there was difference between the malnourished and the healthy control groups but no difference between the well-nourished and the healthy control groups. The cause of this slow muscle relaxation in dialysis patients is unclear but two possible mechanisms could be argued. Type II fibre atrophy has been reported in uraemic patients [62], and since type II fibres have fast-twitch contractile characteristics [63] and a high rate of energy utilization [64] compared with type I, their decrease could result both in slowed relaxation and a reduction in energy liberation. This prompts the question as to whether changes in relaxation rate might be related to the altered proportions of the type I (slow-twitch) and type II (fast-twitch) fibres. The other possible mechanism is related to the fact that the resting concentration of ATP in the quadriceps of dialysis is low, and the relaxation speed of the isolated rat soleus muscle is proportional to its content of ATP [65].

Slow relaxation of intact human muscle is not confined to dialysis patients but has been reported in various conditions. Studied in vivo, relaxation of the human quadriceps from a brief stimulated tetanus is slow in osteomalacia. This is consistent with the demonstration by Rodney and Baker [66] that the soleus muscle of vitamin-D-depleted rats relaxes slowly when studied in vitro. The very slow relaxation of the quadriceps in hypothyroidism has also been reported [67], and a lesser degree of slowing has also been reported in Duchenne muscular dystrophy [67,68]. Lastly, malnutrition from whatever cause leads to slow muscle relaxation. All these would argue against uraemia as a sole cause of the abnormality. In this study, the muscle was slow in all patients and was further slowed in the malnourished group, perhaps suggesting that the nutritional status plays a major role in the pathogenesis.

Conclusions

Proximal muscle weakness, though invariable as a symptom, was subtle or absent on clinical examination. Quadriceps force measurements, however revealed unequivocal weakness in most of the patients, particularly those with malnutrition. There was no evidence of defective electromechanical activation both in terms of impaired neuromuscular transmission or impaired excitation–contraction coupling. Impaired short-term energy supply may explain this weakness and requires further investigations. Inadequate contractile machinery (smaller muscle cells) is very likely to contribute to the observed weakness.

The other most prominent abnormality of quadriceps muscle function observed in this study was slowing

of relaxation. This might be related to the altered proportions of the muscle fibres or altered energy supply and to malnutrition.

In contrast to other studies, anaemia, electrolyte disturbances (hyperkalaemia, hypocalcaemia), excess parathormone, and acidosis were not related to the muscle weakness or the relaxation abnormalities.

The only significant predictor of loss of muscle strength and abnormality of relaxation in this study was the nutritional state. A regular assessment of the nutritional state is required to ensure adequate nutrition and prevent these abnormalities of the skeletal muscles.

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