Muscle fatigue in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) and its response to a manual therapeutic approach: A pilot study

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1. Introduction

Chronic fatigue syndrome (CFS) or Myalgic Encephalomyelitis (ME), as it has been known in the UK since coined by Ramsay in 1955, is a clinically accepted condition now referred to in Britain as CFS/ME1 which is characterised by generalised abnormal muscle fatigue. Other common symptoms include sleep disturbance, headaches, cognitive dysfunction, depression, increased sensitivity to light and sound, back and neck pain, sore throat, and irritable bowel and bladder pain.2,3

The prevalence of CFS/ME in the UK has been estimated as 0.5% when co-morbid psychological disorders were excluded.4 A UK Government working group in January 2002 estimated that a general practice with 10,000 patients is likely to have between 30 to 40 CFS/ME patients.5 Prognosis of this complex disorder is recognised as being highly variable.6 It is not surprising that CFS/ME imposes substantial economic costs on society, mainly in the form of informal care and lost employment. Treatments need to be developed which recognise these impacts.6

CFS/ME is listed in The 10th Revision of the International Statistical Classification of Diseases and Related Health Problems, Volume 10 (ICD-10), under ‘Diseases of the Nervous System’ (code G93.3). Criteria for CFS have been long established by the U.S. Centers for Disease Control and Prevention (CDC)7 although there remains no universally recognised diagnostic test. However CFS/ME has recently been officially acknowledged as a disease entity by the UK Government.1 Since the pathophysiology of the disorder is a source of controversy, a universally accepted treatment for CFS/ME remains highly unlikely at this present time.

One of the main symptoms of CFS/ME is that of generalised abnormal muscle fatigue which occurs after relatively mild activity.2,7,8 Fatigue may be defined as a progressive impairment of maximal force generating capacity that develops during muscular activity.9 A muscle is said to fatigue when the point at which a contraction can no longer be maintained, the “failure point”, has been reached. In people with CFS/ME the onset of fatigue was found to occur after only a few seconds of maximal-effort muscle contractions.10

A previous study of patients with CFS/ME11 has demonstrated that the reduced capacity for dynamic exercise is also associated with reaching exhaustion much more rapidly than normal subjects, at which point these patients have relatively reduced intracellular concentrations of ATP.
Paul et al.\textsuperscript{12} investigated the delayed recovery from fatiguing exercise in CFS/ME patients. Recovery was examined following 3 sessions of 10 maximum voluntary isometric contractions over a 24 h period. Paul and co-workers found that the healthy control group in this study showed no significant difference in all 3 test sessions whereas the patient group showed a significant increase in recovery time as they progressed through the 24 h period.

Muscle fatigue has previously been quantified by studying the median frequency shift in the sEMG power spectrum. This has been shown to be a useful objective indicator of muscular fatigue during isometric muscle testing.\textsuperscript{13,14} The reliability of sEMG and isometric torque has been well reported for isometric knee extensor testing.\textsuperscript{13,15,16} Integrated EMG (iEMG) has been suggested to give a better means of assessment of isometric muscle function than raw EMG. Zakaria and co-workers\textsuperscript{17} showed excellent reliability of non-normalised iEMG of the vasti muscles, which was supported by Onishi et al.\textsuperscript{18} who investigated the iEMG of vastus lateralis, and concluded that iEMG may be used to predict muscle force in kinesiological research.

The reliability of isokinetic machines to investigate isometric and isokinetic torques has been well published. Farell and Richards\textsuperscript{19} reported a high level of reliability in tests performed for both static and dynamic exercise, and there have been many studies published using these devices to investigate quadriceps function. Isometric torque produced by the quadriceps has been shown to be a useful measure of recovery in muscle function pre and post treatment. Peak torque during voluntary quadriceps muscle strength tests has been measured following knee injury\textsuperscript{20}, and during recovery of muscle strength after high tibial osteotomy.\textsuperscript{21} Agre et al.\textsuperscript{22} investigated the efficacy of a 12-week home quadriceps muscle strengthening exercise program by investigating isometric torque and endurance. To assess endurance Agre and co-workers\textsuperscript{22} used a measure of tension time index (TTI) defined as being the product of isometric endurance time and 40% of maximal torque.

It has been clinically observed by the principal author that the lower extremity, particularly the quadriceps, is the most common region affected by muscular fatigue in CFS/ME. Also many prior studies have focussed on quadriceps when assessing different aspects of fatigue in CFS/ME.\textsuperscript{12–14} Thus although other muscle groups throughout the body are affected in most CFS/ME patients, the quadriceps may be used as an indicator of improvement in muscle fatigue following manual treatment.

The aim of this study was to evaluate the efficacy of a manual treatment protocol for CFS sufferers. This was achieved by determining whether any of the major CFS/ME symptoms were improved following the manual treatment protocol and to assess changes in exercise induced fatigue pre and post treatment. The objectives were to identify and quantify one possible source of muscular fatigue from the peak torque, impulse torque and sEMG signal measured during the isometric contraction of the quadriceps.

2. Methods

2.1. Participants

Prior to any testing ethical approval was granted by the local ethics committee. Volunteers were recruited using advertisements placed in local and national press with the first nine patients who fulfilled the Centers for Disease Control and Prevention (CDC) criteria\textsuperscript{7} assigned to the treatment group (CFS1). Participants were only enrolled after independent corroboration from their GP. No payments were received from any member of CFS1 for their treatment during the year long trial. All participants were identified as having no other patho-physiological explanation for their symptoms and were all certified by their GP as having no other coexisting pathology and fulfilling the CDC criteria.\textsuperscript{7} All participants met the inclusion criteria: aged between 18 and 60, not pregnant, and none of the CFS groups had received any physical therapy for their present symptoms during the previous 6 months.

There were two groups of CFS patients, the first group (CFS1: 5 men and 4 women: age range 20–53 years; mean age 35.3 years) received only osteopathic treatment\textsuperscript{23} for 1 year while patients in the other group, who were referred by their general practitioners, (CFS2: 5 men and 4 women: age range 22–55 years; mean age 36) were allowed to pursue treatment regimens of their own choice, excluding manual treatment. These included herbal and other alternative therapies, or allopathic approaches including antidepressants. None of the CFS patients were considered to be from the extreme end of the symptomatic spectrum (i.e. bedridden, with intense sensitivity to any external stimuli). The control group (NORM: 5 men and 4 women: age range 22–53 years; mean age 36.1 years) were normal volunteers in good general health and with no history of significant neurological abnormality (see Table 1).

To ensure that the no volunteer was suffering from a unipolar depression or primary anxiety state all the subjects who volunteered were included only after being independently reviewed by a consultant psychiatrist as suffering with CFS/ME, and not in any depressive or anxiety state. The psychiatrist, who had considerable clinical experience working in an NHS clinic specialising in CFS/ME, conducted an hour long consultation with each subject using both the Hospital Anxiety and Depression Scale HADS system\textsuperscript{24} plus the much more precise Schedules for Clinical Assessment in Neuropsychiatry SCAN system which provides a comprehensive, accurate and technically specific means of describing and classifying psychiatric phenomena.\textsuperscript{25,26}

The purpose of the exclusion criteria was to reduce the likelihood that a psychiatric disorder could explain the symptom picture in participants and confirmed that the diagnosis of the cohort of eighteen CFS/ME sufferers was as robust as possible.

2.2. Treatment

The manual treatment of each CFS/ME participant [CFS1 patients 1–9] consisted of the following techniques:\textsuperscript{27,28}

Each treatment session lasted for approximately 30 min with the following techniques applied. The individual time for the techniques are shown in brackets.

1. Effleurage to aid drainage in thoracic and cervical lymphatic vessels (5 min).
2. Gentle articulation of thoracic and upper lumbar spine, and the ribs. This was achieved by both long and short lever techniques (5 min).
3. Soft tissue massage of the paravertebral muscles, the trapezius, levator scapulae, rhomboids and muscles of respiration (10 min).
4. High and Low velocity manipulation of the thoracic and upper lumbar spinal segments using supine and side-lying combined leverage and thrust techniques (This technique was only used when there was obvious restriction in one or more apophyseal joints but not in every session).

Table 1

<table>
<thead>
<tr>
<th>Demographic data of participants.</th>
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<tbody>
<tr>
<td>Gender M:F</td>
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<tr>
<td>-----------</td>
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<tr>
<td></td>
</tr>
<tr>
<td>CFS1</td>
</tr>
<tr>
<td>CFS2</td>
</tr>
<tr>
<td>NORM</td>
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</tbody>
</table>

SD, Standard deviation.

5. Functional techniques to the sub-occipital region and the sacrum (5 min).
6. Stimulation of the cranio-sacral rhythm by functional-cranial techniques (5 min).29

The treatment protocol listed above continued weekly over a 12 month period. The treatment altered slightly depending on the physical state of the patient and on the symptom picture at that particular stage in their therapy. The treated participants were advised to aid the lymphatic drainage of the head and spine through a very gentle self massage routine that stimulates flow to the terminals of the lymphatics at the subclavian veins. As in a standard osteopathic practice, advice was also given to help improve general health.27 All participants were advised to avoid any stress whether physical or emotional where possible. No new activities that exerted physical strain on the body were allowed.

2.3. Isometric and EMG testing

Knee extensor tests were conducted on a Kin-Com AP isokinetic dynamometer. Participants were seated comfortably in the dynamometer chair with the tibia at 90° to the thigh, and an angle of 90 between the alignment of the spine and the femur. The pelvis was stabilised with a seatbelt and the right thigh with a wide strap. The centre of rotation of the knee was aligned with the point of rotation of the dynamometer lever. The lever was aligned along the lateral side of the leg with the padded lever arm extending in the front of the shin, just above the ankle. Torque data was collected at a sampling rate of 100 Hz.

Surface EMG (sEMG) signals were recorded for rectus femoris using silver/silver chloride electrodes in a bipolar configuration at a sample rate of 1000 Hz, with an inter-electrode distance of 2 cm over the belly of rectus femoris. The skin was cleaned with electrode skin preparation, and the electrodes were attached parallel to the muscle fibres on the longitudinal midline of the muscle 10 cm above the superior border of the patella. sEMG data was collected with an MT8 radio telemetry EMG system (MIE Medical Research Ltd.). The signals from the electrodes were processed through differential amplifiers (gain of 4000, CMRR 110 dB, and bandwidth of 4–1000 Hz).

Participants were seated on the isokinetics machine and asked to exert as much force as possible against the lever arm for 5 s, the subject then rested for 3 min. The peak torque was noted and from this a safe “exercising” level was determined at 33% of this peak value. The participants then underwent a controlled exercise protocol consisting of 10 reps of pushing at their safe exercising level for 20 s followed by a 10 s rest period. After a further 3 min rest the participants were then instructed to push as hard as they could for as long as they could.

The torque and sEMG were recorded during all exercising reps and the final maximal push. Peak torque, impulse torque, iEMG, and median power frequency were found. Paired t-tests were conducted on the data from peak torque, impulse torque, iEMG and median frequency for the final push at the beginning and end of the 12 month period for all three groups. Paired t-test were also conducted on the median frequency shift and iEMG during the first and last push of the ten repetitions on each visit to determine if the participants’ fatigue changed on the two visits during the exercise programme. The dynamometer and sEMG readings were blinded with the analysis of the data being undertaken by a researcher who had no details of which group the participants were allocated into. The participants were all given code numbers and were all ambulant with no obvious signs of illness at the time of testing. The CFS1 group received treatment at a separate clinic 4 miles away.

After each test the each participant’s final push was rated on the Borg Scale of Perceived Exertion. The participant was asked to score the perceived amount of strain they felt during the maximal push and as long as the difference between the real (based on heart rate) and perceived exertion during the initial tests did not increase in the repeat test twelve months later, then any torque measurement improvement did not imply that the participant was simply applying more effort at the end compared to the beginning of the project.30

2.4. Method of collection and analysis of questionnaire data

The symptoms were investigated utilising The Profile of Fatigue Related States31 which had already been used in the principal author’s prior clinical trial.32 The Profile of Fatigue Related States (PFRS) is a multidimensional measure incorporating nearly all the symptoms associated with CFS/ME.33 The PFRS has four scales assessing emotional stress, cognitive difficulty, fatigue and somatic symptoms.

Statistical analysis of the outcome of the participant groups and not participant group was carried out. Kruskal–Wallis test was used to test for significant differences in questionnaire responses, as percentages of maximum scores possible, between the three treatment groups. Related sample Wilcoxon Signed Ranks Tests were also conducted to investigate the change within each treatment group over the 12 month period. Non-parametric tests were used rather than parametric one-way and two-way analyses of variance, because the assumptions of normality might be inappropriate for percentage changes. A p-value of less than 0.05 was used as the cut-off for significance.

3. Results

3.1. Torque and impulse torque

Both the peak and impulse torque showed significant increases in the treated participant group over the year. The peak torque showed a 27% increase (p = 0.038), whereas the impulse torque showed a 29% increase (p = 0.027), Table 2. This indicates an improvement in the quadriceps ability to produce torque and sustain it during the maximal push following treatment. No such changes were seen in both the untreated participant group and the normal control group, see Table 2.

Table 2

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The peak torque and impulse torque in groups CFS1, CFS2 and NORM.</th>
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<tbody>
<tr>
<td>Peak torque (Nm)</td>
<td>CFS1 (0 months)</td>
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<tr>
<td>Mean (SD)</td>
<td>47.42 (38.2)</td>
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<tr>
<td>Mean difference</td>
<td>12.89</td>
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<tr>
<td>t – test</td>
<td>p = 0.038</td>
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<tr>
<td>Impulse torque (Nms)</td>
<td>CFS1 (0 months)</td>
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<tr>
<td>Mean (SD)</td>
<td>782 (713.8)</td>
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<tr>
<td>Mean difference</td>
<td>231.31</td>
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</table>

SD, Standard deviation.
3.2. Electromyography (EMG)

There was no significant difference in mean iEMG between the treated and untreated groups over the course of the 12-months, Table 3. This would indicate that the same number of motor units are being recruited by all participants during the exercise at the beginning and end of the year.

3.3. Median frequency data from 1st and 10th repetition treated ME

The median frequency shift of the EMG showed no significant difference in the treated patient group, untreated patient group and the normal control group over the year, Table 3. This indicates that all subjects are fatiguing by the same amount during the exercise at the beginning and end of the year.

3.4. Questionnaire

The estimated median increase in the PFRS result showed a significant difference between the groups \( (p = 0.006) \). This was reinforced by a significant improvement in PRFS scores in most symptoms, notably fatigue, pain and cognitive function were reported between the beginning and end of the 12 month period for the treated CFS/ME group only \( (p = 0.021) \), Table 4. A significant reduction in back pain was also found between the beginning and end of the 12 month period for treated CFS/ME group only \( (p = 0.028) \), Table 5, although the scores between the three groups did not reach significance \( (p = 0.065) \).

4. Discussion

The results from this study showed improved peak and impulse torque which is a direct measure of the muscles ability to produce and maintain a force. This demonstrates that there was a significant improvement in quadriceps muscle function following treatment. It should be noted that the reduced fatigability of the quadriceps was not achieved by any direct treatment on the lower extremity, or by any exercise regime to improve muscle strength in the legs.

It is important to realise that the massage techniques used could have been beneficial simply because the treatment reduced stress, improved relaxation and not due to improved lymphatic drainage. The author’s treatment programme was based solely on the hypothesis that by articulatory techniques of the thorax and the soft tissue plus cranial techniques which are all designed to improve the respiratory mechanisms and blood and lymphatic fluid movement within the body\(^{24,25} \) and reduce disturbed afferent sympathetic impulses, the overall sympathetic nervous system eventually begins to function normally thus further improving the central lymphatic pump\(^{26,37} \) which increases toxic drainage in all body tissues, including skeletal muscle.

The significant improvements in the major symptoms of CFS/ME following twelve months of treatment together with clinical findings, albeit palpatory, of a reduction of cervical and thoracic lymph engorgements, plus relaxation of cervical and thoracic paravertebral musculature have supported this hypothesis and give further evidence to support the use of the manual therapeutic approach. However it can be argued that the improvement noted in CFS1 group was due to the fact that they received regular and frequent treatment compared with the patients in CFS2 group who were unlikely to have as much care and attention from any therapist. A two-tailed paired \( t \)-test showed no significant differences in iEMG and Frequency shift between 0 months and 12 months in groups CFS1, CFS2 and NORM for the 1st and 10th repetition of the controlled exercise protocol or between the beginning and end of the maximal push (See Table 3). This implies that the level of fatigue was the same in the two visits. This finding indicates that the fatigue seen in CFS/ME is not due to any abnormality in the motor unit suggested by prior studies such as defect in the muscle membrane,\(^{23} \) or minor necrotic and microscopic structural changes.\(^{38} \)

However, a two-tailed paired \( t \)-test showed significant difference in the isometric tests for the final maximal push, in both peak and impulse torque, between the beginning and end of the 12 month in the treated group CFS1.Control groups CFS2 and NORM showed no significant difference in the same between 0 and 12 months (see Table 2).

Although this could be due to the controlled exercise protocol of 10 repetitions at 33% of maximal not inducing a fatigued state, the final maximal contraction did produce a greater impulse torque indicating significant functional improvements of the quadriceps in the treated patients, and no change in those who had no treatment.

The success of the treatment would imply that the fatigue in CFS/ME is possibly due to reduced blood and/or lymph flow and oxygenation. McCully and co-workers\(^{39} \) investigated the association of CFS/ME with reduced blood flow and oxidative delivery to skeletal muscle. Muscle blood flow was measured with doppler ultrasound after cuff ischaemia and exercise. Muscle oxygen

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>CFS1 (0 months)</th>
<th>CFS1 (12 months)</th>
<th>CFS2 (0 months)</th>
<th>CFS2 (12 months)</th>
<th>NORM (0 months)</th>
<th>NORM (12 months)</th>
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<tbody>
<tr>
<td>iEMG (µV/s)</td>
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<tr>
<td>Mean (SD)</td>
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<td>Mean difference</td>
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<tr>
<td>Mean difference</td>
<td>21</td>
<td>10</td>
<td>-10</td>
<td>10</td>
<td>27</td>
<td>10</td>
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<tr>
<td>Median Frequency (Hz)</td>
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<tr>
<td>Mean (SD)</td>
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<tr>
<td>Mean difference</td>
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<td>-3</td>
<td>-2</td>
<td>-2</td>
<td>2</td>
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<tr>
<td>Mean difference</td>
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<td>0.4184</td>
<td>-7</td>
<td>2</td>
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### Table 4

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<tr>
<th></th>
<th>CFS1 (0 months)</th>
<th>CFS1 (12 months)</th>
<th>CFS2 (0 months)</th>
<th>CFS2 (12 months)</th>
<th>NORM (0 months)</th>
<th>NORM (12 months)</th>
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<tbody>
<tr>
<td>Wilcoxon signed ranks test</td>
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<tr>
<td>PRFS</td>
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<tr>
<td>Mean (SD)</td>
<td>162 (41)</td>
<td>103 (70)</td>
<td>129 (44)</td>
<td>148 (43)</td>
<td>14 (18)</td>
<td>11 (13)</td>
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<tr>
<td>Mean difference</td>
<td>-0.021</td>
<td>-0.260</td>
<td>3</td>
<td>5</td>
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</tbody>
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SD, Standard deviation.
delivery was measured as the rate of post-exercise and post-ischaemic oxygen-haem re-saturation using continuous wavelength near-IR spectroscopy. Muscle metabolism was measured using P magnetic resonance spectroscopy. No significant difference was noted in the patient and control groups. McCull and co-workers concluded that CFS/ME patients showed no deficit in blood flow or oxidative metabolism.

If reduction of blood flow is not the cause for the fatigue then one only has to look at the lymphatic drainage capabilities to find a highly plausible reason for the functional impairment of the muscle. With the lack of any other reliable clinical method to confirm varicosities in lymphatic vessels, palpation in all the 18 CFS/ME patients in this study revealed engorged lymphatic vessels in the cervical and thoracic regions indicating impaired central drainage. Clinically in some patients these tortuous beaded vessels are superficial and large enough to be seen as in the photograph below. In this CFS/ME patient one can clearly see five separate varicose ‘megalymphatic’ superficial vessels at the anterior medial aspect of the right shoulder inferior to the right clavicle, the central one being the most pronounced. These are definitely lymphatic and not blood vessels since lymph fluid is creamy white in colour containing no red blood cells. Thus the surface varicosities are the same colour as the surrounding skin and do not have the blue/purplish hue seen in varicose veins. Visual evidence is rare, however, the author routinely palpates the same beaded vessels just below the surface of the skin in the chests of all CFS/ME patients.

Oedematous changes in muscles undergoing sustained low-level isometric contractions have been have been implicated as a major influence of the amount of fatigue. One of the major reasons for this oedema is the lack of adequate lymphatic drainage. The techniques of massage and manipulation employed on the patients in this study were specifically used to encourage movement of the bodily fluids including lymph drainage, eliminate dysfunction in the motion of the tissues, relax muscular tension and release compressed bones and joints. Kurz and co-workers have shown that histamine and serotonin were released from the oedematous tissue following manual lymphatic drainage and that circulation improved through increased output of adrenaline and noradrenaline.

The improvement of central lymph drainage following the manual treatment advocated by the authors has been shown to aid the intra muscular lymphatics and subsequently reduce the fatigue. The main drainage vessel of the lymphatics contains smooth muscle walls controlled by sympathetic nerves. Dysfunction of sympathetic control of the thoracic duct may lead to a reflux of toxins in the resultant retrograde lymph flow causing varicose lymphatic vessels predominantly in the abdomen, neck and chest plus affecting the flow of CSF into the lymphatics. Disturbance of normal sympathetic control as seen in CFS/ME offers a possible explanation regarding the reduced muscle function seen in this study. Spinal manipulation has been hypothesized as a method to improve afferent and efferent sympathetic activity and may aid the symptoms associated with CFS/ME.

In addition to the data collected by the physiological tests and PFRS questionnaires, patients were subjected to rigorous physical examinations during treatment sessions which occurred up to once a week for the duration of the trial. The Kruskal-Wallis tests showed significant differences in PFRS scores between groups in the within-group changes, $p = 0.006$, with significant reductions in most symptoms, notably fatigue, pain and cognitive function reported between the beginning and end of the 12 month period for the treated CFS/ME group only (see Table 4).

In subjective terms the cervical and thoracic paravertebral muscles demonstrated improved tissue texture and the thoracic spine was more mobile and the cervical and thoracic lymphatics less tender and less engorged following the year of osteopathic treatment. These clinical findings were strengthened by a separate back pain questionnaire which was developed by the principal author and used in an earlier study on CFS/ME patients. A Kruskal-Wallis tests showed no significant difference in changes in pain in thoracic and lower cervical regions of spine between the different groups $p = 0.065$. A significant reduction in back pain was reported between the beginning and end of the 12 month period for the treated CFS/ME group only (see Table 5).

The fact that members of the treatment group CFS1 had regular treatment and received encouragement and advice for the year could explain the improvement. However the question of bias was addressed by CFS2 patients being allowed to choose their own treatment rather than receiving no treatment or being given a therapy not of their own choice. Also as mentioned earlier the benefit of the manual treatment may be due to other factors rather than improvement in the sympathetic tone and increased lymphatic drainage. Although the authors acknowledge there is a potential non-comparability of these 3 groups due to the method of recruitment.

### 5. Conclusion

These findings suggest that post-exercise muscle function in CFS/ME is improved following specialised osteopathic intervention and that the fatigue in this disorder is not due to myopathic changes but as a consequence of other extrinsic causes. The authors suggest the
disturbance of lymphatic drainage to be one possible aetiopathological factor in the observed muscle fatigue. The findings of this study indicate the necessity for clinicians to investigate the possibility of lymphatic dysfunction of the musculature and indeed the central lymphatic drainage when diagnosing and treating CFS/ME.

References