A single-blind randomized controlled trial to evaluate the effect of 6 months of progressive aerobic exercise training in patients with uraemic restless legs syndrome

Christoforos D. Giannaki1,2, Georgios M. Hadjigeorgiou2,3, Christina Karatzafes2,4, Maria D. Maridaki5, Yiannis Koutedakis2,4, Paraskevi Founta6, Nikolaos Tsianas6, Ioannis Stefanidis2,7 and Giorgos K. Sakkas2,4,7

1 Department of Life & Health Sciences, University of Nicosia, Nicosia, Cyprus, 2 Centre for Research and Technology—Hellas, Trikala, Greece, 3 Faculty of Medicine, Department of Neurology, University of Thessaly, Larissa, Greece, 4 Department of PE and Sport Science, University of Thessaly, Trikala, Greece, 5 Department of PE and Sport Science, University of Athens, Athens, Greece, 6 Nephrology Clinic, General Hospital of Trikala, Trikala, Greece and 7 Faculty of Medicine, Department of Nephrology, University of Thessaly, Larissa, Greece

Correspondence and offprint requests to: Giorgos K. Sakkas; E-mail: gsakkas@med.uth.gr

Keywords: depression, exercise with no resistance, haemodialysis, sleep disorder, sleep quality

ABSTRACT

Background. Uraemic restless legs syndrome (RLS) affects a significant proportion of patients receiving haemodialysis (HD) therapy. Exercise training has been shown to improve RLS symptoms in uraemic RLS patients; however, the mechanism of exercise-induced changes in RLS severity is still unknown. The aim of the current randomized controlled exercise trial was to investigate whether the reduction of RLS severity, often seen after training, is due to expected systemic exercise adaptations or it is mainly due to the relief that leg movements confer during exercise training on a cycle ergometer. This is the first randomized controlled exercise study in uraemic RLS patients.

Methods. Twenty-four RLS HD patients were randomly assigned to two groups: the progressive exercise training group (n = 12) and the control exercise with no resistance group (n = 12). The exercise session in both groups included intradialytic cycling for 45 min at 50 rpm. However, only in the progressive exercise training group was resistance applied, at 60–65% of maximum exercise capacity, which was reassessed every 4 weeks to account for the patients’ improvement. The severity of RLS symptoms was evaluated using the IRLSSG severity scale, functional capacity by a battery of tests, while sleep quality, depression levels and daily sleepiness status were assessed via validated questionnaires, before and after the intervention period.

Results. All patients completed the exercise programme with no adverse effects. RLS symptom severity declined by 58% (P = 0.003) in the progressive exercise training group, while a no statistically significant decline was observed in the control group (17% change, P = 0.124). Exercise training was also effective in terms of improving functional capacity (P = 0.04), sleep quality (P = 0.038) and depression score (P = 0.000) in HD patients, while no significant changes were observed in the control group. After 6 months of the intervention, RLS severity (P = 0.017), depression score (P = 0.002) and daily sleepiness status (P = 0.05) appeared to be significantly better in the progressive exercise group compared with the control group.

Conclusion. A 6-month intradialytic progressive exercise training programme appears to be a safe and effective approach in reducing RLS symptom severity in HD patients. It seems that exercise-induced adaptations to the whole body are mostly responsible for the reduction in RLS severity score, since the exercise with no applied resistance protocol failed to improve the RLS severity status of the patients.

Clinical Trial Registry number. NCT00942253.
INTRODUCTION

Restless legs syndrome (RLS) prevalence in haemodialysis (HD) patients reaches ~30%, and it is significantly higher than in the general population [1]. Despite the high prevalence and great impact of the syndrome in the HD population, limited data are available regarding any non-pharmacological treatment options to reduce symptom severity.

Uraemic RLS has attracted increasing attention during the last decade since published evidence revealed that this form of secondary RLS could induce further reductions in the patient’s quality of life, depression and sleep quality [2–4], whereas the symptom severity was associated with an increased risk of death [4,5]. In addition, recent studies from our group shed light on a possible association between uraemic RLS and muscle atrophy [4,5]. In addition, recent studies from our group shed light on a possible association between uraemic RLS and muscle atrophy [4,5]. In addition, recent studies from our group shed light on a possible association between uraemic RLS and muscle atrophy [4,5]. In addition, recent studies from our group shed light on a possible association between uraemic RLS and muscle atrophy [4,5].

Subjects and Methods

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Subjects

Twenty-four uraemic RLS patients were recruited from the HD units of the University Hospital of Larisa and the General Hospital of Trikala, both located in the region of Thessaly in central Greece. RLS diagnosis was based on the criteria set by the International RLS Study Group (IRLSSG) [9], while the severity of the symptoms was assessed using the IRLSSG severity rating scale [10]. The study adhered to the Declaration of Helsinki and ethical approval was obtained by the Human Research and Ethics Committee at the University of Thessaly and the two hospitals, while all patients gave their written informed consent.

The inclusion criteria were dialysis for at least ≥3 months with adequate dialysis delivery (Kt/V) and with stable clinical condition. The exclusion criteria included diagnosed neuropathies or reasons for being in a catabolic state within 3 months prior to the start of the study or being unable to exercise. None of the recruited patients were engaged in any systematic exercise training programme, and none of them has been treated with any medication for RLS prior to the study. A neurologist skilled in RLS (GMH) examined the patients in order to assess any potential augmentation phenomena during the study period, using the standard criteria [9].

Aerobic exercise training

The patients were randomized in a 1:1 fashion to either progressive exercise training or a no-resistance exercise (control) group. The randomization procedure was completed using customized randomization software. After the randomization procedure, patients were asked to change their HD day or shift (morning or afternoon session) in order to match with the intervention arm in which they were randomized. Patients were randomized separately based on the host hospital (Hospital 1, n = 12, Hospital 2, n = 12). The exercise training intervention programme included aerobic exercise (cycling) for 45 min during the HD session three times per week for a 6-month period. Cycling in the progressive exercise training group was performed in a recumbent cycle ergometer (Model 881 Monark Rehab Trainer, Varberg, Sweden) at an intensity of 60–65% of the patient’s maximal exercise capacity (in Watts), which was estimated during a previous HD session using a maximal ergometer ramp test [11]. The exercise intensity was readjusted every 4 weeks to account for the patients’ improvement. The no-resistance programme also involved cycling during the dialysis session for 45 min, three times per week, for a 6-month period on the same ergometer, but without the application of resistance. The patients of both groups exercised under the supervision of an exercise physiologist, during different dialysis days in order to sustain the single-blind design. In order to avoid any potential acute effects of exercise on the examined variables (RLS severity), all assessments performed 48 h after the last exercise session. Functional capacity of the patients was assessed using a battery of test including the North Staffordshire Royal Infirmary test (NSRI), the sit to stand 5 repetitions (STS5) and the sit to stand 60 seconds (STS60) as previously described [2].

Haemodialysis procedure

The patients received the HD therapy (Fresenius 4008B, Oberursel, Germany) three times per week with low-flux, hollow-fiber dialysers and bicarbonate buffer, with each session lasting ~4 h. All patients had a forearm arteriovenous fistula as a vascular access to receive the HD treatment. An enoxaparin dose of 40–60 mg was administered intravenously before the beginning of each HD session. EPO therapy was given after the completion of the HD session in order to normalize haemoglobin levels within 11–12 (g/dL).
Subjective sleep quality, depression and daily sleepiness status assessment

The patient’s subjective sleep quality levels were assessed by using a weekly sleep diary [12]. The HD patient’s depression score was evaluated by using the self-rating depression scale developed by Zung [13]. Finally, the HD patient’s daily sleepiness status was assessed by using the Epworth sleepiness scale (ESS) [14].

Biochemical assessment

The patient’s routine monthly laboratory results were recorded including iron, ferritin haematocrit, haemoglobin, albumin and dialysis efficiency parameters. A single-pool Kt/V was calculated from pre- and post-dialysis BUN measurements using the Daugirdas II equation [15] at baseline and at the end of the 6-month intervention. The biochemical analysis was performed at the clinical biochemistry laboratory of the University Hospital of Larissa under standard hospital procedures.

Statistical analysis

The baseline values of each outcome measure were compared with the values obtained at 6 months by generalized linear model (GLM) repeated measures. Categorical variables were analysed using Chi-square analysis. Continuous variables were analysed using an independent sample t-test. In the case of outcome variables which changed in the same direction in both the progressive exercise and control groups, between-group comparisons were also performed (comparing Δ-change values) to determine whether the change in one group was significantly greater than that of the other group. Spearman’s rank correlation test was used to assess the relationships between the examined variables. All statistical analyses were performed using the SPSS version 18.0 (SPSS Inc. Chicago, Illinois). Data are presented as mean ± SD and the level of statistical significance was set at P ≤ 0.05.

RESULTS

All of the patients successfully completed the 6-month intervention programme with no adverse effects and no augmentation phenomena to report. The patient characteristics at baseline are presented in Table 1. No significant differences in the patients’ basic characteristics were found between the two groups (P > 0.05). None of the basic characteristics were significantly changed after the intervention period, except for the Kt/V which significantly improved in the progressive exercise training group compared with its respective baseline value (1.10 ± 0.0 baseline versus 1.25 ± 0.1 post exercise, P = 0.041). In contrast, no significant differences were found in Kt/V for the control group (1.2 ± 0.0 baseline versus 1.2 ± 0.4 post exercise, P > 0.05). None of the biochemical indices measured in the current study changed statistically after the 6 months intervention in either of the groups.

Changes in IRLS severity score, sleep quality, daily sleepiness and depression score are presented in Table 2. At baseline, no significant differences were observed between the two groups in sleep quality, daily sleepiness status, depression score and IRLS score (P > 0.05). However, after the 6-month intervention, statistically significant improvements were found in sleep quality (P = 0.038), depression score (P = 0.000) and IRLS score (P = 0.003) in the progressive exercise training group compared with its respective baseline values. In contrast, no significant changes were observed in the examined variables in the control group (P > 0.05). Moreover, Δ-change values were different between the two groups in depression and IRLS scores (P > 0.05). After the 6-month intervention period, RLS severity (P = 0.017) (Figure 1), depression score (P = 0.002) and daily sleepiness status (P = 0.05) appeared to be significantly improved in the progressive exercise training group compared with its respective baseline values. In contrast, no significant differences were found in the examined variables in the control group (P > 0.05). Moreover, Δ-change values were different between the two groups in depression and IRLS scores (P > 0.05).

Table 1. Patient characteristics at baseline divided into two groups according to the assigned intervention

<table>
<thead>
<tr>
<th>Variables</th>
<th>Exercise group</th>
<th>Control group</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Female/Male</td>
<td>3/9</td>
<td>4/8</td>
</tr>
<tr>
<td>Age (year)</td>
<td>59.2 ± 11.8</td>
<td>58.0 ± 10.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.7 ± 3.6</td>
<td>26.5 ± 4.4</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.1 ± 0.0</td>
<td>1.2 ± 0.0</td>
</tr>
<tr>
<td>Months in HD</td>
<td>24.0 ± 15</td>
<td>30 ± 26</td>
</tr>
<tr>
<td>Iron (µg/dL)</td>
<td>55.0 ± 37.0</td>
<td>72.2 ± 17.9</td>
</tr>
<tr>
<td>Ferritin (ng/dL)</td>
<td>208.5 ± 88.0</td>
<td>216.9 ± 111.0</td>
</tr>
<tr>
<td>Hct (µL)</td>
<td>34.4 ± 6.2</td>
<td>38.5 ± 3.3</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10.9 ± 2.1</td>
<td>12.7 ± 1.1</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.1 ± 0.2</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>98 ± 21</td>
<td>101 ± 18</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.4 ± 1.2</td>
<td>5.4 ± 1.3</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>312 ± 212</td>
<td>298 ± 289</td>
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</table>

Medication

<table>
<thead>
<tr>
<th></th>
<th>Exercise group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive</td>
<td>8 (66%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Anticholesteremic</td>
<td>6 (50%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Cardiac supportive</td>
<td>7 (58%)</td>
<td>8 (66%)</td>
</tr>
<tr>
<td>Peptic disease therapy</td>
<td>2 (16%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (25%)</td>
<td>5 (41%)</td>
</tr>
<tr>
<td>Diabetes prevalence</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Cardiovascular disease prevalence</td>
<td>2 (17%)</td>
<td>3 (25%)</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± SD. No statistical differences were observed between the two groups. BMI, body mass index; Kt/V, dialysis efficiency; Hct, haematocrit; Hb, haemoglobin.
be significantly better in the progressive exercise group compared with the control group.

Moreover, the Δ-change values in sleep quality correlated significantly with the Δ-change values in Kt/V ($r = 0.946$, $P = 0.000$). Functional capacity was improved after the 6 months of the training regime however only in the Exercise group compared to the control (Table 3).

**DISCUSSION**

This is the first randomized controlled exercise intervention study investigating the effects of progressive exercise training...
on RLS symptoms in HD patients with RLS. In the current study, it was shown that a 6-month intradialytic progressive aerobic exercise training regime was safe (no adverse effects were reported), effective in reducing the severity of RLS symptoms and beneficial in improving sleep quality and depression score. Such benefits were not observed in the control group.

Recently, exercise training was shown to be a safe and effective low-cost approach in reducing the RLS symptom severity in HD patients [8]. Moreover, acute exercise appeared to be very effective in reducing acute motor symptoms often seen during HD session in the same type of patients [16].

Apart from the effect of exercise training on RLS symptoms, it is well known that this type of non-pharmacological approach can also confer many beneficial physiological adaptations that impact on the patient’s quality of life and health [17] adding significant clinical value to this approach. In addition, the application of exercise training as a monotherapy or in combination with the approved pharmacological treatment can significantly limit augmentation and rebound phenomena as well as a number of side effects because it allows for a lower pharmaceutical dosage for the amelioration of the RLS symptoms [7].

Our data show that intradialytic progressive exercise training effectively reduced ureaemic RLS symptoms by almost 60%, without adverse effects or augmentation phenomena. In line with the reduction in RLS severity, both sleep quality and depression score significantly improved with the exercise training programme, further highlighting the beneficial effect of exercise on these important health-related parameters. Interestingly, while there were no differences between the groups at baseline, after the 6 months of intervention, RLS severity, depression score and daily sleepiness status appeared to be significantly better in the progressive exercise group compared with the control group (Table 2).

Notably, this is the first study to show that some specific exercise-induced adaptations or responses must be responsible for the improvements seen in the RLS severity score and not just leg movement, which we know confers acute relief (as this is the first study to employ an exercise training control group, i.e. exercise with no resistance, and to thus also account for any placebo effect previously unaccounted for in past exercise versus non-exercise studies). What mechanism(s) by which progressive exercise training may reduce RLS symptomatology is still unclear, however, in a recent study in non-uraemic RLS patients, an inverse relationship between β-endorphin release after exercise training and the periodic limb movements index was observed [18]. The amelioration of RLS symptoms through an increase in the opioid levels such as β-endorphins appears to be one of the strongest candidates as a mechanism, since it is known that RLS is related to a defective opioid system in the brain in this type of patients [19] while in previous studies, opioid treatment resulted in a successful improvement of RLS symptom severity [20]. In addition, a possible pathway by which progressive exercise training could affect RLS severity is the exercise-induced improvements in HD efficiency. In the current study, a significant improvement in \( K_r/V \) was found only in the progressive exercise group. We should note that some studies associated inadequate dialysis with RLS [21,22], while others do not support this hypothesis [5,23]. Interestingly, the application of home short HD sessions resulted in significant improvements in RLS symptom severity score in a recent study by Jaber et al. [24]. In the HD population, inadequate dialysis could induce sleep deprivation and significantly reduce sleep quality [25]. In the past, we have shown how aerobic exercise training improves sleep quality in HD patients with RLS [8]. In the current study, the changes in sleep quality after the exercise training in the progressive exercise group correlated strongly with the respective changes in \( K_r/V \) (\( r = 0.946, P = 0.000 \)), thus indicating a possible association of HD adequacy with sleep, possibly mediated by the known favourable systemic effects of exercise.

The effect of dialysis efficiency on the severity of RLS symptoms is still controversial [25,26]. Interestingly, in the current study, the \( K_r/V \) index appeared to be significantly increased after the progressive exercise training intervention confirming previous data in HD patients with unknown RLS status [27]; however, the Δ changes in \( K_r/V \) correlated only with the Δ change in sleep quality and not with the Δ change in IRLS severity score, continuing this discrepancy with \( K_r/V \).

Studies have shown that sleep quality is diminished in HD patients [28], while it seems that this phenomenon is more intense in the patients with RLS [2,3]. The data of the present study reveal that exercise training significantly improved sleep quality even though the assessment was done by a questionnaire (which is a less sensitive method than polysomnography). Changes in sleep quality could be a result of improvement in depression score or vice versa [29]; however, no significant correlation between the depression score and the sleep quality was observed in our study. It is possible that exercise training could have influenced these two parameters in an independent way; however, further research is needed in order to address this issue. On the other hand, exercise training failed to improve further the levels of daily sleepiness; however, we should note that the mean values of both groups regarding the ESS score were found to be above the cut-off threshold of daily sleepiness (>10). This is also observed by the classical pharmacological treatment used in RLS (dopamine agonists) showing no improvements in daily sleepiness in patients with idiopathic RLS [30]. It seems that daily sleepiness, unless it is very severe, does not change after either exercise or medication treatment; however, more work is needed on this issue to reach firm conclusions.

**Limitations**

Even though RLS is not a sleeping disorder, it would be very helpful if we were able to perform an overnight polysomnographic study in order to objectively evaluate sleep quality and quantity as well as an RLS-related movement disorder occurring during sleep called periodic limb movements in sleep. In addition, the IRLS severity score was not assessed during the 6-month period and, therefore, it is not possible to assess the course of IRLS score change during the study time.
limited number of exercise sessions were characterized as ‘incomplete’, i.e. when the patients were unable to complete the full 45 min cycling due to personal reasons. Unfortunately, those events were not systematically recorded, thus we are unable to comment on whether the level of compliance, which we however gauge as very high, could affect the final outcomes. Finally, we were not able to assess the levels of β-endorphin during the course of the study or during an exercise bout and have to thus rely on available bibliography to surmise a possible mechanism.

CONCLUSIONS

As this is the first study to employ a no-resistance exercise control, and we observed an improvement in RLS symptoms severity only with progressive exercise training, we conclude that the exercise-induced amelioration of RLS symptoms is possibly mostly due to chronic exercise-induced adaptations rather than due to an acute relief conferred by leg movements per se. Six months of intradialytic progressive exercise training appeared to have a positive effect on uraemic RLS symptoms with parallel changes in the patients’ sleep quality and depression. Further research is needed in order to clarify the exact mechanism by which systematic exercise training could affect the dopaminergic system of the brain in the HD patients with RLS.

ACKNOWLEDGEMENTS

We thank all HD patients who volunteered and participated in this study as well as all the staff at the dialysis units of the University Hospital of Larissa, Greece and General Hospital of Trikala, Greece for their expert advice and valuable help during the course of the study.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

REFERENCES


Received for publication: 28.12.2012; Accepted in revised form: 17.5.2013