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Influence of Selected Aerobic Exercises on Serum Vitamin D Level in Patients with Multiple Sclerosis

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Abstract

Background: Multiple sclerosis (MS) is the most common permanent neurological disorder affecting young adult causing strength deficits. Aim of the study: This study was conducted to investigate influence of selected aerobic exercises on serum Vitamin D level and lower limb performance in patients with multiple sclerosis. Subjects and methods: 30 patients with relapsing remitting MS recently diagnosed with early stage of MS, vitamin D insufficiency less than 20- 30 ng/mL, age from 20 to 40 years old and body mass index less than 25 kg/m² were recruited, assessed for and assigned into 2 groups. They received treatment program as follows: control group (A) received conventional medical treatment (Corticosteroids, Interferon beta medications, Dimethyl fumarate, muscle relaxants, medications to reduce fatigue) in addition to vitamin D supplementation only, while experimental group (B) received conventional medical treatment, vitamin D supplementation in addition to selected aerobic exercises. The outcome measures included serum vitamin D level by lab test, timed 25 walk test by measure timing of performance of lower limb gait in multiple sclerosis. Results: both groups showed significant difference in the outcome measures in the post treatment assessment, but the selected aerobic exercises (B) showed a more significant improvement over the control group at p-value >0. 001. Conclusion: selected aerobic exercises is an effective physical therapy modality when added to the conventional medical treatment, so it may provide better outcomes for serum vitamin D level and lower limb performance in patients with MS.

Key words: Selected Aerobic Exercises, Multiple Sclerosis, Vitamin D, 25 foot walk test.

INTRODUCTION

Multiple sclerosis (MS) is the commonest non-traumatic disabling disease to affect young adults. There is increasing incidence and prevalence of MS in both developed and developing countries. MS is a complex disease; many genes modestly increase disease susceptibility in addition to several well defined environmental factors, in particular vitamin D or ultraviolet B light (UVB) exposure, obesity and smoking (Roller and Gowan, 2017). Low 25-OH-D serum levels (around 20 ng/mL) are usually observed in MS patients as early as the beginning of the disease, i.e.at the stage of the clinically isolated syndrome (CIS) or of the first relapses (Ascherio et al., 2014). it has been showed that vitamin D deficiency associated with an increased relapse rate leading to increased disability that affect functional activity (Kampmanet al., 2012). It was assumed that ankle dorsiflexion; knee flexion and extension; hip flexion, extension, abduction, and adduction; and trunk lateral flexion are the most common affected muscles in patients with multiple sclerosis (Zackowski, 2014). No specific recommendations for exercise treatment exist that are universally valid. Since exercise programs have not sufficiently been investigated in more severely disabled patients, these recommendations are restricted to MS patients with a maximum expanded disability status scale (EDSS) score of 7 (Romberg, 2004). it has been reported that exercise training associated with systemic anti-inflammatory effects which may be cause vitamin D deficiency in MS cases (Lira et al., 2009). Exercise programs should specifically target weaker muscles, and should preferably encompass multisegmental complex movements (White et al., 2004). There is a gap in the available literatures that identify the role of aerobic exercises with vitamin D in treatment of multiple sclerosis, so this study may add a piece of information to the physical therapists, in the governmental hospitals and private clinics about the most recent rehabilitation programs when dealing with patients in early stages of MS (Cakit, 2010).

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SUBJECTS AND METHODS

Design

This is a randomized control trial (pre-test post-test experimental design study) single blind test that was approved and accepted by the Research Ethical Committee, Faculty of Physical Therapy, Cairo University, (P.T.REC/012/002176) and the Pan African Clinical Trial Registry database under the identification number PACTR202005730797920. Also, the patients signed an informed consent form prior to participation in the study, after the purpose and procedures of the study were fully explained to all patients in accordance with the principles set forth in the Helsinki Declaration.

Participants

The eligibility of 30 participants out of 50 (15 in each group) referred by a neurologist from outpatient clinics of kasr Al Aini Medical school, Cairo University were determined by conducting a preliminary power analysis with a power 80

Their age ranged from 20 to 40 years of both genders. They were recently diagnosed as patients with relapsing remitting MS, EDSS (Expanded Disability Status Scale) score less than 5 and Vitamin D insufficiency less than 20- 30 ng/mL. Patients were excluded if they used vitamin D supplements in the past 3 months, suffered any additional illness that would restrict their function, or suffered from a relapse within the last 4 months, as defined by Polman (Polman et al., 2011), relapse of any diseases and any corticosteroids intake in the past month, active inflammation at the start of the study (flu, cystitis etc), renal disease, elevated levels of calcium or parathyroid hormone, switching of imunomodulatory drugs in past 3 months, hypersensitivity to vitamin D preparations, cognitive impairment interfering with the subject's ability to provide an informed consent, history of hyperparathyroidism, liver disease, tuberculosis, sarcoidosis and kidney stones (Lassmann, 1999).

Sample Size

G Power (version 3.1.9.2) calculated the sample size using data from a pilot study with three participants in each group. It yielded an effect size of 0.52 for the main outcome Vitamin D and the error I rate was set at 5%, while power of error II rate was set at 90%, alpha level at 0.05. Because of the 15% drop out rate, a minimum of 29 participants was needed for this analysis. The IBM SPSS statistics 25 software was used for statistical analysis. The level of significance for all statistical tests was set at $p < 0.05$.

Randomization

Then, the patients that were randomly assigned by coin tossing into 2 groups, Group (A) that received conventional medical treatment in addition to vitamin D supplementation only, while group (B) received in addition to group A, selected aerobic exercises in the form of treadmill, stretching and strengthening exercises. Treatment was applied twice weekly for 6 weeks in a total of 12 sessions for each patient and the outcome measures were applied pre and post treatment (Figure 1).

Outcome measures

Serum vitamin D lab analysis

The 25-hydroxy vitamin D test was carried by lab a technician using an arm needle that drew blood sample from a vein and put it into a sample kit that was investigated in the lab. The patient was asked to stop any food intake for 4 to 8 hours before the test. Blood samples taken in the morning. Samples left to clot at room temperature for 30 min and then centrifuged. Aliquots of the serum supernatant had been frozen and stored at–80 °C and subsequently thawed and analyzed in one batch. Serum estrogen (E2) (reference range, 18.4–201 pmol/l), and vitamin D (25(OH)D3) (range, 30–80 ng/ml).

Timed 25 Foot Walk Test (T25FWT)

The T25FWT is a quantitative mobility and leg function performance test has been described as the "best characterized objective measure of walking disability and can be used across a wide range of walking disabilities" in MS. It is the first component of the multiple sclerosis functional composite to be administered at each visit (Phan et al., 2012).

Trial 1

Make sure that the stopwatch is set to 0:00. For the T25FWT, the subject was directed to one end of a clearly marked 25-foot course (clearly defined on the Floor or on the wall) and instructed to stand just behind the starting line. Point out where the 25-foot course ends, and then instruct the patient to walk 25 feet as quickly as possible, but safely without slowing down until passing the finish line. Timing begins when the lead foot is lifted and crosses the starting line. The examiner should walk along with the patient while completing the task. Stop timing when the lead foot crosses the finish line. The examiner should then record the subject's walk time to within 0. 1 second, rounding as needed. Round up to the next tenth if hundredth's place is > =0. 05, round down if hundredth's place is <0. 05. Once the time is recorded, be sure to reset the stopwatch.

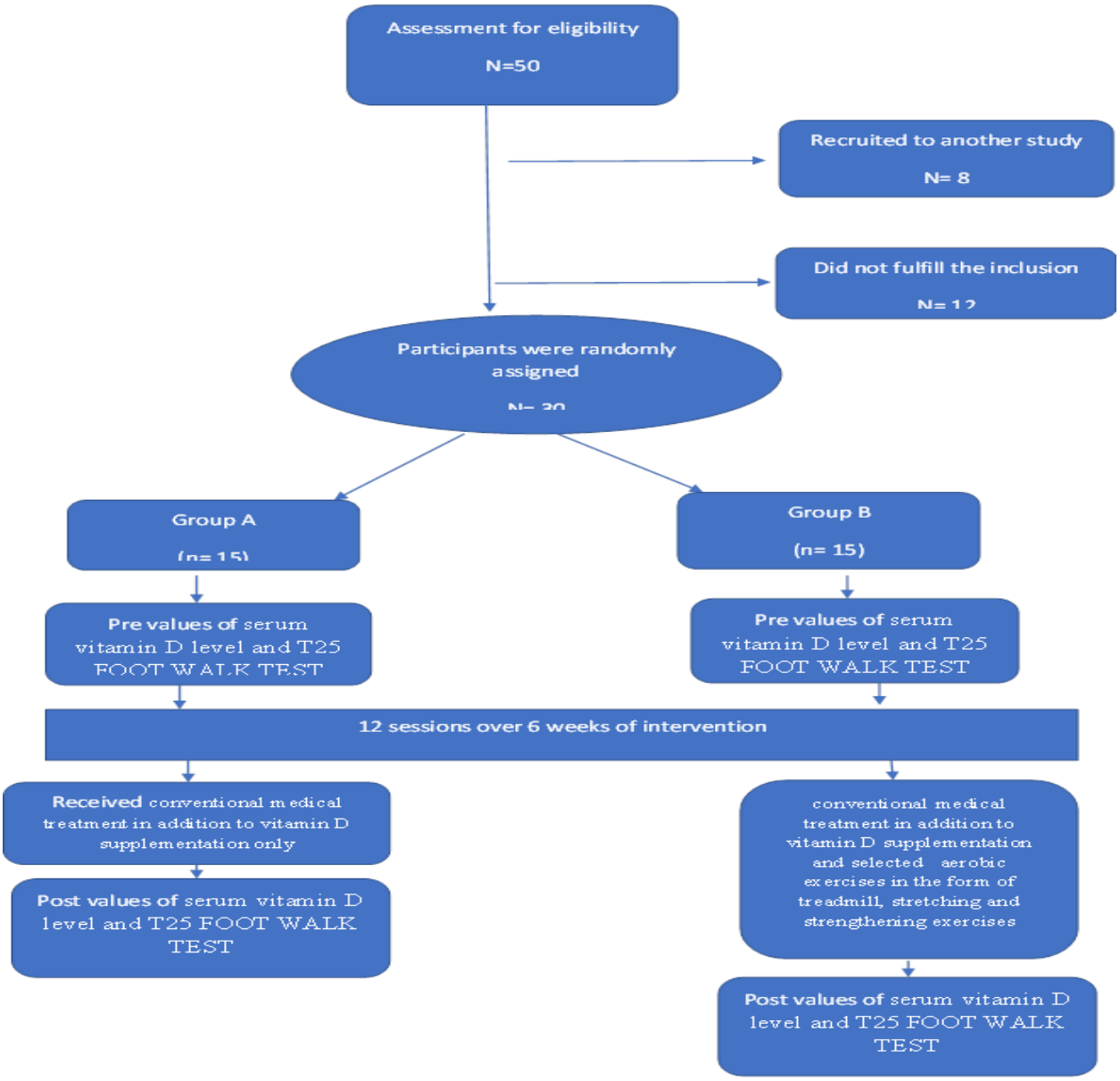

Figure 1: Flowchart of the study

Trial 2

After completing the first timed walk, position the patient in standing just behind the line, repeat the same instructions, and have the patient complete the walk again.

Stretching exercises for the muscle group

Stretching for hip flexors/extensors, knee flexors/extensors, ankle dorsiflexors/invertors/evertors using Thomas test stretch for hip muscle flexors, straight leg raising for hamstring muscles stretch, soleus and gastrocnemius muscles stretch, stretch of ankle invertors and ankle invertors and dorsiflexors while the patient in long-sitting with a towel or belt looped under the foot. The patient pulled on the lateral side of the towel to cause the heel and foot to turn outward (Peeler & Anderson, 2007).

Strengthening exercises

Bilateral strengthening of hip flexors muscles from half crock lying position, by raising lower limb straight forward up to the level of the opposite flexed lower limb from a fully extended lower limb, then lower it down to rest over the plinth and relax (Wagner et al.,2010). Bilateral strengthening of hip extensors muscles from prone position, with proper resistance

was secured around patient's fully extended exercising leg just above the ankle joint posteriorly. The patient raised it straight backward as far they could, held it for 5 seconds, then lowered it gradually and smoothly down (Ayotte et al 2007). Bilateral strengthening of knee flexors started from prone position, and proper resistance was applied just above the ankle joint posteriorly with fully extended lower limb, then patient raised leg backward to 90 degrees of knee flexion, held it for 5 seconds, then rested it back on the bed gradually and smoothly (Wk Lee et al., 2015). Bilateral strengthening of knee extensors was done with the patient siting on bed edge; while feet free from the ground and knee in 90 degrees of flexion. The therapist's hand applied proper resistance just above the ankle joint anteriorly as the patient pushed the therapist hand forward to complete knee extension, held it for 5 seconds, and then returned to the starting position (Beynnon et al., 2005). Strengthening of ankle dorsiflexors and planterflexors started from an erect standing position with weight, as the patient lifted heels and walked several steps on toes then relaxed, and was instructed to discontinue if there was pain in ankle during the exercise. Then to walk several steps on heels, repeat several times until muscle feels tired with increasing a few steps each session (Chinn & Hertel, 2010). Exercises were repeated 25-30 times.

Electrical treadmill for aerobic exercise program:

Zan 800, Germany made**,** provided with control panel to display the exercise parameters, its speed, inclination and timer were adjustable. It was used for aerobic and anaerobic exercise program. Warm up exercises proceeded treadmill by walking on the treadmill for 5 minutes at a speed of 1.5 KM/HR with zero inclination. During the active phase the duration gradually increased from 10 to 20 minutes while walking with 2 inclinations. It was repeated 2 to 3 times per week for 6weeks with an intensity of 60-80% of maximal heart rate (Leonard et al, 2017). Cooling down followed after the active phase in the form of walking on the treadmill for 5 minutes at speed of 1 KM/HR with 2 inclinations and gradually decreasing speed until zero as adapted from (Abd El Kader & Sedrak, 2009).

statistical Analysis

Subject characteristics were compared between both groups using t-test. Chi- squared test was used for comparison of sex distribution between groups. Mann–Whitney U test was conducted for comparison of EDSS between groups. Normal distribution of data was checked using the Shapiro-Wilk test for all variables. Levene's test for homogeneity of variances was conducted to test the homogeneity between groups. Mixed MANOVA was performed to compare the effects of treatment on vitamin D and timed 25 walk test between the group A and B as between group comparison and between pre and post treatment in each group as within group comparison. Post-hoc tests using the Bonferroni correction were carried out for subsequent multiple comparison.

RESULTS

Subject characteristics

Table 1 showed the subject characteristics of both groups. There was no significant difference between both groups in the mean age, weight, height and BMI ($p > 0.05$). Also there was no significant difference in sex distribution between groups ($p = 0.68$).

Table 1. Comparison of subject characteristics between group A and B.

	Group A	Group B	
	$\bar{x}$±SD	$\bar{x}$±SD	p- value
Age (years)	30.06 ± 4.77	29.4 ± 6.37	0.74
Weight (kg)	65.53 ± 7.04	63.5 ± 7.77	0.45
Height (cm)	166.33 ± 7.13	165.06 ± 7.04	0.62
BMI (kg/m²)	23.81 ± 3.31	23.36 ± 2.88	0.69
EDSS, Median	4	4	1
Males/females	6/9	4/11	0.43

$\bar{x}$, Mean; SD, standard deviation; p value (Probability value)

Effect of treatment on vitamin D and timed 25 walk test:

Mixed MANOVA revealed that there was a significant interaction of treatment and time ($F = 40.06$, $p = 0.001$). There was a significant main effect of time ($F = 250.24$, $p = 0.001$). There was a significant main effect of treatment ($F = 10.86$, $p = 0.001$).

Within group comparison

Both groups showed significant increase in serum vitamin D level post treatment compared with that pre-treatment ($p < 0.001$). There was a significant increase in timed 25 walk test in the group A post-treatment compared with that pre-treatment ($p < 0.001$), however, there was no significant difference in timed 25 walk test in the group A in pre and post treatment ($p = 0.09$) (Table 2).

Between group comparison

There was no significant difference between group A and B in all variables pre-treatment ($p > 0.05$). There was a significant increase in serum vitamin D level and timed 25 walk test of group B compared with that of group A post- treatment ($p < 0.01$) (Table 2).

DISCUSSION

Our results revealed that the control and experimental groups had significant improvement in post treatment outcome measures (serum vitamin D level, timed 25foot walk test), although the improvement was more significant in the experimental group (B). This variation in the amount of improvement between the two groups was due to the effect of selected aerobic exercises in improving lower limb muscle strength.

Table 2. Mean serum vitamin D and timed 25 walk test in group A and B.

	Pre treatment			Posttreatment				
	Group A	Group B	p value	Group A	Group B	p value	Pre vs post (group A) p value	Pre vs post (group B) p value
	x̄±SD	x̄±SD		x̄±SD	x̄±SD			
Serum vitamin D (ng/ml)	20.47±4.08	21.33±3.3	0.52	25.2±4.24	31.86±2.7	0.001	0.001	0.001
Timed 25 walk test (sec)	85.26±9.64	84 ± 8.84	0.71	83.2±9.47	74.33±8.48	0.01	0.09	0.001

x̄, mean; SD, standard deviation; p-value, level of significance <0.05.

Studies investigating the role of vitamin D supplementation with aerobic exercise in MS are conflicting and no consensus has been reached regarding the use of vitamin D (Sintzel et al., 2018). The purpose of this study was to investigate the influence of selected aerobic exercises on serum vitamin D level in patients with early stage of multiple sclerosis and lower limb performance. Although current research indicates that MS patients can gain a wide variety of therapeutic and functional benefits from regular activity, the influence of exercise on the progression of MS symptoms remains unclear and additional studies are warranted (White and Dressendorfer, 2004).

According to our knowledge, this was the first study that evaluated the effect of combined vitamin D supplementation with aerobic exercises versus vitamin D supplementation only in patients with early stage of multiple sclerosis.

Effect of vitamin D supplementation on MS

In several studies, low vitamin D serum levels have been associated with an increased relapse rate, increasing disability and an increased lesion load, as seen on magnetic resonance imaging (MRI) (Fitzgerald et al., 2015; Smolders et al., 2019 and Ascherio et al., 2014).

Various experimental settings have implied that Vitamin D receptors especially for 1. 25 dihydroxy vitamin D are present on various cells of the immune system like macrophages and activated T and B cells. The stimulation of these receptors in vitro causes inhibition of inflammatory cytokines production. In a recent study in MS patients, vitamin D supplementation reduces IL-2 mRNA levels in peripheral blood mononuclear cells. They also promote development of regulatory T cells and correlation also has been demonstrated between serum 25-hydroxyvitamin D levels and a more anti-inflammatory ratio of T helper cells type 1 and type 2 (Th1/Th2). Apart from MS a more diffuse protective role of Vitamin D against a variety of inflammatory diseases such as rheumatoid arthritis, type 1diabetes and systemic lupus erythematosus is becoming evident. In MS, the immunomodulation by 1, 25hyroxyvitamin D, can reduce severity by inhibiting proinflammatory cells and increasing anti-inflammatory cells. Further modification in cytokine profile may reduce inflammation and have been demonstrated in MS patients following dietary intake of vitamin D (1000 IU/ day) plus calcium (800 mg/day). However, more studies are essential to identify the exact effect of vitamin D on MS pathology (Harandi et al., 2012).

Our results were in harmony with a preliminary Iranian study conducted by Etemadifar and Janghorbani, 2015 that assessed the safety and efficacy of high-dose vitamin D supplementation in women with MS. The authors advocated for adding high-dose vitamin D3 supplementation to the routine care of women with MS.

Also, according to Hupperts et al., 2017, a high sample randomized, double-blind, placebo-controlled, multicenter, phase 2 studies found no differences between low versus high vitamin D groups for other clinical parameters such as EDSS.

Similarly, Ascherio et al. (2014) found that increase in 25(OH) D levels was associated with a reduction of 0. 16 steps in the average EDSS. The annualized change in EDSS was lower among patients with high vitamin D levels as compared with those low vitamin D levels.

Also, Soilu-Hänninen et al., 2012 conducted a 1-year, randomized, double-blind, placebo-controlled trial with vitamin D3 in patients with MS. They found that, there was a tendency toward reduced disability accumulation as measured by EDSS and toward improved timed tandem walk.

In line with the current study, the CHOLINE trial evaluated the effect of high-dose vitamin D (100, 000 IU every other week) versus a placebo in 96 weeks. They observed a lower progression of EDSS in the vitamin D group but no statistical difference between the two groups (Camu et al., 2019).

On the contrary, Zheng et al., 2018 that conducted a meta-analysis to evaluate the efficacy of vitamin D supplementation in MS patients, no significant beneficial effect on EDSS was found.

In regard to this, Martínez-Lapiscina et al., 2020 conducted a meta-analysis of six studies in 2019 where the effect on EDSS progression was reviewed, and effect of vitamin D supplementation on disability progression was nonsignificant.

Also, Mosayebi and colleagues, 2011 evaluated in a prospective study the effects of vitamin D3 supplementation at a dose of 300, 000 IU/month versus placebo in a randomized trial. They did not find any differences between groups on EDSS.

Effect of Exercise on Vitamin D in MS

Exercise and physical activity are considered as the most effective, non-pharmacological interventions in MS. However, little is known about the underlying mechanism and the role of vitamin D coordinating these adaptations. This was explained by observation of improving vitamin D status with

modest lifestyle modifications as recently suggested. The National Health and Nutrition Examination Survey (NHANES III) reports indicated that physical activity is related to serum 25(OH)D3 either due to enhanced vitamin D metabolism or increased sun exposure. Wanner et al. reported significantly higher levels of 25(OH)D3 in those who exercised outdoors than in those who exercised indoors (Wanner et al., 2015).

Recently, studies have demonstrated primary exercise benefits of improved balance and increased walking capacity, with secondary benefits of reduced fatigue, enhanced mood, improved Quality of Life (QOL), and decreased perceived disability immediately following an 8-week strength-training program and an aerobic exercise intervention in patients with multiple sclerosis. Despite the demonstrated benefits, mild attrition in exercise intervention studies is a concern that raises a question about the feasibility of exercise programs for people with MS regardless of any primary or secondary benefits (Swank et al., 2013).

Moreover, it was reported that exercise training is associated with systemic anti-inflammatory effects, with a reduction in pro-inflammatory markers such as IL-6 and TNF-α in plasma which may be cause vitamin D deficiency in MS cases (Lira et al., 2009).

Our results were supported by many studies showings that, walking speed improved following combined or isolated aerobic or resistance training, (Cakit et al., 2010; Van den Berg et al., 2006; Dalgas et al., 2009; Romberg et al., 2004 and Motl et al., 2012).

This was also proved by, Aly et al., 2016 who revealed that swimming exercise in diabetic rats was effective in improving vitamin D status resulting in significantly higher serum vitamin D levels associated with increased vitamin D receptors in muscle, pancreas and adipose tissue.

Additionally, in our current study, regarding the timed 25 walk test, although, the mean difference in timed 25foot walk test between group A and B pretreatment was non-significant, there was a significant decrease in the timed 25 walk test of the group A post treatment compared with that of group B.

White et al., 2004 reported that 8 weeks of twice weekly progressive lower limb resistance training improved leg strength, stepping ability and reduced fatigue while also favorably altering gait.

And another similar study by DeBolt and McCubbin, 2004 founded that 8 weeks of home-based lower body resistance training with elastic bands improved leg extensor power.

On the other hands, pooled data from four studies using the 204 T25FW (s) demonstrated a small but non-significant improvement, as a result of exercise (Carter et al., 2014; Learmonth et al., 2012; Oken et al., 2004 and Tarakci et al., 2013).

Similar finding was observed by **Aivo et al., (2012)** study on patients with vitamin D arm compared to placebo. There was no change in measured EDSS (Expanded Disability Status Scale), & timed 25-foot walk (T25FW), among both groups post treatment.

Aerobic exercises and vitamin D

Hypovitaminosis D causes changes to muscle fibres due to its role within musculoskeletal functions. A deficiency causes large interfibrillar spaces and muscular infiltration of fat, leading to muscular atrophy and changes in muscle type. Whilst vitamin D supplementation significantly increase the diameter and number of type II muscle fibres (Sinha et al., 2013).

Data reporting, optimal 25(OH)D is essential for healthy muscle tissues and may enhance muscle strength. Most research has investigated the role of vitamin D on resistance exercise; however, there is a paucity of evidence reporting whether 25(OH)D affects aerobic exercise. 1, 25(OH)D affects cardiac muscles directly and although 25(OH)D deficiency has been associated with hypertension, there is conflicting evidence regarding the effects of 25(OH)D on blood pressure in normotensive individuals (Ferrington et al., 2016)

Recommendation

More research should be conducted to confirm the using of the selected aerobic exercises in patients with MS, further studies should compare the effect of selected aerobic exercises with different treatment techniques on serum vitamin D level and lower limb performance in MS patients, to investigate the effect of aerobic exercise alone and the long – term follow up of selected aerobic exercises.

CONCLUSION

Selected aerobic exercise is an effective physical therapy modality that may provide better outcomes for a patient with deficient vitamin D and lower limb performance in multiple sclerosis.

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DECLARATION OF COMPETING INTEREST

None, the authors have no competing interests.

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