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Effects of Exercise on the Progression of Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) has a vast array of clinical presentations, yet the science of its pathophysiology has not evolved adequately to target or prevent the sequelae of the disease. What is known, however, is that MS is a chronic inflammatory and neurodegenerative disease of the central nervous system due to demyelination of the axons of white matter resulting from infiltration of lymphocytes and astrocytes. [1] This axonal loss leads to the neurologic and constitutional (or systemic) deficits: visual disturbances, tremors, weakness, fatigue, cognitive impairment, depression/anxiety, poor motor control, and overall very poor quality of life from reduced mobility. [2] The associated inflammation and degeneration is hypothesized to be caused by high imbalance of cytokine activity and disturbances in the blood-brain-barrier (BBB). [3] This pathophysiologic process causing high levels of inflammation, eventually leads to scarring of the neurons, producing plaques on brain MRI (magnetic resonance imaging), which assists in diagnosing MS. All these harmful sequelae are not only debilitating, but also significantly increase the risk of developing comorbidities in addition to direct neurologic damages. This progressive destruction of the CNS promotes a vicious cycle resulting in negative health effects.

The disease and its severity vary substantially among individuals. This disparity is partly due to the different subsets of multiple sclerosis. MS is divided into relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing. This variability in MS leads to difficulties channeling treatment modalities that help all individuals. Relapsing-remitting MS (RRMS) is a main focus of research to date because it is one of the few subtypes that has pharmacologic treatments (including corticosteroids and other biologic medications) which target the relapse phase. However, pharmacologic therapy poses other difficulties because not all medications have been shown to be beneficial and each has its own risks. Besides pharmacologic treatments, other therapies are being sought for the treatment of symptoms and disease progression. Not all have been successful. So, apart from pharmacotherapy, what other therapies are effective for the prevention and/or mitigation of symptoms and disease progression in MS? Recent research is revisiting exercise as a treatment modality. In healthy persons it decreases inflammation and works similarly in patients with MS while also decreasing all the negative side effects of inflammation and neurodegeneration. Nevertheless, MS patients have long been advised to refrain from physical exercise. The advice stemmed from the misconception that symptoms tended to transiently worsen when the body temperature increased. [4] These apparent conflicting findings underlie the need to explore how aerobic/anaerobic exercise compared to sedentary lifestyles influence the quality of life and progression of MS over an individual's life span.

Indeed, physical exercise may be proven beneficial for MS patients. Moreover, exercise has other health benefits. Hence, it could become a highly recommended treatment that would deserve a high priority among therapeutic options. Many patients with MS are not informed about adjunctive treatment options such as exercise for reducing disease severity and progression.

Discussion

The evidence thus far, has confirmed that exercise has a surplus of benefits for patients suffering from MS. Overall the most consistent findings have been improvements in gait, fatigue, cognition and cardiopulmonary function. [5, 6] In the randomized control trial by Giancario et. al, evaluating fatigue and cognitive function with aerobic and anaerobic training. There were significant improvements in motor function, cognition, cardiopulmonary function, and decreased fatigue. Although these findings are slightly limited by the small sample size. Benefits from exercise have been shown to be independent of an **i**ndividual**'s** weight or baseline physical capacities before exercise routines began. [7] These findings were evidenced by a single randomized control trial by Negaresh et al, evaluating depression, fatigue, cognition in an 8-week aerobic training program, with regards to baseline weight status. These benefits notwithstanding some of the most debilitating factors in patients with MS, other than physical impairments, are the reduction in cognition and the persistent fatigue. [1] The diminished cognitive faculty can be a severe burden when patients attempt to accomplish everyday tasks. [6] Fifty percent of patients with MS experience fatigue at least once a week, which is chiefly due to the disease process, but also partly due to the pharmacologic treatments that are commonly prescribed. [7] As the disease progresses and the older the individuals are, the worse both cognitive decline and fatigue become. [6] The declines are what prompted a systematic review of clinical trials by Sokolov et al, comparing different interventions and their impact on fatigue and cognition. Exercise, especially in a multimodal approach, was shown to be superior to pharmacologic therapy to mitigate those symptoms. Further advancements in technology will be able to solidify this evidence further by evaluating cognition more in depth. Data from testing the effects of exercise on cognition have been promising. Learning/memory as assessed by specific cognition tests (viscoelasticity of brain tissue in the hippocampus as measured by magnetic resonance elastography or MRE) and fatigue levels as determined by VO2 all showed significant improvements in a pilot study by Sandroff et al, after a 12-week aerobic exercise program guided by ACSM. [8] This study has the limitation of technology for more insight into the changes that occur. Fatigue has also been shown to decrease when assessed using the fatigue severity scale after exercise, in a blind randomized control trial by Negaresh et al. Measurements of fatigue were done after completing as little as an 8-week interval training program of exercise 3 days a week. There were significant improvements in mood, fatigue, motor performance. [7] These findings are independent of weight status prior to the trial, however, a longer duration study would be needed to strengthen the evidence. With this short duration of exercise producing such favorable results, it would be interesting to investigate how much improvement could be derived from exercise over a longer period of time.

In addition to memory and fatigue, other indicators of disease remission and progression provide insight about the benefits of exercise. Pathophysiologic markers associated with MS, including imbalances in neurotrophic factors, and levels of BBB markers that reflect disease severity, are useful tools for this purpose. In a recent systematic review by Negaresh et al, reviewing effects of exercise on pathophysiological biomarkers in MS individuals indicate exercise can reduce said markers, improve brain function and integrity, provide a neuroprotective effect, and significantly reduce inflammatory markers. [9.] Due to inclusion criteria, it's difficult to find a substantial number of studies that qualify. More studies are needed to validate the information further. Inflammation in MS is known to be partly due to higher cytokine levels. Exercise has been shown to mildly lower leptin and TNF (tumor necrosis factor) levels, which are increased in patients (or persons) with chronic inflammation from any disease state. This was shown in a randomized control trial by Majdinasab et al, investigating response of various cytokines and adipokines in response to acute aerobic exercise, with levels being examined at hour 1 and hour 6 post exercise. Limitations of the study include cytokine measurements only taken from serum as well as the timing of the sample measurements. These findings indicate that exercise can act as an anti-inflammatory agent, thus achieving one of the main goals of treatment in MS patients. [3]

Another malady due to MS is poor respiratory health, which. has been shown to contribute to sedentary behavior and can discourage MS patients from participating in physical activity. Respiratory muscles improve with exercise as well, which then improves fatigue and overall quality of life. This statistically significant finding was revealed in a quasi-experimental study evaluating respiratory strength, fatigue, quality of life, and functional performance after a five-week training program of combined progressive resistance respiratory muscle therapy. [10] Although individual's baseline differences were variable in this study, these findings are favorable.

All these findings mentioned thus far, were from studies that focused on combined exercise training programs or just mild aerobic activity. Since then, significant findings emerged from studies that evaluated aerobic and anaerobic exercise separately. Results from evaluating each type of exercise separately indicated the importance of incorporating a mixed exercise program. Different effects are produced by aerobic and anaerobic exercises. Aerobic activity has been shown to improve the immune system as evidenced by evaluation of T-cell changes (increases CD39 cells and decrease in their counterparts CD31 cells) in a controlled, single blind, randomized control trial by Mahler et al. Thus, improving the immune system in an immunocompromised person.[11] Anaerobic workouts improve energy metabolism by increasing fatty acid oxidation.[11] Significant improvements in depression and cholesterol levels from both anaerobic and aerobic training were also found in evaluating individuals under hypoxic conditions. Thus, the effects of exercise help fight against acute health problems while also preventing chronic comorbidities. Again, duration of study is a limitation but findings are consistent with exercise improving many aspects of these patients' lives overall.

Lastly, data reflecting neuroprotection were found with activities such as walking and running on the treadmill. In a 2016 randomized control study investigating aerobic exercise and its neuroprotective capabilities, the findings indicate these exercise modalities increase brain-derived neurotrophic factor (BDNF) levels. Because BDNF serves as a neuroprotective mechanism, increasing or maintaining its level is crucial for preventing the progression of MS. The increase in cytokines associated with MS already decreases BDNF significantly. BDNF levels increased about 10% after a 24-week exercise intervention program compared to the group that was sedentary.[12] This same study also measured results from combined resistance and endurance training, showing improvements in muscle strength and mobility. Individuals were much more capable and stable in just performing walking tests.[12] Improvements in mobility and strength indicated that not only is exercise safe for patients with MS, but also that being sedentary can actually speed up the disease process and contribute to the inflammation and degeneration.

Among the experimental and systematic reviews, studies on mice are available. These experiments, while not as convincing as human studies, still indicate promising results. One evaluated mice with autoimmune encephalitis. This disease process is similar to the infiltration and demyelination associated with MS. Exercise was shown to delay the disease onset and the rise in disability scores in mice who exercised compared with mice that were sedentary as evidenced by observation of their behavior or physical condition and by evaluation their white and gray matter. [1]

Summary

Overall, the evidence to date indicates that exercise mitigates the manifestations of multiple sclerosis, not only by reducing symptoms but also by harnessing a neuroprotective effect, which attenuates the neurodegeneration. This conclusion has been derived from experimental studies and systematic reviews that incorporated various means of measuring cognitive and physiologic benefits, including imaging, blood samples and multiple surveys/exams. Because MS is not completely understood at the cellular level, the studies themselves have not been able to target everything at the cellular level. Research on the effects of exercise on MS is ongoing and additional results should provide further insight. Nonetheless, MS is a very intricate and complex disease process. It will take time to further understand how and what specific exercise modalities will prove to be the most beneficial and provide the most neuroprotection. Many of these studies had some limitations, the most common one being small sample sizes. Another weakness was the short duration of follow up. It's very difficult to enroll large sample sizes and to monitor participants for long periods of time. Furthermore, many of the studies examined RRMS patients and did not evaluate the other subsets of MS, thus limiting the generalizability of the findings. These limitations notwithstanding, all studies had similar exercise modalities, such as treadmill walking/running and upper/lower body cycling, which was a strength.

In view of the limited evidence, further investigation is needed to confirm the neuroprotective effects and the reductions in the overall negative effects of MS with increased understanding of the disease pathophysiology at a cellular level. Long term studies are needed as well to evaluate reduction in the disease progression and severity. Larger sample sizes and sampling from different subsets of MS patients will be needed as well to increase the validity and generalization of the results. Some studies even suggested using a broader version of initial disability scales that range from mildly disabled and severely disabled in order to measure the varying effect from exercise.[3]

Conclusion

Aerobic and anaerobic exercise, both providing different benefits, are crucial for optimal care of MS patients and should be part of the practitioner's treatment plan. Many patients with MS are left without many options. If exercise is implemented early in the disease, the patient's quality of life can improve and associated debility can be minimized. Exercise prescriptions can be initiated by providing referrals for supervised physical activity after determining the patient's baseline limitations, which vary from individual to individual. Many studies have already been initiated to further investigate all ~~of~~ the current findings and affirm the importance of exercise as a treatment tool. Unless an individual has a specific contraindication to exercise, some form of exercise should be started.

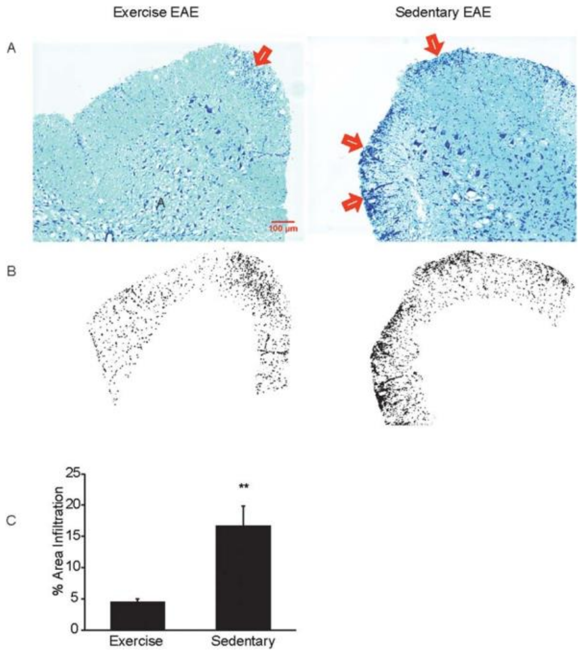

Figure A: Shows the ventral region of the lumbar spinal cord in mice comparing exercise vs. sedentary behavior. Figure B: Shows ventral white matter tracts. Figure C: indicates the amount of infiltration in exercise vs. sedentary mice [1].

REFERENCES

1. Pryor WM, Freeman KG, Larson RD, Edwards GL, White LJ. Chronic exercise confers neuroprotection in experimental autoimmune encephalomyelitis. *Journal of Neuroscience Research*. 2015;93(5):697-706. doi:10.1002/jnr.23528.
2. Guillamó E, Cobo-Calvo Á, Oviedo GR, et al. Feasibility and Effects of Structured Physical Exercise Interventions in Adults with Relapsing-Remitting Multiple Sclerosis: A Pilot Study. *Journal of Sports Science & Medicine*. 2018;17(3):426-436. http://search.ebscohost.com.pacificatclassic.pacific.edu/login.aspx?direct=true&db=a9h&AN=131385245&site=ehost-live. Accessed June 14, 2019.
3. Majdinasab, N., Motl, R., Mokhtarzade, M., Zimmer, P., Ranjbar, R., Keytsman, C., Cullen, T., Negaresh, R. and Baker, J. (2018). Acute responses of cytokines and adipokines to aerobic exercise in relapsing vs. remitting women with multiple sclerosis. *Complementary Therapies in Clinical Practice*, 31, pp.295-301.
4. Gold SM, Schulz K-H, Hartmann S, et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. *Journal of Neuroimmunology*. 2003;138(1-2):99-105. doi:10.1016/S0165-5728(03)00121-8.
5. Giancario Coghe, F. C. (2018). Fatigue, as measured using the Modified Fatigue Impact Scale, is a predictor of processing speed improvement induced by exercise in patients with multiple sclerosis: data from a randomized controlled trial. *Journal of Neurology*, 1328-1333.
6. Sokolov AA, Grivaz P, Bove R. Cognitive Deficits in Multiple Sclerosis: Recent Advances in Treatment and Neurorehabilitation. *CURRENT TREATMENT OPTIONS IN NEUROLOGY*. 20(12). doi:10.1007/s11940-018-0538-x.
7. Negaresh R, Motl R, Mokhtarzade M, et al. Effect of Short-Term Interval Exercise Training on Fatigue, Depression, and Fitness in Normal Weight vs. Overweight Person With Multiple Sclerosis. *EXPLORE*. 2019;15(2):134-141. doi:10.1016/j.explore.2018.07.007.
8. Sandroff BM, Johnson CL, Motl RW. Exercise training effects on memory and hippocampal viscoelasticity in multiple sclerosis: a novel application of magnetic resonance elastography. *Neuroradiology*. 2017;59(1):61-67. doi:10.1007/s00234-016-1767-x.
9. Negaresh, R., Motl, R., Zimmer, P., Mokhtarzade, M. and Baker, J. (2019). Effects of exercise training on multiple sclerosis biomarkers of central nervous system and disease status: a systematic review of intervention studies. *European Journal of Neurology*, 26(5), pp.711-721.
10. Ray AD, Udhoji S, Mashtare TL, Fisher NM. A Combined Inspiratory and Expiratory Muscle Training Program Improves Respiratory Muscle Strength and Fatigue in Multiple Sclerosis. *Archives of Physical Medicine and Rehabilitation*. 2013;94(10):1964-1970. doi:10.1016/j.apmr.2013.05.005.
11. Mähler A, Balogh A, Csizmadia I, et al. Metabolic, Mental and Immunological Effects of Normoxic and Hypoxic Training in Multiple Sclerosis Patients: A Pilot Study. *Frontiers in Immunology*. 2018;9. doi:10.3389/fimmu.2018.02819.

12. Wens I, Keytsman C, Deckx N, Cools N, Dalgas U, Eijnde BO. Brain derived neurotrophic factor in multiple sclerosis: Effect of 24 weeks endurance and resistance training. *European Journal of Neurology*. 2016;23(6):1028-1035. doi:10.1111/ene.12976.