Effect of low-intensity aerobic cycling ergometer on disease severity and depression of patients with myasthenia gravis in “Dr. Soetomo” General Hospital Surabaya

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Short Running Title: Low-intensity Aerobic Cycling Ergometer Improves Disease Severity and Depression in Myasthenia Gravis

TITLE: Effect of Low-intensity Aerobic Cycling Ergometer on Disease Severity and Depression of Patients with Myasthenia Gravis in Dr. Soetomo General Hospital Surabaya

ABSTRACT

Background and Objectives: Myasthenia gravis (MG) is a chronic autoimmune disease characterized by muscle weakness. Muscle weakness leads to impairment of daily activities and leads to psychiatric symptoms, including depression. The lack of exercise methods in MG patients is a problem in rehabilitation. This study evaluates the effect of an 8-week low-intensity aerobic exercise program on Myasthenia Gravis Composite (MGC) and Beck Depression Inventory (BDI) scores in MG patients.

Materials and Methods: This is a randomized controlled trial conducted from May to June 2023. Twenty subjects were randomly divided into treatment group and control group. The treatment group received low-intensity aerobic exercise with cycle ergometer 3 sessions per week for 8 weeks. Both groups were informed about lifestyle changes and effective breathing exercises. MGC and BDI scores were measured and compared before and after intervention.

Results: In the treatment group, MGC and BDI scores was significantly decreased with strong effect size after 8 weeks (5.4 ± 2.32 to 2.4 ± 1.84, *p* = 0.001, Cohen's D = 1.57; and 10.4 ± 2.88 to 5.9 ± 2.77, *p* = 0.001, Cohen's D = 1.86). In the control group, MGC and BDI scores were not significantly different (5.4 ± 2.68 to 6.0 ± 2.49, *p* = 0.193, Cohen's D = 0.44; and 10.4 ± 1.71 to 9.6 ± 1.65, *p* = 0.247, Cohen's D = 0.39). The MGC score strongly correlated with the BDI score (r = 0.50).

Conclusion: 8 weeks of low-intensity aerobic exercise with cycling ergometer reduces disease severity and depression severity in myasthenia gravis.

Keywords: Aerobic exercise, cycle ergometer, myasthenia gravis, depression, neuromuscular disease.

Abbreviations: Myasthenia gravis (MG), Myasthenia Gravis Foundation of America (MGFA), Myasthenia Gravis Composite (MGC), Beck Depression Inventory (BDI), Montreal Cognitive Assessment Score Indonesia Version (MoCA-INA), Joint National Committee (JNC), New York Heart Association (NYHA), Wong Baker Faces Scale (WBFS), Early Onset Myasthenia Gravis (EOMG), Late Onset Myasthenia Gravis (LOMG), Respiratory Muscle Training (RMT), Force Vital Capacity (FVC), Force Expiratory Volume in One Second (FEV_1), Body Mass Index (BMI), Quantitative Myasthenia Gravis (QMG)

TITLE: Effect of Low-intensity Aerobic Cycling Ergometer on Disease Severity and Depression of Patients with Myasthenia Gravis in Dr. Soetomo General Hospital Surabaya

INTRODUCTION

Myasthenia gravis (MG) is a chronic autoimmune disease with an incidence of 1 to 2 per 10,000 population. Typical clinical symptoms of MG are muscle weakness that fluctuates due to antibody activity in neuromuscular junction[1]. Weakness of these muscles affects the severity of MG patients and decreases functional capacity[2]. Although fatigue in patients with MG correlates with the ability to perform ADL, there was no significant correlation between fatigue and walking and no between functional capacity and quality of life in MG patients[3–5]. MG patients show varying severity, the higher the severity, the higher the possibility that the patient has myasthenia crisis which can lead to death[6]. Myasthenia crisis is a severe and life-threatening condition characterized by generalized muscle weakness with a respiratory compromise that requires ventilatory support[7].

Assessment of the severity of MG is developed to evaluate the patient's clinical condition and response to intervention (treatment or exercise). In 2012, the Myasthenia Gravis Foundation of America (MGFA) recommended the use of the Myasthenia Gravis Composite (MGC) scale in evaluating daily practice to assess the severity of the disease[8]. The MGC scale is an assessment that combines objective assessment by the examiner with subjective reporting by the patient. The MGC scale provides a better assessment of all degrees of severity with a validated assessment score[9].

Patients with myasthenia gravis often complain of psychiatric symptoms. All chronic diseases, including MG have a psychological impact on patients, such as anxiety and depression. Limitations of activity due to muscle weakness and fatigue in MG patients make it difficult for patients to do activities outside the home and in everyday life are the causes of these psychiatric symptoms[10]. Other causes such as unstable MG symptoms, long term duration of disease and long term treatment, especially the use of steroids, are thought to worsen the depression in MG patients[10,11]. There is relationship between the symptoms of depression and the severity of the disease in MG patients, especially during exacerbations and the development of the disease in which MG patients with dysphagia, dysphonia and the crisis of myasthenia gravis have higher levels of depression and anxiety disorders[11]. Measurement tools that are widely used to identify depression symptoms was Beck Depression Inventory (BDI) developed by Beck in 1976. BDI are shown by a scale that displays 21 symptoms of depression. The higher the score of BDI, the worse the symptoms of depression and vice versa[12].

Physical exercise in MG patients, especially aerobic exercise can increase muscle strength, reduce fatigue, and improve the severity and psychological status of MG patients[13]. Aerobic exercise with cycle ergometer for 8 weeks shows a decrease in depression status and MGC scale in MG patients[13,14]. Eight weeks of light-intensity cycle ergometer aerobic exercise improves the functional and aerobic capacity of adult MG patients[15].

There is still a lack of high-quality evidence regarding the effectiveness of aerobic exercise for MG patients[16,17]. This study objective was to analyze effect of low-intensity aerobic exercise using cycle ergometer to the severity of the MG and degree of depression in MG patients.

MATERIALS AND METHODS

This study is a randomized controlled trial with pre-test and post-test group study design. This study conducted at the Medical Rehabilitation Outpatient Clinic at Dr. Soetomo General Hospital, Surabaya, Indonesia from April to June 2023. Ethical clearance for this study was issued by Hospital Ethical Committee with ethical clearance number 0601/KEPK/II/2023.

The subjects of this study were 20 MG patient obtained using consecutive sampling. Inclusion criteria for this study were: 1) confirmed myasthenia gravis patients class I - IIb based on MGFA, 2) Men or women aged 18-59 years, 3) cooperative patients, 4) normal cognitive function (Montreal Cognitive Assessment Indonesia Version / MoCA-INA Score ≥ 26), 5) receive myasthenia gravis treatment at Dr. Soetomo General Hospital, 6) able to do low-intensity aerobic exercise with a cycle ergometer for 30 minutes, 7) willing to join the study and sign the informed consent, 8) given approval by neurologist to join the study. The exclusion criteria were: 1) myasthenia crisis, 2) currently undergoing a routine aerobic exercise program 2-3x/week in the last 1 month, 3) history of cardiorespiratory disease (ischemic heart disease, resting heart rate ≥ 120, stage II hypertension according to the Joint National Committee (JNC) VII criteria with systolic blood pressure > 160 mmHg, arrhythmia, heart failure class II-IV according to the New York Heart Association (NYHA) criteria, and uncontrolled restrictive or obstructive airway disease), 4) history of systemic disease (kidney failure, liver disease such as liver cirrhosis, uncontrolled diabetes mellitus with random blood sugar levels < 80 or > 250 mg/dL), 5) Static and dynamic sitting balance disorders, 6) being pregnant, and 7) pain in the lower limbs with Wong Baker Faces Scale (WBFS) > 4 which interferes with ambulation. Criteria for drop out were: 1) subject is not willing to continue for any reason, 2) subject unable to finish the exercise in two consecutive sessions, 3) subject is absent from training more than 2 times consecutively or more than 20% of total attendance (maximum 3 absences from training), 4) subject's condition is worsening (signs of myasthenic crisis or being classified as myasthenia gravis class III or more based on the MGFA), and 5) subject died. Simple randomization performed to divide subjects into treatment group and control group with 10 subjects in each group.

The treatment group received low-intensity aerobic exercise using a cycle ergometer, education about lifestyle changes, and effective breathing exercises. Subjects were introduced to the training protocol in the first session. The intervention in this study performed in 3 sessions every week for 8 weeks with the duration of each exercise being 30 minutes, consist of warming up 5 minutes, core 20 minutes and cooling down 5 minutes. Intensity of aerobic exercise measured using Target Heart Rate (Heart Rate Rest + 30% Heart Rate Rest) with an activity level of 11 – 12 on the BORG scale. The control group received education about lifestyle changes, and effective breathing exercises. The MGC and BDI scales were measured before the intervention and after 8 weeks of the intervention in both groups. A comparison of MGC scores and BDI scores was carried out in each group and in both groups before and after 8 weeks of intervention. Data analyzed using SPSS version 26. Paired t test used to compare the MGC and BDI scores within each group before and after intervention. Independent t test used to compare the MGC and BDI scores in the two groups before and after intervention. The p value is considered significant if $p < 0.05$.

RESULTS

The total 20 subjects divided into two groups (treatment and control) with 10 subjects in each group. All subjects were able to complete the exercises until the last session.

No adverse effects were observed in study subjects during low-intensity cycle ergometer exercise.

The average age of subjects in the treatment group was 49.2 ± 5.18 while in the control group it was 45.1 ± 6.33 years with an age range of 36 -54 years. The gender proportion in both groups was similar but majority of the subjects were female (70%). The average Body Mass Index (BMI) in the treatment group was 22.36 ±3.41 kg/m^2 while the control group was 23.49 ±3.57 kg/m^2. In the treatment group, the average age of subjects when diagnosed with MG was 35.80 ± 8.89 years, while in the control group it was 34.5 ± 7.05 years. Based on the MG classification in terms of age of diagnosis, 85% of the subjects (n=17) were Early Onset Myasthenia Gravis (EOMG) type. All subjects had generalized MG type (100%). Based on the MGFA classification, all subjects were class 2 MG type consist of class 2a (4 subject, 20%) and class 2b (16 subject, 80%). The treatment group received MG therapy longer (7.6 ± 3.53 years) than the control group (6.2 ± 3.26 years). Subject characteristics can be seen in table 1.

Table 1. Characteristic of Subject

Profile	Treatment (n=10)	Control (n=10)	Total (n=20)	*p*
Sex (n (%))				
Male	3 (30)	3 (30)	6 (30)	
Female	7 (70)	7 (70)	14 (70)	
Age (years)				
Mean ±SD	49.2 ± 5.18	45.1 ± 6.33	47.15 ± 6.01	0.130[b]
Median (min-max)	49.5 (38-55)	45 (36-54)	48 (36-55)	
BMI (kg/m^2)				
Mean ±SD	22.36 ± 3.41	23.49 ± 3.57	22.92 ± 3.45	0.479[b]
Median (min-max)	23.1 (18-27.6)	23.3 (17.9-29.3)	23.1 (17.9-29.3)	
Age at diagnosis (years)				
Mean ±SD	35.80 ± 8.89	34.5 ± 7.05	35.15 ± 7.84	0.722[b]
Median (min-max)	35 (19-50)	33.5 (20-46)	34 (19-50)	
Type of MG (n (%))				
General	10 (100)	10 (100)	20 (100)	
MGFA classification (n (%))				
Class 2a	2 (10)	2 (10)	4 (20)	
Class 2b	8 (70)	8 (70)	16 (80)	
Onset classification MG (n (%))				
EOMG	8 (80)	9 (90)	17 (85)	
LOMG	2 (20)	1 (10)	3 (15)	
Duration of therapy (months)				
Mean ±SD	7.6 ± 3.53	6.2 ± 3.26	6.9 ± 3.39	0.416[c]
Median (min-max)	7.5 (4-13)	5 (3-12)	5.5 (3-13)	
Dose of Pyridostigmine (mg)				
Mean ±SD	189 ± 103.97	162 ± 75.1	175.5 ± 89.35	0.485[c]
Median (min-max)	180 (60-300)	180 (60-240)	180 (60-300)	
Methyl prednisone (n (%))				
Yes	2 (20)	1 (10)	3 (15)	
No	8 (80)	9 (90)	17 (85)	
Other medicine (n (%))				
No	7 (70)	7 (70)	14 (70)	

Symbicort	1 (10)	0 (0)	1 (5)	
Atorvastatin	1 (10)	1 (10)	2 (10)	
Amlodipine	1 (10)	0 (0)	1 (5)	
Lisinopril	0 (0)	1 (10)	1 (5)	
Furosemide	0 (0)	1 (10)	1 (5)	
Comorbid (n (%))				
No	5 (50)	5 (50)	10 (50)	
Asthma	1 (10)	1 (10)	2 (10)	
Dyslipidemia	1 (10)	2 (20)	3 (15)	
Hypertension	2 (20)	1 (10)	3 (15)	
Valvular Heart Disease	1 (10)	1 (10)	2 (10)	
Thymectomy (n (%))				
Yes	3 (30)	1 (10)	4 (20)	0.582[a]
No	7 (70)	9 (90)	16 (80)	
IPAQ (n (%))				
Mild	4 (40)	5 (50)	9 (45)	
Moderate	6 (60)	5 (50)	11 (55)	
Physical Activity (Minutes/Week)				
Mean ±SD	680 ± 135.04	680.20 ± 142.58	680 ±135.15	0.595[c]
Median (min-max)	735 (510-840)	675 (522-840)	735 (510-840)	

BMI = Body Mass Index; MGFA = Myasthenia Gravis Foundation of America; EOMG = Early-onset MG; LOMG = Late-onset MG; IPAQ = International Physical Activity Questionnaire; METs = Metabolic Equivalent; [a] = Fisher Exact test; [b] = Independent t test; [c] = Mann-Whitney U test.

The average MGC score in the treatment group at baseline was 5.4 ± 2.32. After 8 weeks, there was a decrease in the MGC score by 3 points with an average MGC score of 2.4 ± 1.84. There was a significant difference between the MGC scores in the treatment group at baseline compared to weeks 8 (table 2). In the control group, the MGC score at initial measurement was around 5.4 ± 2.68 points. The control group showed an increase in the MGC score of 0.6 points with a mean MGC score of around 6 ± 2.49. There was no significant difference between the MGC scores in the control group (table 2). Comparison of MGC scores at week 8 between the two groups showed statistically significant results with a strong effect size (table 3).

Table 2. MGC Score within both groups at baseline and week 8

MGC Score	Treatment (n = 10)					Control (n=10)				
	Baseline	Week 8	Delta[#]	p[£]	Effect size[€]	Baseline	Week 8	Delta[#]	p[£]	Effect Size[€]
Mean ± SD	5.4 ± 2.32	2.4 ± 1.84	- 3.0	0.001*	1.57	5.4 ± 2.68	6 ± 2.49	0.6	0.193	0.44
Med (min-max)	6 (2-8)	2 (0-6)			(strong)	5(2-10)	6(2-10)			(weak)

[£]paired t test; [€]Cohen's D; [#]Delta of mean at week 8 and baseline; *p < 0.05 (considered significant)

Table 3. MGC Score between groups at week 8

Group	MGC Score (Mean ± SD)	Delta[#]	p[a]	Effect size[€]
Treatment (n = 10)	2.4 ± 1.84	-3.0	0.002*	1.73 (strong)
Control (n = 10)	6.0 ± 2.49	0.6		

[a]Independent t test; [#]Delta of mean at week 8 and baseline; [€]Cohen's D; *p < 0.05 (considered significant)

The BDI score in the treatment group after 8 weeks decreased by 4.5 points, while the group experienced a decrease of 0.8 points. There was a significant difference between depression scores in the treatment group (p = 0.001) while the control group did not show a significant difference (p = 0.247). The effect size value in the treatment group was 1.86, which means that aerobic cycle ergometer training for 8 weeks had a strong effect on changes in BDI scores, while the effect size value in the control group was 0.39 and had a weak effect on changes in BDI scores (table 4). The effect size value in the treatment group was 1.86, which means that aerobic cycle ergometer training for 8 weeks had a strong effect on changes in BDI scores, while the effect size value in the control group was 0.39 and had a weak size effect on changes in BDI scores (table 4). Comparison of BDI scores at the end of the measurement between the two groups showed significant results (p = 0.002) with a strong effect size value (table 5).

Table 4. BDI Score within both groups at baseline and week 8

BDI Score	Treatment (n = 10)					Control (n=10)				
	Baseline	Week 8	Delta#	p£	Effect size€	Baseline	Week 8	Delta#	p£	Effect size€
Mean ± SD	10.4 ± 2.88	5.9 ± 2.77	- 4,5	0.001*	1.86	10.4 ± 1.71	9.6 ±1,65	- 0.8	0.247	0.39
Med (min-max)	11 (6-14)	6 (2-9)			(strong)	10.5 (8-13)	9 (8-13)			(weak)

£paired t test; €Cohen's D; #Delta of mean at week 8 and baseline; *p < 0.05 (considered significant)

Table 5. BDI Score between groups at week 8

Group	BDI Score (Mean ± SD)	Delta#	*p*a	Effect size€
Treatment (n = 10)	5.9 ± 2.77	- 4.5	0.002*	1.71 (strong)
Control (n = 10)	9.6 ±1.65	- 0.8		

aIndependent t test; #Delta of mean at week 8 and baseline; €Cohen's D; *p < 0.05 (considered significant)

The results of the Pearson correlation between the MGC score and the BDI score show significant correlation (p = 0.023 ; r = 0.505). This means that the higher the decline in the MGC score, the greater the decline in the BDI score.

DISCUSSION

In this study, there was a decrease in the severity of disease in the group that received aerobic cycle ergometer training for 8 weeks. Reducing the severity of MG by 3 points in MGC indicates clinically significant improvement in MG patients[18]. The results of this study are consistent with the study by Westerberg (2018) who stated that MG disease activity decreased after MG patients did physical exercise for 12 weeks, although the decrease in MGC scores in this study was only 1 point[14]. The study by Rahbek et al. (2017) reported that 6 MG patients who underwent aerobic exercise for 8 weeks showed a reduction in the severity of MG disease[13].

There are two basic theories regarding the effect of aerobic exercise on the severity of MG disease. First, aerobic exercise can improve cardiorespiratory fitness by increasing cardiac output and cardiac performance. Second, there is an increase in the endurance of skeletal muscles due to changes in biogenesis that occur in muscle cell mitochondria, causing metabolic adaptation and an increase in the lactate threshold so that complaints of fatigue are reduced[19].

In this study, the MGC scale was used to estimate the severity of MG by assessing the improvement of ocular, bulbar, respiratory and upper and lower extremity muscle weakness. There was a significant increase in respiratory function based on the MGC score in the group that received aerobic cycle ergometer training in this study. Complaints of shortness of breath reported by subjects when carrying out activities were reduced by 70%. The results of this study are in accordance with the theory that aerobic exercise can improve cardiorespiratory fitness and reduce fatigue. Lower extremity muscle strength, especially hip flexors, in the MGC score showed an increase, although in this study it was only 10%. Rhythmic and dynamic movements of the large muscles of the pelvis occur during aerobic exercise on a cycle ergometer. Cycling exercise has been shown to improve neuromuscular control and lower extremity muscle activation thereby increasing pelvic muscle strength[20,21].

MGC scores for speech and swallowing function decreased by 30% in this study. Improvements in speech and swallowing function were reported by Hsu (2020) in the results of their prospective study regarding the effects of Respiratory Muscle Training (RMT) exercises in MG patients. RMT training is a special exercise that trains the respiratory muscles both in inspiration and expiration, therefore the results of this RMT exercise show an increase in lung function, especially force vital capacity (FVC) and force expiratory volume in one second (FEV_1) as well as the Quantitative Myasthenia Gravis (QMG) score for speech, swallowing, breathing and lung function[22].

There are limited evidence discussing the effects of aerobic cycle ergometer training on speech and swallowing function in patients with MG. In this study, the improvement in speech and swallowing function on the MGC score possibly caused by combination of cycle ergometer training and effective breathing exercises, which have an effect on respiratory muscle training, especially expiratory muscles, which play a role in helping speech and swallowing function. Further study is needed to evaluate the effects of aerobic exercise on speech and swallowing function in the future.

The results of this study showed a decrease in the level of depression in the group that received aerobic cycle ergometer training for 8 weeks. In the treatment group there was a decrease in BDI scores of 4.5 points, while in the control group there was a decrease of 0.8 points. The results of this study are in line with the study by Farrugia (2018) reported improvements in depression symptoms in 10 MG patients who received physical and psychological exercise treatment for 10 weeks[23].

A randomized controlled trial study conducted by Birnbaum (2021) shows different results from this study. In 43 MG patients who underwent aerobic exercise at home for 12 weeks, the patient's depression level did not decrease at the end of the measurement. Aerobic exercise in this study used a rowing ergometer, moderate intensity, which was carried out in 3 x 40 minute sessions per week for 12 weeks. Differences in the type and intensity of aerobic exercise used, longer duration of exercise programs, and aerobic exercise programs carried out without supervision from the researcher team, are factors that differentiate the reduction in depression levels in previous studies[24].

Study by Rahbek (2017) also reported different results from this study. Eight MG patients who underwent aerobic exercise with a cycle ergometer for 3 sets, 10 to 12 minutes with an intensity of 70% to 85% of maximum heart rate for 8 weeks, showed that depression scores increased, although not significantly[13]. In this study, the BMI of the subjects was included in the obesity level 1 category with an average BMI of 25.6 ± 4.8 kg/m^2 and the intensity of the aerobic exercise used was moderate to high intensity, whereas this study used low-intensity aerobic exercise (30% Heart Rate Rest + Heart Rate Rest). Differences in BMI and exercise intensity are factors that help differentiate the depression score results of this study from previous studies.

High-intensity physical exercise should be avoided in MG patients because it can increase muscle weakness and symptoms of central and peripheral fatigue. In neuromuscular diseases, there is a decrease in functional muscle fibers due to the patient's sedentary lifestyle, causing muscle atrophy. This causes MG patients to experience fatigue very quickly when doing heavy physical activity. In patients with MG, weakness not only occurs in the extremity muscles but also in the heart and lung muscles, causing a decrease in cardiopulmonary fitness which worsens the effects of fatigue[25].

High-intensity exercise affects changes in heart rate, oxygen consumption, respiratory and ventilation rates, lactic acid production, muscle glycogen content, mechanical stress and body temperature. In MG patient, this can cause significant complaints of fatigue, which can worsen the severity of the disease and increase the severity of depression(17,26). In Rahbek (2017) study, one explanation for the persistent level of depression in MG patients who did aerobic exercise was related to an increase in body temperature after exercise. This increase in temperature resulted in a threefold increase in the severity of MG disease after moderate to high intensity aerobic exercise compared to the group that only performed resistance exercise[13].

Study by Tripathi (2023) reported that physical exercise can cause feelings of satisfaction and euphoria. In the group that received high intensity exercise, this exercise caused negative feelings such as fatigue, irritability and loss of energy, in contrast to the group that received light to moderate intensity physical exercise which caused positive emotional effects[27].

Exercise exerts beneficial psychological and immunological effects in MG patients. Improvement in symptoms of depression and anxiety after exercise has been reported in many chronic diseases. Physical exercise increases the release of endorphins and has been reported to be beneficial in a variety of neuromuscular diseases. β-Endorphin is a peptide considered a neurotransmitter and neuromodulator with long-term effects on the human body and mind. β-Endorphin is a strong analgesic, euphoric and antidepressant so physical exercise can be an additional therapy for patients who have complaints of depression[27].

This study has limitations. First, the type of intervention given in this study does not allow it to be carried out in a blinded manner. Evaluation of post-treatment is carried out by the researchers themselves, not carried out in a disguised manner, so that it can cause measurement bias, namely examination bias. Second, the subjects of this study are not representative of the general MG population because only patients with generalized type MG and MGFA classifications IIa and IIb were eligible to participate in this study. Third, the study duration was short to allow assessing the long-term effects of aerobic exercise with a cycle ergometer in patients with MG.

CONCLUSION

Low-intensity aerobic exercise with a cycle ergometer reduces the severity of the disease and reduces the level of depression in MG patients. There is also a positive relationship between the degree of severity and the level of depression where a decrease in the MGC score will be accompanied by a decrease in the BDI score in MG patients.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR'S CONTRIBUTIONS

Conceptualization: TDP, MA, DP, IS, PS. Data curation: TDP, MA, DP, IS, PS, SM. Methodology: TDP, MA, DP, PS, IS, SM. Project administration: TDP. Visualization: TDP. Writing - original draft: TDP. Writing - review and editing: TDP, MA, DP, IS, PS, SM. All authors have read and approved the submitted manuscript. The manuscript 9 has not been submitted elsewhere nor published elsewhere in whole or in part.

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