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Original Research

Effects of Oxidative Damage during Ruesi Dadton Exercise in Mild Cognitive Impairment: Randomized Controlled Trial

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ABSTRACT

International Journal of Exercise Science 15(3): 1528-1537, 2022. This study aimed to investigate the effect of biomarkers of oxidative stress (OS) in 8-isoprostane (8-iso) and 8-hydroxy-2'–deoxyguanosine (8-OH-dG) on mild cognitive impairment (MCI) during a 12-week Ruesi Dadton (RD) exercise. A total of 274 enrolled participants were classified into blocks based on age and formal educational years, and randomly assigned into two groups: RD and control (CON). The participants' cognitive functions were tested using Mini-Mental State Examination and Montreal Cognitive Assessment (MoCA) scores to screen for MCI. Urine samples of approximately 30 mL were collected from both groups pre- and post-intervention. All participants signed consent forms before participating in the program. Participants in the RD group were instructed to perform 15 postures of RD exercise in 60 min, three times a week for 12 weeks. A 2 x 2 (group x time) repeated multivariate analysis, with MoCA score, 8-iso, and 8-OH-dG as covariates, was performed to analyze the between-subject differences across group [V = 0.143, F(2,60) = 5.020, p = 0.010, d = 0.209] and within-subject differences across interaction between group [V = 0.143, F(2,60) = 5.020, p = 0.010, d = 0.408]. There were significant differences from univariate data regarding both 8-iso (F1,61 = 10.081, P = 0.002, d = 0.406) and 8-OH-dG (F(1,61) = 5.965, P = 0.018, d = 0.312) levels. Moreover, results from both biomarkers in the RD group revealed significant improvements in 8-iso (p < 0.001) and 8-OH-dG (p = 0.003), whereas there were no improvements in the CON group. In conclusion, RD decreased biomarkers of OS during 12 weeks of RD exercise in MCI. These results indicate that in MCI, RD could improve lipid peroxidation and DNA oxidation by 8-iso and 8-OH-dG, respectively.

KEY WORDS: 8-isoprostane, 8-hydroxy-2'–deoxyguanosine, Mild Cognitive Impairment, Mind-body exercise, Oxidative stress

INTRODUCTION

Mild cognitive impairment (MCI) can be described as pre-dementia or pre-Alzheimer's disease (AD). Its prevalence, which is approximately 6−26% varies depending on the demographic and

risk factors of the sample population (8, 12, 16, 29). Amyloid-beta plaque and the neurofibrillary tangle of tau in the brain are the hallmarks of MCI and AD (35, 42). Mitochondria plays a key role in generating reactive oxygen species (ROS) and mediating cell apoptosis signals (26). Overproduction of mitochondrial ROS or imbalance between ROS production, antioxidant systems, and energy metabolism leads to OS, resulting in the production of superoxide anion and hydrogen peroxide (3). Tau is a protein that localizes in neurons, mostly in microtubule cytoskeleton in axons and also in mitochondria, nucleus, plasma membrane, and synapses (17). Therefore, accumulation of amyloid-beta in mitochondria can lead to MCI and AD (10). Additionally, aggregation of amyloid-beta leads to oxidative stress (OS), mitochondrial dysfunction, and energy failure that develop into plaque pathology (9).

OS could detected in early AD and MCI by biological fluids such as cerebrospinal fluid, blood, and urine. (6, 20). The biomarkers that evaluate the effects of exercise in AD and MCI consist of neuropathological hallmarks, neurotrophic factors, inflammatory factors, OS markers, metabolic biomarkers, and genotypes (30). During physical exercise, the release of brain-derived neurotrophic factors reduces inflammation, OS, and brain apoptosis (2). Exercise has been shown to benefit patients with MCI and AD through several pathways (27, 44). The biomarker for OS during exercise in such patients involves lipid and DNA damage (31). An example is 8-hydroxy-2'–deoxyguanosine (8-OH-dG), which is determined to be a biomarker of DNA oxidation in MCI and AD during exercise (30), Similarly, isoprostane isomers such as 8-isoprostane (8-iso), malondialdehyde, and acrolein are biomarkers of lipid peroxidation (5, 30). Moreover, previous studies have shown that physical exercise and physical activity decreased OS (18, 34, 43).

In the AD mouse model, it was revealed that all exercise modalities can improve OS (4). A recent study of combined physical and cognitive virtual reality-based training in MCI found significant improvements in cognitive parameters, ROS production rate, and OS at both 8-OH-dG and 8-iso levels in the experimental group (34). The efficacy of mind-body exercise cannot be studied in animal models, but there were evidences that Tai Chi and yoga improved OS levels (11, 41), although rarely in MCI. Similarly, healthy older adults who performed Ruesi Dadton (RD) showed improved OS and antioxidant levels (23).

RD is a traditional Thai mind-body exercise. It is a collection of evidence knowledge of 127 postures (15), of which 15 postures were selected and applied by The Ministry of Public Health, Thailand, to promote general health for the Thai population. Performance of RD involves slow movements with deep breathing and inspiration breath holds. In healthy older adults, RD was found to improve physical function (22), mental health (39), and quality of life (37). In MCI patients, stress was reduced in RD group at week 6, 8, and 10 when compared to control (CON) group (25). Furthermore, RD exercise has been shown to improve all physical and executive functions (24). We hypothesize that OS will decrease after RD exercise. Therefore, this study aimed to investigate the efficacy of a 12-week RD on 8-iso (lipid peroxidation) and 8-OH-dG (DNA oxidation) in MCI.

METHODS

Participants

The inclusion criteria were individuals aged 50–80 years old with body mass index of 19–27.5 kg/m^2, Montreal Cognitive Assessment (MoCA) score of < 26, Mini-Mental State Examination (MMSE) score of ≥ 24, and diagnosed MCI by a neurologist. Exclusion criteria were those with blood pressure > 160/100 mmHg, knee pain or inability when cross sitting, regular exercise within 2 years, neurological disease, history of severe diseases or diseases that involve cognition (cancer, cardiovascular disease, alcoholism, mental symptoms, neurological diseases, and brain accident). Participants were recruited between June and July 2020 (Figure 1). After excluding the samples that did not pass the criteria, 66 urine samples were analyzed (RD group, n = 34 and CON group, n = 32). The experiment was performed according to the ethical standards of the Helsinki Declaration. All participants provided written informed consent prior to participation. This study was approved by the Human Research Ethics Committee No. 1 of the Faculty of Medicine, Thammasat University, Thailand (approval no. 119/2562) and registered in the Thai Clinical Trials Registry (TCTR20200727001). Additionally, this research was conducted in accordance with the recommendations of ethical issues relating to scientific discovery in exercise science from the International Journal of Exercise Science (36).

RD was demonstrated and practiced for 2 days prior to the 12-week intervention, which required 60 min exercise, three times a week for 12 weeks; a total of 36 sessions. On the first day of training, breathing technique was demonstrated until the participants can be followed. RD breathing in one loop equals to the RD movements in one step or posture. Abdominal breathing involved holding the breath for about 5–10 seconds and then gently breathing out. On the second day, RD movements were combined with breathing. The 15 RD postures have been shown in a previous study (22). The main RD procedure included deep breathing and slow stretching in Thai style. The other components for RD exercise included self-massage, isometric contraction, core strengthening, eye-hand co-ordination, and balancing. The movements were combined in diagonal and various starting positions. Most of the RD movements started with cross-sitting positions; however, various starting positions were practiced for the whole body, such as sitting, supine lying, prone lying, and side lying. RD practice was conducted by two traditional Thai medical doctors. Movements were supervised and corrected by physical therapist (researcher PK). Supervision, an RD model, and video visualization in the local language were provided during the 12-week period of practicing RD. Participants in both groups received information from the neurologist about basic knowledge of MCI and dementia except for the effect of exercises. The CON group can live their normal lives as before with no intention in practice mind-body exercise until finish intervention.

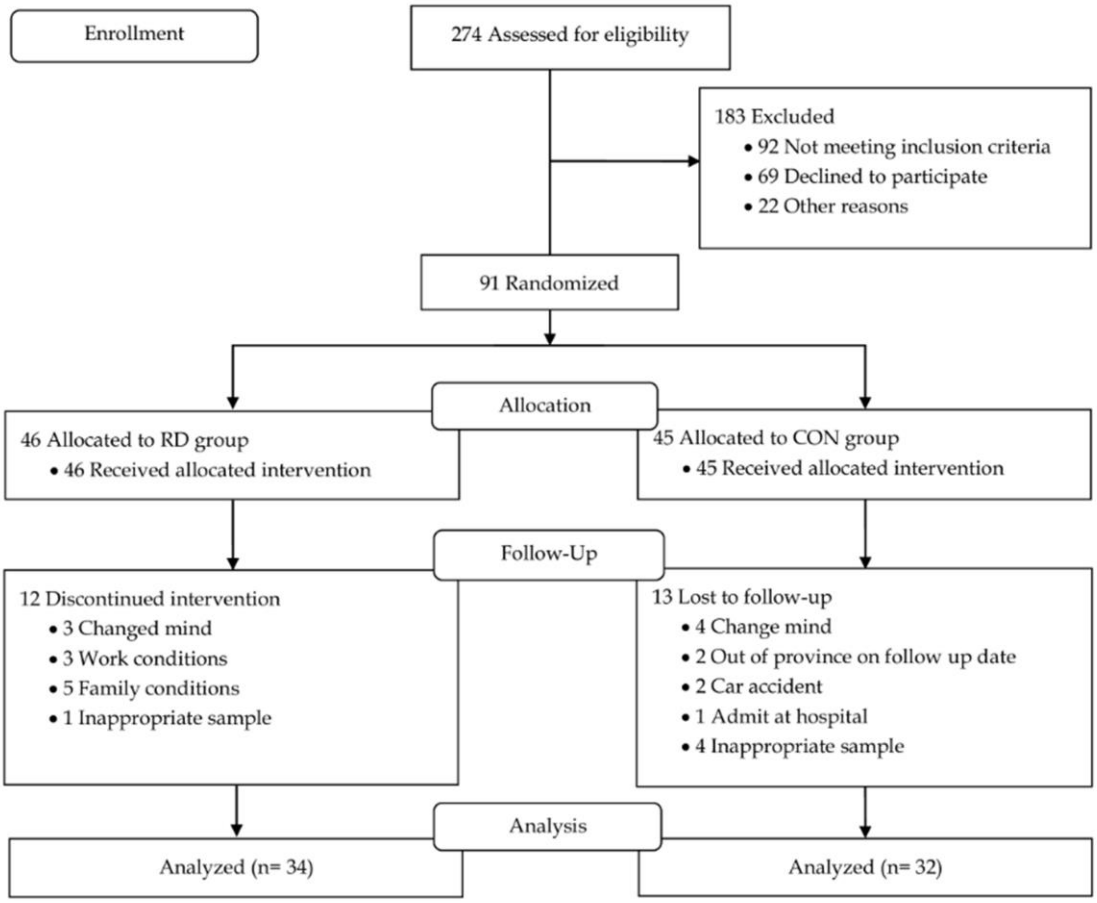

Figure 1. Study flowchart
Note: Reusi Dadton (RD), Control (CON)

Protocol

The cognitive function tests (MoCA and MMSE) were screened by researcher PK. Participants in both groups received information from the neurologist about basic knowledge of MCI and dementia except for the effect of exercises at the same day of pre-test. There was allocation by block randomized based on age and education level by researcher in order of number recruitment. The participants were assigned to two blocks; in the first block, the participants were classified into groups of < 65 and ≥ 65 years old, while in the second block, they were classified into those who continued to formal education at ≤ 6 and > 6 years old. After all participants have been assigned into blocks, randomization was performed within each block to equally allocate them into the RD and CON groups.

Urine sample was collected pre-intervention and 12 weeks post-intervention. The participants will be given a small plastic bottle and use the mid-stream in the bottle and keep it in a cold place after waking up until they go to the Hua Don Tambon Health Promoting Hospital to prevent urine fermentation. A total of 30 mL-morning urine samples will be collected with an ice box and immediately centrifuged at 3,000 rpm at 4 °C for 10 min and then transferred into stock tubes. Samples will be stored at -80 °C until further analysis. Urine 8-iso and 8-OH-dG will

be measured by the enzyme-linked immunoassay-based method using a kit provided by Cayman Chemical (Ann Arbor, USA) according to the manufacturer's instruction. The laboratory data were completed at the Research and Development Center of Thai Herbal Products, Faculty of Thai Traditional and Alternative Medicine, Ubon Ratchathani Rajabhat University. The collection and analysis of laboratory OS data were completed by researcher AD. They were only aware of the number of participants but were blinded toward each sample's group. The analysis data with participant number codes were then sent to researcher PK for continued calculation.

Statistical Analysis

All statistical analyses were performed using SPSS version 24. 0.05 is the alpha level used for the determination of significance. A 2 x 2 (group x time) repeated multivariate analysis of covariance (MANCOVA) was used to analyze the effects of the urine biomarkers by controlling the difference at baseline of MoCA and both OS markers. Pillai's Trace (V) was used to report the multivariate results because it is suitable for unequal sample sizes. G*Power 3.1 was used to calculate Cohen's d effect size from MANCOVA by partial eta squared at 0.10, 0.25. 0.40 to indicate small, medium, and large effect sizes, respectively. Independent t-test was used for demographic data and to compare the difference between groups, and paired t-test was used to compare the difference in time point duration (pre- and post-analysis) of 8-iso and 8-OH-dG. Additionally, the significant level of interaction between time points and groups was set as $p < 0.025$ (cut off 0.05/2).

RESULTS

The baseline demographic characteristics of participants are presented in Table 1. Age, educational year, body weight, and MMSE were not significantly different. However, there were significant differences in MoCA scores and 8-iso and 8-OH-dG levels in the RD and CON groups. Thus, MANCOVA, with control of MoCA score and both OS markers, was performed to measure interaction between both biomarkers.

Table 1. Demographic characteristics, cognitive functions, and OS levels in the RD and CON groups

	RD (n = 34)	CON (n = 32)	p
Age (years)	60.5 ± 5.6	61.3 ± 7.9	0.605
Education (years)	7.3 ± 3.9	7.9 ± 4.2	0.543
Body weight (kg)	54.9 ± 6.5	56.0 ± 6.7	0.476
MMSE score	26.9 ± 1.9	26.3 ± 1.8	0.128
MoCA score	20.3 ± 3.4	18.3 ± 2.9	0.012*
8-iso	0.7 ± 0.5	0.4 ± 0.2	0.008*
8-OH-dG	12.9 ± 9.2	7.3 ± 3.5	0.002*

Notes: Reusi Dadton (RD), Control (CON), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), 8-isoprostane (8-iso), 8-hydroxy-2-deoxy Guanosine (8-OH-dG).

Table 2 shows that biomarkers of OS, 8-iso and 8-OH-dG, were measured for both groups pre- and post-12-week intervention. Repeated-measures MANCOVA, with control of baseline

MoCA, 8-iso, and 8-OH-dG, revealed that there was a significant multivariate effect between-subjects across groups [V = 0.143, F(2,60) = 5.020, p = 0.010, d = 0.209] and within-subjects across interaction between group [V = 0.143, F(2,60) = 5.020, p = 0.010, d = 0.408]. However, no significant multivariate effect across within-subjects time points (regardless of both groups) at V = 0.042, F(2,60) = 1.304, and p = 0.279. A significant difference was observed in the univariate between-group analysis; higher levels of both 8-iso (F(1,61) = 10.081, P = 0.002, d = 0.406) and 8-OH-dG (F(1,61) = 5.965, P = 0.018, d = 0.312) were found in the RD group compared to that in the CON group.

Table 2. OS levels by groups across treatment time points

	Measures		Main Effects			Group vs. Time					
						RD			CON		
			Mean	SE	N	Mean	SE	N	Mean	SE	N
8-iso	Time	Pre	0.56[a]	0.000	66	0.56[a]	0.000	34	0.56[a]	0.000	32
		Post	0.49[a]	0.031	66	0.38[a]	0.046	34	0.60[a]	0.048	32
	Group	RD	0.47[a]	0.023	34						
		CO	0.58[a]	0.024	32						
8-OH-dG	Time	Pre	10.16[a]	0.000	66	10.16[a]	0.000	34	10.16[a]	0.000	32
		Post	9.86[a]	0.747	66	7.83[a]	1.099	34	11.89[a]	1.136	32
	Group	RD	9.00[a]	0.549	34						
		CO	11.02[a]	0.568	32						

Notes: Reusi Dadton (RD), Control (CON), Standard error (SE), 8-isoprostane (8-iso), 8-hydroxy-2-deoxy Guanosine (OH-dG). [a]Covariate appearing in the model are evaluated at the following value: 8-iso = 0.56, 8-OH-dG = 10.16, MoCA score = 19.35.4.

To determine the significance of each biomarker, Table 3 shows the mean and standard deviation across different time points (pre- and post-intervention) by independent and paired t-tests. Pre- and post-intervention were significant in the RD group regarding both 8-iso ($p < 0.001$) and 8-OH-dG (p = 0.003) levels, whereas it was not significant for the CON group regarding both 8-iso (p = 0.057) and 8-OH-dG (p = 0.063) levels. However, RD and CON showed significance at baseline but not after 12 weeks regarding both 8-iso and 8-OH-dG levels.

Table 3. OS levels at time point

Variables	RD (n = 34)		CON (n = 32)	
	Pre	Post	Pre	Post
8-iso	0.7 ± 0.5†	0.4 ± 0.3**	0.4 ± 0.2†	0.5 ± 0.4
8-OH-dG	12.9 ± 9.2	9.8 ± 7.7*	7.3 ± 3.5	9.8 ± 7.5

Notes: Reusi Dadton (RD), Control (CON), 8-isoprostane (8-iso), 8-hydroxy-2-deoxy Guanosine (8-OH-dG). *p < 0.05, significant difference within-group. **p < 0.001, significant difference within-group.
†p < 0.05, significant difference between-group.

DISCUSSION

Although the baseline characteristics, particularly the biomarkers, showed significant differences, randomization and control were performed before allocation. The main finding of

RD in improving OS levels was confirmed by the significant difference showed by 2 x 2 repeated MANCOVA in the interaction of multivariate and univariate regarding both 8-iso and 8-OH-dG levels. The results of the independent *t*-test revealed a significant improvement in all OS in the RD group, but not in the CON group. Therefore, our hypothesis that a 12-week exercise of RD can improve biomarkers of OS in MCI was proven.

For many decades, oxidative damage has been known to be involved in many degenerative diseases, particularly neurological problems (3, 6). The potential mechanism of RD in reducing OS in MCI and AD by dysfunction of mitochondria and abnormal accumulation of metals lead to the production of ROS. Moreover, holding deep breathing during RD could enhance the oxygen in blood mediated to the brain. Consequently, RD showed an increase in vital capacity of older adults (22). To the best of our knowledge, this is the first study to investigate the effect of mind-body exercise on OS in MCI. Related studies have found that physical exercise can decrease OS in MCI and AD using different biomarkers (7, 13, 18, 28, 32, 43). Additionally, Tai Chi and yoga were shown to have beneficial effects for other neurodegenerative diseases in ameliorating OS levels arising from events such as Parkinson disease (14), and anxiety (1). Furthermore, a systematic review and meta-analysis showed that mind-body exercise (Tai Chi and yoga) and high-intensity aerobic training were efficient at decreasing OS in unhealthy persons (27).

8-iso was regarded as a biomarker for late-onset AD (33). A study in older adults revealed that 8-iso levels improve significantly after 12 weeks of performing Tai Chi (21). When comparing other types of exercise, 8-iso showed a controversial result (19, 34, 40). The OS by 8-iso in this study shows similar results in improvement after 6 weeks of combined physical and cognitive virtual reality-based training (34) and 12 weeks of arm swing in MCI (40). However, 16 weeks of aerobic exercise did not show a significant difference in 8-iso (19).

A study that combined physical and cognitive virtual reality-based training showed a better significant difference in 8-OH-dG than 8-iso (34), which is consistent with the present findings. Moreover, it was found that electroacupuncture attenuated 8-OH-dG in the AD rat model (45). In summary, the present study confirmed the effects of RD on MCI by attenuating 8-iso and 8-OH-dG, which are biomarkers for identifying damage to lipid and DNA, respectively (30, 38).

Further studies should consider RD in promoting brain health in older adults with MCI. However, this study had some limitations, including an imbalance of sample size from both groups, inappropriate urine samples that were more mucous-like to analyze in some participants, leading to a decrease in number of participants, and both biomarkers could indicate other diseases, such as diabetes and hypertension. Although the urine sample was more convenient and safer with minimal risk for participants than drawing blood sample because it was non-ivasive method. Further studies involving a larger sample size and comparing the results from other sources, such as blood samples, should be conducted in the future.

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