RANDOMIZED TRIAL EVALUATING EFFECTS OF EXERCISE ON OLFACTION IN PATIENTS WITH EARLY-STAGE DEMENTIA

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ABSTRACT

Importance: Olfactory dysfunction has been well-described in Alzheimer's disease (AD). Options for improving olfaction are limited, and few studies have prospectively attempted to improve hyposmia. A previous meta-analysis has shown that exercise provides global benefit to patients with AD.

Objective: We aim to prospectively evaluate what effect exercise has on olfaction and general cognition in patients with AD.

Design: Sub-study of a randomized, controlled clinical trial of 26 weeks duration.

Setting: Tertiary referral center.

Participants: Individuals with early-stage AD and adequate visual and auditory abilities to perform all cognitive testing were included into this study. Only individuals with MMSE of 16-30 and scored 0.5 (very mild) or 1.0 (mild) on the Clinical Dementia Rating Scale (CDR) were enrolled.

Interventions: Participants were randomized into either an aerobic exercise program or stretching program. Aerobic exercise typically consisted of treadmill walking for 150 minutes per week with similar times of stretching exercises for the control arm.

Main Outcomes and Measures: Patients completed the UPSIT (University of Pennsylvania Smell Inventory Test) and MMSE (Mini-Mental State Examination) prior to and after the 26 weeks program.

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Results: This study included 18 patients with 9 patients in the control arm and 9 in the exercise arm. The groups showed no statistical difference (p=0.537) between pre-treatment and post-treatment olfactory scores. There were 3 patients in the exercise arm versus 1 patient in the control arm that had an improvement in olfactory score (p=0.288). The groups showed no significant difference in post-intervention average MMSE (p=0.884), though more patients improved in the exercise arm.

Conclusion: Although more patients in the exercise arm versus the control arm improved in normative olfactory score and MMSE scores, it may be hard to predict statistical significance due to small sample size. This is suggestive that exercise may play a role in aiding certain patients. Reproduction of this study with a larger sample size and shorter intervention length may provide further clarity.

Trial Registration: clinicaltrials.gov NCT01128361

Keywords: Olfactory dysfunction; Dementia; Alzheimer's disease.

INTRODUCTION

Olfactory dysfunction worsens with age and has been well-described in Alzheimer's Disease (AD). [1, 2] This dysfunction is thought to precede clinical dementia by several years thus researchers have posited smell testing as a way to screen for the disease. [3, 4] The loss of smell may be associated with even greater morbidity, as appetite and mood may be affected. Unfortunately, an option for improving olfaction is limited.

There has been a wealth of animal research, [5-10] and epidemiologic studies [11-14] supporting exercise positively impacts brain health. Suggested hypotheses behind this include increased brain-derived neurotrophic factor (BDNF) [15] and other important neurochemicals [16] supporting brain growth and survival, stimulation of neurogenesis, [9] enhanced neuronal survival, [17] and increased synaptic development and plasticity. [18] Despite this compelling data suggesting exercise is related to brain health, there is a relative lack of data on the role of exercise in olfaction. We hypothesize that exercise can have similar effects on the olfaction centers as it does in other areas of the brain.

As an adjunct to an institutional study evaluating effects of aerobic exercise in patients with early evidence of dementia, we prospectively evaluated what effect, if any; aerobic exercise plays on olfaction in patients with AD. We, additionally, examined any correlation between global functioning and olfaction after an aerobic exercise regimen.

METHODS

This sub-study was an adjunct to The Alzheimer's Disease Exercise Program trial (ADEPT: ClinicalTrials.gov, NCT01128361). This was a randomized, controlled, 26-week study comparing aerobic exercise (AEx) vs. a non-aerobic stretching and toning control program (ST). Individuals with mild cognitive impairment and early-stage AD. Stretching exercises are often used as a control for exercise intervention. [19, 20] Participants were recruited from March 14, 2014 until September 26, 2014 and randomized in a 1:1 ratio. Follow-up testing was

completed by April 17, 2015. Details of the full study protocol have been previously published. [21] All testing was performed at the University of Kansas Medical Center. The intervention was administered at 16 YUMA of Greater Kansas City Facilities. There were no changes to study methods after trial commencement.

Participants

A convenience sample of volunteers were recruited through print advertising, community talks, memory clinic referral and existing research participant databases. The study covered TMCA membership and certified personal trainer fees. We included all sedentary patients, 55 years of age and older, with diagnosis of Mild Cognitive Impairment of the Alzheimer's type, or probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). [22] Only individuals with a MMSE of 16 to 30 and scored 0.5 (very mild memory loss) or 1.0 (mild) on the Clinical Dementia Rating scale (CDR) were enrolled. [23] Patients must have adequate visual and auditory abilities to perform all aspects of their cognitive testing. All medications were continued. All patients had normal rhinologic exams and no evidence of sinus disease on imaging. Patients with abnormal brain imaging that could explain their cognitive decline, other neurologic or psychiatric diseases, co-morbidities limiting exercise, or CDR 0.5 uncertain dementia were excluded from the study.

Interested individuals completed a telephone screen of medical history followed by in-person screening of those who remained interested and appeared eligible. All participants provided institutionally proved, written, informed consent under the study protocol (#11969) approved by the KU Medical Center Institutional Review Board.

Interventions

Patients meeting the inclusion criteria were randomly placed into a 26-week aerobic or stretching exercise regimen at their local Greater Kansas City Youth Men's Christian Association (YMCA). Patients attended 3 nonconsecutive days per week of professionally guided aerobic or stretching exercises each lasting 40 minutes. Patients in the AEx group walked on a treadmill for 20 minutes at 1.7 mph and 0% grade with an increasing speed and grade to maintain heart rate at 50-70% of the maximum achieved heart rate (as determined during VO2peak testing at baseline). [21] Exercise duration and speed progressed as tolerated for each subject every week until the subject reached approximately 40 minutes duration. Heart rate zones for weeks 1-4 were 40-55%, weeks 5-18 were 50-65% and weeks 19-26 were 60-75%. Exercise instructors supervised a maximum of two subjects at one time unless deemed a sufficient fall risk then one-on-one supervision was provided.

The ST Group performed a series of non-aerobic exercises that rotated weekly (core strengthening, resistance bands, modified tai chi, modified yoga). Participants wore HR monitors and were asked to keep their HR below 100 bpm. Trainers helped adjust intensity to reduce HR as necessary. Subjects are required to attend at least 80% (62 of the 78 sessions) of the aerobic or stretching exercise sessions during the course of the study. Patients could drop out at any time.

Outcomes measures

Evaluate the patients' olfaction, we used the University of Pennsylvania Smell Inventory Test (UPSIT), [24] a 40-question validated, multiple-choice scratch and sniff test. To evaluate patient cognition, we utilized the Mini-Mental State Examination (MMSE). [25]

On the day of consent, patients were asked to complete the UPSIT and the MMSE. Upon completion of their regimen, patients were asked to complete the same tests. Patients were scored based on age and gender specific norms. Patients UPSIT scores were translated into normative values based on age and sex as follows: 0 for normosmia; 1 for mild microsmia; 2 for moderate microsmia; 3 for severe microsmia, 4 for anosmia. [26] Patients' MMSE were also scored out of 30 points and before and after values were compared. There were no changes in trial outcomes one the trial commenced.

Sample size, randomization, blinding and safety

Our enrollment size of 30 was limited by the primary protocol's ability to enroll patients up to a certain date as well as cessation after they met an enrollment goal of 80. Participants were blocked randomized upon successful completion of the exercise and stratified by age (split at 75) and sex, to balance treatment arms. The randomization sequences were constructed prior to study start by the KU Department of Biostatistics.[21] The allocation schedule was creating using SAS software, and sequentially numbered index cared were placed in sealed envelopes groups by age and sex strata. [27] Envelopes were opened after baseline testing by staff not involved in outcome measure testing. The clinical evaluator (ZA) was blinded to the randomization assignment and participants were asked not to discuss regarding their intervention with testing staff. Participants were not blinded to intervention arms. At the time of consent, the phrases "aerobic exercise" and "non-aerobic activities" were used rather than "intervention" and "control."

Statistical methods

SPSS statistical analysis software (Version 15, SPSS, Chicago, IL) was used to perform all statistical analysis. Wilcoxon Signed ranks tests and Mann-Whitney U tests were used to detect differences between pretreatment and post treatment test results. Non-parametric correlations were used to analyze relationships between UPSIT scores, normative olfactory scores, and MMSE scores. Fisher exact tests were used to compare patients with improvement in UPSIT, normative olfactory scores and MMSE scores between treatment arms. Logistic regression was performed to determine if you could predict whether patients fell into the control arm or the exercise arm based on the differences in UPSIT, normative olfactory scores, and MMSE scores. P values of <0.05 were considered significant.

RESULTS

This was a single institution prospective study that enrolled a total of 30 patients and ultimately included 18 patients (Figure 1). There were 12 patients lost to follow up and were excluded from the study. There were 9 patients in the control arm, and 9 patients in the exercise arm. The average age was 79 years (SD=6) for the control

arm, and 75 (SD=8) for the exercise arm. Total, there were 6 females (33.3%) (Table 1).

Table 1 Patient Demographics

	Control (n=9)	Exercise (n=9)
Age, mean (SD), years	79 (6)	75 (8)
Sex, n (%)		
Male	7 (78)	5 (56)
Female	2 (22)	4 (44)
Education, n (%)		
Some High School	1 (11)	0 (0)
High School or equivalent	4 (44)	3 (33)
Some College[b]	1 (11)	1 (11)
College degree	0 (0)	2 (22)
Postgraduate degree	3 (33)	3 (33)
CDR[c],n (%)		
0.5	6 (67)	3 (33)
1.00	3 (33)	6 (67)

[a]Mean age of all participants (across groups)

[b]Short of degree requirements

[c]Clinical Dementia Rating scale

When comparing UPSIT scores for the control arm, the median pretreatment score was 19 (IQR= 12.5-25.5) while the median post treatment score was 16 (IQR=10-22). The difference between pre and post-treatment medians was not found to be statistically significant (p=0.528). For the exercise arm UPSIT scores, the median pretreatment score was 19 (IQR -15.25-22.75) while the median posttreatment was 19 (IQR=12.5-25.5). There was also no statistically significant difference found between these medians (p=0.725). When comparing the differences between the pre-treatment and post-treatment UPSIT scores for the control arm versus the exercise arm, there was no statistical difference found (p=0.658).

When comparing normative olfactory data for the control arm, the median pretreatment score was 4 (IQR= 3-4) while the median post treatment score was also 4 (IQR=2.5-4). The difference between pre and post-treatment medians was not found to be statistically significant (p=0.317). For the exercise arm normative olfactory data, the median pretreatment score was 3 (IQR = 3-4) while the median post treatment was also 3 (IQR=2-4). There was also no statistically significant difference found between these medians (p=0.257). When comparing the differences between the pre-treatment and post-treatment olfactory scores for the control arm versus the exercise arm, there was no statistical difference found (p=0.537).

For the MMSE scores within the control arm, there was a median pretreatment score of 23 (IQR=20-26) and a median post treatment score of 22 (IQR=18-26). The difference between pre and post-treatment medians was

not found to be statistically significant (p=0.157). Within the exercise arm, the median pretreatment score was 25 (IQR=23-27) while the median post treatment score was 23 (IQR=21-25). There was also no statistically significant difference found between these medians (p=0.436). When comparing the mean differences between the pre-treatment and post-treatment MMSE scores for the control arm versus the exercise arm, there was no statistical difference (p=0.857). Figure 2 demonstrates differences between normative olfactory data and MMSE for the control arm and exercise arm.

Although median olfactory score among patients did not significantly differ, patients undergoing exercise were 4.2 times more likely to have an improvement in olfactory score compared to patients in the control arm (p=0.288). When looking at raw UPSIT scores, patients were equally likely to have improvement in scores among treatment arms (p=0.68). The median improvement for the control group was 3 (IQR = 1.5- 6.750 while the median improvement for the exercise arm was 4.25 (IQR = 1.25-8). There was no statistical difference found between improvement in the control arm versus the exercise arm (p=0.884). Furthermore, patients in the exercise group were also 4.2 times more likely to have an improvement in MMSE score when compared to patients in the control arm (p=0.288). These changes are depicted in Figure 3. Of note, patients who did show improvement, regardless of treatment arm, had near significant improvement in raw UPSIT scores.

Overall, there was not found to be any correlation between normative olfactory scores and MMSE in both the pretreatment group (p=0.867) and the post-treatment group (p=0.488). Furthermore, there was no correlation between UPSIT scores and MMSE in both the pretreatment group (p=0.646) and the post-treatment group (p=0.171). We also analyzed if there was any correlation between changes in the olfactory scores and changes in the MMSE scores however this was not statistically significant (0.429). There was also no statistically significant correlation between changes in the UPSIT scores and changes in the MMSE scores (0.615). Based on multivariate analysis, there was no way of predicting which treatment arm patients were in based on changes in UPSIT score, changes in normative olfactory scores and changes in MMSE scores.

There were 8 adverse events possibly or definitely related to the intervention or cardio respiratory exercise testing: 3 mild, 2 moderate and 1 severe in the ST group and 2 mild severity in the AEx group. Common mild adverse events possibly or probably related to the intervention included low back, hip, knee or foot pain. Moderate severity adverse events included lower extremity pain (n = 1), and chest pain (n = 1). The severe event was back pain related to spinal stenosis possibly exacerbated by exercise.

DISCUSSION

Anosmia and severe hyposmia have been noted to cause severe impairment to quality of life. [28, 29] Murine models have also demonstrated a worsening of Alzheimer's-like tau pathology after inhibition of the olfactory system. [30] With depression also being a frequent comorbidity in AD, [31] it is important to address methods of improving patients' day to day happiness and possibly slow progression of disease.

Numerous studies have established olfactory dysfunction in patients with AD, but no study has tried to improve olfaction. In our study, we prospectively evaluated if an exercise program in patients with mild AD improved olfaction and cognition. Overall, we saw no significant improvement in patients' mental status or in

olfaction. Although there were more patients in the exercise arm versus the control arm that improved in normative olfactory score, it may have been hard to predict statistical significance due to the small sample size. Therefore, if studies were conducted in larger sample, it may produce different results. This can also be said of those patients who had improvement in MMSE score. Furthermore, patients who had an improved UPSIT score, regardless of treatment regimen, had nearly significant increases in their scores. This could suggest that there may be another underlying component causing the improvement in olfaction. However, this improvement in raw UPSIT olfaction score for these 8 patients only caused a concomitant improvement in normative olfaction score for 4 patients, 3 of which were in the exercise arm. This is suggestive that although it was not a statistically significant increase, exercise may play a role in causing these changes in normative olfaction scores.

It is known that an odor identification task within the UPSIT relies heavily on memory. [32] Therefore, it could be possible that these improvements in normative olfactory scores in the exercise group could be attributed to improved memory rather than improved olfactory function. However, given that there was no correlation with changes in MMSE and changes in olfaction this is less likely and there truly is improvement in olfaction with exercise.

One of the challenges we encountered during our study was our high dropout rate as 10/28 patients (35.7%) did not complete the study. We mostly attribute this to the length of the study. A 26-week exercise regimen is challenging to complete, even for otherwise healthy patients. It is possible that participants simply lost interest, did not perceive any benefit, or found their training to be too cumbersome. Additionally, while our patients' dementia was mild, the UPSIT test may have been difficult to complete. There may have also been variability in testing secondary to nurse administration of the examination, as this varied from visit to visit.

Olfactory dysfunction has greater presence in the elderly population. The average age of patients in our study was 77 years. That age correlates to about a 20% reduction in olfaction. [33] This finding is known to be worse in males as they have a 33% reduction in olfaction by that age. Therefore, it is possible that underlying age-related deficits in smell were also difficult to overcome with exercise. Our study also included more males than females (6 female, 12 male), so there may be more bias related to age and gender related deficits in olfaction.

The mechanism of olfactory dysfunction has many theories. Post-mortem studies of individuals with AD show deposition of tau protein and β-amyloid within the olfactory bulb and olfactory system. [34] The significance of increased amyloid burden is controversial. In-vivo measurements of β-amyloid in AD patients using Pittsburgh Compound B (PiB) PET imaging showed no difference in olfaction between β-amyloid positive patients and controls. [35] Global neural atrophy is one of the hallmarks of dementia. A previous study noted atrophy of the olfactory bulb and tract in early AD, [36] however a subsequent study has shown no correlation between olfactory bulb size, olfactory dysfunction, and AD. [37] Another study showed that UPSIT scores correlated highly with odor-induced blood oxygen level-dependent signals at the primary olfactory cortex on fMRI. [38] A rodent model demonstrated decreased nitric oxide production in the olfactory bulbs of tau mice, [39] which could correlate to previous fMRI observations; however, no human study has verified these findings. Finally, a previous study has shown improvement in olfaction after administration of donepezil. [40] This correlates with research demonstrating

the central cholinergic system as the chief neuromodulator for olfaction. [41] Future research aimed at manipulating these molecular and biochemical inputs may help olfaction in this patient population.

CONCLUSION

Our results are suggestive that exercise may play a role in aiding patients with olfactory dysfunction. Reproduction of this study with a larger sample size as well as a control group with patients without dementia may provide further clarity.

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