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REDUCING THE RATE OF BIOLOGICAL AGING BY YOGA AND MEDITATION IN MAJOR DEPRESSION

MADHURI R. TOLAHUNASE[a], RAJESH SAGAR[b] AND RIMA DADA[c1]

[ac]Lab for Molecular Reproduction and Genetics, Department of Anatomy, All India Institute of Medical Sciences (AIIMS), New Delhi, India.

[b]Department of Psychiatry, All India Institute of Medical Sciences (AIIMS), New Delhi, India

ABSTRACT

We report findings on the modifications in biological aging at the cellular level after 12 week in a group of patients with major depressive disorder (MDD) treated with yoga- and meditation- based lifestyle intervention (YMLI) (n = 29) or routine drug therapy (RDT) (n = 26). Our secondary outcome was change in depression severity. Fifty-five patients visiting psychiatry OPD and diagnosed with MDD were randomly assigned to receive either YMLI or RDT. Primary outcome was determined with the assessment of the systemic biomarkers of biological aging at the cellular level. Secondary outcome was determined with Beck Depression Inventory II (BDI-II) scale. There were significant improvement in the 12-week levels of systemic biomarkers of biological aging at the cellular level in YMLI group compared to RDT group [decrease in reactive oxygen species, 8OH2dG, cortisol, and IL-6 and increase in total antioxidant capacity, telomerase activity, brain derived neurotrophic factor, and sirtuin 1] (all P<0.05). However, it did not differentially improve telomere length (P=0. 092). These findings were in parallel with significant reduction in BDI-II scores (P<0.001) and remission rates (64% in YMLI group and 22% in RDT group, P=0.003).MDD patients treated with YMLI show significantly slower rate of biological aging at the cellular level, and in parallel reduce depression severity, in comparison to those treated with RDT at 12-week post-intervention point. This reduces the incidence of complex lifestyle diseases in this cohort of patients, which arise earlier in them. The results of this study suggest that reducing the rate of biological aging by YMLI provides increased long term remission and increases both healthspan and lifespan in MDD.

KEYWORDS: Major Depressive Disorder, Biological Aging, Lifestyle, Biomarker, Yoga, Meditation, Telomeres

Yoga and meditation are mind-body interventions (MBIs) that have been used successfully for treating major depressive disorder (MDD) (Streeter, Gerbarg, Whitfield et al., 2017). They can be used as a lifestyle intervention since regular practitioners show higher resilience to adversities of modern lifestyle, which significantly contribute to pathogenesis of MDD, accelerated biological aging, and increased risk for other chronic non-communicable diseases (NCDs). Current first-line drug treatment for MDD that is based on monoamine hypothesis, is suboptimal and associated with complications (Forte, Baldessarini, Tondo et al., 2015). Recent imaging studies have reported that yoga decreases age associated decline in gray matter. More recent genetic studies (Buric, Farias, Jong et al., 2017; Tolahunase, Sagar, Khan et al., 2016) have suggested that MBIs modify expression of genes associated with cellular pathways of aging. On the other hand,drug treatments have ~40% failure rate, numerous side effects, and relapses. An et al., (An, Wang, Li et al., 2017) have reported that drug treatment in MDD adversely affect nervous system.

MDD is a recurring illness, and not only residual symptoms remain after the acute episode but also adverse effects are seen after drug therapy (Sakurai, Suzuki, Yoshimura et al., 2017; Saragoussi, Touya, Haro et al., 2017). Recently published studies (López-Otín, Blasco, Partridge et al., 2013) have reported that hallmarks of aging are mainly associated with cellular function and include: oxidative stress [reactive oxygen species (ROS) and total antioxidant capacity (TAC)]; telomere metabolism [telomerase activity and telomere length]; DNA damage [8-hydroxy 2'-deoxy guanosine (8OH2dG)], nutrition sensing [sirtuin 1], and intercellular communication [cortisol, Il-6, and brain derived neurotrophic factor (BDNF)]. As MDD is associated with accelerated aging and earlier onset of complex lifestyle diseases, it is important to analyze the impact of YMLI on the rate of biological aging and the severity of disease in MDD.

Objective of this trial was to compare the systemic markers of biological aging at the cellular level and parallel changes in depression severity in MDD patients treated with either YMLI or routine drug therapy (RDT) for 12 weeks. The findings of this assessment are reported in this article.

METHODS AND MATERIALS

Fifty-five patients who were diagnosed as MDD at psychiatry outpatient unit were selected for the study

[1]Corresponding Author

based on the inclusion criteria of - age between 20 and 60 years; BDI II ≥ 19 and ≤ 45; and no comorbidity with major medical or surgical disorder. The study was initiated after ethical clearance (ESC/T-370/22-07-2015) from the institute ethics committee and the registration of the trial [Clinical Trial Registry of India (CTRI) REF/2014/09/007532]. An informed consent was obtained before inclusion of patients in the study. Response was defined as demonstrating 60% drop in the BDI-II score or, having a BDI-II score ≤ 9. Three patients dropped out from the intervention. Patient characteristics are described in Table 1.

Table 1: Demographics and Clinical Variables

	Group		P-Value
	YMLI (n = 29)	CONTROL (n = 26)	
Age (years), mean ± SD	38.54 ± 11.16	36.84 ± 9.88	0.554
Sex, *n* (%)			
Female	17 (55)	16 (58)	1.000*
Male	12 (45)	10 (42)	
Marital status, *n* (%)	25 (86)	24 (92)	0.672*
Smoker, *n* (%)	4 (14)	3 (12)	1.000*
Alcoholic, *n* (%)	5 (17)	6 (26)	0.739*
Kuppuswamy SES scale, mean ± SD	17.28 ± 6.44	18.27 ± 5.86	0.594
BMI score, mean ± SD	28.18 ± 7.56	26.79 ± 8.26)	0.518
ROS (RLU/min/10^4 neutrophils), mean ± SD	3274.65 ± 784.76	3416.68 ± 824.56	0.516
TAC (mmol Trolox equiv/L), mean ± SD	6.12 ± 2.08	6.54 ± 1.94	0.443
8OH2dG (pg/ml), mean ± SD	1316.52 ± 121.72	1288.84 ± 98.42	0.361
Telomerase activity (RTA/cell), mean ± SD	13.58 ± 4.45	15.26 ± 5.81	0.231
Telomere length (IU/cell), mean ± SD	0.62 ± 0.22	0.73 ± 0.27	0.102
Sirtuin 1 (ng/ml), mean ± SD	27.64 ± 5.80	26.56 ± 7.22	0.542
Cortisol (ng/ml), mean ± SD	430.67 ± 35.84	428.56 ± 33.34	0.823
IL-6 (pg/ml), mean ± SD	4.17 ± 0.59	3.96 ± 0.62	0.204
BDNF(ng/ml), mean ± SD	12.34 ± 4.43	13.18 ± 4.32	0.481
BDI-II score, mean ± SD	30.23 ± 5.45	32.61 ± 6.18	0.135

Abbreviations: BDI-II, Beck Depression Inventory II; BDNF, brain derived neurotrophic factor; BMI, Body mass index; CI, Confidence Interval; *n*, number; SD, standard deviation; SES, socioeconomic status; YMLI, yoga- and meditation-based lifestyle intervention

Interventions

Participants were randomized into YMLI group or routine drug therapy (RDT) group (control), after recruiting and screening eligible subjects. Baseline characteristics were recorded before intervention. Participants underwent 12-week pre-tested (Bijlani et al., 2005). YMLI program comprising theory and practice sessions. The sessions were taught by registered, specialized yoga instructor at AIIMS, New Delhi. YMLI is based on Patanjali's ashtanga (eight limb) yoga and include a set of asanas (physical postures), pranayama (breathing exercises), and dhayna (meditation). YMLI included interactive lectures on lifestyle, lifestyle diseases, and the importance of their prevention. The Hawthorne effect was insignificant because of YMLI's emphasis on environmental enrichment and self-awareness.

Outcomes

The primary outcomes were systemic markers of biological aging at the cellular level: oxidative stress [reactive oxygen species (ROS) and total antioxidant capacity (TAC)]; telomere metabolism [telomerase activity and telomere length]; DNA damage [8-hydroxy 2'-deoxy guanosine (8OH2dG)], nutrition sensing [sirtuin 1], and intercellular communication [cortisol, Il-6, and brain derived neurotrophic factor (BDNF)]. Methodological details of the procedures have been described previously (Tolahunase, Sagar, & Dada, 2017).

Secondary outcome was self-rated measure of Beck Depression Inventory II [BDI II] scale. All investigations were carried out at baseline and after 12 weeks.

Statistical Methods

In this trial, chi-square test and Fisher's exact tests were used to compare categorical characteristics at baseline; Student's t-test was used to compare normally distributed continuous variables and the nonparametric continuous data were compared using Wilcoxon rank-sum test (Table 1). Baseline to end-of-study changes were analyzed using paired samples t-test. To assess the statistical significance of differences between groups at each time point we used independent samples t-test and Fisher's exact test.A value of $p < 0.05$ was considered statistically significant.

RESULTS

Baseline demographic and clinical data are presented in Table 1. Both YMLI and RDT groups were similar in all parameters at baseline. The most important finding of this study is that there was significant improvement in the 12-week levels of systemic biomarkers of biological aging at the cellular level in YMLI group compared to RDT group [decrease in ROS, 8OH2dG, cortisol, and IL-6, and increase in TAC, telomerase activity, BDNF, and sirtuin 1) (all $P<0.05$). However, YMLI did not significantly improve telomere length ($P=0.092$) (Table 2). These findings were in parallel with significant reduction in BDI-II scores ($P<0.001$) and remission rates (64% in YMLI group and 22% in RDT group, $P=0.003$)

Table 2: Between-group analysis of the change in systemic biomarkers of biological aging and depression severity after interventions in the study

	YMLI (n=29) (12 week – Baseline) Mean Change (CI)	CONTROL (n=26) (12 week – Baseline) Mean Change (CI)	P Value [1]
Primary outcome **Systemic markers of biological aging**			
Oxidative Stress			
ROS (RLU/min/10^4 neutrophils)	-878.81 (-1206.06, -427.57)	124.64 (46.88, 178.43)	< 0.001[†]
TAC (mmol Trolox equiv/L)	1.92 (1.46, 3.84)	-0.15 (-0.51, 0.21)	< 0.001
DNA damage			
8OH2dG (pg/ml)	-112.54 (-276.54, - 76.63)	38.42 (-36.43, 121.43)	< 0.01
Telomere metabolism			
Telomerase activity (IU/cell)	6.32 (2.96, 9.36)	-0.43 (-1.42, 0.41)	< 0.001
Telomere length (IU/cell)	0.18 (0.00, 0.36)	0.03 (-0.11, 0.19)	0.092
Nutrition sensing			
Sirtuin 1 (ng/ml)	7.44 (2.96, 11.82)	-0.78 (-0.41, 1.17)	< 0.001
Intercellular communication			
Cortisol (ng/ml)	-146.74 (-212.43, -86.45)	31.62 (-8.76, 71.42)	< 0.001[†]
IL-6 (pg/ml)	-0.86 (-1.28, -0.51)	0.61 (0.27, 1.02)	< 0.001
BDNF (ng/ml)	4.68 (2.20, 8.16)	0.04 (-0.82, 0.85)	< 0.001
Secondary outcome **Depression severity**			
BDI-II scores	-6.13 (-9.54, -3.69)	1.55 (-1.24, 3.16)	< 0.001

[†] Wilcoxson signed rank test; [1] independent samples t test.
Abbreviations: BDI-II, Beck Depression Inventory II; BDNF, brain derived neurotrophic factor; BMI, body mass index; CI, Confidence Interval; *n*, number; SD, standard deviation; YMLI, yoga- and meditation- based lifestyle intervention.

DISCUSSION

In this study we were interested in determining whether 12 week YMLI and RDT modify the rate of biological aging at the cellular level in parallel to changes in depression severity in MDD patients. The results suggest that the levels of systemic biomarkers at the cellular level following YMLI are significantly different from those observed following RDT. These findings are encouraging since they strengthen the evidence that YMLI may significantly slow the rate of biological aging. These effects on biological aging are reflected clinically as significant differences in the reduction of depression

severity and in the remission rates between YMLI and RDT groups.

Maintaining oxidative stress levels in physiological range when cells are exposed to psychological stress and environmental insults and poor social habits appear to be crucial in reversing the pathobiology of MDD and providing a cure (Lindqvist, Dhabhar, James et al., 2017). This may involve improved processing of substrates to mitochondria. In addition, improved nutrition sensing due to increase in the levels of sirtuin 1 may decrease the substrate overload on mitochondria by decreasing proteostasis. Sirtuin 1 also modify the expression of the anti-oxidant genes through epigenetic effects. Both proteostasis and epigenetic effects involve sirtuin 1 deacetylation reactions. Furthermore, findings from previous research have shown that sirtuin 1 increases cell survival and neurogenesis through mTOR signaling and BDNF expression (Guo, Qian, Zhang et al., 2011). Caloric restriction is known to increase sirtuin 1 expression, and previous study from our lab (Tolahunase, Sagar, & Dada, 2017) has shown for the first time that YMLI increases sirtuin 1 level independent of caloric restriction.

YMLI-induced oxidative eustress (oxidative stress in physiological range) may contribute to genomic stability as demonstrated by decrease in the levels of DNA damage marker (decrease in 8OH2dG, a marker of oxidative stress) and increase in the levels of telomerase activity. Maintaining telomere length is crucial to prevent stem cell exhaustion and cellular senescence. Improved genomic stability may be crucial to maintaining healthy stem cells and to increase neuroplasticity in the brain and decrease exaggerated stress and inflammatory responses through improved somatic tissue environment. Oxidative stress also causes genome wide hypomethylation and YMLI significantly decreases these levels and optimizes the levels of dysregulated transcripts to normal levels (Dada, Faiq, Mohanty et al., 2016). Significant decrease in cortisol and IL-6 and increase in BDNF suggest reversal of the adverse effects of biological aging in the brain and in regulatory feedback systems. However, due to a relatively low number patients in our study, assessment after a short duration, these findings must be validated in large sample size.

One of the great burdens in MDD is accelerated biological aging that contribute to high relapse rates, high rates of suicide, rapid decline in cognitive function, and increased risk and earlier onset of complex lifestyle diseases. Our assessment of the changes in biological aging at 12-week after YMLI intervention, supported by evidences from the literature (Tolahunase, Sagar, & Dada, 2017), suggest that YMLI, a MBI, improved clinical outcome in MDD in contrast to drug therapy, and that it provided remission by effectively reversing the pathobiology of MDD so that long term remission is possible, with fewer side effects. Since MDD is increasingly being recognized as a mind-body disorder and residual somatic symptoms are common after current first line treatments (Sakurai, Suzuki, Yoshimura et al., 2017), increased remission after YMLI may be due to reversal of the accelerated biological aging in somatic tissues parallel to improved nervous system functions.

Thus, YMLI intervention can reduce the rate of biological aging and severity of MDD. It is also associated with fewer relapses, improved patient compliance, and overall quality of life of patients and their caregivers.

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COMPETING INTERESTS

The authors declare no competing financial interests.

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