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Original Article

Study of cytokine as a predictor of antidepressant effects of physical exercise in depression

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Abstract: Background and aims: Exercise is an effective therapy for major depressive disorder (MDD) and has been demonstrated to have anti-inflammatory effects in non depressed subjects. In this study, we tested the extent to which inflammatory markers interleukin 1-β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) can be used to predict response to exercise treatment after an incomplete response to an serotonin reuptake inhibitor (SSRI). Methods: MDD patients who partial responders to a selective SSRI were randomized to receive one of two doses of exercise: 20 kilocalories per kilogram of body weight (KKW), or 5 KKW for 15 weeks were enrolled in this study from cangzhou central hospital. Blood samples were collected before initiation and again at the end of the 15-week exercise intervention. The serum samples were analyzed using a multiplexed ELISA for IL-1β, IL-6, TNF-α. Results: A significant positive correlation between change in IL-1β and depression symptom scores was observed ($P = 0.044$). There was no significant change in the level of any cytokine following the 15-week intervention, and no significant relationship between exercise dose and change in mean cytokine level. Conclusions: Our results confirm antidepressant medications that the decreasing IL-1β to positive depression treatment outcomes.

Keywords: Physical exercise, cytokines, major depressive disorder

Introduction

Major depressive disorder (MDD) is a mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities [1]. MDD significantly affects a person's family and personal relationships, work or school life, sleeping and eating habits, and general health. According to the World Health Organization (WHO), it is predicted to be the second-leading cause of disease burden worldwide after HIV in 2030 [2]. The prevalence of depressive disorders and their associated socioeconomic burden are of growing concern. Evidence suggests that of those receiving adequate medication trials, most will not achieve remission following initial treatment and nearly one-third will not achieve remission even following several treatment steps [3]. The identification of moderators of treatment response is a critical step in the pursuit of developing methods to better match patients with treatments. These moderators could be used to develop new diagnostic methods that subtype patients into groups with differences in underlying pathophysiology as well as for personalizing treatment [4].

Physical exercise has been shown to be effective as a independent and as an augmentation treatment for MDD [5-8]. Madhukar et al. recent work suggested gender and family history as significant regulators of treatment response for exercise management [9]. In addition, they examined changes in Brain-Derived Neurotrophic Factor (BDNF) associated with exercise treatment and found higher levels of BDNF at baseline predicted a significantly greater decrease in depressive symptoms following exercise augmentation. These findings, together with previous studies revealing that treatment outcome, to be certain extent, may be relied on underlying genetic factor, demonstrate there may be underlying biological moderators related to antidepressant response to physical exercise

and support the further verification of biological biomarkers associated with treatment response of exercise [10-14].

Cytokines have potential for biomarker development in MDD [15-18]. Recent studies have shown that these markers are high in depressed patients when compared to healthy controls. Elevations of interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) have been affirmed in a meta-analysis [19]. Additionally, antidepressant treatment has been shown to decrease levels of cytokine in MDD. In a recent meta-analysis findings confirmed that cytokines are reduced following treatment with SSRIs. Studies have also demonstrated that elevated baseline TNF-α and IL-6 relate to treatment failure for SSRIs [20-22]. To our knowledge, few studies have determined the relationship between physical exercise and cytokine markers in a depressed sample.

This report tests the extent to which inflammatory markers (IL-1β, IL-6, TNF-α) can be used to predict response to exercise treatment after an incomplete response to an SSRI. It also examines how the inflammatory markers change with exercise.

Patients and methods

Subjects

In the treatment with exercise augmentation for depression (TREAD) study, adults with MDD who failed to remit with an adequate trial of a single SSRI were recruited with an exercise augmentation regimen at the Department of Nursing, Cangzhou Central Hospital between January 2010 and December 2014. Blood samples were collected from these subjects for analysis of the cytokine markers at both before (baseline) and at the end of treatment. TREAD recruited adults, age 18-60, with MDD, who were currently taking an adequate dose of a single SSRI but were non-responders as defined by a score of ≥ 14 on the 17-Hamilton Rating Scale of Depression (HRSD17), following > 6 weeks and < 6 months treatment. Participants were excluded for presence of psychosis or if they regularly engaged in physical activity.

Written informed consents conforming to the tenets of the Declaration of Helsinki were obtained from each participant prior to the study. The Medical Ethics Committee of the department of neurosurgery, the first affiliated hospital of Henan university, approved this study.

Interventional treatment

Participants were randomly divided into two groups: the low dose group with a target energy expenditure of 5 kilocalories per kilogram of body weight per week (KKW) and the high dose group with 20 KKW over 15 weeks. Subjects engaged in aerobic exercise (treadmill, cycle ergometers or a combination) at self-selected exercise intensity. The exercise dose was completed in a combination of supervised and home-based sessions, and participants logged actual activity using a web based system.

Diagnosis

Self-report and clinician-rated measures were collected prior to the first exercise session of each week. Trained personnel blinded to group assignment completed clinician-rated assessments. The primary outcome assessment was the 30-item clinician-rated Inventory of Depressive Symptomatology (IDS-C_{30}); additional assessments of depressive symptoms included the 30-item self-rated Inventory of Depressive Symptomatology (IDS-SR_{30}) and the ($HRSD_{17}$).

Sample collection and analysis

Of the 121 randomized TREAD participants, 100 signed additional consent for blood analysis at baseline (95 samples were available); 63 of these completed the study and provided week 15 samples. Resting blood samples were collected at baseline and following the 15-week intervention. All samples were drawn in the morning; participants fasted a minimum of 3 hours prior to blood draw, and were at least 24 hours from the last exercise session. Ten ml of peripheral venous blood was drawn and centrifuged at 900 rpm for ten minutes at room temperature to separate the blood components. Serum was subsequently frozen at -80°C until the time of analysis. We analyzed samples in duplicate using a multiplexed chemo-iluminesce ELISA method (MesoScale Discovery, Gaithersburg, MD) for IL-1β, IL-6, and TNF-α. All data were calibrated using standard curves generated for each cytokine.

Table 1. The demographic, clinical and laboratory characteristics of tested samples

Parameter	Total (n)	Mean ± SD	20 KKW (n)	Mean ± SD	5 KKW (n)	Mean ± SD	X^2/t	*P* value[&]
Age	95	46.15±9.23	50	44.83±8.65	45	49.32±9.34	1.78	0.07
Male (%)	95	20	50	15.19	45	25	1.16	0.21
IDS-C	95	34.41±7.12	50	33.51±5.94	45	35.16±8.77	1.21	0.16
IDS-SR	91	32.51±9.76	47	31.86±4.87	44	33.26±1.76	1.50	0.39
HSRD	95	18.10±6.83	50	17.97±2.81	45	18.26±4.93	0.83	0.41
IL-1β	93	0.10±0.03	49	0.09±0.07	44	0.10±0.03	0.69	0.49
IL-6	95	0.87±0.54	50	0.98±0.76	45	0.81±0.69	0.03	0.95
TNF-α	94	5.45±1.76	50	5.32±1.58	44	5.54±1.7	2.76	0.07
BMI	95	30.89±3.61	50	30.36±7.01	45	31.44±4.13	0.87	0.39
SF-36	91	80.11±8.97	47	80.68±9.83	44	79.77±8.72	0.2	0.84
RE (%)	95	67.63	50	67.89	45	67.35	0.13	0.71
FH (%)	95	67.63	50	67.98	45	67.31	0.03	0,94
Duration	94	20.18±8.12	49	18.31±8.25	45	22.07±9.19	1.5	0.12

[&]Tested for differences between 20 KKW and 5 KKW exercise groups on each demorgraphic/clinical characteristic in a separate model. Note: SD = standard deviation; KKW = Kilocalories per kilogram per week; IDS-C = Inventory of Depressive symptoms-Clinician Rated; HRSD = Hamiliton Rating Scale for Depression; SF-36 = SF-36 Physical Health; RE = Recurrent of MDD; FH = Family History of MDD. N = Number of patients involved in the investigation.

Table 2. Spearman correlation coefficients between the change in each cytokine level and the change in depression severity for all completers and within each dose group

Depression severity	Group	n	r_s	*P* value	n	r_s	*P* value	n	r_s	*P* value
		IL-1β			IL-6			TNF-α		
HRSD	Total	63	0.23	0.028	62	0.25	0.07	61	-0.01	0.96
	5 KKW	32	0.12	0.420	32	0.24	0.15	31	-0.19	0.29
	20 KKW	31	0.38	0.040	30	0.17	0.31	30	0.18	0.29
IDS-C	Total	61	0.24	0.040	61	0.21	0.09	62	0.05	0.69
	5 KKW	31	0.21	0.260	32	0.24	0.16	32	-0.04	0.81
	20 KKW	30	0.28	0.120	29	0.17	0.42	30	0.09	0.63
IDS-SR	Total	62	0.24	0.048	60	0.02	0.90	59	-0.01	0.37
	5 KKW	32	0.16	0.360	30	0.13	0.45	31	-0.15	0.37
	20 KKW	30	0.32	0.049	30	-0.03	0.26	28	-0.10	0.61

Note: Change was operationally defined as week 15 cytokine level minus baseline cytokine level. Note: KKW = Kilocalories per kilogram per week; IDS-C = Inventory of Depressive symptoms-Clinician Rated; HRSD = Hamiliton Rating Scale for Depression.

Statistical analysis

Data were initially assessed for normality and log-transformed where appropriate. Baseline descriptive data were expressed as mean ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. Differences between groups were assessed using unpaired *t*-test or Mann-Whitney test for continuous variables, and by Chi squared test for categorical variables. We performed an Analysis of Covariance (ANCOVA) on each cytokine level at week 15, while controlling for baseline cytokine level, BMI, and the physical subscale of the SF-36. Multivariate analysis using stepwise logistic regression was completed for all significant variables in univariate analysis. All analyses were performed using SPSS 18.0. Two-tailed tests with a 5% level of significance were used throughout.

Results

The characteristics of patients

A total of 121 baseline samples were collected and analyzed by using cytokine assay. One baseline value for TNF-α was greater than five standard deviations above the sample mean and thus excluded from further analysis. Two participants had missing baseline values for IL-1β and were also excluded. An additional participant sample had no value for 15 week IL-1β this participant was included in the mixed model but excluded from the correlation analysis. **Tables 1** and **2** show the number of participants who were included in each analysis.

Table 3. Effect of physical exercises on change of cytokine levels from baseline to week 15

	n	Baseline	Week 15	Δ_M	*P* value[&]
Groups			IL-1β		
Total	63	0.10±0.07	0.13±0.28	0.03±0.27	0.38
5 KKW	32	0.10±0.06	0.11±0.05	0.01±0.07	0.77
20 KKW	31	0.09±0.05	0.16±0.45	0.07±0.43	0.21
Groups			IL-6		
Total	62	0.89±0.77	0.77±0.25	-0.12±0.97	0.58
5 KKW	32	0.87±0.57	0.79±0.65	-0.08±0.97	0.87
20 KKW	30	0.91±0.79	0.74±0.46	-0.17±0.82	0.56
Groups			TNF-α		
Total	63	5.77±1.74	5.60±1.76	-0.18±0.79	0.18
5 KKW	32	6.18±1.57	5.68±1.67	-0.32±1.08	0.41
20 KKW	31	5.28±1.62	5.29±1.64	0.01±0.83	0.91

Note: Δ_M = Mean change in cytokine levels; KKW = Kilocalories per kilogram per week; Each cytokine was measured in pg/ml. [&]From Wilcoxon signed rank test (two-tailed) for mean change.

Table 4. ANCOVA results for effect of different exercise groupson cytokine at week 15

			IL-1β			
Exercise Groups	n	M	SE	95% CI	F	*P* value
5 KKW	32	0.11	0.05	0.02-0.21	0.87	0.38
20 KKW	31	0.18	0.04	0.07-0.28		
			IL-6			
Exercise Groups	n	M	SE	95% CI	F	*P* value
5 KKW	32	0.76	0.08	0.65-0.89	0.21	0.68
20 KKW	30	0.79	0.08	0.62-0.91		
			TNF-α			
Exercise Groups	n	M	SE	95% CI	F	*P* value
5 KKW	32	5.52	0.16	5.21-5.91	0.71	0.41
20 KKW	31	5.79	0.18	5.32-6.05		

Note: M = Least Squares Mean; SE = Standard Error; 95% CI = 95% Confidence Interval for the expected mean value; KKW = Kilocalories per kilogram per week.

Participants' baseline demographic and clinical characteristics as well as mean baseline cytokine levels for all participants and for each exercise dose group are reported in **Table 1**.

Correlation analysis between the cytokine level and depression symptoms

Spearman correlation coefficients between the change in each cytokine level and the change in depression severity for all completers and within each dose group are shown in **Table 2**. The analysisi of Spearman correlations for all completers revealed a significant positive relationship between change in IL-1β and change in IDS-C30 (rs = 0.24, $P = 0.040$), change in HRSD17 (rs = 0.23, $P = 0.028$), and change in IDS-SR_{30} ($r_s = 0.24$, $P = 0.048$). Significant associations were also observed in the high dose exercise group, with significant positive relationships between change in IL-1β and change in $HRSD_{17}$ ($r_s = 0.38$, $P < 0.05$) as well as change in IDS-SR ($r_s = 0.32$, $P < 0.05$), respectively. Correlations between change in depression severity and change in other cytokines were not significant.

Association between change in cytokine level and physical exercise therapy

Mean cytokine levels at baseline and week 15, as well as change in the means for all completers and by dose group, are reported in **Table 3**. There was no significant change in any of the mean cytokine levels over the study period in the entire sample or within either exercise-dose group. Further, we assessed exercise group effect on cytokine level. The ANCOVA of each inflammatory cytokine outcome, controlling for baseline cytokine level, BMI, and SF-36 physical health, revealed no significant effect of any exercise group in any of the individual cytokine mean values at week 15 (p's > 0.35) (**Table 4**).

Discussion

Our results suggest that cytokines may be useful biomarkers of the antidepressant effect of exercise. We found a significant positive correlation between changes in IL-1β and depressive symptoms on all three symptom measures used in TREAD, such that participants who experienced larger drops in IL-1β level also had larger decreases in symptom scores. This relationship maintained significance in the higher dose 20 KKW subgroup, but not in the lower dose 5 KKW subgroup, demonstrating a dose response relationship. Contrary to Madhukar H results, we did not find that exercise augmentation treatment lowered mean cytokine levels or that a higher dose of exercise had a stronger effect on mean cytokine levels.

Our results that a change in IL-1β associates with change in symptom severity, on the other

hand, is similar with a growing body of research on cytokines and SSRI treatment [23]. For instance, Song et al. [24] found that responders to SSRI treatment had lower end treatment IL-1β than non-responders. The recent meta-analysis by Hannestad et al. [25] also suggested reductions in IL-1β associate with better consequence with SSRIs. Our finding is significant, however, in that it is the first replication of this relationship in a sample treated with exercise. We also found significant correlations between alteration of IL-1β and change in depressive symptom severity in the 20 KKW group but not in the 5 KKW group. This suggests a dose-response effect on IL-1β might have been found in a larger or better characterized sample.

We did not find that exercise augmentation treatment lowered mean cytokine levels or that a higher dose of exercise had a stronger effect on mean cytokine levels. This finding is in disagreement with both studies of exercise in healthy and medically ill samples, and with studies of SSRI treatment in depressed samples [26]. Similarly, we failed to find a dose effect on cytokine change. It is probable that pretreatment with SSRIs in this sample obscured our ability to detect change in cytokine levels, since SSRIs are known to lower cytokines. Similarly, SSRI pretreatment likely reduced baseline depressive symptoms in our sample. Future research examining the effect of exercise on inflammatory cytokines in treatment MDD patients would provide the information necessary for comparison to previous SSRI trials.

While it is clear that there is a substantial relationship between inflammation and depression, several mechanisms appear to be involved and may play key roles across patients. Indeed, subsets of MDD patients have an altered peripheral immune system, which includes both impaired cellular immunity, and an increase in the levels of proinflammatory cytokines. Furthermore, studies indicate that innate immune cytokines can influence pathophysiological domains, such as neurotransmitter metabolism, neuroendocrine function and regional brain activity, all of which are relevant to depression. Moreover, administration of high levels of proinflammatory cytokines has been shown to cause changes in behaviour, such as low mood, fatigue, anxiety, sleep disturbances, anhedonia and cognitive dysfunction, all of which closely resemble symptoms observed in MDD [27-31]. Not only has exercise been shown to be broadly anti-inflammatory, but it has been specifically demonstrated to act on these pathways such as disruption of synthesis, reuptake and metabolism of neurotransmitters, alteration of hypothalamic-pituitary-adrenal (HPA) axis function to reverse the effects of inflammation [32-34]. Any or all of these mechanisms could be involved in the efficacy of exercise as a treatment of MDD, and future studies better depicting baseline cytokine and its change among the period of exercise therapy may clarify which hypothesis are most important in clinical recovery.

In summary, our results demonstrate that exercise may play a crucial role in effective treatment of MDD within specific subpopulations. For instance, chronic increased levels of inflammatory cytokine is closely related to metabolic syndrome and insulin resistance, in turn, of these syndrome may be accompanied with treatment-resistant depression [35]. Considering exercise generally decrease cytokine levels, counterpoise insulin resistance, and improves several feature of metabolic syndrome [36, 37]. Thus, it is reasonable that exercise may be extremely effective as a single-handed or combined therapy for MDD in patients with inflammatory conditions.

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Disclosure of conflict of interest

None.

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