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Research paper

The effect of cognitive behavioral therapy on the circulating proinflammatory cytokines of fibromyalgia patients: A pilot controlled clinical trial

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ABSTRACT

Objectives: There is no consensus over the effect size of cognitive behavioral therapy (CBT) in the treatment of fibromyalgia (FM). This study aims to evaluate the effect of CBT on FM patients, through assessing circulating proinflammatory cytokines.

Methods: A controlled, single-blind, parallel clinical trial was performed with 21 FM patients in each group. Sixteen FM patients in the intervention group (CBT) and 17 FM patients in the control group (waiting-list) completed the study. For the intervention group, traditional face-to-face CBT was performed for groups of 10 and 11 patients in 20 sessions. Fibromyalgia Impact Questionnaire (FIQ), widespread pain index (WPI), circulating IL-6, IL-8, and TNF-α level were evaluated before and after the intervention using enzyme-linked immunosorbent assay. Intention-to-treat analysis was performed as the primary analysis.

Results: The average changes of factors examined were as follows: FIQ score −0.61 ± 5.5 in the waiting-list group and 10.2 ± 14.9 in the CBT group ($p = 0.012$); WPI −0.33 ± 1.1 in the waiting-list group and 2.4 ± 3.1 in the CBT group ($p = 0.002$); serum IL-6 level −0.05 ± 0.86 pg/ml in the waiting-list group and 1.5 ± 2.4 pg/ml in the CBT group ($p = 0.002$); serum IL-8 level − 0.55 ± 0.2.5 pg/ml in the waiting-list group and 5 ± 5.9 pg/ml in the CBT group ($p = 0.002$); serum TNF-α level 0.67 ± 1.8 pg/ml in the waiting-list group and 0.7 ± 1.6 pg/ml in the CBT group ($p = 0.89$).

Conclusion: Reductions in proinflammatory cytokines after CBT compared with a waiting-list control group confirm the potential value of these biomarkers as surrogate outcome measures in FM.

1. Introduction

Fibromyalgia (FM), one of the most common rheumatologic disorders, is estimated to affect up to one in 20 patients in primary care which is predominantly prevalent in women [1,2]. It is characterized by chronic widespread musculoskeletal pain, cognitive dysfunction, fatigue, and sleep disturbance [3].

In spite of the health burden of FM, its pathophysiology has remained controversial. It has been suggested that FM is simply caused by somatization of distress [4]; so psychological factors play a major role in the predisposition, onset, and perpetuation of FM [5]. For this reason, psychological therapies are widely used to reduce the symptoms of FM and improve the daily functioning of the patients. Cognitive behavioral therapy (CBT), which attempts to change negative thought patterns and introduce behavior modification to cope with pain, is considered as one the main psychological treatments of FM [6]. Although the efficacy and tolerability of CBT in reducing the key symptoms of FM have been reported in many investigations as compared to the recommended pharmacotherapies (pregabalin and/or duloxetine) [6], some preliminary questions have remained unanswered regarding the significance of CBT in FM treatment. Further, CBT has proved to yield mild to moderate effects in different investigations and there is still no consensus regarding the magnitude of the effect of CBT on FM symptoms [6].

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To date, evaluation of the efficacy of CBT in FM patients has mainly relied on self-reporting (subjective) assessments [6]. Meanwhile, accumulating evidence suggests a remarkable role for systemic inflammation in the pathogenesis of FM [7]. In addition, the circulating level of proinflammatory cytokines has been reported to be enhanced in FM patients compared to healthy controls [8,9]. Accordingly, we hypothesized that proinflammatory cytokines may be considered useful surrogate markers of the outcome in evaluating the treatment efficacy in FM patients.

In this study, we evaluated the effect of CBT on the circulating levels of relevant proinflammatory cytokines in FM patients including IL-6, IL-8, and TNF-α. To the best of our knowledge, this is the first study to evaluate the effect of CBT on the serum proinflammatory cytokines of FM patients.

2. Patients and methods

This study was approved by the ethics committee of Iran University of Medical Sciences under the code of IR.IUMS.REC 1395.95-03-196-29435 and was registered in the Iranian Registry of Clinical Trials under the code of IRCT2012100610960N2. Written consent was obtained from patients before their participation in the study.

Women between 18 and 64 years of age who had the diagnosis of FM entered this controlled, parallel-designed, clinical trial. The diagnosis of FM was done using American College of Rheumatology (ACR) criteria [10]. Accordingly, the diagnosis of FM was made if (1) the WPI was larger than 7 and the Symptom Severity Score (SS) was greater than 5, or the WPI was 3–6 and the SS was higher than 9; (2) symptoms remained at a similar level for at least 3 months; and (3) no other disorder was found that would otherwise explain the pain.

The exclusion criteria were a history of any chronic inflammatory conditions such as rheumatic diseases, metabolic diseases, infection, and any other concurrent disorder that could potentially affect the serum cytokine levels. The diagnosis of these comorbidities was based on a detailed history-taking, as well as clinical and laboratory examinations assessed by the involved rheumatologist. The patients with severe psychiatric disorders who were unable to follow behavioral techniques were also excluded. The diagnosis of severe psychiatric disorders was based on a detailed history-taking and clinical evaluation performed by the involved clinical psychologist. The criteria of diagnosis were based on DSM-5 (Diagnostic And Statistical Manual Of Mental Disorders, Fifth Edition) diagnostic classification [11]. Since vitamin D deficiency is reported to affect the outcome of treatment in FM, patients with vitamin D deficiency were also excluded from the study [12]. The patients who missed more than five CBT sessions were excluded from the study as well.

The sample size was calculated based on the standard deviation (SD) of 5.54 pg/ml for the circulating levels of IL-8, obtained from the study of Kosek et al., who evaluated the circulating levels of IL-6, IL-8, and TNF-α in the serum samples of FM patients in comparison with healthy volunteers [13]. With an effect size of 4.78 pg/ml, power of 80%, and significance level of 5%, 21 patients in each group were considered sufficient to detect a clinically important difference between circulating cytokine levels of the two study groups, based on a two-tailed *t*-test of the difference between means. Note that the circulating cytokine levels were assumed to be normally distributed.

During the recruitment process, a number of 21 consecutive FM patients who met the eligibility criteria of the study were allocated to the intervention (CBT) group. The next 21 consecutive eligible FM patients were enrolled in the CBT waiting-list and were considered as the control group in this study. The intervention group was asked not to take any other FM treatments concurrent with the CBT course. The control group was asked not to take any FM treatments while they are waiting for the beginning of the CBT course. Group assignment was kept confidential from the investigators who were responsible for the laboratory examinations and data collection.

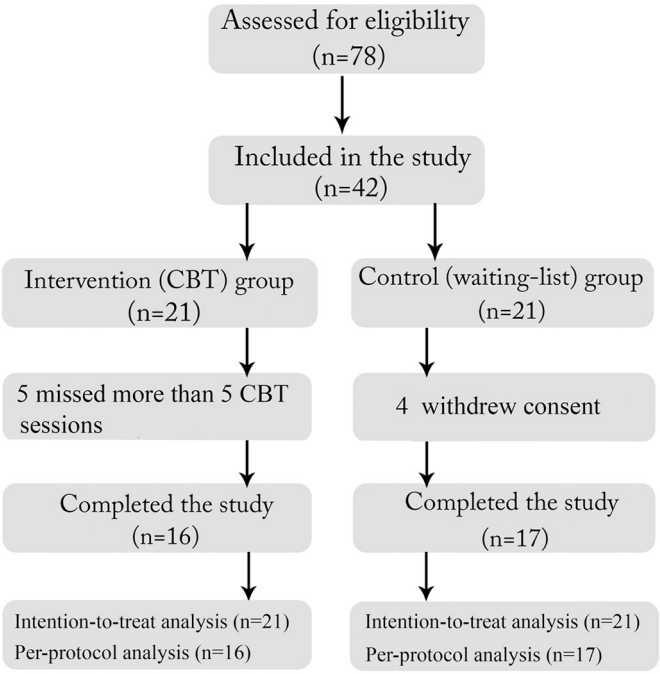

Fig. 1. The flowchart of the study population.

Five patients in the intervention group missed more than five CBT sessions and thus were excluded from the study. Four patients in the waiting-list decided not to continue participating in the study. Fig. 1 demonstrates the flowchart of the study population.

Traditional face-to-face CBT, including monitoring thoughts and feeling and correcting the inaccurate thinking patterns, was implemented with the same general content as previously described [14]. Meanwhile, some modifications were made considering the timeline of the project and our center facilities. While Karlsson et al. offered once weekly sessions lasting 3 h for 6 months, we offered twice weekly sessions lasting 2 h over 10 weeks. In total, 20 CBT sessions were performed for 10- and 11-patient FM groups.

The CBT courses were provided by a psychotherapist. Briefly, the CBT course consisted of 4 main sections including: i) identifying the troublesome situations in the patients' life (2 sessions); ii) becoming aware of one's own interaction between thoughts, emotions, and behaviors (2 sessions); iii) identifying the negative or inaccurate thinking (irrational beliefs) patterns (4 sessions); and iv) reshaping and restructuring negative or irrational beliefs pattern and changing the unproductive behaviors (12 sessions).

Persian version of Beck Depression Inventory-II (BDI-II) [15] and Beck Anxiety Inventory-II (BAI-II) [16] were used for evaluating the baseline depression and anxiety level in the two study groups. Beck inventory score ranges from 0 to 63, where an score of 0–9 shows normal to minimal depression or anxiety, score of 10–18 represents mild to moderate depression or anxiety, an score of 19–29 reflects moderate to severe depression and anxiety. Finally, a score of 30–63 reveals severe depression or anxiety.

The primary outcomes of the study were measured objectively through assessing the circulating levels of IL-6, IL-8, and TNF-α. On the other hand, the secondary outcomes were evaluated subjectively using the Fibromyalgia Impact Questionnaire (FIQ) in Persian [17] and the widespread pain index (WPI) [18]. The Persian version of FIQ had already been validated in the earlier investigation, and its reliability for measuring the health status of Persian-speaking FM patients was approved [19].

2.1. Primary outcome measures

A total of 5 ml of peripheral blood sample was taken from the patients of the intervention group immediately before the start of the first CBT session and at the end of the last CBT session. The same amount of blood was withdrawn from the patients of the control group immediately being assigned into the waiting-list and 2.5 months after the assignment. After collecting the blood samples, the blood serum was extracted and kept at −80 °C for later examinations. After the completion of CBT courses, the serum levels of IL-6, IL-8, and TNF-α were evaluated using an enzyme-linked immunosorbent assay (ELISA) and according to the manufacturer's protocols (Human IL-6 ELISA,BE69157, IBL Co; Human IL-8 ELISA, BE69160, IBL Co; and Human TNF-alpha Quantikine ELISA,DTA00C, R&D System Co).

2.2. Secondary outcome measures

FIQ was scored on a scale of 0–100: higher FIQ scores indicated a larger spectrum of problems related to FM. WPI was scored on a scale of 0–19, capturing the number of areas where the patient had pain over the last week. For the intervention group, FIQ and WPI were measured before the beginning of the first CBT session and at the end of the last CBT session. For the control group, FIQ and WPI were assessed immediately after assigning the patients into the waiting-list and 2.5 months after the assignment.

2.3. Statistical analyses

Statistical analyses of the data were performed using SPSS for Windows, version 16. Descriptive analyses were provided as the mean ± standard deviation (SD) or number and percentage. The primary analysis of the data was performed on the intention-to-treat population using the Last Observation Carried Forward (LOCF) imputation method. Per-protocol analysis including only the completers was done as the secondary statistical analysis. The changes of the outcome measures in the two study groups were compared using independent sample *t*-test or its nonparametric counterpart, Mann-Whitney *U* test. The Pearson/Spearman's correlation coefficient test was employed to examine the potential correlation between variables. Binary logistic regression was used to control for one single potential confounder at a time. A p-value of < 0.05 was considered significant.

3. Results

A total of 42 FM patients were included in this study (21 patients in each group). The mean age of the patients was 46.5 ± 7 years (range: 29–57 years). The mean disease duration was 22.4 ± 11.8 months (range: 2–48 months). None of the patients were smokers or alcoholic and all of them were married. The intervention group attended 17.1 ± 1.5 CBT sessions on average. The elapsed period between the two assessment points was 2.5 months in the CBT group and 3 months in the waiting list group. The clinical and demographic characteristics of the patients are reported in detail in Table 1.

Table 1
Clinical and demographic characteristics of FMS patients.

Variable	Intervention (CBT) group (n = 16)	Control (waiting-list) group (n = 17)	p value
Age (year)	45.4 ± 7.5	47.5 ± 6.4	0.32
BMI (kg/m^2)	29.8 ± 6.2	30.1 ± 7	0.46
Job			
• Housewife	11 (68.7)	13 (76.5)	0.58
• Employed	5 (31.3)	4 (23.5)	
Menopause			
• Pre	12 (75)	14 (82.4)	0.69
• Post	4 (25)	3 (17.6)	
Higher education[a]			
• Yes	9 (56.3)	7 (41.2)	0.33
• No	7 (43.7)	10 (58.8)	
Serum vitamin D level (ng/ml)	37.3 ± 11.7	35.6 ± 12.4	0.39
Duration of disease (month)	23.2 ± 11.5	21.6 ± 12	0.44
Beck Depression Inventory	18.23 ± 8.6	18.55 ± 8.9	0.71
Beck Anxiety Inventory	21.5 ± 7.6	21.1 ± 7.2	0.66

[a] Education after completion of high school, FMS: fibromyalgia syndrome; BMI: body mass index; NS: non-significant. The data are shown as mean ± SD and number (%).

3.1. Between group intention-to-treat analysis

Intention-to-treat analysis included all 21 randomized patients of the study groups. The average baseline and final self-reported measures of the two study groups are presented in Fig. 2 as well as Table 2. The mean change of FIQ score was −0.61 ± 5.5 in the waiting-list group and 10.2 ± 14.9 in the intervention group (p = 0.012). Also, the mean change of WPI was −0.33 ± 1.1 in the waiting-list group and 2.4 ± 3.1 in the intervention group (p = 0.002).

The mean baseline and final serum cytokine levels of the two study groups are demonstrated in Fig. 3 as well as Table 2. The mean changes of the studied parameters were as follows: serum IL-6 level changed −0.05 ± 0.86 pg/ml in the waiting-list group and 1.5 ± 2.4 pg/ml in the intervention group (p = 0.002); serum IL-8 level changed −0.55 ± 2.5 pg/ml in the waiting-list group and 5 ± 5.9 pg/ml in the intervention group (p = 0.002); serum TNF-α level changed 0.67 ± 1.8 pg/ml in the waiting-list group and 0.7 ± 1.6 pg/ml in the intervention group (p = 0.89). After adjusting for one single potential cofounder at a time using binary regression model, the change of serum IL-8 was still significantly greater in the CBT group. The change of serum IL-6 was also significantly greater in the CBT group when adjusted for all cofounders but the depression score (odds ratio = 2.1, 95% CI: 0.955–7.8, p = 0.06) (Table 3).

3.2. Between-group per-protocol analysis

Per-protocol analysis included 17 patients in the waiting-list group and 16 patients in the intervention group who completed the study. According to the results, the mean changes were as follows: FIQ score change was −0.76 ± 6 in the waiting-list group and 13.5 ± 15.8 in the intervention group (p = 0.002); WPI change was −0.41 ± 1.2 in the waiting-list group and 3.2 ± 3.3 in the intervention group (p = 0.001); serum IL-6 change was −0.6 ± 96 pg/ml in the waiting-list group and 1.9 ± 2.5 pg/ml in the intervention group (p = 0.001); serum IL-8 change was −0.7 ± 2.8 pg/ml in the waiting-list group and 6.6 ± 5.9 pg/ml in the intervention group ($p < 0.001$); and serum TNF-α change was 0.8 ± 2 pg/ml in the waiting-list group and 0.9 ± 1.8 pg/ml in the intervention group (p = 0.15).

3.3. Correlation analysis

The mean changes of IL-8 in completers were significantly correlated with the mean variations of IL-6 ($r = 0.690$, $p < 0.001$). The same situation was true for IL-8 in completers which was significantly correlated with mean WPI changes ($r = 0.447$, p = 0.009). Also, the mean WPI change in completers was significantly correlated with the mean change of FIQ (p = 0.407, p = 0.019). No other significant correlation was observed between the alterations of the evaluated parameters.

4. Discussion

Along with the subjective assessments of outcomes including WPI

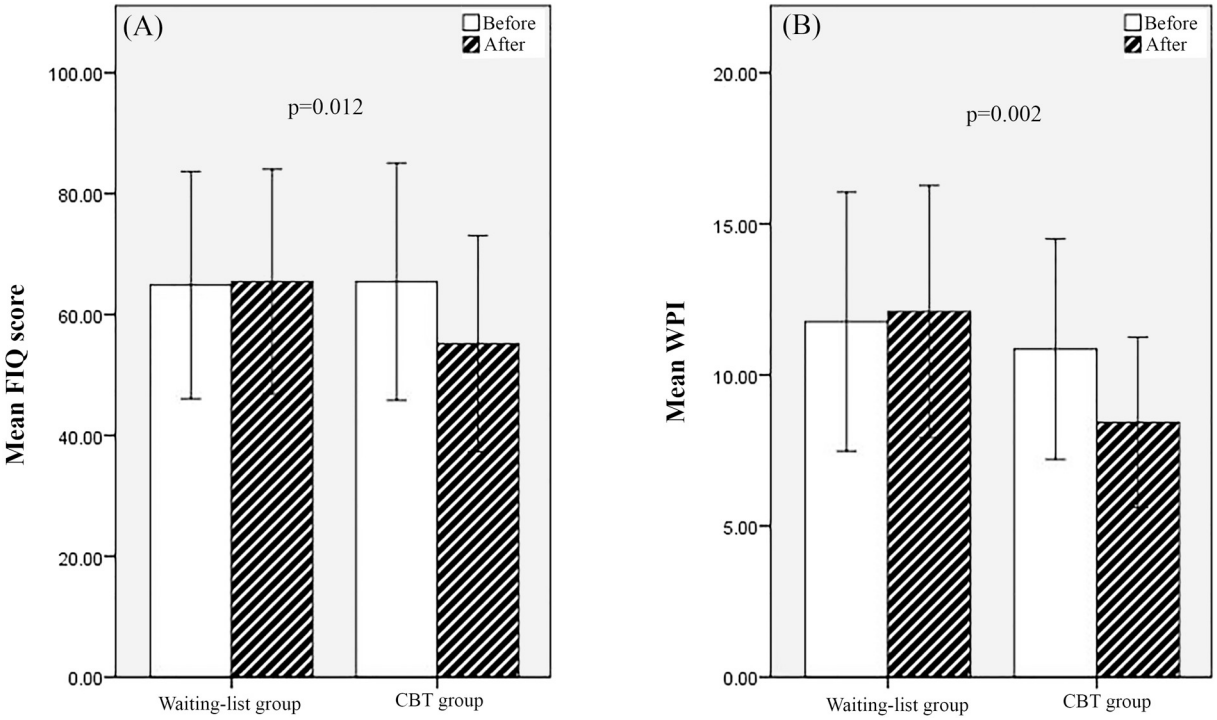

Fig. 2. The results of self-reported assessments in the case and control group at baseline and at the end of the study. $p < 0.05$ is considered significant.

and FIQ, we monitored the changes of relevant proinflammatory cytokine levels (IL-6, IL-8, and TNF-α) following the CBT to assess the value of other outcome measures. Based on our results, CBT intervention in FM significantly reduced the serum levels of IL-6 and IL-8, but not TNF-α. Further, subjective measures were significantly improved in the intervention group in this study.

Recently, Bernardy et al. performed a meta-analysis on the available randomized controlled trials (RCTs) to evaluate the efficacy, acceptability, and safety of CBT in FM patients. According to their study, CBT provided the same efficacy compared to drug therapy (pregabalin and/or Duloxetine), with superiority for coping with pain and tolerability. Nevertheless, the exact effectiveness of CBT in FM treatment has still remained unclear [6]. As all the included RCTs in this meta-analysis had used self-reporting assessments to measure the efficacy of CBT, we thought one can evaluate the efficacy of CBT from a different point of view.

According to the earlier investigations, IL-6 and IL-8 were more relevant with FM symptoms than TNF-α. The study of Mendieta et al. indicated elevated concentrations of IL-6 and IL-8 in FM patients. Further, both cytokines were correlated with clinical scores of the disease. They concluded that IL-6 and IL-8 could be considered as the most constant inflammatory mediators in FM. TNF-α concentration, however, was undetectable in FM patients of their study [20]. Wallace et al. found no significant difference between FM patients and controls by measuring TNF-α, while IL-8 was significantly higher in sera, and IL-6 was significantly higher in stimulated and un-stimulated peripheral blood mononuclear cells of FM patients compared with controls [21]. Our results also support stronger association between IL-6 plus IL-8 and FM symptoms than TNF-α.

In contrast to the study of Mendieta et al., suggesting a significant correlation between cytokines' concentration (IL-6 and IL-8) and FIQ scores [20], we did not find any correlation between these cytokines and FIQ score. On the other hand, a significant correlation was found between serum IL-8 level and WPI scores of the patients in our study.

Serum cytokines had been used as markers for the efficacy of FM treatment in other investigation as well. Parkitny and Younger evaluated the therapeutic role of low-dose Naltrexone in FM through assessing its effect on serum cytokine levels. According to their results, low-dose Naltrexone therapy was associated with reduced plasma concentrations of several proinflammatory cytokines including IL-6 and TNF-α [22]. In line with the results of Parkitny and Younger, our results also revealed that serum cytokines could be used as biomarkers of treatment efficacy in FM patients.

The positive effect of CBT on lowering proinflammatory cytokines in patients with the major depressive disorder had been reported earlier. Moreira et al. assessed the changes of circulating proinflammatory

Table 2
Comparison of the baseline and final outcome measures between the two study groups.

(Intention-to-treat) Outcome measure	Control (waiting-list) group (n = 21)		Intervention (CBT) group (n = 21)		p value[a]
	Baseline	Final	Baseline	Final	
FIQ score	64.8 ± 18.8	65.4 ± 18.5	65.4 ± 19.6	55.2 ± 17.9	0.012
WPI	11.8 ± 4.3	12 ± 4.2	10.9 ± 3.6	8.4 ± 2.8	0.002
Serum Il-6 (pg/ml)	3.4 ± 3.7	3.4 ± 3.5	3.6 ± 3.7	2.1 ± 2.1	0.002
Serum Il-8 (pg/ml)	30.5 ± 6.4	31 ± 7	30.9 ± 5.4	25.9 ± 8.2	0.002
Serum TNF-α (pg/ml)	34.6 ± 7.7	34 ± 7.2	33.5 ± 6	32.8 ± 6.1	0.89

The data are shown as mean ± SD and number (%).
CBT: cognitive behavioral therapy; FIQ: Fibromyalgia Impact Questionnaire; WPI: widespread pain index.
[a] The change of outcomes measures were compared.

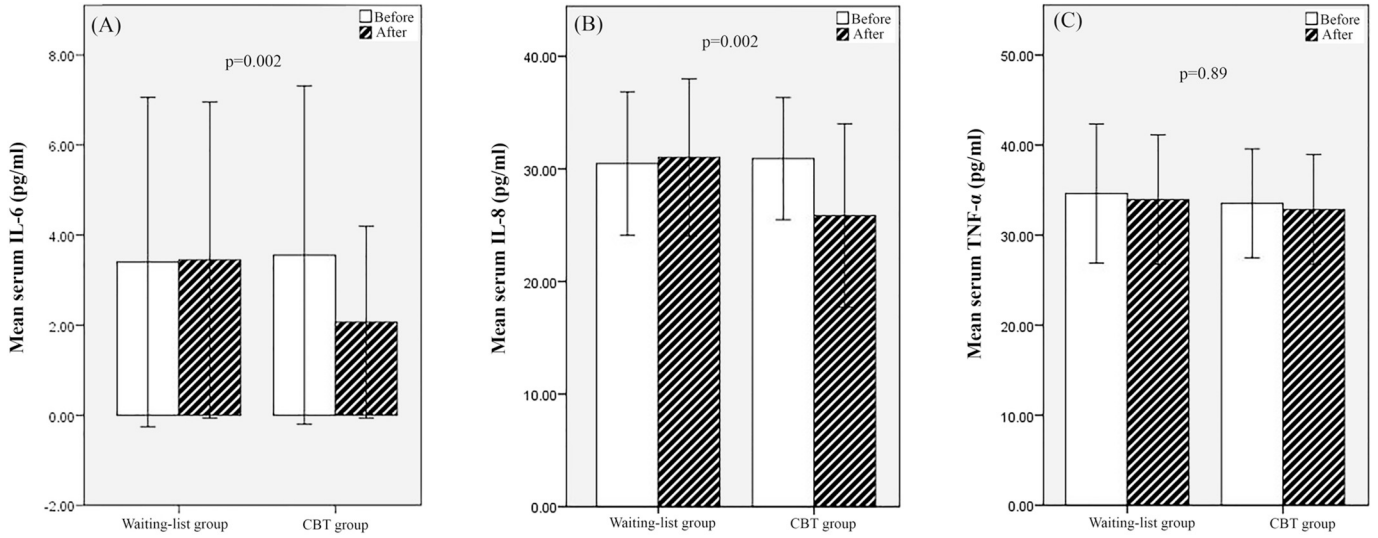

Fig. 3. The circulating levels of proinflammatory cytokines in the case and control group at baseline and at the end of the study. $p < 0.05$ is considered significant.

Table 3
Logistic regression analysis showing the predictive values of IL-6 and IL-8 as surrogate markers of CBT effect in the treatment of FM patients before and after controlling for a single potential confounder at a time.

Outcome measure	Odds ratio	95% CI	p value
Serum IL-6 not adjusted	2.73	1.2–7.3	0.04
Serum IL-6 adjusted for age	2.6	1.05–7.6	0.05
Serum IL-6 adjusted for BMI	2.9	1.11–7.2	0.039
Serum IL-6 adjusted for BDI	2.1	0.995–7.8	0.06
Serum IL-6 adjusted for BAI	2.05	1.15–7.1	0.04
Serum IL-8 not adjusted	1.44	1.1–1.9	0.008
Serum IL-8 adjusted for age	1.5	1.1–2	0.01
Serum IL-8 adjusted for BMI	1.81	1.19–2.4	0.02
Serum IL-8 adjusted for BDI	1.31	1.06–1.8	0.01
Serum IL-8 adjusted for BAI	1.42	1.04–1.9	0.009

BMI: body mass index; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory.

cytokines (IL-6 and TNF-α) following the CBT intervention in major depressive disorder. According to their report, CBT resulted in a significant reduction in serum levels of IL-6 and TNF-α [23]. Several other investigations have also reported the positive effect of CBT in reducing inflammation in depressed patients [24,25]. Note that this study has been the first attempt to examine the effect of the CBT on the reduction of proinflammatory cytokines in FM patients.

The results of the current study, in combination with the results of earlier investigations, confirm the value of CBT as an efficacious non-pharmacologic treatment for FM. As a safe and efficacious FM treatment, CBT's importance is further highlighted knowing that the CBT has no probable side-effects associated with FDA approved drugs for FM treatment [26,27].

This study had some limitations which should be mentioned. Loss of follow-up could be regarded as the main limitation of this study, which led to exclusion of five and four patients in the intervention and control groups, respectively. This loss of follow-up might have adversely affected the power of the study. In this respect, the absence of significant changes in TNF-α may have been related to its lesser relevance to FM symptoms. Alternatively, it might be due to the inadequate power of the tests to detect a change, particularly as another recent study did find a significant decrease in TNF-α in addition to IL = 6 [22]. Further, the sample size of this study was not large enough to perform multivariate analysis and consider the role of confounding factors in the effect of CBT. The absence of random assignment was another weakness which increases the likelihood of group difference in dimensions that are relevant to the outcomes under study. This weakness was caused by recruiting the patients of waiting-list as the control group, as we found it unethical to deny participants' access to any treatment.

The durability of the CBT effect was not evaluated that which could be regarded as a determinant characteristic when compared with conventional pharmacologic therapy. Regarding the generalisability of our results, it should be noted that this was a single-centered study on female FM patients who referred to a public hospital. All patients were satisfied with the course of CBT and stated their willingness to participate in future CBT courses as well.

5. Conclusion

CBT not only improved the self-reported measures including FIQ and WPI, but also resulted in a significant decrease in the serum concentration of IL-6 and IL-8, as the main proinflammatory mediators in FM pathogenesis. Thus, this method could be considered as a safe and effective non-pharmacological treatment for FM management.

Conflict of interests

The authors of this article declare no conflict of interest to disclose.

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