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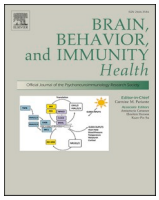

Inflammatory markers changes following acceptance-based behavioral psychotherapy in generalized anxiety disorder patients: Evidence from a randomized controlled trial

Lucas Gandarela [a,b,*], Thiago P. de A. Sampaio [b,c], Lia Marçal [d], Emmanuel A. Burdmann [d], Francisco Lotufo Neto [b,c], Marcio A. Bernik [a,b]

[a] Experimental Pathophysiology Program, School of Medicine, University of São Paulo, São Paulo, Brazil
[b] Department and Institute of Psychiatry, Anxiety Disorders Program, University of São Paulo, São Paulo, Brazil
[c] Department of Clinical Psychology, Institute of Psychology, University of São Paulo, São Paulo, Brazil
[d] LIM 12, Division of Nephrology, School of Medicine, University of São Paulo, São Paulo, Brazil

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ABSTRACT

Introduction: Generalized anxiety disorder (GAD) has been associated with elevated levels of C-reactive protein (CRP) and proinflammatory cytokines. Despite robust evidence as an effective treatment for GAD, research on the effects of cognitive-behavioral therapies (CBT) in the inflammatory profile of patients with clinical anxiety has presented mixed results.
Objective: The present study aimed to investigate the effect of an acceptance-based behavior therapy (ABBT) on inflammatory biomarkers and their association with anxiety levels in GAD patients in comparison to supportive therapy as an active control.
Methods: Peripheral inflammatory biomarkers (CRP, IL-1β, IL-4, IL-6, IL-10, TNF-α) were measured in 77 GAD patients who participated in a 14-week 10-session randomized clinical trial of group ABBT (experimental, n = 37) or supportive group therapy (ST: active control group, n = 40).
Results: The concentrations of IL-1β decreased in the control group and the concentrations of IL-6 increased in the experimental group from baseline to post-treatment, whereas no difference was identified in IL-4, IL-10, TNF, or CRP. Although anxiety and depression levels decreased in both treatment conditions, no correlation with inflammation markers was found for most clinical and biological variables. A negative correlation between changes in IL-6 and IL-10 and anxiety symptom score changes was identified.
Conclusions: The present study results found that a short trial of acceptance-based behavior therapy did not change the proinflammatory profile which may be associated with GAD. Additional research is needed to evaluate the influence of other inflammation-related variables, longer periods of follow-up as well as the effect of supportive therapy on peripheral inflammatory biomarkers in GAD patients.

1. Introduction

Generalized anxiety disorder is a chronic and debilitating condition. In addition to an important psychosocial impairment, GAD and its symptoms are associated with an increased risk for metabolic syndrome (Carroll et al., 2009) and cardiovascular disease (Batelaan et al., 2014; Eaker et al., 2005), which are both associated with chronic systemic inflammation (Hotamisligil, 2006).

Inflammation has been associated with anxiety in several studies involving experimental animal models (Schrott and Crnic, 1996; Yang et al., 2016; De Miranda et al., 2011), healthy volunteers with anxious symptoms (Maes et al., 1998; Pitsavos et al., 2006; O'Donovan et al., 2010), and anxiety disorders (Vogelzangs et al., 2013; Belem da Silva et al., 2017; Renna et al., 2018). Major depressive disorder, a frequent anxiety disorder comorbidity, has also been extensively correlated with inflammation (Howren et al., 2009; Dowlati et al., 2010; Milaneschi et al., 2021). In GAD patients, raised levels of C-reactive protein (CRP) and some peripheral cytokines have been associated with measures of

* Corresponding author. , Anxiety Disorders Program Institute of Psychiatry, University of São Paulo, R.Dr. Ovidio Pires de Campos, 785 São Paulo, São Paulo, 05403Brazil.
E-mail addresses: lucasgandarela@hotmail.com, lucasgandarela@hotmail.com (L. Gandarela).

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anxiety severity (Khandaker et al., 2016; Tang et al., 2018; Costello et al., 2019). Although health-related variables such as Body Mass Index (BMI) and medication use may play a role in the GAD-inflammation interactions (Copeland et al., 2012), it is plausible that persistent exaggerated neurobiological sensitivity to threat associated with anxiety disorders could increase the risk for repeated activation of biological stress systems such as inflammatory systems (O'Donovan et al., 2013). Brain regions associated with threat processing can activate biological stress-response systems such as the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) (Dickerson and Kemeny, 2004; Thayer et al., 2012). Meanwhile, increased levels of glucocorticoids (Sheridan et al., 2000) and catecholamine (García--Bueno et al., 2008) can bind to specific receptors on immune cells that modulate the release of inflammatory cytokines. Accordingly, psychoneuroimmunology research on GAD suggested that chronic systemic inflammation might also be relevant to its pathophysiology (Michopoulos et al., 2017).

Cognitive-behavioral therapies (CBT) hold the strongest evidence in the psychological treatment of GAD (Papola et al., 2023). On the other hand, studies on the effect of CBT on the inflammatory biomarkers of patients with clinical anxiety have presented mixed results. While cognitive therapy has been shown to reduce increased levels of circulating cortisol among GAD patients (Tafet et al., 2005), CBT showed no effect on IL-8 and CRP in depression and anxiety patients (Memon et al., 2017). Acceptance-based behavior therapy (ABBT) is a psychological treatment adapted from traditional CBT specifically for GAD (Roemer and Orsillo, 2009), incorporating strategies from other acceptance-based therapies such as Acceptance and Commitment Therapy (ACT) (Hayes et al., 1999). Instead of targeting the substitution of dysfunctional thoughts that cause anxiety as traditional CBT, ABBT tries to help patients become less attached to their thoughts and increase their stress tolerance (Vøllestad et al., 2012). GAD patients treated with ABBT showed significant reductions in GAD symptoms compared with waitlist control (Roemer et al., 2008) and comparable to applied relaxation (Hayes-Skelton et al., 2013) in randomized trials.

The effects of acceptance-based behavior therapy on the inflammatory cytokines of GAD patients have not been evaluated in the literature within a randomized controlled clinical trial (RCT).

The present study measures peripheral inflammatory biomarkers in GAD patients who participated in a 14-week RCT of ABBT for GAD compared to active control, a supportive group therapy protocol (ST). We predicted a reduction in proinflammatory markers (IL-1β, IL-6, TNF-α and CRP) and an increase in anti-inflammatory markers (IL-4 and IL-10) associated with the improvement of anxiety measures in the ABBT group versus the control group.

2. Material and methods

Subjects in this study took part in a parallel-arm RCT that investigated the effect of ABBT on a variety of clinical symptoms compared to ST in GAD patients (de Almeida Sampaio et al., 2020) (Clinical Trials identifier NCT03930095). The present study compared the effects of the ABBT protocol on the inflammatory biomarkers compared to a control treatment condition.

This trial was conducted under the Declaration of Helsinki and Ethical Guidelines for Clinical Studies and was approved by the research ethics committee of the University of São Paulo (USP) Medical School, São Paulo, Brazil.

All outcome measures reported here were not analyzed until data collection was complete. Data collection occurred between February and July 2016. Biological variables were measured between August 2017 and May 2018.

2.1. Participants

Participants were recruited from the Anxiety Disorders Program outpatient clinic waiting list (Institute of Psychiatry, USP Medical School), and media advertisements. Eligible patients were aged between 18 and 65 years, were literate, and had a principal diagnosis of GAD as determined by the MINI-International Neuropsychiatric Interview for DSM-IV and ICD-10 (MINI) (Sheehan et al., 1998). Exclusion criteria were: (a) bipolar disorder (b) psychotic disorder (c) current substance abuse/dependence (d) current moderate/severe suicide risk (e) current psychological treatment. Patients diagnosed with comorbid depression and under pharmacological treatment with stable dosages for at least three months were not excluded from our study. Participants were asked to maintain the same medication dosage of psychotropics throughout the intervention if possible.

Based on Roemer and Orsillo's results (Roemer et al., 2008), a comparison of two means using R software was conducted for sample size estimation (Chow et al., 2007). Considering the primary clinical outcome of this trial (Depression Anxiety Stress Scale – 21 items), in order to achieve 80% power and expecting an approximate 25% dropout rate, a total of N = 92 participants were needed.

2.2. General procedure

The experiment and the data collection took place in the Anxiety Disorder Clinics, Institute of Psychiatry, USP Medical School. After confirming eligibility, all participants provided informed consent for the study.

A random number generator (http://www.randomization.com) was used to generate a random number for each participant and randomly allocate each enrolled participant to one of the two treatment groups, in a 1:1 ratio, following the method of randomly permuted blocks (Matts and Lachin, 1988). Randomization was stratified into two blocks according to current psychotropic medication use. Accordingly, randomization occurred in two steps: (1) randomization of patients with current psychotropic use and (2) randomization of patients with no current psychotropic use. An unblinded research assistant was responsible for patients' randomization and assignment to interventions.

Both interventions consisted of 10 two-hour group sessions within a 14-week period.

Briefly, the ABBT protocol (Roemer et al., 2008) consisted of psychoeducation about anxiety and GAD from an acceptance-based behavioral perspective (which emphasizes the role of experiential avoidance in suffering and functional impairment) and the applicability of these concepts to each patient's clinical symptoms and a variety of mindfulness practices.

Our active control condition, the Supportive Therapy group, followed the standards for brief supportive psychotherapy (Markowitz, 2014) and consisted of stimulating patients to suggest themes for discussion and participate to receive and offer mutual support. Nondirective psychoeducation on GAD features was offered in a generic way. No instructions based on the acceptance-based approach of GAD, meditation, or mindfulness techniques were allowed in the ST groups.

2.3. Measurements

2.3.1. Measurements of inflammatory biomarkers

Blood samples were collected before the first session (week 1) and after the 10th session (week 14) of ABBT or ST. At each collection, a sample of 10 mL venous blood was taken from all participants: 5 mL of whole blood in an EDTA tube and 5 mL in an anticoagulant-free vacuum tube.

The samples were then centrifuged at 4000 rpm for 20 min at 4 °C, aliquoted, and frozen at −80 °C.

High sensitivity CRP, expressed in mg/L, was measured by the immunoturbidimetric method by Cobas 8000 modular analyzer (Roche Instrument Center, Rotkreuz, Switzerland) at the Laboratory Division - USP General Hospital. Participants with CRP values above 10 mg/L in any of the measurements were removed from statistical analysis (N = 5)

since such values probably indicate acute inflammatory or infectious states and not low-grade systemic inflammation associated with cardiovascular and metabolic risk (Copeland et al., 2012; Wagner et al., 2015; Pearson et al., 2003).

Serum levels of IL-1β, IL-4, IL-6, IL-10, and TNF-α, expressed in pg/mL, were quantified by Luminex Xmap technology using a commercial multiplex immunoassay kit (Bio-Plex Pro Human, Bio-Rad Inc., USA) according to the manufacturer's instruction. Lower levels of detection (LOD) for TNF-α, IL-4, IL-6, and IL-10 were 1.25; 0.06; 0.15, and 0.42, respectively. Undetectable measures for TNF-α, IL-4, IL-6, and IL-10 at baseline and post-treatment were replaced by half the LOD as previously suggested (Wagner et al., 2015). For high-sensitivity CRP and IL-1β, all values were detectable at baseline and post-treatment.

2.3.2. Clinical rating scales

Anxiety and depression symptoms were measured at three time points: at baseline (week 0), before the sixth session (week 6), and after the last session (week 14). Quality of life and daily functional measurements were also assessed, but only at baseline and after the last session.

Anxiety symptom severity was measured using the Brazilian Portuguese version (Kummer et al., 2010) of the Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959). At baseline, each participant was allocated to one of the evaluators on a first-come, first-served basis after completing the self-administered questionnaires. All measurements were then assessed by the same evaluator at all time points. The evaluators were masked to any information regarding the participants' group allocation and participants were instructed by the therapists not to mention any aspect of the intervention to the evaluators. Raters were four clinical psychologists who were part of the Anxiety Disorder Clinics staff and trained in administering the scales. Internal consistencies for the HAM-A were 0.84, 0.81, and 0.80 across the three time points.

Depression and anxiety symptoms severity was measured using the Brazilian Portuguese version (Vignola and Tucci, 2014) of Depression, Anxiety and Stress Scale – 21 items (DASS-21) (Lovibond and Lovibond, 1995). DASS-21 is a self-report scale that separately measures the scores of depression, anxiety, and stress. Internal consistencies for DASS-depression were 0.89, 0.87, and 0.9 across the three-time points; for DASS-stress, 0.8 at all three time points; and for DASS-anxiety, 0.79, 0.77, and 0.8 at the three time points respectively.

Quality of life was measured using the Brazilian abridged version (da Rocha and Fleck, 2009) of the self-rated quality of life inventory – WHOQOL (Berlim et al., 2005). It comprises 24 items divided into four domains: physical health, psychological, social relationships, and environment. Higher scores indicate higher quality of life.

Functional impairment was measured using the Sheehan Disability Scale (Sheehan and Sheehan, 2008), a three-item, self-rated scale designed to assess family, work, and social impairment in the previous week. For each item, responses range from 0 (not at all) to 10 (extremely) presented along a continuum graphically represented by a horizontal line. Total scores range from 0 to 30 and higher scores represent higher disability.

Self-report questionnaires were answered through the software Research Electronic Data Capture (REDCap) (Harris et al., 2009), a digital platform for data collection hosted at the University of São Paulo.

2.4. Statistical analyses

Baseline characteristics of experimental and control groups were compared using Fisher's exact test and the independent sample *t*-test for categorical (sex, education, marital status, psychotropic medication use, comorbidities) and continuous variables (age, HAM-A scores, DASS-depression scores), respectively.

Values of IL-1β, IL-4, IL-6, IL-10, TNF-α, CRP, Sheehan global score, and WHOQOL-physical health score were log-transformed to correct for skewed distributions. Primary analyses of these variables were conducted using log-transformed values.

Mixed Effects Linear Models (MLMs) were used to compare measures of inflammatory markers and clinical outcomes from baseline to post-intervention for each condition and between groups.

To take the effects of potential confounding factors into account, MLMs were repeated for each inflammatory marker, and HAM-A scores adjusted for sex, age, baseline HAM-A score, and diagnosis of depression (Sheehan et al., 1998) as covariates.

Concerning the association between clinical outcomes and the biomarker levels, Spearman's correlation coefficient of residual gains in the percentage of each variable over time was calculated (Rankin and Tracy, 1965).

All statistical tests were conducted with the statistical software SAS (version 9.4). An alpha value of 0.05 was established throughout the analysis.

Since this study has an exploratory nature and used only a few scientifically preplanned comparisons, no correction for multiple comparisons was executed.

3. Results

Of the 92 adults who participated in the overall RCT, blood samples were obtained at least once from 82 participants (41 of each group). Five participants were excluded from the analysis due to CRP levels above 10 mg/L at one of the measurements (4 of the experimental group and 1 of the control group). 77 patients with GAD were then included in the statistical analyses (Fig. 1).

3.1. Baseline demographic and clinical characteristics

Demographic characteristics by treatment group are presented in Table 1. Participants were predominantly women (75%) with a mean age of 36 years (SD 12), who were single or divorced (78%) with completed higher education (70%). The most common psychiatric comorbidities were depression (62%) and panic disorder (46%). According to clinical scales, both groups displayed moderate to severe anxiety symptoms and moderate depressive symptoms at baseline. 27 (35%) participants were under the use of psychopharmacological treatments (control n = 13, experimental n = 14), out of which 17 (control n = 08, experimental n = 09) were using antidepressants, six were using benzodiazepines, two were using non-benzodiazepine anxiolytics and five participants were unable to specify. There were no significant group differences in terms of baseline demographic and clinical characteristics. There was also no significant difference in participants' main comorbidities between groups.

Regarding attrition, the rate of participants who discontinued the study was higher than expected. Therefore, blood samples from these participants at the end of the study were not available (control group: 43%, experimental group: 51%). However, there was no difference in dropout rates between groups. Participants who discontinued the study did not differ from completers in terms of demographic characteristics such as sex, education, and marital status or severity of depressive and anxiety symptoms. However, the former presented a higher rate of current diagnosis of depression.

3.2. Intervention effects on inflammatory biomarkers

Raw values of the inflammatory biomarkers and clinical outcomes at baseline and post-intervention are depicted in Table 2 and the results of the mixed-effects models examining change across all time points are in Table 3.

Mixed effects linear models revealed a group × time interaction on log-transformed IL-1β ($F(1,35) = 7.01$; $p = 0.01$), IL-4 ($F(1,38) = 4.45$; $p = 0.04$) and IL-6 ($F(1,38) = 11.36$; $p < 0,01$) but not in other biomarkers (Table 3). However, in post-hoc tests concerning IL-4, only one trend towards a significant difference between conditions at the post-

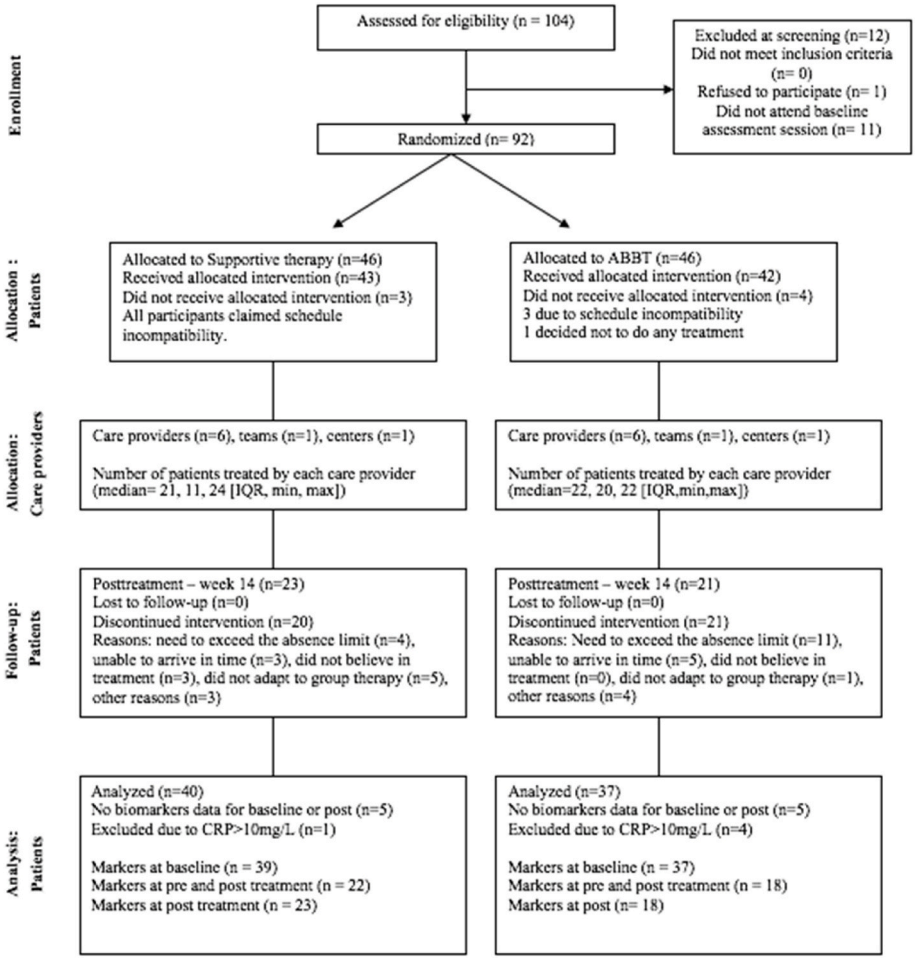

Fig. 1. Flow chart of participants following the guidelines of the modified CONSORT flow diagram for individual randomized controlled trials of nonpharmacologic treatments (Boutron et al., 2017). ABBT, acceptance-based behavior therapy; CRP, C reactive protein.

treatment was observed ($t = 1.85$, $p = 0.07$).

IL-1b levels decreased significantly in the control group from baseline to post-treatment (difference = −1.1; $t = 2.83$; $p = 0.01$) and differed from the experimental group at the endpoint (difference = 0.52; $t = 2.86$; $p = 0.01$). Moreover, a significant increase in IL-6 was detected in the experimental group over time (difference = 0.22; $t = -3.16$; $p < 0.01$), showing a difference between the groups at post-treatment (difference = 0.20; $t = 3.02$; $p < 0.01$) (Fig. 2).

MLMs for each inflammatory biomarker adjusted for age, sex, initial HAM-A score, and diagnosis of depression showed no effect on the results.

There were some outliers in each biomarker which were excluded from analysis since they showed no influence in the results.

3.3. Intervention effects on clinical outcomes

MLMs identified time effect on several clinical outcomes: HAM total score ($F(2,94) = 36.54$, $p < 0.0001$), HAM psychic score ($F(2,95) = 41.98$, $p < 0.0001$) HAM somatic score ($F(2,94) = 20.12$, $p < 0.0001$), DASS-depression ($F(2,95) = 7.1$, $p = 0.001$), DASS-anxiety ($F(2,95) = 9.65$, $p = 0.0002$) and DASS-stress ($F(2,95) = 23.69$, $p < 0.0001$).

Time effect was also detected for measurements of quality of life and disability: WHOQOL-psychological ($F(1,47) = 28.32$, $p < 0.0001$), WHOQOL-physical health ($F(1,47) = 27.14$, $p < 0.0001$), WHOQOL-social ($F(1,47) = 6.51$, $p = 0.014$), WHOQOL-environment ($F(1,47) = 12.9$, $p = 0.001$) and Sheehan total score ($F(1,43) = 27.03$, $p < 0.0001$). A reduction in anxiety and depression symptoms severity, disability scores, and an improvement in quality of life subscale scores were observed for both interventions between pre and post-treatment.

Group effects were also identified by MLMs on DASS-anxiety ($F(1,95) = 5.4$, $p = 0.02$), DASS-stress ($F(1,95) = 10.16$, $p = 0.002$), WHOQOL-psychological symptoms ($F(1,47) = 10.09$, $p = 0.003$) and WHOQOL-environment ($F(1,47) = 4.88$, $p = 0.032$).

However, no group x time effect was detected for any clinical measurements (Table 3).

3.4. Association of clinical outcomes with inflammatory biomarkers

A negative correlation between changes in IL-6 concentrations across time points and changes in both DASS-stress subscale and the HAM-A somatic subscale was identified. A negative correlation between changes in HAM-A somatic subscale scores and IL-10 concentrations from pre-to post-treatment was also detected. No other correlations between clinical outcomes and inflammatory biomarker changes during the study were identified (Table 4).

4. Discussion

This exploratory study shows the challenges of assessing the effect of psychological treatment on biological markers in patients with anxiety disorders. It investigated the effect of an acceptance-based behavior therapy on inflammatory biomarkers in GAD patients compared to an active control condition. We also investigated the association between changes in the anxiety symptoms severity and these inflammatory

Table 1
Baseline demographic and clinical characteristics.

	Total sample (n = 77)	Control (n = 40)	Experimental (n = 37)	*p-value*
Sex				
Female (%)	58 (75%)	31 (77%)	27 (73%)	0.79
Male (%)	19 (25%)	9 (23%)	10 (27%)	
Mean Age years (SD)	36 (12)	35 (11)	37 (13)	0.3
Education				
Elementary school (%)	1 (1%)	0 (0%)	1 (3%)	0.75
High School (%)	22 (29%)	12 (30%)	10 (27%)	
Higher Education (%)	54 (70%)	28 (70%)	26 (70%)	
Marital status				
Married/living together (%)	17 (22%)	10 (25%)	7 (19%)	0.75
Single/divorced (%)	60 (78%)	30 (75%)	30 (81%)	
Current psychotropic use				
Yes(%)	27 (35%)	13 (33%)	14 (38%)	0.641
Antidepressants	17 (22%)	08 (20%)	09 (24%)	0.785
Benzodiazepines	06 (08%)	01 (03%)	05 (14%)	1
Non-benzodiazepines anxyolitics	02 (03%)	01 (03%)	01 (03%)	1
Mood stabilizer	01 (01%)	00 (00%)	01 (03%)	–
Unspecified	05 (07%)	02 (05%)	03 (08%)	0.667
No(%)	50 (65%)	27 (67%)	23 (62%)	
Comorbidities				
Current major depression	48 (62%)	25 (63%)	23 (62%)	1.00
Current panic disorder	30 (39%)	13 (33%)	17 (46%)	0.25
Agoraphobia	23 (30%)	15 (38%)	8 (22%)	0.14
Social Phobia	17 (22%)	10 (25%)	7 (19%)	0.59
Suicide risk	11 (14%)	6 (15%)	5 (14%)	1.00
Mean Baseline HAM-A score (SD)	27.8 (9.8)	27.8 (8.8)	27.7 (11)	0.94
Mean Baseline DASS-depression score (SD)	16.7 (10.5)	18.1 (10.9)	15.2 (9.8)	0.23

Table 2
Means (M) and standard deviations (SD) of outcomes raw values before and after treatment in GAD patients.

Outcome	Intervention	Pretreatment M (SD)	Posttreatment M (SD)
IL-1β (pg/mL)	ABBT	0.39 (0.65)	0.70 (1.00)
	ST	0.36 (0.67)	0.17 (0.12)
IL-4 (pg/mL)	ABBT	0.10 (0.06)	0.17 (0.19)
	ST	0.13 (0.15)	0.08 (0.03)
IL-6 (pg/mL)	ABBT	0.18 (0.07)	0.40 (0.38)
	ST	0.25 (0.26)	0.19 (0.14)
IL-10 (pg/mL)	ABBT	0.72 (0.83)	0.84 (0.86)
	ST	0.81 (0.74)	0.69 (0.51)
TNFα (pg/mL)	ABBT	8.87 (5.54)	10.62 (4.43)
	ST	8.04 (4.37)	8.60 (3.32)
HsCRP (mg/L)	ABBT	2.08 (1.85)	2.00 (2.25)
	ST	1.72 (1.94)	1.65 (1.69)
HAM-A	ABBT	27.67 (10.97)	17.57 (8.13)
	ST	27.83 (8.84)	20.26 (8.37)
HAM-A psychic	ABBT	16.03 (4.77)	9.17 (4.01)
	ST	15.16 (4.96)	7.00 (3.41)
HAM-A somatic	ABBT	11.80 (5.04)	7.00 (4.19)
	ST	12.58 (7.02)	5.00 (3.65)
DASS-depression	ABBT	18.05 (10.92)	11.57 (8.82)
	ST	15.19 (9.84)	9.11 (10.43)
DASS-anxiety	ABBT	16.00 (8.38)	9.39 (7.64)
	ST	13.03 (7.94)	6.78 (7.17)
DASS-stress	ABBT	26.20 (7.86)	17.57 (7.56)
	ST	22.81 (7.94)	12.00 (7.20)
WHOQOL-physical	ABBT	47.33 (16.79)	64.45 (15.17)
	ST	51.94 (17.22)	72.82 (10.76)
WHOQOL- psychological	ABBT	37.30 (17.04)	52.54 (15.17)
	ST	46.18 (13.94)	62.50 (13.71)
WHOQOL- social	ABBT	44.38 (19.47)	52.54 (18.37)
	ST	49.33 (24.72)	62.50 (19.65)
WHOQOL- environment	ABBT	46.88 (14.17)	54.89 (16.61)
	ST	50.43 (15.94)	64.07 (12.23)
Sheehan total score	ABBT	18.65 (7.04)	11.04 (6.76)
	ST	17.11 (6.86)	7.00 (5.39)

biomarkers.

Contrary to our predictions, there wasn't a reduction of proinflammatory markers IL-1β, IL-6, TNF-α, and CRP, nor an increase in anti-inflammatory markers IL-4 and IL-10 in the experimental group over time. The concentrations of IL-1β decreased in the control group and the concentrations of IL-6 increased in the experimental group from baseline to post-treatment, whereas no significant difference was identified in IL-4, IL-10, TNF-α, or CRP. Anxiety and depression levels decreased in both groups after treatment. There was also an improvement in quality of life and disability levels in both groups. However, no difference between groups was identified throughout the interventions.

A negative correlation was found between changes in IL-6 and changes in stress scores and somatic anxiety symptoms from baseline to post-treatment. A negative correlation was also detected between changes in IL-10 and changes in somatic anxiety symptoms during treatments. No other correlations between biological markers and clinical symptoms were found, including depression symptoms.

Overall, the present study results add to the available evidence that, while the efficacy of behavioral treatment for anxiety disorders is well established, its effects on the markers of systemic inflammation are mixed. While psychosocial interventions have been associated with enhanced immune system function, most of the studies have aimed at the treatment of individuals with medical systemic illnesses such as HIV, cancer, and autoimmune disorders, with associated anxiety symptoms (Shields et al., 2020). One possibility is that the efficacy of psychosocial interventions on inflammation may only occur in individuals at higher levels of systemic inflammation linked to medical conditions, which may not exist in all patients with primary anxiety disorders. The effects of inflammatory processes may only be measurable when contributing factors are present. In fact, our participants' average CRP levels suggest a low level of baseline inflammation. Future studies should incorporate stratification based on baseline inflammation levels to enhance our understanding of whether patients with higher C-reactive protein levels could derive greater physical health benefits from psychological treatments for anxiety.

Anxiety and depression symptoms severity, as measured by HAM-A and DASS-21 anxiety, stress, and depression subscales, decreased in both groups. Depression and anxiety symptoms have been associated with elevated levels of proinflammatory markers (Duivis et al., 2013; Kohler et al., 2017; Milaneschi et al., 2021). Since there was no superiority of the experimental group against the control condition over time, as shown by the absence of group × time interaction, this could be a reason for the lack of decrease of proinflammatory markers in the experimental group in comparison to the control group. Contrary to our predictions, the efficacy of supportive therapy seems to happen almost as a norm among psychological intervention trials, which usually offer supportive therapy as a form of control intervention (Markowitz, 2014; Bernik et al., 2018). The increased efficacy of non-directive supportive therapy has been shown in depressed patients in comparison with other commonly used control groups such as waitlist or "treatment-as-usual" (Cuijpers et al., 2012). These latter interventions are regarded as worse control situations because they mimic a nocebo condition. Participants randomized to no-treatment controls may improve less than would be expected compared to participants not enrolled in a trial and may decrease natural help-seeking behaviors. On the other hand, nonspecific treatment component controls may result in substantial improvements in anxiety and mood disorders, requiring large sample sizes to be adequately powered (Mohr et al., 2009). The presence of common and unspecific factors in all forms of psychotherapy (e.g. therapeutic alliance, patient expectancy, and therapeutic rituals) may be a possible explanation for supportive therapy's efficacy (Weinberger, 1995). Investigating the effect of supportive therapy on inflammatory markers compared to a no-intervention control would help elucidate our results

Table 3
Results of the mixed-effects models examining change across all time points.

Outcome	Unadjusted			Adjusted for covariates[a]		
	df	F value	p	df	F value	p
IL-1β						
Treatment	35	4.11	0.05	33	4.15	0.05
Time	35	1.37	0.25	33	3.07	0.09
Treatment x Time	35	7.01	0.01[b]	33	6.65	0.01[b]
IL-4						
Treatment	38	0.78	0.38	36	0.9	0.35
Time	38	0.11	0.75	36	0.01	0.93
Treatment x Time	38	4.45	0.042[b]	36	4.17	0.049[b]
IL-6						
Treatment	38	2.41	0.13	36	2.31	0.14
Time	38	1.67	0.20	36	0.64	0.43
Treatment x Time	38	11.36	0.002[b]	36	11.77	0.002[b]
IL-10						
Treatment	38	0.04	0.85	36	0.09	0.76
Time	38	0.13	0.72	36	1.65	0.21
Treatment x Time	38	1.98	0.17	36	1.55	0.22
TNF-α						
Treatment	38	1.54	0.22	36	1.21	0.28
Time	38	0.23	0.64	36	0.17	0.68
Treatment x Time	38	0.63	0.43	36	0.73	0.40
CRP						
Treatment	38	2.28	0.14	36	3.09	0.09
Time	38	0.25	0.62	36	0.01	0.91
Treatment x Time	38	0.84	0.37	36	0.95	0.34
HAM-A total						
Treatment	94	2.92	0.09			
Time	94	36.54	<0.0001[b]			
Treatment x Time	94	0.78	0.46			
HAM-A psychic						
Treatment	95	3.44	0.07			
Time	95	41.98	<0.0001[b]			
Treatment x Time	95	0.34	0.71			
HAM-A somatic						
Treatment	94	1.46	0.23			
Time	94	20.12	<0.0001[b]			
Treatment x Time	94	1.33	0.27			
DASS-depression						
Treatment	95	1.06	0.31			
Time	95	7.1	0.001[b]			
Treatment x Time	95	0.6	0.55			
DASS-anxiety						
Treatment	95	5.4	0.022[b]			
Time	95	9.65	0.0002[b]			
Treatment x Time	95	0.01	0.99			
DASS-stress						
Treatment	95	10.16	0.002[b]			
Time	95	23.69	<0.0001[b]			
Treatment x Time	95	0.51	0.60			
Sheehan total score						
Treatment	43	3.68	0.62			
Time	43	27.03	<0.0001[b]			
Treatment x Time	43	2.79	0.10			
WHOQOL-physical						
Treatment	47	3.25	0.08			
Time	47	27.14	<0.0001[b]			
Treatment x Time	47	0.07	0.79			
WHOQOL- psychological						
Treatment	47	10.09	0.003[b]			
Time	47	28.32	<0.0001[b]			
Treatment x Time	47	0.03	0.86			
WHOQOL-social						
Treatment	47	3.39	0.07			
Time	47	6.51	0.01[b]			
Treatment x Time	47	0.39	0.54			
WHOQOL-environment						
Treatment	47	4.88	0.03[b]			
Time	47	12.9	0.001[b]			
Treatment x Time	47	1	0.32			

[a] Adjusted for sex, age, HAM-A total score and depression diagnosis at baseline.
[b] p value ≤ 0.05.

and clarify the potential biological effects of this type of intervention.

In agreement with the present study results, previous studies have shown no difference in immune function after diverse short-term psychosocial interventions for anxious patients. No significant differences in cell-mediated immunity were found in panic disorder patients after 6 weeks of CBT or CBT plus benzodiazepines (Koh and Lee, 2004). Similarly, CBT or mindfulness-based therapy showed no effect on IL-8 or CRP in patients with depression and anxiety after 8 weeks of treatment (Memon et al., 2017). More recently, an eight-week intervention of Acceptance and Commitment Therapy showed no effect on CRP, plasma cortisol, IL-1 receptor antagonist, and adiponectin concentrations in adults with overweight and psychological distress compared to a no-treatment control (Järvelä-Reijonen et al., 2020). On the other hand, cognitive-behavioral therapies were able to reduce inflammatory markers in short-term psychological trials for depressive symptoms (Moreira et al., 2015; Ma et al., 2022).

A negative correlation between changes in anxiety symptoms, as indicated by the HAM-somatic subscale and DASS-stress subscale, and changes in IL-6 from baseline to posttreatment was identified. This might explain why, to our surprise, a CBT-derived therapy such as ABBT was associated with an increase in IL-6 levels throughout treatment. However, anxiety and depression symptoms have been associated with increased levels of IL-6 in previous studies (Pitsavos et al., 2006; Duivis et al., 2013; Milaneschi et al., 2021). It is possible that other unmeasured variables such as health-related characteristics may play a role as a confounding factor in this correlation since it has been suggested that BMI and smoking mediates the effects of somatic symptoms of anxiety on IL-6 levels (Duivis et al., 2013). Another possibility is that IL-6 may also exert an anti-inflammatory function according to the concentrations of other proinflammatory cytokines and the signaling path activated by IL-6 (Xing et al., 1998). Future studies on the relationship between somatic anxiety symptoms and IL-6 profile might help clarify our current findings.

A negative correlation between IL-10 changes and somatic anxiety symptoms change was also detected from pre-to post-treatment. Although few studies have focused on the relationship between IL-10 and anxiety symptoms, IL-10 levels were negatively associated with HAM-A psychic and somatic symptoms in poststroke patients (Ying et al., 2023) and seem to mitigate the anxiogenic effects of proinflammatory IL-1b in male rats (Munshi et al., 2019).

Anxiety symptoms severity, as indicated by the HAM-A and DASS-21 subscales, decreased in both groups, but no correlation was observed between most anxiety change scores (HAM-A total, HAM-A psychic, and DASS-anxiety subscale) and the changes in the inflammatory biomarkers. This lack of correlation was against our predictions, but it appears to be the norm among many intervention trials (Memon et al., 2017; Koh and Lee, 2004; Moreira et al., 2015). One possible explanation is that brief psychological interventions appear to be effective in improving anxiety symptoms but may not change chronic processes such as systemic low-grade inflammation.

An important possible confounding variable for our results was the relationship between depressive symptoms change along treatment and levels of inflammation markers. Depressive symptoms, according to the DASS-depression subscale, reduced in both groups throughout time, but no group x time difference was identified. No correlation between changes in DASS-depression scores and changes in biological markers was detected in our analyses.

A third of our participants were under the use of pharmacological treatment, mostly antidepressants. Antidepressant medications, especially serotonin reuptake inhibitors, may reduce levels of IL-6 and TNF-α (Hannestad et al., 2011). Although this might have played a role as a confounding variable in our study, we addressed it by including only participants with stable dosages for the last three months, asking patients to maintain medication dosages if possible throughout the intervention, and by using stratified randomization based on the current use of psychotropic medications. Accordingly, there was no difference in the

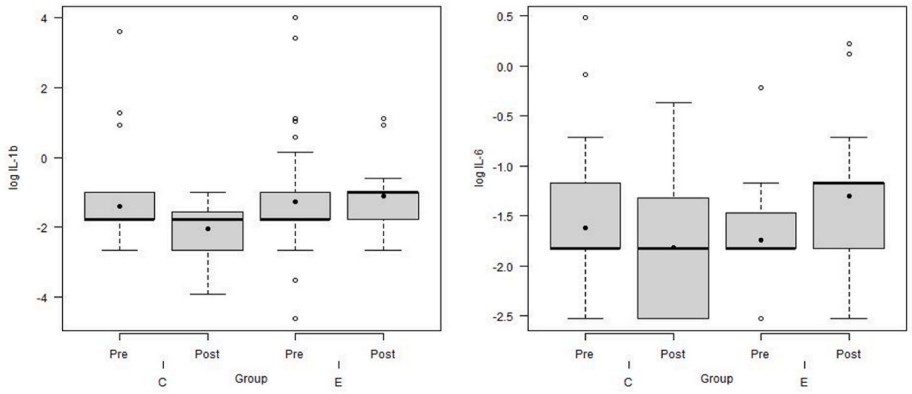

Fig. 2. Log-transformed values of IL-1beta and IL-6 according to intervention (C = control, E = experimental) at pre and post treatment.

Table 4
Spearman correlation coefficient of residual gains (%) over time between clinical outcomes and inflammatory biomarker levels.

		IL-1β	IL-4	IL-6	IL-10	TNF-α	CRP
HAM-A Total Score	Correlation	0.27	0.09	−0.22	−0.12	−0.01	0.07
	n	36	39	39	39	39	39
	p-value	0.11	0.58	0.18	0.47	0.97	0.67
HAM-A Psychic Score	Correlation	0.045	−0.049	−0.174	0.107	0.084	0.053
	n	37	40	40	40	40	40
	p-value	0.791	0.765	0.284	0.512	0.605	0.746
HAM-A Somatic Score	Correlation	0.059	−0.168	−0.343	−0.393	−0.044	−0.148
	n	36	39	39	39	39	39
	p-value	0.732	0.307	0.033*	0.012*	0.791	0.368
DASS-depression	Correlation	−0.262	−0.021	−0.160	−0.221	−0.088	0.076
	n	34	37	37	37	37	37
	p-value	0.134	0.903	0.345	0.189	0.603	0.656
DASS-stress	Correlation	−0.133	−0.095	−0.315	−0.156	−0.181	−0.216
	n	37	40	40	40	40	40
	p-value	0.434	0.561	0.047*	0.338	0.264	0.181
DASS-anxiety	Correlation	0.009	0.122	−0.043	0.004	−0.016	0.023
	n	37	40	40	40	40	40
	p-value	0.957	0.455	0.793	0.981	0.923	0.886
Sheehan total score	Correlation	−0.123	−0.070	−0.064	−0.113	0.023	0.039
	n	36	39	39	39	39	39
	p-value	0.450	0.670	0.699	0.493	0.892	0.814
WHOQOL physical health	Correlation	−0.029	0.072	−0.004	0.072	−0.120	−0.093
	n	37	40	40	40	40	40
	p-value	0.865	0.661	0.981	0.660	0.462	0.567
WHOQOL- psychological health	Correlation	0.012	−0.156	−0.186	−0.109	−0.092	0.020
	n	37	40	40	40	40	40
	p-value	0.946	0.337	0.251	0.504	0.571	0.903
WHOQOL- social	Correlation	−0.130	−0.086	−0.028	−0.026	−0.117	0.050
	n	37	40	40	40	40	40
	p-value	0.444	0.599	0.072	0.872	0.473	0.758
WHOQOL- environment	Correlation	0.070	−0.034	0.091	0.153	0.091	0.084
	n	37	40	40	40	40	40
	p-value	0.682	0.836	0.575	0.347	0.579	0.606

number of participants under pharmacological treatment between groups.

The concentration of the proinflammatory marker IL-1β decreased in patients in the control group, but patients in this group also showed reduced anxiety symptoms. The unpredicted clinical efficacy of supportive therapy in comparison with more structured psychotherapies has been a common finding in many trials (Markowitz, 2014; Bernik et al., 2018; Cuijpers et al., 2012) and its effect on a proinflammatory marker might be an interesting target for future studies.

There were methodological limitations in the present study which together reduce its overall impact. Dropout rates for the clinical trial were higher than expected (54% in the experimental group and 50% in the control group), which accounted for an important reduction in blood sample collection at the endpoint. This high dropout rate was probably an important reason for our study to be likely underpowered, which along with the inherent variability among participants regarding cytokine values, might have contributed to the lack of statistically significant results in our study. Based on our experience in this study, some strategies to increase adherence to biological markers evaluation in a randomized clinical trial with anxiety disorder patients could be suggested: sensitize participants about the importance of blood collection to the study, reduce possible avoidance strategies (previous questioning about blood-needle-injection discomfort/phobia, flexible schedule for blood collection), active search for dropout participants, baseline blood collection at week zero. Also, as is always possible with studies with biomarkers, unmeasured or underlying variables associated with inflammatory mechanisms may have influenced our results: metabolic factors (weight, waist circumference, glycemic levels, lipid profile), lifestyle factors (alcohol use, smoking, sleep, physical activity) or comorbidity with medical conditions (cardiovascular, autoimmune). Those confounding factors are only partially dealt with by randomization.

Despite the limitations, there are many important findings in the present study. To our knowledge, it is the first RCT that investigated the effect of a psychological treatment on peripheral inflammatory cytokines and acute phase protein in GAD patients. Most trials of psychosocial interventions on inflammatory markers investigated populations with medical conditions, emotional symptoms that do not meet the criteria for a diagnosis, or other psychiatric disorders with more established inflammatory alterations such as depression. Our study also indicates that inflammatory biomarkers do not increase after effective psychotherapies for anxiety symptoms in patients with GAD. This is in contrast to antidepressant medications, which are considered a first-line treatment for GAD and have been associated with an increase in C-reactive protein (Verhoeven et al., 2023).

4.1. Conclusions

This is a study with negative findings. The present study results suggest that a short trial of ABBT not improve a patient's proinflammatory profile, which may be associated with GAD, in comparison with supportive therapy. Additional research is needed to evaluate the influence of other inflammation-related variables in the effect of an acceptance-based behavior therapy, longer periods of follow-up as well as the effect of supportive therapy in peripheral inflammatory biomarkers in GAD patients.

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CRediT authorship contribution statement

Lucas Gandarela: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Thiago P. de A. Sampaio:** Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Lia Marçal:** Methodology, Formal analysis, Data curation. **Emmanuel A. Burdmann:** Supervision, Resources, Funding acquisition. **Francisco Lotufo Neto:** Supervision, Resources, Funding acquisition, Conceptualization. **Marcio A. Bernik:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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