Does Psychotherapy Reduce Inflammation in Patients with Major Depressive Disorder?

Alvin Mantey B.S, Henry A. Nasrallah, MD
Department of Psychiatry and Behavioral Science, UC College of Medicine, Cincinnati, OH

University of CINCINNATI

Abstract

Background
It is well-established that major depressive disorder is associated with elevated serum inflammatory biomarkers such as IL-6, CRP, TNF-alpha and cortisol. These elevated biomarkers are also linked to the somatic symptoms seen in depression such as pain and low energy. Antidepressant pharmacotherapy and neuromodulation (ECT) have been shown to reduce the levels of inflammatory biomarkers in responding patients. Psychotherapy, especially CBT, is well known to improve depressive symptoms. Here, we review the literature of controlled studies reporting the effects of psychotherapy on serum pro-inflammatory biomarkers.

Methods
We conducted a systematic search of online databases (i.e., PubMed, Web of Science, Google Scholar, PsychINFO and Cochrane Library) up to January 2023, using key words such as psychotherapy, inflammation, CBT, and inflammatory biomarkers.

Results
Seven studies met our inclusion and exclusion criteria, including 4,972 subjects. All reported a decline in one or more inflammatory biomarkers, including IL-6 and CRP in responders, but not in non-responders.

Discussion
There is a strong relationship between depression and various pro-inflammatory biomarkers. Evidence-based psychotherapeutic interventions, such as CBT, appear to be associated with a reduction in pro-inflammatory biomarkers, similar to what's observed with antidepressant pharmacotherapy. This suggests that psychotherapy can modulate the immune status of patients with depression. There are also numerous studies reporting that adjunctive anti-inflammatory agents, including NSAIDs, omega-3 fatty acids, COX-2 inhibitors and minocycline, potentiate the antidepressant efficacy. Future studies should examine the potential use of anti-inflammatory agents, especially omega-3 since it is relatively safe, in patients with depression receiving psychotherapy which may potentiate efficacy.

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Methods

We conducted a systematic search of online databases (i.e., PubMed, Web of Science, Google Scholar, PsychINFO and Cochrane Library) up to January 2023, using key words such as psychotherapy, inflammation, CBT, and inflammatory biomarkers. The numerous studies found were then selected based on the inclusion and exclusion criteria outlined and were reviewed.

Inclusion:

- Studies must be randomized controlled trials and above on hierarchy of evidence
- Studies must be reported in English as a language
- Studies must have been done within the last 23 years
- Studies consist of the use of psychotherapy alone

Exclusion:

- Studies done before the year 2000
- Studies below randomized-control trials on hierarchy of evidence
- Studies consisting of other forms of wellness therapy

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Table 1. Selected research studies with study arms, biomarker focus and study results.

Results and Analysis

Authors (Year), Psychotherapy	Biomarkers Studied	Results
Strawbridge R, Marwood L, King S, et al. (2020) Type of Psychotherapy General psychotherapy	TNFα, IL-6, CRP, IL-10, IL-8, IL-12, IL-7, IL-15, IL-16, IL-17, MCP1, MCP4, Mip1b, Eotaxin, sICAM1, sVCAM1, SAA, TARC, Tie2, IP-10, IFNγ, Eotaxin3, TNFβ	After treatment, non-responders had higher CRP (OR = 0.234 [95% CI −3.659, −0.015], p = 0.023), MCP4 (OR = 0.014 [95% CI −12.775, −0.051], p = 0.038) and TARC (OR = 0.039 [95% CI −7.459, −1.344], p = 0.001) and lower IFNγ (OR = 9.331 [95% CI 0.294, 5.996], p = 0.026). When not adjusting for age, gender and BMI, both IL-6 (OR = 0.062, p = 0.027) and sICAM1 (OR = 0.002, p = 0.037) were also elevated significantly in non-responders
Eisendrath SJ, Gillung E, Hartzler A, James-Myers M, Wolkowitz O et al. (2016) Type of Psychotherapy Mindfulness-based Cognitive Therapy	CRP	Mean CRP decreased from 1.82 mg/L at T1 to 1.32 at T2 (t (20) = 2.21, p=0.0517). This represented an effect size of 0.66 (Cohen's d, moderately large).
M.S. O'Toole, D.H. Bovbjerg, M.E. Renna, M. Lekander, D.S. Mennin, R. Zachariae (2018) Type of Psychotherapy Cognitive behavioral therapy, mindfulness-based therapy and guided imagery	CRP, IL-6, IL-8, TNF-α, IFN- γ	The overall combined effect size from pre to post psychological intervention on pro-inflammatory biomarker levels was statistically significant, showing an attenuating effect, although of a small magnitude (s' g = 0.15, p = .008, CI [0.04–0.26]). However, this effect was not maintained into the follow-up period (g < −0.01, p = .964, CI [−0.19–0.18]). Looking at the individual biomarkers assessed across studies, only C-reactive protein (CRP) was found to significantly decrease following psychological intervention
Berk LS, Bellinger DL, Koenig HG, Daher N, Pearce MJ, Robins CJ, et al. (2015) Type of Psychotherapy Religious cognitive behavioral therapy vs. Conventional cognitive behavioral therapy	CRP, TNF-α, IL-1β, IFN-γ, IL-6, IL-12-p70, IL1ra, IL-4, IL-10	CRP (r = −0.03, p = 0.810), TNF-α (r = −0.03, p = 0.745), IL-1β (r = 0.02, p = 0.887), IFN-γ (r = 0.08, p = 0.440), IL-6 (r = 0.07, p = 0.507), IL-12 (r = −0.05, p = 0.675), IL-1ra (r = −0.00, p = 0.984), IL-4 (r = −0.00, p = 0.984), IL-10 (r = 0.04, p = 0.736)
Ma H, Xu J, Li R, et al. (2022) Type of Psychotherapy Cognitive behavioral therapy	IL-6	Peripheral levels of IL-6 were significantly lower after CBT intervention in individuals with depression, with a small effect (SMD = 0.38, 95% CI: 0.07, 0.69, p = 0.02).
Thornton LM, Andersen BL, Schuler TA, Carson WE III. (2009) Type of Psychotherapy Small group therapy	White blood cell count, neutrophil count, and T helper: suppressor ratio	There was a significant Study Arm × Time effect, with the intervention arm showing reductions. WBCs (estimates = -0.11, SE = 0.04, p = 0.005); Neutrophil count (estimates = -0.07, SE = 0.03, p = 0.006); T helper: suppressor ratio (estimates = -0.04, SE = 0.02, p = 0.02)
Harley J, Luty S, Carter J, Mulder R, Joyce P. (2010) Type of Psychotherapy Interpersonal therapy and Cognitive behavioral therapy	CRP	They found that patients with elevated pre-treatment CRP (n = 21) experienced poorer symptomatic improvement than people with lower CRP (n = 147). Patients with a baseline CRP ⩾ 10 mg/L experienced an average 36.3% reduction in depressive symptoms compared to 55.1% in people with lower baseline CRP.

Conclusion and Future Directions

There is a strong relationship between depression and various pro-inflammatory biomarkers. Evidence-based psychotherapeutic interventions, such as CBT, appear to be associated with a reduction in pro-inflammatory biomarkers, similar to what's observed with antidepressant pharmacotherapy. This suggests that psychotherapy can modulate the immune status of patients with depression. There are also numerous studies reporting that adjunctive anti-inflammatory agents, including NSAIDs, omega-3 fatty acids, COX-2 inhibitors and minocycline, potentiate the antidepressant efficacy. Future studies should examine the potential use of anti-inflammatory agents, especially omega-3 since it is relatively safe, in patients with depression receiving psychotherapy which may potentiate efficacy. Future studies should also measure the resolution of inflammation by measuring the levels of pro-inflammatory markers before and after psychotherapy.

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