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REVIEW OPEN ACCESS

Do Inflammatory Cytokines Mediate the Therapeutic Benefits of Exercise in Depressive Disorders? A Scoping Review of Recent English Literature

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Abstract

Introduction: Studies have investigated the pathogenesis of depression, with few focusing on the elevation of pro-inflammatory cytokine levels in depression. This article undertakes a scoping review of the available research to explore the current understanding of the role of pro-inflammatory cytokines in depression. Furthermore, the ability of exercise to reduce depression severity through lowering these cytokine levels is examined.

Method: Analysis of online research articles was used to investigate the intended objective, and 18 English-based papers published between 2010-2020 were selected. These studies examined pro-inflammatory cytokine levels in healthy, depressed, diseased and/or physically active patients or research animals as a primary or secondary outcome. Other inclusion criteria such as number of participants and appropriate control selection were used to further refine the search results.

Results: Based on the conducted search, sufficient evidence seems to exist to support an association between elevated levels of pro-inflammatory cytokines, IL-6, TNF-α, IL-1β and incidence of depression. Exercise increases the production and release of anti-inflammatory cytokines and reduces baseline levels of pro-inflammatory cytokines. These anti-inflammatory properties of physical activity supported by exercise-focused studies, can explain the mechanism behind reduced depressive symptoms after a period of regular exercise.

Discussion: The available data supports an association between elevated pro-inflammatory cytokine levels and depression, and the antidepressant effects of exercise. However, there is no evidence of causality between elevated levels of pro-inflammatory cytokines and depression. Whether pro-inflammatory cytokine levels changed as a result of regular exercise, the specific types of pro-inflammatory cytokines that experienced the change, and the extent to which they did, depended on the participant, and the exercise activity.

Conclusion: Measuring the levels of pro-inflammatory cytokines can potentially provide an objective method for diagnosing depression. Due to the potential anti-inflammatory effects of exercise, programs can be designed as a non-pharmacological treatment in mild cases and augment the effectiveness of drug therapy in severe cases.

Keywords: depression; exercise; cytokines; inflammation; inflammatory cytokines; IL-6; TNF-α; IL-1β

Introduction

In recent years, there has been a significant increase in the number of individuals suffering from depressive disorders, prompting many studies to focus on its pathogenesis and search for better, more effective management and treatment plans. There is a substantial body of evidence that points to the possible role of the immune system, particularly pro-inflammatory cytokines, in the development and prognosis of depressive disorders [1]. Cytokines, a broad group of secreted proteins, influence cell communication and initiate immune functions through stimulating cascades of various, sometimes redundant, cytokines within target cells [2]. These proteins are critical in promoting proper brain development and function by supporting neural integrity, neurogenesis, and synapse remodeling [3]. Chronic elevations of pro-inflammatory cytokines, such as Interleukin 6 (IL-6), Tumour Necrosis Factor-alpha (TNF-α), and Interleukin-1-beta (IL-1β) prompts disruptions in behaviour through changes in neurotransmitter functions, leading to neuropsychiatric dysfunction [3]. These findings led to the cytokine hypothesis of depression, theorizing that increased levels of circulating pro-inflammatory cytokine secretion correlate to increased risks of developing depression [1]. In support, the administration of cytokines to humans and lab animals in various studies have resulted in behavioural changes that are consistent with depressive behaviours [3].

Exercise has shown to be an effective treatment, alone or in combination with other factors, for major depressive disorder (MDD), and it causes an anti-inflammatory response in the body by altering the production and secretion of pro-inflammatory cytokines [4]. For instance, exercise

training studies conducted in middle-aged, overweight men have shown significant reductions in IL-6 concentrations in response to aerobic exercise interventions ranging from 12 to 24 weeks [5]. Exercise can be incorporated into a management and treatment plan for patients with depressive disorders through understanding which pro-inflammatory cytokines are affected during exercise and how this influences other inflammatory variables.

Data collected from various studies show an increased level of pro-inflammatory cytokines in some depressed patients, however, there is no evidence suggesting a causative relation between the increased levels of inflammatory cytokines and depression. If higher inflammatory cytokine levels do contribute to depressive disorders, there is little understanding behind how these pro-inflammatory cytokines influence the central nervous system (CNS) to instigate depression. It remains unclear whether the increased inflammatory cytokine levels observed are a consequence of a pre-existing inflammation in depressed patients or it is the cause of the induced inflammation in these patients. Moreover, the type and duration of exercises necessary to induce a sufficient anti-inflammatory response to effectively manage depressive disorders are not well understood.

This review aims to identify the effects of decreasing pro-inflammatory cytokines IL-6, TNF-α, and IL-1β through exercise on reducing depression symptoms.

Methods

This paper was constructed based on some of the Preferred Reporting Items for Systematic Reviews and Meta-analysis for Scoping Reviews (PRISMA-ScR) guidelines [6]. The search engine Google scholar, and the databases MEDLINE and EMBASE were used. This paper was formulated from publications written in English between the years 2010-2020. Studies were established as significant and relevant by inclusion of key terms: inflammatory cytokines, IL-6, TNF-α, IL-1β, IL-10, IL-1RA, depression, depressive disorder, exercise, and/or physical activity. These preliminary inclusion criteria were used to conduct the search in specified search engines to extract a subset of studies.

A more refined inclusion criteria to further narrow down the experimental papers required them to have 10 participants per experimental/control condition to ensure better reliability and replicability of the collected data. Next, studies with a control that appropriately matched the treatment condition(s) were kept as they provide a basis for comparison. In the case of animal studies that were included, the specimens were allowed ample time to adapt to their environment before the experimentation took place, in order to eliminate any environmental confounding factors.

All authors independently examined relevant studies to increase consistency. Using the preliminary inclusion criteria, a subset of potentially eligible studies was selected; followed by a sequential evaluation of each study by title, abstract, and full text using the more refined eligibility criteria lead to final study selections. Disagreements on study selection and data extraction were resolved through consensus and discussion (Figure 1). Considering all the mentioned criteria, a total of 18 articles were included and a quick summary of each article is provided (Table 1).

Information about baseline cytokine levels, depressive symptom presence and severity, and level of physical activity were collected from the studies. The reported association between depression severity and cytokine levels, and changes in their levels after an exercise intervention were reviewed.

Results

The database search revealed many studies that contained the key terms: depression, inflammatory cytokines, exercise, and physical activity, within the last decade. 18 papers were found to satisfy all inclusion criteria after title, abstract, and full-article reviews. These included 7 controlled experiments on human and rat subjects, and 11 literature, scoping, or systematic review papers.

In a 2015 study, mice were subjected to unpredictable chronic mild stress (UCMS) and the anti TNF-α agent infliximab was administered to some groups to test their cognitive abilities [7]. The behavioural analysis of the control, UCMS, and UCMS with infliximab groups showed that mice subjected to UCMS expressed depressive-like symptoms [7]. However, the group administered infliximab expressed no depressive-like symptoms and behaved similarly to the control group that was not subjected to any stressors [7]. The data presented by this study supports an association between TNF-α levels and depression [1,8-9]. The study also focused on Brain-derived Neurotrophic Factor (BDNF) levels in the hippocampus [7]. BDNF is a polypeptide growth factor found in the CNS that plays a role in neuronal maturation, synapse formation, and synaptic plasticity (10–12).

Previous studies have identified decreased expression of BDNF in different brain regions of individuals with mood disorders such as depression, followed by an increase in its expression after administration of traditional antidepressants [12]. BDNF levels remained relatively unchanged in the presence of infliximab, while the mice inflicted with UCMS in the absence of infliximab presented lower BDNF levels [7]. Since TNF-α can access the CNS it has the ability to affect BDNF levels [7]. It can be hypothesized that TNF-α expression in hippocampal regions can negatively impact BDNF levels. The observed difference in BDNF levels indicates that mice who showed depressive-like behaviours had potentially lowered neural development regulation [7]. This is consistent with other study findings that associated depression with neuropsychiatric dysfunction [3].

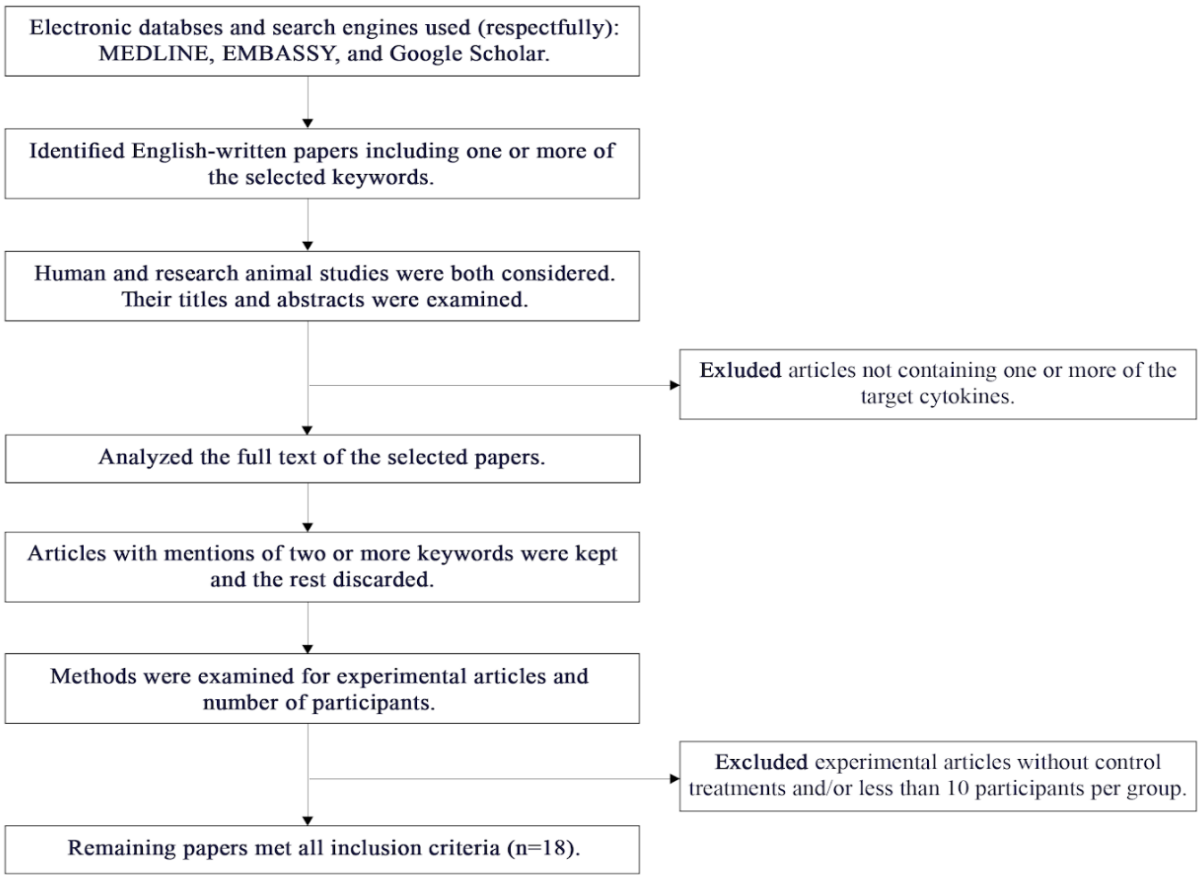

Figure 1. The step-by-step procedure used to identify relevant papers to be included in this scoping review article.

Table 1. Summary of studies included.

Ref #	Study Title	Main Objective	Experimental vs Review	Human vs Animal
1	Cytokine levels in depressed and non-depressed subjects, and masking effects of obesity	To investigate the effects of cytokines on the pathogenesis of depression	Experimental	Human
2	Cytokines in inflammatory disease	To discuss inflammatory cytokines and their correlation and role in the genesis of inflammatory impacts	Review	N/A
3	Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications	To explore specific gene polymorphisms and neurotransmitter systems that may confer protection from or vulnerability to specific symptom dimensions of cytokine-related depression	Review	N/A
4	Pro-inflammatory cytokines as predictors of antidepressant effects of exercise in major depressive disorder	To examine how inflammatory markers change with exercise, and if these changes are associated with exercise intensity or changes in symptom severity	Experimental	Human
5	Effects of exercise combined with caloric restriction on inflammatory cytokines	To explore the specific factors associated with diet and exercise that can contribute to changes in inflammatory markers	Experimental	Human

Ref #	Study Title	Main Objective	Experimental vs Review	Human vs Animal
7	TNF-alpha inhibition prevents cognitive decline and maintains hippocampal BDNF levels in the unpredictable chronic mild stress rat model of depression	To investigate the effects of anti-inflammatory Infliximab on UCMS-induced memory acquisition and retention impairments in rats	Experimental	Animal
8	Exercise reduces depression and inflammation but intensity matters	To determine the effects of exercise intensity on depression severity	Experimental	Human
9	Exploring the Potential Antidepressant Mechanisms of TNFα Antagonists	To explore the potential antidepressant mechanisms of TNFα	Review	N/A
10	Brain-derived neurotrophic factor and its clinical Implications	To explain the role of brain derived neurotrophic factor (BDNF), and its clinical implications	Review	N/A
11	BDNF - A key transducer of antidepressant effects	To determine the role of BDNF in mediating antidepressant mechanisms	Review	N/A
12	BDNF at the synapse: Why location matters	To explain the role of BDNF in different parts of synapse and brain	Review	N/A
13	Role of inflammatory cytokines in depression: Focus on interleukin-1 β (Review)	To document recent literature regarding the impact of IL-1β on the pathophysiology of the depression	Review	N/A
14	Pro- and anti-inflammatory cytokines expression in rat's brain and spleen exposed to chronic mild stress: Involvement in depression	To explore the expression of pro-inflammatory and anti-inflammatory cytokine in rat's brain and spleen subjected to chronic mild stress and their role in depression	Experimental	Animal
15	The P2X7 Receptor-Interleukin-1 Liaison	To summarize the key role of P2X7 polymorphism in IL-1β production	Review	N/A
16	Interleukin-1beta Promoter (− 31T / C and − 511C / T) Polymorphisms in Major Recurrent Depression	To compare alleles and genotype layout between patients with major recurrent depression and healthy people	Experimental	Human
17	Exercise as an anti-inflammatory therapy for rheumatic diseases — myokine regulation	To identify myokines regulated by exercise that can elicit an anti-inflammatory response	Review	N/A
18	The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease	To discuss the mechanisms by which exercise exerts anti-inflammatory effects, and their implications in disease prevention and treatment	Review	N/A
20	Immune and Neuroprotective Effects of Physical Activity on the Brain in Depression	To explore the immunomodulatory mechanisms and pathways that cause the benefits of physical activity in depression	Review	N/A

Depression has been associated with systemic diseases where an up regulation of inflammatory markers possibly causes an inflammatory state [1,13]. A study conducted in 2011 focused on differences in sucrose preference, locomotor activity, body weight gain, and cytokine gene expression in Wistar rats subjected to chronic mild stress (CMS) as compared to the control group [14]. The study reported significant decreases in sucrose preference and locomotor activity in the CMS group compared to the control group, with no correlation between time and group [14]. Weight gain was significantly reduced within the CMS group, before subjection to stress and after, and between the CMS group and the control [14]. Further examination of the rats showed increased expression of IL-1β mRNA, TNF-α mRNA, and IL-6 mRNA in the CMS group with decreased expression of IL-10 mRNA and BDNF mRNA [14]. The ratio of TNF-α to IL-10 and ratio of IL-6 to IL-10 was significantly higher in the CMS group compared to the control [14].

Research exploring the possible role of IL-6 in depression pathogenesis has associated a functional polymorphism of the promoter region of the IL-6 gene, stimulating increased production, with depression [3]. In addition, certain SNPs that change the function of P2X7 receptor of IL-1β, which plays a role in IL-1β production, maturation and release [15], have been linked to the onset of depression in the elderly [13]. Based on the results of a 2011 study conducted on Wistar rats, exposure to chronic stress can be one of the mechanisms that promotes such polymorphic changes in the IL-6 promoter gene and P2X7 receptor, leading to increased cytokine levels [14]. Research conducted on mice showed that P2X7 receptor blockade or knockout leads to antidepressant effects, but similar results in humans have yet to be found [4,15]. Another study found that the systematic administration of IL-1β to rats caused depressive symptoms to arise, similar to symptoms that commonly occur in cytokine immunotherapy treatments [16]. This study made an association between a polymorphism of the IL-1β promoter gene, increasing IL-1β production, and increased risk of major recurrent depression (MRD) and the occurrence of depression in schizophrenic patients [16].

A study conducted in 2013 measured the antidepressant effects of exercise in individuals that have major depressive disorder (MDD) [4]. Individuals were placed in high and low dose exercise groups based on the amount of energy expenditure per kilogram of body weight per week [4]. The study reported a positive correlation between changes in IL-1β levels in relation to changes in depression severity test scores [4]. Higher TNF-α baseline levels were linked to greater reduction in depression severity independent of exercise dose over the course of the intervention (12 weeks) [4]. No correlation was observed between IL-6 and TNF-α levels and depression severity in either exercise group [4]. Moreover, no significant changes in group mean cytokine levels and individual mean cytokine levels were observed at the beginning and the end of the intervention [4].

A 2018 study featured three groups, High-intensity Interval Training (HIT), Moderate-intensity Continuous Training (MCT), and a control group that did not partake in any physical activities [8]. Upon examining inflammatory markers in the different groups after the completion of the intervention, lower levels of TNF-α and depression were observed in the MCT group in comparison to the control group [8]. In the HIT group, increased IL-6 levels and decreased depression severity were observed when compared with the control group [8]. A greater decline in depression severity was observed in the MCT group compared with the HIT group [8]. There were no significant differences in measured IL-1β levels between MCT, HIT, and control groups [8].

Discussion

This study provides a review of the associations between IL-6, TNF-α, and IL-1β levels on the incidence of depression, as well as the antidepressant properties of physical activity in relation to changes in select pro-inflammatory cytokine levels.

As expected, most studies reported elevated levels of one or more pro-inflammatory cytokines in depressed subjects. However, the inconsistencies in the type of pro-inflammatory cytokines observed in such subjects were not initially accounted for. Which of IL-6, TNF-α, or IL-1β are elevated seems to be random or based on some other factors unique to the patient or their specific depressive disorder that have not been identified yet. Further, current studies lack the evidence to support a temporal relationship between elevated pro-inflammatory cytokines and depression, meaning it is unclear whether pro-inflammatory cytokine levels are elevated before development of depression or after. This lack of evidence causes an inability to draw any causality relations. The type of pro-inflammatory cytokines affected by exercise differed between participants within a study and between studies. Mode, intensity, and duration of exercise can contribute to this observed difference, as well as a variety of other myokines produced during exercise that may mediate its indirect anti-inflammatory effects [17].

Although IL-6 is a pro-inflammatory cytokine, its elevated levels during exercise seem to trigger the release of anti-inflammatory cytokines IL-10 and IL-1RA, and the hormone cortisol [18], and IL-6 and other myokines may potentially have indirect anti-inflammatory effects [17]. Increased IL-6 levels suppress TNF-α production and secretion through negative feedback as TNF-α is one of the promoters of IL-6 production [17-18]. The secreted IL-1RA inhibits the actions of IL-1β and IL-10, potent anti-inflammatory promoter, down regulates or completely inhibits the expression of some pro-inflammatory cytokines [18]. IL-6 produced during exercise induces higher production of cortisol, which has anti-inflammatory effects and down regulates production of TNF-α and IL-1β, further contributing to the antidepressant effects of exercise [18].

Depression is most often diagnosed through clinician-rating scales. These tests generally follow the format of self-reported answers from patients, and conclusions are drawn based on the responses that the individual provides, as well as judgement from the clinician [19]. Although this type of diagnostic tool is a valid method for diagnosing depression in individuals, there is still some degree of subjectivity involved in the diagnostic process. Thus, a more objective diagnostic tool based on physiological markers could prove beneficial. Based on the results of this paper, it can be suggested that inflammatory cytokines have the potential to be used as biomarkers of depression to help diagnose patients with depressive disorders; IL-6 and TNF-α levels specifically have been shown to be elevated in depressed patients [4]. With this objective test, a more decisive diagnosis can be provided for patients suspected to have depression. Since this test is based on physiological states that the patient cannot control, it

eliminates the potential for information bias when patients answer diagnostic questionnaires about their symptoms. This bias may stem from cultural beliefs, societal stigmas, personal mindset, or not being comfortable with the physician.

These findings not only propose a new possible diagnostic tool for depression, it can also suggest potential methods to expand the range of treatments that can be prescribed to reduce depressive behaviours in individuals. Accumulation of visceral fat is followed by an increased release of adipokines IL-6 and TNF, and the development of low-grade inflammation [18,20], which has been suggested as one of the contributing factors in depression [20]. The reduction in visceral fat mass may be a potential mechanism behind the anti-inflammatory and antidepressant effects of exercise [18]. We speculate that reducing the amount of visceral fat through exercise can lower the production and secretion of these pro-inflammatory cytokines and potentially alleviate depressive severity and symptoms. Thus, fitness routines, with a focus on moderate-intensity continuous training [8], can be created with aims to decrease IL-6 and TNF-α levels, in hopes that it will lead to the management of depression. This is especially useful for patients with pharmaceutical complications, who require an alternative treatment to medication.

Selective serotonin reuptake inhibitors (SSRIs) are a widely used type of antidepressants that have been shown to decrease the elevations in IL-6, TNF-α and IL-1β [4]. Studies focusing on depressed patients observed that elevated levels of baseline IL-6 and TNF-α correlated with SSRI treatment failure [4]. Based on the information presented in this study, exercise routines could aid in modifying treatment plans for depressed individuals that are unresponsive to SSRIs. Exercise routines can potentially lower the baseline levels of IL-6 and TNF-α enabling SSRIs to have better efficacy in improving depressive symptoms. However, before such exercise routines are prescribed, there needs to be further research performed to determine whether exercise can sufficiently change baseline levels of IL-6 and TNF-α, and if so, which form of exercise is the most effective in achieving this goal.

This scoping review has some limitations. To make the project manageable, a small sample of eligible studies were included. Furthermore, most studies that were considered included participants that were Caucasian leading to a lack of generalizability to other ethnic groups. Along with the narrow ethnicity, more participants fell under the category of female than male. This could be attributed to the higher prevalence of depression in females than in males; but still remains a limiting factor as, again, it reduces the generalizability of this data to the male population. In addition, only inflammatory cytokines IL-6, TNF-α, IL-1β, IL-10, and IL-1RA were taken into consideration.

Conclusions

Pro-inflammatory cytokines, particularly IL-6, TNF-α, and IL-1β, have strong associations with the occurrence of depression. This review aimed to shed some light on the mechanisms behind this association, but nothing concrete can be said until further research is conducted to provide more evidence on the ideas discussed. Based on general consensus, exercise helps to better one's mood, and some of the possible mechanisms behind this phenomenon were mentioned and discussed. With additional research on the specific impacts of exercise on targeted cytokines, workout programs can be designed as a treatment method for patients with depressive disorders. Understanding how to utilize exercise as a treatment method can open the door for future research on the development of unconventional treatments for a variety of other diseases and disorders.

List of Abbreviations Used

BDNF: brain derived neurotrophic factor
CMS: chronic mild stress
CNS: central nervous system
HIT: high-intensity interval training
IL-6: interleukin 6
IL-1β: interleukin 1 beta
IL-1RA: interleukin 1 receptor antagonist
IL-10: interleukin 10
MCT: moderate-intensity continuous training
MDD: major depressive disorder
MRD: major recurrent depression
SERTs: serotonin transporters
SNPs: single nucleotide polymorphisms
SSRIs: selective serotonin reuptake inhibitors
TNF-α: tumor necrosis factor alpha
UCMS: unpredictable chronic mild stress

Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethics Approval and/or Participant Consent

Since this is a scoping review article, there were no participants and therefore no need for consent. Additionally, this study did not require review from any institutional research ethics board.

Authors' Contributions

KA: Made substantial contributions for the acquisition, analysis, and interpretation of data for the work, drafting and revising the manuscript, and gave final approval of the version to be published.
FA: Made contributions for the acquisition, analysis, and interpretation of data for the work, drafting and revising the manuscript, and gave final approval of the version to be published.

AA: Contributed to the acquisition, analysis and interpretation of data for the work, drafting and revising the manuscript, and gave final approval of the version to be published.

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