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Revisiting the Role of Mindfulness-based Stress Reduction in the Management of Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a type of arthritis characterized by a chronic inflammatory disorder that primarily affects the lining of the synovial joints resulting in progressive disability in the movement of diarthrodial joints and arthralgia. It is a debilitating disease associated with premature death and socioeconomic burdens. Its pathogenesis is multifactorial with an individual course of progression where psychological stress is considered to be one of the risk factors associated with RA progression. Most of the therapeutic interventions rely upon the use of NSAIDs, DMARDs, tumor necrosis factor Inhibitors, and more recent T-cell costimulatory blocking agents, B-cell depleting agents, and Interleukin-1 antagonists but, all these modalities lead to severe side effects and havoc on the quality of life of RA patients. Recently, psychological stress is a prominent risk factor that is associated with the pathogenesis of RA and induces flare response in RA patients which indicates the implication of intervention of psychological treatment to RA patients. Recently, Mindfulness-Based Stress Reduction (MBSR) perceived to be an effective modality for the management of RA that has the potential to improve the quality of life of RA patients under medication. However, the extent of this contribution to MBSR is not clear, therefore this review aims to understand the effects of MBSR in patients with RA by searching related literature on databases like Google Scholar, PubMed, Embase, and Web of Science. This study encompasses different interventions of MBSR, such as mindfulness meditation, mindfulness yoga, mindfulness exercise, etc, as a therapeutic modality for RA.

Keywords: Rheumatoid Arthritis (RA), Psychological Stress, Pathogenesis, Meditation, Yoga, Mindfulness-Based Stress Reduction (MBSR)

INTRODUCTION

Rheumatoid arthritis is a systemic, chronic inflammatory autoimmune disorder where the immune system targets and attacks the synovia, and degrades the bones and other tissues. It appears to be a disabling and painful inflammatory pathological condition that leads to loss of mobility due to joint destruction that may lead to crooked appendages and arthralgia [1]. It is a progressive disease that typically starts in small diarthrodial peripheral joints, and progresses to proximal joints if left untreated. Joints [2,3,4]. It is a systemic inflammatory disorder that not only affects the synovia, causing its hyperplasia but also results in the production of autoantibodies that attack the synovial membrane. Chronic inflammation destroys bone and cartilage in the long run leading to the formation of Boutonniere and swan-neck deformity, and crooked appendages resulting in restricted but painful articular movement of diarthrodial joints in RA patients. Further, it causes other systemic disorders like cardiovascular disorders, pulmonary diseases, psychological disorders, and skeletal disorders [5]

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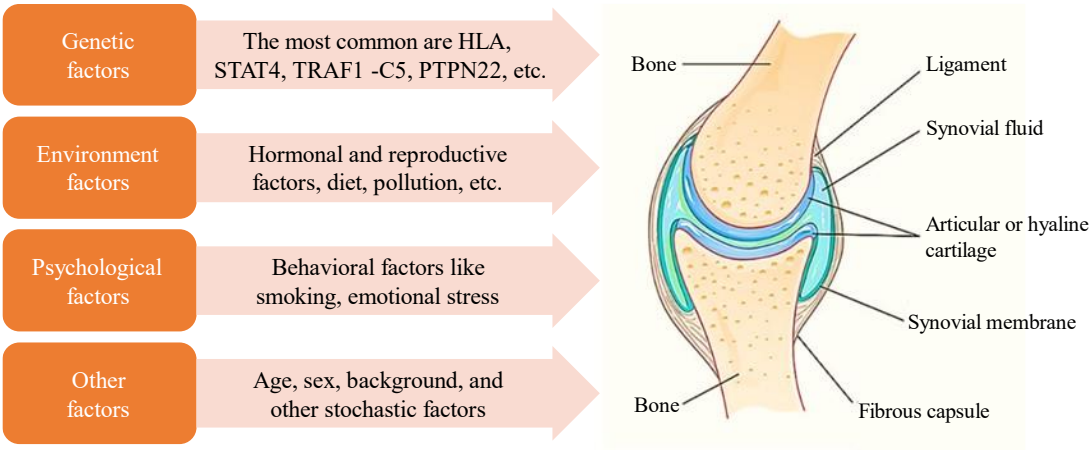

Figure 1. The predisposition of several interacting factors contributes to the pathogenesis of rheumatoid arthritis. Genetic factors such as HLA [7], STAT4 [8], TRAF1-C5 [9], PTPN22 [10, 11] are major risk factors that are triggered by interacting environmental factors [12] leading to initiation of autoimmunity and further interacting factors help in the propagation of the disease. Different regions of genes differently acting upon the onset of disease; HLA has a shared epitope which results in the preferential presentation of citrullinated antigens in RA patients. Another region containing PTPN22 induces cellular hyperreactivity by disrupting PTPN22 and PAD4 (Peptidyl Arginase Deaminase 4) interactions leading to hypercitrullination, TRAF1-C5, and STAT4 predisposition resulting in increased inflammation in the synovia. Many more genes are associated with RA pathogenesis [13]. Gut microbiota [14,15] and psychological factors have been shown to redefine the pathological conditions associated with RA. *Abbreviations:* HLA, Human Leukocyte Antigen; TRAF1-C5, Tumor necrosis factor receptor (TNFR)-associated factor-1; PTPN22, Protein tyrosine phosphatase non-receptor type 22; STAT4, Signal transducer and activator of transcription 4.

constituting a major autoimmune disorder that leads to an increased risk of morbidity and mortality in the population [6].

PATHOGENESIS OF RA

Rheumatoid arthritis (RA) is a chronic inflammatory pathological disorder that results from a complex interaction of genetic and environmental factors like tobacco, pollution, and gut health (Figure 1). Environmental factors are said to be triggering factor that leads to the formation of autoantibodies, such as rheumatoid factors (RF), antibodies against post-translational modified proteins like citrullination (ACPA) and carbamylation (anti-CarP antibodies) which leads to the formation of immune complexes reactive to own tissue of the joint [16].

The immune complexes thus formed bind to type I FcγRs (Fragment Crystallizable Gamma Receptors) present on the cell surface of fibroblast-like synoviocytes (FLS) and fibroblast cells of the synovia leading to the production of ROS, proinflammatory cytokines, Chemokines, and MMPs (Matrix Metalloproteinase) [17]. The chemokines attract immune cells like T and B lymphocytes, neutrophils, monocytes, and fibroblast cells into the synovium [18] which upon exposure to proinflammatory environment produce elevated levels of pro-inflammatory cytokines, chemokines, and matrix metalloproteinases that contribute to progressive degradation of the cartilage and bones in one hand and hyperplasia of synovial tissue in another hand leading to the formation of abnormal tissue called pannus, which further invades and destroys local articular structures [5, 18]. Thus, these immune cells attracted by the autoantibody-associated immune complexes attack the synovium leading to inflammation and thickening of the joint or articular capsule which gradually degrades the cartilage and bones of diarthrodial joints [19, 20].

Psychological Factors in the Pathogenesis of RA

Recently an association of psychological factors like psychological stress and emotions has been established. In particular, psychological stress has been recognized as an important risk factor that can induce and modulate the disease condition of RA in the long term. Psychological stress and mood disorders evident of depression and anxiety are more frequent due to tenderness, joint pain, and fatigue resulting in flare responses in RA patients [21,22]. The association of family or professional stress has been reported to activate proinflammatory effects that aggravate disease conditions showing a positive correlation between psychological stresses and RA pathogenesis [23]. A strong relationship between different types of psychological stresses and the pathogenesis of RA has been established which shows gender specificity in their action that was found to be prominent only in women [24]. Further psychological stresses are prevalent in RA patients due to pain and debility [25-27] which not only affect the quality of life but also deteriorate the condition of disease in RA patients. About 25% of RA patients reported experiencing anxiety and about 16% of RA patients show anxiety concomitant with depression [22]. It shows distress in RA patients is common [28] and bidirectional. Joint pain and tenderness are common and concomitant with depression and other mood disorders [29], which cumulatively alter the behavior of patients resulting in poor recovery of RA patients and increased mortality risk [30-32].

The mechanism of psychological stress-mediated pathogenesis of RA is not very clear but it has been reported that psychological stress activates the amygdala, which is an almond-shaped structure in the temporal lobe, lying just beneath the uncus having reciprocal connections with the hypothalamus through the fornix and stria terminalis and with the PAG through the ventral amygdalofugal pathway [33-36]. The amygdala upon activation sends a distress signal in the form of glutamate neurotransmitters (Glu) to the hypothalamus and other parts of the brain [37] that leads to activation of the hypothalamic region. The hypothalamus upon activation releases CRH (Corticotropic hormone) which activates the anterior region of the pituitary to secrete ACTH (Adrenocorticotropic hormone) [38]. The neurotransmitters released from the amygdala and amygdala-induced anterior cingulate cortex, orbitofrontal cortex, and prefrontal cortex pass through the midbrain to stimulate the sympathetic nervous system [39,40]. The activated sympathetic nervous system prepares the system for fight and flight response by stimulating the adrenal medullae which synthesize and drain a large amount of EN and NE in the body [41] (Figure 2).

On the other side, the adrenal cortex secretes the cortisol hormone after adrenal activation by ACTH which causes an increase in blood pressure, atherosclerosis, diabetes, immune suppression, osteolysis, and myolysis in the long term [45,46]. Though cortisol is known to be an anti-inflammatory factor, chronic elevations due to stress response can lead to the immune system becoming “resistant” to this stress hormone and therefore it leads to increased production of inflammatory cytokines and continually elevated levels of proinflammatory cytokines that further exert deleterious effect to the immune system [47,48]. However, work establishing the relationship of continually elevated levels of cortisol and RA pathogenesis is seriously lacking and if some literature is available, it is mostly poor and misleading. It has been however reported that cortisol signaling in fibroblast-like synoviocytes (FLS), myocytes, osteoblasts, and osteocytes show an inflammatory effect in RA which is contrary to the effect of cortisol in macrophages, mast cells, and chondrocytes [49] which gives primary insight into the role of endogenous cortisol in the pathogenesis of inflammatory bone diseases like RA.

Therapeutic Implication of MBSR in RA

Mindfulness-Based Stress Reduction program or simply MBSR, is a group of interventions propounded and formulated by Dr. Jon Kabat-Zinn in 1979 to deal with patients suffering from stress disorders due to life’s difficulties and physical and mental illness [50]. Mindfulness is a momentous awareness of thoughts and feelings of bodily sensations and ambiance which refers to an open, nonjudgemental, curious, and accepting state of mind [51]. Mindful meditation is the meditation practice in which the subject has an attentive awareness of the body’s rhythmic movement and

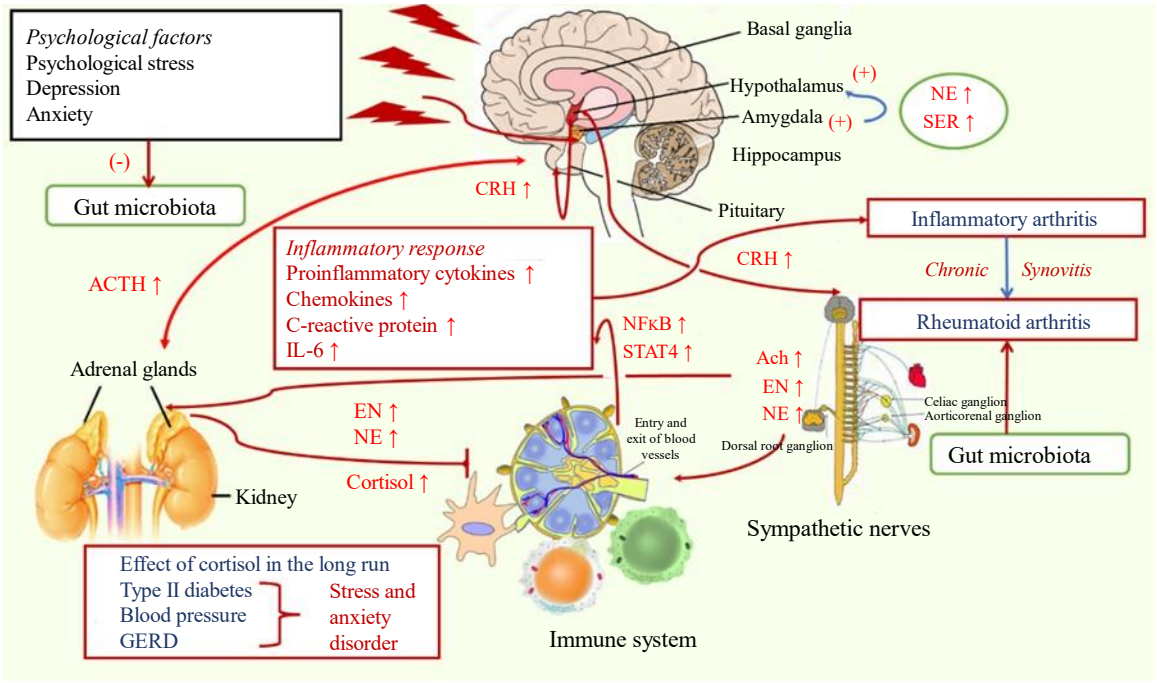

Figure 2. Effect of psychological factors in the pathogenesis of RA. Psychological factors like psychological stress, depression, anxiety, etc., activate the amygdala to secrete NE and SER which activates the hypothalamus to release CRH. CRH stimulates the anterior region of the pituitary gland to secrete ACTH that works on the adrenal glands which in turn secrete cortisol hormone which in the long run leads to type II diabetes, hypertension, stress, and anxiety disorder. Adrenal glands secrete EN and NE neurotransmitters which are also secreted by the sympathetic nervous in large amounts after being activated by neurotransmitters released by the amygdala leading to the onset of fight and flight response [42]. The neurotransmitters EN and NE activate NFκB [43] and STAT4 proteins [44] in immune cells like macrophages, dendritic cells, etc., which bind to DNA to induce the transcription of proinflammatory cytokines, and chemokines forming a pro-inflammatory environment. The inflammatory ambiance results in inflammatory arthritis initially which slowly transforms into rheumatoid arthritis in the long run affecting diarthrodial joints. Psychological stress results in the disturbance of normal gut microbiota that is associated with the formation of autoantibodies forming immune complexes [15]. The immune complexes attack the synovial membrane by attracting various immune cells that form an inflammatory microenvironment at the joint. *Abbreviations:* CRH, Corticotropin-Releasing Hormone; ACTH, Adrenocorticotropic Hormone; ACh, Acetylcholine; EN, Epinephrine; NE, Norepinephrine; SER, Serotonin; IL-6, Interleukin-6; NFκB, Nuclear Factor Kappa B; STAT4, Signal transducer and activator of transcription 4.

environment moment-to-moment without being judgmental and reactive [52]. Mindfulness meditation is one of the interventions in a group of interventions constituting the MBSR program. Likewise, mindful yoga including different asanas, mindful respiration, mindful exercise, and/or a combination of all these is part of the MBSR [53]. Apart from stress, it is now applied for the treatment of a variety of disorders including anxiety, insomnia, depression, skin diseases, pain, hypertension, immune disorders, COPD, diabetes, and even cancer, and found to be very effective in different populations [54]. The MBSR interventions have been found effective and beneficial in a variety of pathophysiological conditions such as depression, anxiety, stress, insomnia, addiction, psychosis, pain, hypertension, weight control, cancer-related symptoms, and prosocial behaviors which suggests its substantial role in the management of these chronic diseases [55-59]. Randomized controlled trial studies of MBSR showed a reduction in RA disease activity for up to 4 to 6 months [60] which started a debate on the possible role of MBSR in the management of RA.

Table 1. Different therapeutic interventions in RA.

Class	Drugs	Mechanism
NSAIDs	Aspirin, celecoxib, Celebrex, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Indomethacin, Ibuprofen, Ketoprofen, Naproxen	Relieve pain, inflammation, and fever. Some inhibit. Some newer drugs such as naproxen and Celebrex are COX-2 inhibitors [62].
DMARDs	Methotrexate, Hydroxychloroquine, Sulfasalazine, Leflunomide	Most DMARD inhibits the immune responses of monocytes and T and B cells. Sulfasalazine and D-penicillamine also affect fibroblast and/or endothelial cell proliferation. Many DMARDs inhibit the production of cytokines [63].
Cortisol	Prednisolone, Prednisone, Dexamethasone, hydrocortisone	Works through glucocorticoid receptors [62] which can repress the NFκB pathway [64].
Other biological agents		
Anti-TNF-α antibody	Infliximab, etanercept	Neutralize TNF-α and TNF-β by binding [65]
Costimulation Blockers	Abatacept	Binds to CD80 and CD86 on antigen-presenting cells (APC), thereby blocking interaction with CD28 on T cells [66].
IL-1 inhibitors	Anakinra	Block IL-1 receptor thus blocking the action of IL-1α and IL-1β [67].
B-cell targeted therapies	Rituximab	Binds to CD20 molecules on some B cells leading to depletion of B cells in synovium [68].

RA is managed mostly by a pharmacological intervention that is comprised of different drugs and different routes of application given symptomatically; to relieve pain NSAIDs (Non-Steroidal Antiinflammatory Drugs) such as celecoxib, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Indomethacin, Ibuprofen, Ketoprofen, etc.; to relieve from inflammation, cortisol (glucocorticoids) is recommended [61] to control inflammation in the long run, a DMARD (Disease Modifying Anti-Rheumatic Drugs) such as methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide, and other inhibitors are prescribed (Table 1).

These modalities efficiently relieve the pain and complications of RA but they are associated with adverse effects that drastically affect the quality of life of RA patients. The long-term use of NSAIDs may lead to gastric irritation, peptic ulcer, gastrointestinal bleeding, kidney impairment, cardiovascular disorders, etc., use of corticoids may lead to diabetes, osteoporosis, cataract, metabolic syndrome, etc., DMARD use may lead to hepatic dysregulations, pneumonitis, hematologic disorders, nephrotoxicity, etc., and use of other biomolecules may lead to infections, neutrophil disease cellulitis, stomatitis, mucosal disorders, etc., causes severe degradation in life leading to irritability and stress response [69, 70]. The adverse effects of these current medications can also be repressed by undergoing the MBSR program [71, 72]. However, the mechanism of the effect of MBSR on reducing anxiety and other adverse effects is not yet clear.

It has been shown that different MBSR interventions exert positive effects on RA patients slightly differently, but overall exert its effect by suppressing the activation of NFκB which is associated with the expression of proinflammatory cytokines and factors causing an inflammatory reaction in RA patients [73]. The activation of STAT4 is also suppressed by the MBSR program (Figure 3). Furthermore, a strong association between chronic stress and the profile of gut microbiota has been established [74–76]. Studies in different autoimmune disorders suggest that the MBSR improved the profile of gut microbiota by increasing the relative abundance of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus* bacteria, after an 8-week MBSR program and improved the symptoms of IBD (Irritable Bowel Disease) [77]. Further, the risk of developing autoimmune antibodies is minimized, and suppressing the migration of autoreactive cells to the synovia [15, 78], the healthy gut microbiota is an important factor in suppressing RA pathology.

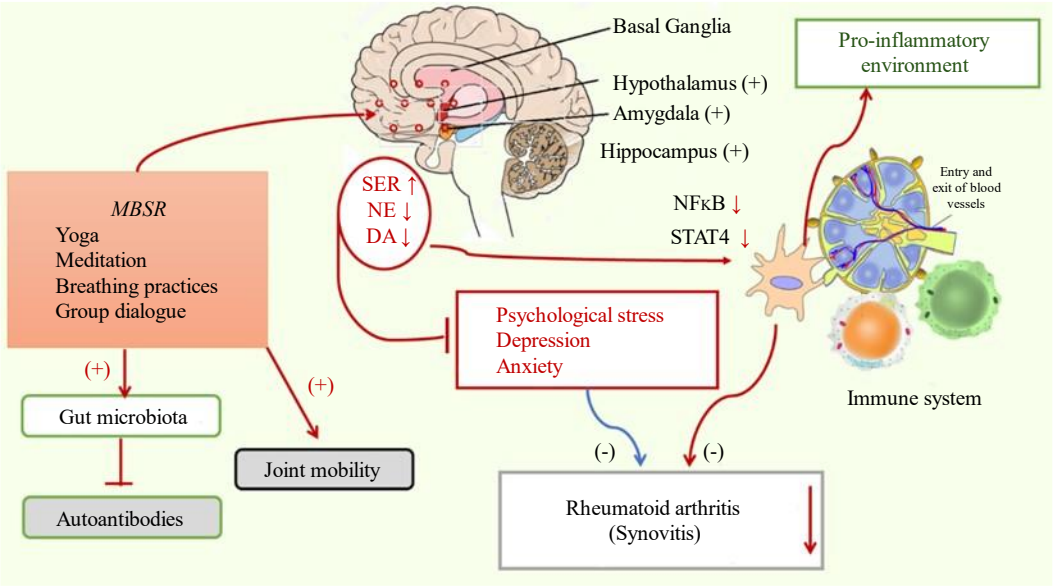

Figure 3. Modulation of RA pathology with MBSR.. The practices of different MBSR regimes can activate different regions of the brain namely the anterior cingulate cortex, frontal and prefrontal cortex, amygdala, hippocampal as well as hypothalamic regions [79–81]. Upon activation, the regions of the brain release neurotransmitters such as SER, NE, and DA which transmit feel-good emotions that relieve psychological stress, depression, and anxiety. The MBSR is associated with downregulated expression of NFκB [73] and STAT4 linked to a higher level of these neurotransmitters, reduces chronic inflammatory state, and thus reduces RA progression. Further, MBSR helps in maintaining the healthy balance of gut microbiota thus minimizing the risk of RA. *Abbreviations:* MBSR, Mindfulness-Based Stress Reduction; DA, Dopamine.

CONCLUSION

On reviewing a large number of literature, it can be concluded that there is a strong correlation between psychological stress of any type and RA pathogenesis [23] which suggests an implication of Mindfulness-Based Stress Reduction Program (MBSR) in minimizing the risk and pathogenesis of RA. Several literatures are suggestive of the positive role of MBSR in minimizing the risk of RA and suppressing the deleterious effect of the continual inflammatory state of the body in RA patients. Furthermore, MBSR exerts a positive impact on gut health by increasing the relative abundance of beneficial bacteria and improves the RA symptoms by suppressing the mobilization of autoreactive immune cells to the joints thus improving the quality of life of RA patients. However, relatively little work has been carried out in this regard, and a detailed and targeted study is urgently required.

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