Stress and Autoimmunity

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A common observation by physicians is the adverse relationship between stress and disease in patients. The association of stress and disease has been particularly true in regard to immune-based diseases, including susceptibility to infection, atopic diseases, and asthma. In addition, there has long been an interest in the relationship between stress and autoimmunity diseases. Autoimmunity results from a dysregulated immune response against self.1 Under normal physiologic conditions autoimmunity may be a phenomenological event without pathologic implications (eg, false positive autoantibody tests). Clinical autoimmune diseases occur when the autoimmune reaction results in tissue damage and destruction. Given the ability of stress and its downstream neuroendocrine alterations to modulate immune function,2 it is reasonable to hypothesize that stress may influence autoimmunity and autoimmune disease. Although studies are conflicting, links between stress and autoimmune and inflammatory diseases, such as rheumatoid arthritis (RA), juvenile RA, systemic lupus erythematosus, and ankylosing spondylitis, likely exists.3–6 Understanding the role that stress may have in either precipitating these diseases or triggering flare in the activity of these diseases could have implications for the treating physicians and patients. Translation of these findings into potential therapeutic interventions may provide a relatively safe and low-cost complement to traditional therapies in the management of these diseases.

Although stress likely has an impact on multiple autoimmune diseases, in the current article, the focus is on RA, using it as a model for stress-autoimmune interactions. The evidence that either supports or contradicts the potential role of stress in triggering autoimmune disease is discussed. Also, the evidence that supports stress as an important factor that may modify disease activity in RA patients is reviewed. Finally, the potential interventions aimed at stress that may one day become part of the therapeutic regimen in RA patients are discussed.

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RA

RA is a chronic, systemic autoimmune disease that primarily targets the synovial membrane of diarthrodial joints. RA affects approximately 1% of the population, and is most common in patients 40 to 70 years old, but can affect patients at any age. Untreated, RA leads to joint damage and destruction, resulting in profound disability and loss of productivity at a substantial societal cost, as well as an increase in mortality. Fortunately, disease-modifying therapies exist. Treatment with methotrexate and other synthetic disease modifying agents clearly improves outcomes in patients with RA. A substantial number of patients require treatment with biologics targeting cytokines (tumor necrosis factor-α [TNF-α], interleukin [IL]-1, IL-6), B cells, and T cell costimulation.

A detailed review of the pathogenesis is beyond the scope of this article and can be found in several recent articles. However, it is important to recognize that the pathogenesis of RA involves a complex interaction of cells of the innate (neutrophils, mast cells, dendritic cells) and adaptive (T cells, B cells) immune systems. Furthermore, it is clear that a cytokine network, including TNF-α, IL-1, and IL-6, is central to the development of the inflammatory response in RA. It is not currently known what triggers the development of RA, nor is it understood what factors trigger flares in disease activity. Therefore, understanding additional modifiable factors that modulate susceptibility or activity of RA is of interest.

Is Stress a Trigger for Development of RA?

Although our understanding of the autoimmune and inflammatory pathways involved in the pathogenesis of RA continues to grow, the initial trigger for the development of RA remains elusive. Current paradigms implicate an aberrant immune response in a genetically predisposed individual to an environmental trigger that has yet to be determined. However, these paradigms do not adequately explain why a genetically predisposed individual might develop an autoimmune disease at a specific point in time.

Indeed, it has long been suggested that psychological stress may be a trigger of RA. In 1942, a retrospective study of 20 RA patients reported that nearly half of the subjects attributed the onset of symptoms with a discrete, emotionally upsetting event. In a subsequent editorial, it was noted that among 43 patients with RA, a significant number of patients mentioned the loss of social support (ie, loss of a spouse) coincident with onset of RA symptoms. These findings were also confirmed in a retrospective study of 30 RA patients compared with 25 osteoarthritis (OA) patients. Finally, a retrospective study of 100 women with RA, suggested that there were two distinct groups of RA patients: a major conflict group whose onset of symptoms occurred within a year of a traumatic life event and a nonconflict group whose disease onset was not associated with a preceding emotional event. Interestingly, the major conflict group had an abrupt disease onset and a more severe disease course while the nonconflict group had a more insidious disease onset and a less severe disease course. Unfortunately, these studies do not provide details with regard to the diagnosis of RA, and some predate the use of diagnostic laboratories, radiological methods, and criteria that form a well-established definition of the diagnosis of RA. However, these studies are among the initial observations that formed the foundation for the hypothesis that psychological stress may be a trigger for the development of RA.

Several retrospective studies have further supported the association of stress preceding RA onset and have used diagnostic criteria for RA. A retrospective study by Stewart and colleagues also confirmed the prior observation that two
subgroups of RA patients exist based on a different reactivity to stress.\textsuperscript{12} In this study, 53 women with RA who met American College of Rheumatology (ACR) Criteria for the diagnosis of RA\textsuperscript{16} were included, and rheumatoid factor (RF) status was determined for each subject. Interviews included measurement of pain, functional status, life events over past 10 years, and disease onset. Interestingly, the seronegative subgroup (negative RF) reported significantly higher rate of negative life events in the two years before disease onset.

Whereas several small retrospective studies have supported the association of stress with the onset of RA, there are also several studies that have failed to confirm this association. A large retrospective case-control study of 532 subjects failed to show a significant association in the occurrence of stressful events before onset of RA.\textsuperscript{17} More recently, a prospective cohort of 9,159 subjects also failed to show a significant increased risk of developing RA in subjects reporting traumatic childhood experiences.\textsuperscript{18} Although the size of the subject populations in these studies is a strength, neither study used rigid diagnostic criteria for the diagnosis of RA. Two additional studies have failed to confirm the hypothesis that stress may be a trigger for the development of RA. In a retrospective study of 60 subjects with ACR-classified RA, no significant association with stressful events preceding onset of disease in either seropositive or seronegative RA could be determined.\textsuperscript{19} Finally, using a retrospective case-control study in which 55 subjects with RA-fulfilling ACR criteria were each matched with three controls, Cature and colleagues\textsuperscript{20} failed to show a significant impact of stressful life events before the development of RA.

Based on the literature to date, the evidence for stress as a trigger for the development of RA remains controversial. The majority of studies supporting the idea of stress as a provoking factor in RA lack the statistical power to determine significance and their retrospective design is not ideal for determining causality. The two largest studies, including one that is prospective, found no significant association with stress and RA—thus favoring a lack of association.\textsuperscript{17,18} However, failure to clearly see a consistent association may not rule out this possibility. The pathogenesis of RA is complex, and the ability to determine the timing of disease onset is often difficult. It is not clear if patients may have evidence of autoimmunity, for example the presence of anticyclic citrullinated peptide antibodies years before the development of clinical disease. Furthermore, the onset of RA in many patients is often insidious, with patients presenting to physicians only after symptoms reach an individual threshold. Indeed, Rimon\textsuperscript{12} was able to show an association of stress in a group of patients with abrupt onset of RA but not in those with an insidious onset. It remains unclear if this reflects the variability of the disease, the difficulty of identifying disease onset, or the complexity of assessing stress and life events retrospectively. Future studies, ideally longitudinal studies, using diagnostic criteria and laboratory data may help resolve these controversies.

**Does Stress Modulate Disease Activity in RA Patients?**

Anecdotally, most physicians caring for patients with RA have observed that patients have increased symptoms during times of stress. Indeed, patients also have reported an association of psychological stress with RA symptoms. In a study of 92 RA patients, psychological stress was found to be the most common self-reported reason for disease flares.\textsuperscript{21} The association of stress and RA flares has been a subject of investigation. Research has often divided stressful events, or stressors, into major and minor stressors. Major stressors are often life events such as death of a relative, severe illness of a relative, or separation from a partner. Minor stressors are often considered day-to-day events that an individual perceives as irritating or stressful. It
is important to consider that a stress-associated increase in symptoms may be due to changes in pain or perception in pain. However, given the influence of stress on immune function, it is also possible that stress may have an impact on the inflammatory pathways that lead to increased synovial inflammation, thereby increasing a patient’s symptoms. In this section the authors review the literature to address the question of whether major stressors or minor stressors modulate symptoms in RA patients.

Major stressors
It has been hypothesized that major stressors such as death of loved ones, natural disasters, or divorce can modulate disease activity with studies showing both a suppressive role and an exacerbating role. A case report of a woman with RA reported disease remission after death of her husband and daughter. This report prompted a further study of 25 RA patients, of whom 6 had experienced death of a family member in the previous 6 months. Joint tenderness was significantly lower for the bereaved group suggesting that major stressors may exert an immunosuppressive effect in RA patients.

In contrast, several studies have demonstrated that major stressors may be associated with a flare in RA activity. In a prospective study of 78 subjects with RA, those who experienced major life stressors in the preceding 6 months showed significantly increased pain with daily minor stressors. Additionally, in a 15 year follow-up study of Rimon’s original study, the major conflict group whose disease onset was associated with traumatic life events later had significantly higher incidence of disease exacerbations with similar stressful events. These studies support the hypothesis that major stressors are associated with an increase in RA symptoms.

Several studies have not shown association with major life events and RA disease activity. In a 5-year prospective study of 78 recently diagnosed RA patients, there was no significant relationship between major life stressors and disease activity, as measured by erythrocyte sedimentation rate (ESR) and a disease activity score. However, disease activity was predicted by coping and social support at the time of diagnosis. In a multicenter prospective cohort study of 370 RA subjects meeting ACR criteria for RA, yearly interviews over the course of 3 years showed no significant association with major life events and disease activity, as determined by Ritchie Index, Health Assessment Questionnaire (HAQ), and Visual Analog Scale (VAS). A 2-year prospective study of 238 RA patients meeting ACR criteria for RA showed no significant relationship between negative life events and worsened functional disability measured by the HAQ. Additionally, studies by Dekkers and colleagues and Thomason and colleagues found no significant correlation between major life events and disease activity as measured by ESR.

Although data remains conflicting, at this time it appears that major stressors are not significantly associated with RA disease activity at the population level. The studies that demonstrate an association of major stressors with RA symptoms use pain as the outcome, whereas those that do not show the effect use measures that might better reflect inflammation. Could pain and inflammation in RA be differentially affected by major stressors? Additional studies using several standardized clinical diseases activity scales that have more recently been developed may be able to answer this question. Prospective studies performed with larger RA cohorts using either patient-driven disease activity scales such as the RA Disease Activity Index (RADAI) or the Clinical Disease Activity Index (CDAI), or multidimensional scales that combine physician measures, patient report, and laboratory markers, such as the disease activity score-28 (DAS28) or simplified disease activity index (SDAI), would
permit more sensitive assessment of disease activity and help to demonstrate an association of major stressors and RA activity.\textsuperscript{30}

\textbf{Minor stressors}

The majority of studies investigating the association of stress and RA-disease activity have focused on minor stressors, are hassles encountered on a daily basis, including interpersonal relations, work stress, and financial stressors. The majority of these studies have consistently demonstrated an association of increased RA symptoms with minor stressors. A 12-week prospective study of 41 women with RA diagnosed based on ACR criteria found a significant relationship between minor stressors and joint tenderness and pain.\textsuperscript{31} Additionally, in a subgroup of 20 patients who experienced a highly stressful week during the study, significant increases in clinician global ratings of disease activity were associated with an increase in numbers of DR\textsuperscript{1} CD3 cells and IL-2 receptor were seen, which supports the hypothesis that minor stressors are associated with increased disease activity.\textsuperscript{31} In the previously mentioned study by Potter and Zautra,\textsuperscript{22} patients found daily stressors and negative affect significantly correlated with increased joint tenderness. Further supporting the association of minor stressors with RA activity is a 5-year prospective study of 50 RA patients. The investigators observed that patients with higher levels of daily stress had more joint swelling and erosions at study entry, and progression of these erosions continued over the course of the study.\textsuperscript{32} Finally, interpersonal workplace stressors and financial stress have also been evaluated and found to significantly predict arthritis symptoms, including pain, as well as nonarthritis health complaints in both RA and OA patients.\textsuperscript{33,34}

The role of mood disturbances in the stress-disease activity paradigm has also been evaluated. From a cohort of 138 RA patients, 74 patients were randomly assigned to undergo a controlled stress induction. Interestingly, those patients with history of two or more episodes of major depression had significantly increased pain as measured by Short Form-36 (SF-36), Western Ontario and McMaster Osteoarthritis Index (WOMAC), and DAS28 measure of tenderness.\textsuperscript{3} Similarly, in another study of 14 RA patients, it was found that increases in joint inflammation were significantly correlated with increased soluble interleukin-2 receptor (sIL-2R) levels and increases in mood disturbance significantly correlated with declining sIL-2R levels and increased pain, suggesting that mood disturbances contribute to pain perceptions despite levels of underlying inflammation.\textsuperscript{35} Similarly, increased daily stressors were associated with increased pain but decreased joint inflammation evidenced by diminished IL-2R, suggesting a role for mood disturbance in pain perception.\textsuperscript{36} Collectively, the above studies suggest depression and other mood disturbances could increase vulnerability of RA patients to stress, thus accounting for differences in pain experienced by each person.

Only a few published studies have not shown an association with minor stressors and disease activity. In the study by Dekkers and colleagues,\textsuperscript{28} 54 patients with newly diagnosed RA completed the Life Experience Survey, were assessed for coping skills and social support, as well as health status measures where evaluation included ESR and VAS. No significant correlation was observed between minor stressors and ESR or pain. A retrospective study of 66 RA patients found no significant correlation with psychosocial stress and pain; other disease activity markers were not evaluated.\textsuperscript{37}

Taken together, the weight of the published evidence supports the association of minor stressors and RA disease activity. However, from these studies, it is not always clear if the increase in RA disease activity is immune mediated and through increased synovial inflammation, through changes in pain and pain perception, or both. The
majority of studies cite pain as the most common measure of disease activity. Regardless of the mechanism, pain remains an important target in therapeutic intervention as it can significantly influence quality of life in RA patients. Undoubtedly, the relationship between stress and rheumatic disease is complex, and the mechanism of influence has not been elucidated through the studies available at this time.

Mechanisms of Stress-Associated RA Flares

As discussed above, minor stressors appear to be associated with increase symptoms in RA patients. The studies do not clearly distinguish if these symptoms are secondary to increases in inflammation and synovitis or alterations in pain. A thorough discussion of how stress can affect pain is beyond the scope of this article. However, it is important for the reader to appreciate the possibility that some of the stress-associated increase in symptoms in RA patients may be related to the effects of stress on pain pathways.38 An alternative mechanism by which stress may increase symptoms in RA patients is through modulation of the immune response. Indeed, animal and human studies have demonstrated bidirectional communication of the neuroendocrine system and the immune system and have provided a conceptual framework for how stress may contribute to the pathogenesis of immune-mediated disease. This section discusses possible basic immune mechanisms by which stress may adversely affect symptoms or disease activity in RA patients.

Stress-immune interactions

The impact of stress on immune function has been extensively investigated using subjects with exposure to stressors such as bereavement, marital discord, caregiving for a relative with a chronic illness, and academic examination stress. Initial paradigms supported a potential suppressive effect of stress on immune function, including suppression of natural killer cell function, lymphocyte proliferation, and peripheral blood mononuclear cell (PBMC) production of IL-2 and interferon gamma (IFN-γ).39–44 However, these experimental observations were inadequate to explain the association of stress with increased susceptibility to asthma and atopic diseases, immune-based diseases where T helper (Th)-2 cytokines are increased. Subsequent studies using the medical student examination stress model suggested that stress is associated with a shift in the Th-1 (type-1)/Th-2 (type-2) cytokine balance toward Th-2 cytokine responses.45 These studies were confirmed with multiple in vitro studies where dexamethasone, at concentrations mimicking serum cortisol levels during periods of stress, suppressed IFN-γ production and increased the production of IL-4 and IL-10 by human PBMC, a shift toward a Th-2 cytokine milieu.46,47 More recently, it has been demonstrated that exposure of corticosteroids can increase the sensitivity of PBMC to the immunomodulatory effects of catecholamines, providing evidence for a cooperative effect of multiple stress hormones in regulating Th-1 and Th-2 cytokines.48 These data strongly suggested that stress is not immune suppressive, rather it modulates immune function such that it decreases Th-1 responses while increasing Th-2 responses.

After the identification of the Th-1 or Th-2 cytokine balance, a significant amount of research sought to explain the pathogenesis of autoimmune diseases using the imbalance of these two Th subsets. Initial studies suggested that Th-1 cytokines would support autoimmunity; however, several studies conflicted these data.49 Subsequent studies demonstrated that a third Th subset, the Th-17 cell, may more adequately explain the CD4+ T cell contribution to autoimmune diseases.50,51 Th-17 cells differentiate from naive Th cells when stimulated in the presence of IL-6, transforming growth factor-β, and IL-1β. IL-23 is another key cytokine that supports the Th-17 cytokine response. Indeed, several studies now support a potential role for Th-17 cells in
autoimmune diseases, including RA.\textsuperscript{52–54} Currently, no published studies have shown an association of stress with alterations in IL-17 or IL-23. However, an intriguing in vitro study using T cells from D011.10 ova-specific transgenic mice demonstrated that dexamethasone did not decrease IL-17 and IL-22 production by Th-17 cells.\textsuperscript{55} Although this study did not use “stress” equivalents of dexamethasone, these data, in combination with prior data demonstrating a decrease in Th-1 cytokines, suggest that corticosteroids and, possibly, stress may support a Th-17 milieu.

Regulatory T cells (T-reg) are a CD4\textsuperscript{+} T cell population that suppress immune responses through a variety of mechanisms.\textsuperscript{56} Loss of T-reg function may contribute to autoimmunity and autoimmune disease.\textsuperscript{56} It is of interest to understand whether stress may alter T-reg function, which in turn could modulate the immune balance and contribute to autoimmunity. Consistent with this hypothesis, patients with post-traumatic stress disorder have been found to have lower circulating T reg cells, as defined by intracellular expression of the T-reg transcription factor FoxP3, relative to age and ethnically matched controls.\textsuperscript{57}

The therapeutic success of biologics targeting inflammatory cytokines such as TNF-\textgreek{z}, IL-1\textbeta, and IL-6 highlight the important role that these cytokines play in the pathogenesis of RA.\textsuperscript{58–61} The ability of stress to modulate the inflammatory cytokines represents another potential mechanism by which stressors may increased RA activity. One recent study examined circulating IL-6 levels in a large cohort of spousal dementia caregivers compared with controls.\textsuperscript{62} Over the 6-year period, the average rate of increase in IL-6 levels in caregivers was approximately four times that of control subjects. Several studies also have demonstrated an association of increased IL-6 levels in RA patients with stress.\textsuperscript{63–65} Another study demonstrated that a laboratory acute stressor resulted in higher levels of circulating IL-1\textbeta compared with controls.\textsuperscript{66} Finally, a meta-analysis of 30 studies demonstrated robust effects for an increase in IL-6 and IL-1\textbeta following acute stress.\textsuperscript{67} Together these studies suggest that stress is associated with an increase in proinflammatory cytokines, which may in part contribute to an increase in inflammation in RA patients owing to an increase in stressors.

One additional mechanism by which stress may affect RA is through regulation of telomerase and telomere length in T cells. It has been reported that CD4\textsuperscript{+} T cells from RA patients have accelerated telomere attrition.\textsuperscript{68} This may be due to a defect in the upregulation of telomerase in RA patients, and this has been hypothesized to contribute to a defect in regulation of the T cell pool through excessive T cell loss. Interestingly, a recent study has reported an association of chronic caregiver stress with shorter telomere lengths in PBMC compared with controls.\textsuperscript{69} Therefore, stress could potentially add to the telomere attrition in T cells, which may have an impact on the immune balance and inflammatory status in RA patients.

In summary, stress can modulate the immune response at multiple levels. Stress-induced alterations in Th cell subsets, T-reg, as well as inflammatory cytokines can have significant impact on the immune balance in healthy subjects. Similar changes have been seen in RA patients. Given the association of minor stressors with increased symptoms in RA patients, these stress-associated alterations likely contribute to a proinflammatory milieu in RA patients.

STRESS INTERVENTIONS IN RA MANAGEMENT

Given the potential association of minor stressors with RA flares and disease activity, it is important to understand if stress interventions could play a role in the management of RA. Although it is unlikely that stress management alone would induce remission in
patients, combining stress intervention with pharmacologic intervention may be an effective way to reduce the need for some medications, such as corticosteroids. This would reduce treatment side effects and offer patients safe and complementary interventions in the management of their disease. A large number of studies have sought to determine if stress interventions are safe and beneficial in the management of RA, including a large number of randomized controlled trials summarized in Table 1. This section reviews the published studies investigating psychological interventions such as cognitive behavioral therapy and emotional disclosure, as well as other methodologies that indirectly modulate stress levels such as tai chi, yoga, and patient education.

**Psychological Interventions**

**Cognitive behavioral therapy**

Many studies on cognitive behavior therapy (CBT) for treatment of RA have been conducted and involve therapist-guided training in coping strategies such as relaxation, goal setting, imagery, and cognitive restructuring of negative thoughts related to pain. In a randomized controlled trial of 53 RA patients, each were assigned to the CBT group, social support therapy group, or a nontreatment group. Significant improvements in disease activity as measured by Rheumatoid Activity Index, pain, pain behavior, and anxiety were seen posttreatment and at 6 month follow-up. Sharpe and colleagues conducted a randomized clinical trial of 54 RA patients comparing routine medical care with or without CBT. CBT resulted in significant improvements in joint stiffness, depression, and C-reactive protein (CRP) posttreatment, as well as joint stiffness and depression at 6-month follow-up. At 18 months, patients maintained initial treatment gains with additional significant improvement in anxiety and disability.

In contrast to the above positive studies, other studies have shown no effect on disease activity. In a randomized controlled trial of 63 RA patients, the experimental group received weekly CBT sessions with significant improvements in pain coping, depression, affective pain score, and emotional stabilization. However, no significant effect on disease activity as measured by ESR, CRP, and joint counts was observed. CBT resulted in significant improvement in depression and fatigue but not disease activity in a randomized controlled trial involving individualized CBT in 64 RA patients. Similarly, studies by Parker and colleagues and O’Leary and colleagues showed significant improvement in pain, pain coping, and self-efficacy with CBT, but no effects on disease activity as measured by ESR, CRP, Th subsets, and joint counts. The above studies provide evidence that CBT is an effective therapeutic intervention in RA, especially in the areas of pain, pain coping, self-efficacy, and depression. Effects on disease activity and disability are seen in some studies suggesting a potential role; however, more studies are needed to clarify this effect.

**Emotional disclosure**

Emotional disclosure is a therapeutic modality in which patients write or talk about their thoughts and feelings concerning life events that are not yet disclosed to others. It has been suggested that emotional disclosure has health benefits, thus a few studies have evaluated its role in treatment of RA. In a randomized controlled trial of 72 RA patients in which the experimental group was assigned to talk about stressful events and the control group about trivial topics, significant improvement in affective and physical functioning was seen with no effect on pain or joint counts. Another randomized controlled trial of 51 RA patients found significant improvement in disease activity as measured by physician global assessment 4 months after treatment. Significant improvement in
mood indices but not disease activity was seen in a randomized controlled trial of 34 RA patients who were assigned to write and talk about traumatic personal experiences. In contrast, Keefe and colleagues found no significant benefit of clinician assisted emotional disclosure on pain, disability, or affect. Given as there have been very few published studies on the effect of emotional disclosure on RA disease activity, no conclusions can be made at this time. Though it appears there could be beneficial effects on mood indices and potentially on disease activity, more studies are needed to further delineate the role of emotional disclosure in RA therapy.

Tai Chi

Tai chi is a traditional Chinese martial art that combines slow and graceful movements with mental focus. It has been found to provide benefit to cardiopulmonary function, strength, balance, flexibility, and psychological function. Additionally, it has also been hypothesized to be a therapeutic option in RA. A systematic review including studies by Kirsteins and colleagues and Van Deusen and Harlowe concluded that tai chi provides significant improvement in lower extremity range of motion with no other significant beneficial or detrimental effects on disease activity. Subsequently, several studies have shown therapeutic benefit of tai chi in RA. In a randomized controlled trial of 20 RA patients, the experimental group performed tai chi twice weekly for 12 weeks while the control group underwent RA education along with stretching exercises. Results showed significant improvement in disability index, quality of life, and depression index. Uhlig and colleagues conducted a single group clinical study in which 15 RA patients performed tai chi twice weekly for 12 weeks and underwent baseline, posttreatment, and 12-week follow-up assessments of joint tenderness (DAS28), physical performance tests, functional disability (HAQ), and pain (VAS). Significant improvements in the number of swollen joints, lower limb strength, and endurance was seen at the end of study and follow up, and patients reported increased confidence in movement as well as overall reduced pain. These findings are contradictory to an earlier, similar study that reported no significant improvement in the same measures. The few studies that have been conducted are small, thus improvement in strength of the studies and possibly increased effect could be seen if larger sample sizes were used. Overall, it can be concluded that tai chi can be safely performed without causing exacerbation of disease with evidence for improved lower extremity strength, flexibility, and endurance. It is likely that quality of life and functional disability could be improved with continued tai chi practice as well.

Yoga

Yoga has been found to have positive mood and fitness effects. However, few studies have been conducted to evaluate the effect of yoga on RA disease activity. In a clinical controlled trial of 47 RA patients, the experimental group participated in an 8-week yoga program and showed significant improvements in disease activity (DAS28) and disability (HAQ). Another study of 16 women with RA who practiced yoga for 10 weeks found significant improvements in grip strength after practicing yoga. At this time, no conclusions can be made regarding the effects of yoga on RA disease activity given the paucity of published studies. Beneficial effects of yoga on flexibility, endurance, and mood have been demonstrated in individuals without RA, so it is probable these same effects could be seen RA patients.
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**Abbreviations:** RAI, rheumatoid activity index; RCTs, randomized controlled trials.
Education

Some of the earliest work in educational programs for treatment of RA was done by Lorig through development of the Arthritis Self-Management Program. An early study found that the program resulted in significant improvement in knowledge, behaviors such as exercise and relaxation, as well as diminished pain. A 4-year follow-up study showed long-term benefit as significant decreases in pain and physician visits were found. A larger randomized controlled trial of 544 OA and RA patients found that those who completed the self-management program had significant improvement in cognitive symptoms, communication with physicians, and pain, as well as significant decrease in depression and visits to physicians at 1-year follow-up. Although these studies were predominantly comprised of OA patients, other studies in RA patients have shown similar benefit. A controlled trial of 100 RA patients randomized to a problem-based education group and a control group found significant short-term increases in knowledge, exercise, and joint protection behaviors, as well as significant decreases in pain and disability. The only long-term effects seen were increased knowledge and joint protection. A two-part study by Scholten and colleagues found participation in an educational program resulted in significant postintervention improvement in coping strategies, depression, disability, and compliance with therapy; at 5-year follow-up, significant gains in disability, coping, and compliance were maintained. Likewise, similar improvement in treatment adherence was seen in a randomized controlled trial by Hill and colleagues. A systematic review of 31 randomized controlled trials found significant short-term effects of education on disability, patient global assessment, and depression with no effect on disease activity. No significant long-term effects were seen. The above studies demonstrate that educational interventions have significant short-term effects on disability, depression, pain, knowledge, and perhaps treatment adherence. Long-term benefit is uncertain at this time, warranting future follow-up studies to further evaluate the potential effect on disease activity.

SUMMARY

The importance of stress on immune function and balance has long been of interest, and our appreciation for the effects that stress can have on immune-based diseases continues to grow. Published studies do support the concept that stress can have a significant impact on autoimmune diseases, in particular rheumatoid arthritis. Whereas the effects of stress on onset of RA may be equivocal, the literature supports a role for minor stressors as factors that can contribute to symptom flares in RA patients. Furthermore, stress reduction interventions can have a positive therapeutic effect in RA patients as well. These are of particular interest given that a significant number of patients seek alternatives that can be combined with pharmacologic and biologic therapies to better manage their disease. A need persists to further investigate the effect of stress and stress interventions in RA using more sensitive tools that assess RA activity as well as measurements of stress. Until these studies emerge, it is important for physicians and patients to recognize the potential for stress to impact RA and autoimmune diseases and how stress management should be considered in a multidimensional approach to RA.

REFERENCES


