**CLINICAL REVIEW**

# Integrating Complementary and Alternative Medicine into a Rheumatology Practice

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### *Integrative Medicine*

Integrative medicine reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, and broadly consider appropriate therapeutic approaches, and disciplines to achieve optimal health and healing. Integrative medicine emphasizes compassionate, relationship-centered care and develops an understanding of the patient's culture and beliefs in order to facilitate the healing response. Most importantly, it maintains a patient's health with specific attention to lifestyle choices, such as nutrition, exercise, stress management, and emotional well-being.

Integrative rheumatology applies the principles of integrative medicine to the care of patients with rheumatic and musculoskeletal diseases (RMDs) with scientific evidence that supports both safety and efficacy. Although conventional medicine has limitations, the use of complementary and alternative medicine (CAM) without the supervision of a medical professional can lead to serious consequences, including delay in diagnosis, side effects caused by CAM, and harmful interactions with prescription medications. Conventional medicine as well as CAM should consider the words of Hippocrates:

> "Make a habit of two things: to help, or at least to do no harm."[1]

Many applications of integrative medicine are well matched to rheumatology practice. Conventional medicine treatments are associated with potential for significant adverse effects. Additionally, there is no cure for many rheumatologic disorders, 50%-90% of individuals with chronic illnesses have used at least one form of CAM to manage their symptoms, with 60% of rheumatology patients using CAM.[2]

Rheumatologists should be familiar with integrating the use of CAM into their practice. CAM refers to a group of diverse medical systems, practices, and products that are not generally considered as part of conventional medicine. "Complementary" refers to using a non-mainstream approach together with conventional medicine, while "alternative" refers to using a non-mainstream approach in place of conventional medicine. Furthermore, CAM is influenced by political, social, and cultural issues as well as the health care system.

### *Diet and Nutrition*

When considering the importance of diet and nutrition in the context of integrative medicine, we can refer to the words of Hippocrates:

> Let food be thy medicine and medicine be thy food.[3]

While many still think of medications as conventional medicine and dietary changes as alternative therapies, the rapidly growing field of integrative medicine seeks to combine the best of both. Recent years, an increasing interest in the influence of diet in RMDs led to many research studies exploring the role of nutrition in risk of developing RMDs and the natural history of disease in patients with established RMDs. A recent study by Alunno et al. identified diet as a possible facilitator of lupus and rheumatoid arthritis due to the direct pro-inflammatory properties of some nutrients and the indirect action on insulin resistance, obesity, and associated comorbidities.[4]

The prudent diet and the Mediterranean diet, have received interest by promoting an anti-inflammatory lifestyle. A 2014 publication by Dr. Bing Lu followed a cohort of 93,859 female registered nurses without rheumatoid arthritis who filled out dietary questionnaires every four years between 1991 and 2011. Among the 1181 incident cases of rheumatoid arthritis, there was a trend toward increased risk of rheumatoid arthritis among overweight and obese women. Furthermore, among rheumatoid arthritis cases diagnosed at age 55 years or younger, this association appeared stronger.[5] This study reported the Western diet, associated with high intake of red/processed meat, refined grains, French fries, desserts/sweets, and high-fat dairy products, was associated with an increased risk for developing seropositive rheumatoid arthritis, compared to those who followed the prudent diet, which is associated with high intake of fruits, vegetables, legumes, whole grains, poultry, and fish. Similarly, the Mediterranean diet emphasizes high intake of fruit, vegetables, extra virgin olive oil, fish, and legumes, a low-to-moderate intake of dairy products, eggs, and poultry, and a low intake of sweets, red meat, and wine.[6] Many of the anti-inflammatory effects of the Mediterranean diet are specifically linked to the intake of foods that are rich in polyunsaturated fatty acids as well as extra virgin olive oil, which contains high contents of monounsaturated fatty acids and nonfat micro-components such as phenolic compounds.[7]

***Obesity***

Diet and nutrition play important roles in obesity, a major comorbidity in RMDs. Many studies documented a correlation between obesity and a higher prevalence or worse prognosis of several immune-mediated conditions. There is growing evidence that white adipose tissue is a crucial site in the generation of soluble mediators called adipokines, most of which carry pro-inflammatory activity, including TNF-α, IL-6, lectin, and adiponectin. Elevated levels of inflammatory adipokines further stimulate adipose tissue expansion, particularly in the thorax and around viscera, thus inducing a positive feedback cycle of adipokine secretion and tissue inflammation. These visceral fat stores are thought to be responsible for the generation of elevated markers of systemic inflammation.[8]

Links between obesity and autoimmunity can be seen in many rheumatologic conditions, with several studies identifying the association and likely causality of these links. In psoriatic arthritis, obesity has a pathogenic role in the occurrence and severity of psoriatic arthritis as well as impacting treatment efficacy and safety. Adipose tissue is metabolically active and produces a chronic low-grade inflammation in obese individuals. This chronic low-grade inflammation may be responsible for the increased risk for psoriatic arthritis, increased disease burden, and poor response to therapy.[9] Obesity at 18 years of age was associated with a 35% increased risk of developing rheumatoid arthritis (RA), while obesity in adulthood was associated with a 50% increased risk of developing seropositive rheumatoid arthritis.[10] Finally, obesity increases the incidence of new-onset lupus nephritis and cumulative organ damage.[11]

An annual study examined the relationship of obesity and chronic pain. After thirteen weeks, mice eating the standard American diet had a significant increase in fat mass, serum leptin, and inflammatory cytokines compared to controls. Prolonged exposure to the standard American diet resulted in altered acute nociceptive sensitivity, increased systemic inflammation, and persistent pain.[12]

***Supplementation***

Supplementation involves the use of pills or special types of food in order to improve a person's health and well-being. Many supplements can be used, in conjunction with diet and nutrition, to complement holistic patient care.

Vitamin D is a fat-soluble steroidal substance that plays a crucial role in immune system health. When serum vitamin D level is less than 20 ng/mL, the risk for RA increases considerably.[13] Additionally, low vitamin D is associated with thrombosis in systemic lupus erythematosus.[14] Finally, vitamin D deficiency was found to promote skeletal muscle hypersensitivity and sensory hyperinnervation.[15]

Supplements have widely been used to treat patients with osteoarthritis. Avocado soybean unsaponifiables are a natural blended vegetable extract made from avocado and soybean oils, which have recently been popularized as therapy for osteoarthritis with several studies, demonstrating benefits.[16] Avocado soybean unsaponifiables have had great impact in knee and hip osteoarthritis. Similarly, chondroitin sulfate a naturally-occurring complex carbohydrate helps cartilage retain water. It may be useful in patients with hand osteoarthritis for pain relief and improvement in functioning.[17]

Supplements have been used to systemically promote anti-inflammation. Ginger has antioxidant, anti-inflammatory, antiseptic, and carminative properties. Ginger inhibits LPS-induced NO production, COX and LOX pathways, and peroxynitrite-mediated damage within the body. A study on rheumatoid arthritis patients reported beneficial effects of ginger in alleviating pain and swelling of the RA-involved joints.[18] Likewise, turmeric contains curcumin, a compound with notable anti-inflammatory effects. Curcumin modulates pro-inflammatory cytokine production, inhibits MMP gene expression and NO production, and affects the cyclooxygenase-2 and 5-lipoxygenase pathways. A double-blind, two week tumeric crossover with RA patients reported remarkable improvement in morning stiffness, joint swelling, and walking time.[19] Finally, omega-3 fatty acids, which are unsaturated fatty acids, produce anti-inflammatory lipids, called resolvins and protectins, which inhibit IL-1β, TNF-α, and NF-kβ. Clinical studies have shown omega-3 fatty acids may have a modulatory effect on rheumatoid arthritis disease activity, specifically on the number of swollen and tender joints.[20]

***Stress***

Stress has a long-reported relationship with autoimmunity; and practicing rheumatologists can attest to the importance of stress in the onset and exacerbation of autoimmune disorders, fibromyalgia, and chronic pain.

A 2003 study reported that more than 50% of patients with scleroderma ascribed the cause of their condition to stress.[21] Exposure to acute stress has been linked to altered HPA axis activity and immune function, with IL-1β and IFN-ɣ as predictors of subsequent fatigue. Worrying also increased the swollen joint count, fatigue level, and pain level in a cohort of RA patients. Daily stressors are associated with short-term disease fluctuations, including RA symptoms, fatigue, and arthralgia intensity. [22]

There is overwhelming evidence that the nervous system, can influence the immune system via neuro-immune and neuro-endocrine connections.[23]

Stress exposure activates the HPA axis, resulting in the release of glucocorticoids. While the exact mechanism of how stress can lead to autoimmunity is unknown, recent studies report that glucocorticoids can act as pro-inflammatory agents, particularly in the CNS, depending on the dose, chronicity of exposure, and the organ. One experiment analyzing this effect reported chronic unpredictable stress affects the frontal cortex and hippocampus, enhances the LPS-induced NF-kβ activation,

enhances expression of pro-inflammatory genes (iNOS, IL-1β, and TNF-α), and decreases expression of anti-inflammatory genes (IL-1Ra, IL-10, and MKP-1). Severe acute stress increases HMGB-1 protein levels (NLRP3, IKBα, and NFKB) in the hippocampus. This suggests that HMGB-1 participates in stress-inducing NLRP3 priming, promoting inflammation.[24] One study examined neurogenic neuroinflammation in fibromyalgia and CRPS. Psychological stress was identified as a catalyst, initiating the cascade of events that lead to neuroinflammation, also with other common triggers of infection, autoimmunity, and toxins.[25]

The recent COVID-19 pandemic has multiple stress related impacts. Patients with ankylosing spondylitis and rheumatoid arthritis worsened during the pandemic compared to healthy controls. Patients with chronic illnesses were more vulnerable to the psychological effects of the pandemic, which can worsen disease activity.[26] The new science of immune-autonomics analyzes the effects of stress on the immune system. Immunoautonomics studies the interference between stress, modulated within the brain by the ANS, and the immune system. This emerging science suggests the vagus nerve modulates splenic SNS activity to negatively affect immune conditions, such as RA.[27] Clinical trials and research experiments are being conducted to better understand the relationship between stress and autoimmunity.

***The Relaxation Response***

The stress response was, defined by Han Selye in the beginning of the 20th century. Half a century later, Dr. Herbert Benson and his colleagues built upon the work of Nobel laureate Dr. Walter Hess, who described the relaxation response (RR) a physiological response opposite of the stress response. Although physiological and biochemical changes that occur during the acute stress response have been well-characterized, the contrasting changes that underlie the RR are less understood. The RR is a common pathway of all mind-body therapies, which can be used to effectively and efficiently manage stress.

Mind-body practices are a diverse group of techniques including mindfulness-based stress reduction, meditation, guided imagery, breath work, yoga, massage therapy, spinal manipulation, and acupuncture. Contemporary therapies are increasing understanding of how mind-body techniques can elicit the relaxation response used for stress management. The benefits include, muscle relaxation, a decrease in negative emotions, an increase in positive emotions, promotion of state-dependent learning, and creative enhancement.

Research has shown RR activation enhances expression of genes associated with energy metabolism, mitochondrial function, insulin secretion, telomere maintenance, and reduced expression of genes linked to inflammatory response and stress-related pathways.[28] Interactive network analyses of RR-affected pathways identified mitochondrial ATP synthase and insulin as top upregulated critical molecules and NF-kβ pathway genes as top downregulated critical molecules. Relaxation response elicitation may evoke its downstream health benefits by improving mitochondrial energy production and utilization, thus promoting mitochondrial resiliency through upregulation of ATPase and insulin function. Mitochondrial resiliency might also be promoted by RR-induced downregulation of NF-kβ-associated upstream and downstream targets, thus mitigating stress.[28] Another study reported mind-body interventions, which induce the RR, affect gene expression and disease vulnerability by improving the body's response to oxidative stress, cellular damage, and systemic inflammation.[29]

***Compassionate Care***

Compassion involves looking beyond one's own pain in order to see the pain of others. Physicians are able to provide much-needed compassion in their medical care. Compassionate care is exemplified in this quote by Jalaludin Rumi:

> "Listen with ears of tolerance! See through the eyes of compassion! Speak with the language of love!"[30]

It is important to note that compassion begins with the self. A physician is unable to provide compassionate care to their patients if they are not, first, compassionate towards themselves.

In light of these recommendations, addressing diet, nutrition, supplements, mind-body techniques, stress management, and compassion, physicians are able to implement good medical practices. Integrative medicine, with the help of CAM, aims to empower and support patients, encouraging a more holistic, patient-centered, and compassionate approach to care, which will result in improved patient outcomes and well-being.

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