

ACUPUNCTURE AND RHEUMATOID ARTHRITIS

About rheumatoid arthritis

Rheumatoid arthritis is a chronic condition that can cause pain, stiffness, progressive joint destruction and deformity, and reduce physical function, quality of life and life expectancy.(Östör 2009; DTB 2008) Estimates indicate that around 0.5–1.0% of the UK population have rheumatoid arthritis.(NICE 2008) The condition involves synovial joint inflammation.(Smolen 2003); both T- and B-cells are implicated in the underlying immune pathology, as is the over-production of pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF- α), interleukin-1 (IL-1) and IL-6.(NICE 2008; Panayi 2005; Smolen 2003)

The course of rheumatoid arthritis is variable, following a pattern of relapses and remissions.(Masi 1983) However, within about 2 years of diagnosis, patients usually have moderate disability and, after 10 years, around 30% are severely disabled.(NICE 2008) People with rheumatoid arthritis have a reduced life expectancy compared with healthy controls, and have excess cardiovascular disease mortality.(Goodson 2005)

The cause of rheumatoid arthritis is, as yet, unknown. Infection with a micro-organism in those genetically susceptible, hormonal influences, obesity, diet, and cigarette smoking have all been implicated as risk factors.(Silman 2004)

The aim of treatment is to control pain and inflammation, reduce joint damage, disability and loss of function, achieve low disease activity or remission, and improve quality of life.(NICE 2008; Smolen 2007) A variety of drugs are used, including NSAIDs, analgesics, corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) like methotrexate, and biologicq drugs that block tumour necrosis factor-alpha (TNF) such as etanercept, infliximab or adalimumab.(NICE 2008) None-drug treatments such as physiotherapy may also be used.(NICE 2008)

References

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Rituximab and abatacept for rheumatoid arthritis. *DTB* 2008; 46: 57. 61.

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How acupuncture can help

Systematic reviews have come up with conflicting conclusions regarding the effects of acupuncture treatment for rheumatoid arthritis. One found that the data suggest favourable effects of moxibustion (alone or combined with conventional drugs) on response rate compared with conventional drug therapy.(Choi 2011) The other two reviews found acupuncture to be as good as or better than drugs, but with no consistent advantage over sham acupuncture controls.(Wang 2008; Lee 2008)

More recent trials have been small and do not present a compelling case for upgrading the reviews conclusions. It appears likely that some people may benefit from acupuncture treatment,(Lao 2010) but it is not known what proportion this may be, and to what degree and how acupuncture would compare to other possible interventions. More research is needed.

In general, acupuncture is believed to stimulate the nervous system and cause the release of neurochemical messenger molecules. The resulting biochemical changes influence the body's homeostatic mechanisms, thus promoting physical and emotional well-being. Stimulation of certain acupuncture points has been shown to affect areas of the brain that are known to reduce sensitivity to pain and stress (Hui 2010) It has also be shown to reduce inflammation, by promoting release of vascular and immunomodulatory factors.(Zijlstra 2003; Kavoussi 2007)

Acupuncture treatment may help to relieve pain and improve function in patients with rheumatoid arthritis by:

- decreasing the proinflammatory cytokines IL-1 and IL-6 and increasing the inhibitory cytokines IL-4 and IL-10 (Ouyang 2010);
- inducing vasoactive intestinal peptide expression, an anti-inflammatory neuro-peptide (He 2011);
- inhibiting the function of synovial mast cells (which are substantially involved in the initiation of inflammatory arthritis) (He 2010);
- upregulating plasma adrenocorticotrophic hormone, downregulating serum cortisol levels and synovial nuclear factor-kappa B p 65 immunoactivity, and restoring the hypothalamus-pituitary-adrenal axis (HPAA).(Gao 2010);
- stimulating nerves located in muscles and other tissues, which leads to release of endorphins and other neurohumoral factors, and changes the processing of pain in the brain and spinal cord (Pomeranz 1987; Han 2004; Zhao 2008; Cheng 2009);
- increasing local microcirculation (Komori 2009), which aids dispersal of swelling.

About traditional acupuncture

Acupuncture is a tried and tested system of traditional medicine, which has been used in China and other eastern cultures for thousands of years to restore, promote and maintain good health. Its benefits are now widely acknowledged all over the world and in the past decade traditional acupuncture has begun to feature more prominently in mainstream healthcare in the UK. In conjunction with needling, the practitioner may use techniques such as moxibustion, cupping, massage or electro-acupuncture. They may also suggest dietary or lifestyle changes.

Traditional acupuncture takes a holistic approach to health and regards illness as a sign that the body is out of balance. The exact pattern and degree of imbalance is unique to each individual. The traditional acupuncturist's skill lies in identifying the precise nature of the underlying disharmony and selecting the most effective treatment. The choice of acupuncture points will be specific to each patient's needs. Traditional acupuncture can also be used as a preventive measure to strengthen the constitution and promote general well-being.

An increasing weight of evidence from Western scientific research (see overleaf) is demonstrating the effectiveness of acupuncture for treating a wide variety of conditions. From a biomedical viewpoint, acupuncture is believed to stimulate the nervous system, influencing the production of the body's communication substances - hormones and neurotransmitters. The resulting biochemical changes activate the body's self-regulating homeostatic systems, stimulating its natural healing abilities and promoting physical and emotional well-being.

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The evidence

Research	Conclusion
Systematic Reviews	
Choi TY et al. Moxibustion for rheumatic conditions: a systematic review and meta-analysis. <i>Clin Rheumatol</i> . 2011 Feb 18. [Epub ahead of print]	A systematic review that pooled data from 14 randomised controlled trials testing effectiveness of moxibustion for major rheumatic conditions. Trials were included if moxibustion was used alone (8 trials) or as a part of a combination therapy with conventional drugs (6 trials) for rheumatic conditions. All were of low methodological quality. <u>The data suggested favourable effects of moxibustion alone on response rate compared with conventional drug therapy (p<0.02). The results also suggested favourable effects of moxibustion plus drug therapy on the response rate compared with conventional drug therapy alone (p<0.02). The reviewers concluded that the trials included in this review were of low methodological quality, making it difficult to draw firm conclusions.</u>
Wang C et al. Acupuncture for pain relief in patients with rheumatoid arthritis: a systematic review. <i>Arthritis Rheum</i> 2008; 59: 1249-56.	A systematic review that assessed the efficacy of acupuncture on pain relief in patients with rheumatoid arthritis (RA). In all, 8 randomised controlled trials, involving a total of 536 patients, were included. The outcome measures were pain, measured by tender joint count (TJC) or a pain scale, morning stiffness, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. There were 4 placebo-controlled trials and 4 active-controlled trials. Average study duration was 11 weeks. Six studies reported a decrease in pain for acupuncture versus controls. In addition, 4 studies reported a significant reduction in morning stiffness, but the difference was nonsignificant versus controls. With regard to inflammatory markers, 5 studies observed a reduction in ESR and 3 observed a CRP level reduction; only 1 study showed a significant difference for both ESR and CRP. <u>The reviewers concluded that there were some favourable results in active-controlled trials, but conflicting evidence in placebo-controlled trials concerning the efficacy of acupuncture for RA.</u>
LEE MS ET AL. ACUPUNCTURE FOR RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW. <i>RHEUMATOLOGY</i> 2008; 47: 1747-53.	A systematic review that evaluated the evidence on acupuncture for treating patients with rheumatoid arthritis (RA). It included 8 randomised clinical trials of acupuncture, with or without electrical stimulation or moxibustion. Four trials compared the effects of manual or electro-acupuncture with penetrating or non-penetrating sham acupuncture and failed to show specific effects of acupuncture on pain or other outcome measures. One trial compared manual acupuncture with indomethacin and suggested favourable effects with acupuncture in terms of total response rate. Three trials tested acupuncture plus moxibustion versus conventional drugs and failed to show that it was superior to conventional drugs in terms of response rate, pain reduction or joint swelling. <u>The reviewers concluded that penetrating or non-penetrating sham-controlled trials have failed to show specific effects of acupuncture for pain control in patients with RA.</u>
Clinical studies	
Lao WN et al. Effects of acupuncture on rheumatoid arthritis. <i>International Journal of Rheumatic Diseases</i> . Conference: 14th Congress of Asia Pacific League of Associations for Rheumatology, APLAR 2010 Hong Kong Hong Kong. Conference Publication 2010; 13: 231.	An uncontrolled pilot study that explored the effects of acupuncture on disease activity, pain scores, functional ability and quality of life in 8 patients with RA (6 were positive for rheumatoid factor). No change in disease modifying anti-rheumatic drugs (DMARDs) was allowed 3 months before the study. Tender joint count improved by 33.3% to 100% in six patients. The visual analogue scale for pain score improved by 12.5% to 87.5% in four patients. Disease activity score using 28-joint counts dropped by 3.4% to 29.1% in 6 patients. Health

assessment questionnaire score remained unchanged in five patients and improved by 37% to 60% in two patients. Physical well-being improved by 28.6% to 71.4% and social well-being improved by 4.4% to 75% in half of the patients, emotional well-being improved by 25% to 57.2% in three patients, functional well-being improved by 16.7% to 35.3% in two patients, fatigue sub-scale improved by 10% to 56.5% in three patients. No patients required adjustment of DMARDs, anti-inflammatory drugs or steroid during the therapy. The researchers concluded that their observations suggest acupuncture may be helpful in alleviating pain, improving disease activity, quality of life and functional ability in some patients with RA.

Bernateck M et al. Adjuvant auricular electroacupuncture and autogenic training in rheumatoid arthritis: A randomized controlled trial - Auricular acupuncture and autogenic training in rheumatoid arthritis. *Forschende Komplementarmedizin* 2008; 15: 187-93.

A randomised controlled trial to compare the efficacy of auricular electroacupuncture (EA) with autogenic training (AT) in 44 patients with RA. At the end of the treatment and at 3-month follow-up a clinically meaningful and statistically significant improvement ($p < 0.05$) could be observed in all outcome parameters in both groups. In contrast to the AT group, the onset of these effects in the EA group could already be observed after the 2nd treatment week. In the 4th treatment week the EA group reported significantly less pain than the AT group ($p = 0.040$). After the end of treatment (7th week) the EA group assessed their outcome as significantly more improved than the AT group ($p = 0.035$). The erythrocyte sedimentation rate in the EA group was significantly reduced ($p = 0.010$), and the serum concentration of tumour necrosis factor-alpha was significantly increased compared to the AT group ($p = 0.020$). The researchers concluded that the adjuvant use of both EA and AT in the treatment of RA resulted in significant short- and long-term treatment effects. The treatment effects of auricular EA were more pronounced.

Zanette S de A et al. A pilot study of acupuncture as adjunctive treatment of rheumatoid arthritis. *Clinical Rheumatology* 2008; 27: 627-35.

A double-blind randomised controlled pilot study that looked at the efficacy of acupuncture as an adjuvant treatment in the management of 40 patients with active rheumatoid arthritis (RA). They were allocated to receive a standard protocol of acupuncture (AC) or superficial acupuncture at non-acupuncture points (control AC) for 9 weeks. The primary outcome was achievement of 20% improvement according to the American College of Rheumatology (ACR) 20 criteria but this showed no significant difference between the groups, either at the end of treatment ($p = 0.479$) or after 1 month of follow-up ($p = 0.068$). Only the AC group showed significant improvement over baseline for a range of secondary clinical measures. Nevertheless, it was only statistically superior to the control for the patient and physician global assessment of treatment and physician global assessment of disease activity, not for other clinical and laboratory measures... The researchers concluded that there was no significant difference in the proportion of patients that reached ACR20 between the AC and control AC groups, but that this negative result could be related to the small sample size, selection of patients, type of acupuncture protocol applied, and difficulties in establishing an innocuous and trustworthy placebo group to studies involving acupuncture.

Tam LS et al. Acupuncture in the treatment of rheumatoid arthritis: A double-blind controlled pilot study. *BMC Complementary and Alternative Medicine* 2007; 7: 35.

A randomised double-blind placebo-controlled pilot study of acupuncture to obtain preliminary data on efficacy and tolerability of 3 different forms of acupuncture treatment as an adjunct for the treatment of chronic pain in patients with rheumatoid arthritis (RA). A total of 36 patients were allocated to electroacupuncture (EA), traditional Chinese acupuncture (TCA) or sham acupuncture (Sham). The primary outcome measure was change in the pain score. At week 10, the pain score remained unchanged in all 3 groups. However, the number of tender joints was significantly reduced for the EA and TCA groups. Physician's global score was significantly reduced for the EA group and patient's global score was significantly reduced for the TCA group. All the outcomes except patient's global score remained unchanged in the Sham group. The researchers concluded that the pilot study allowed a number of recommendations to be made to facilitate the design of a large-scale trial, which in turn would help to clarify the existing evidence base on acupuncture for RA.

Research on mechanisms for

acupuncture

He TF et al. Electroacupuncture inhibits inflammation reaction by upregulating vasoactive intestinal Peptide in rats with adjuvant-induced arthritis. *Evid Based Complement Alternat Med* 2011; 2011.

A study in rats that assessed the effects of electroacupuncture with adjuvant-induced arthritis. It was found to markedly decreased paw swelling and the histologic scores of inflammation in the synovial tissue, and reduced body weight loss in an adjuvant-induced arthritis rat model. Electroacupuncture also resulted in an enhanced immunostaining for vasoactive intestinal peptide (VIP), a potent anti-inflammatory neuropeptide, in the synovial tissue. Moreover, the VIP-immunostaining intensity was negatively correlated with the scores of inflammation in the synovial tissue ($p=0.0026$). The researchers concluded that their findings suggest that electroacupuncture may offer therapeutic benefits for the treatment of rheumatoid arthritis, at least partially through the induction of VIP expression.

Ouyang BS et al. Effects of electroacupuncture and simple acupuncture on changes of IL-1, IL-4, IL-6 and IL-10 in peripheral blood and joint fluid in patients with rheumatoid arthritis. [Article in Chinese] *Zhongguo Zhen Jiu* 2010; 300: 840-4.

A randomised controlled trial that explored the mechanism of acupuncture and electroacupuncture on rheumatoid arthritis (RA) in 63 patients. After 3 courses, changes of interleukins in peripheral blood and joint fluid of patients were observed. Both acupuncture and electroacupuncture had significant effects on interleukin (IL)-1, IL-4, IL-6 and IL-10 in the peripheral blood and joint fluid of patients with RA ($p<0.05$ and $p<0.01$, respectively). The researchers concluded that acupuncture and electroacupuncture can decrease the pro-inflammatory cytokines IL-1 and IL-6 and increase anti-inflammatory IL-4 and IL-10.

Gao J et al. Involvement of the hypothalamus-pituitary-adrenal axis in moxibustion-induced changes of NF-kappaB signaling in the synovial tissue in rheumatic arthritic rats [Article in Chinese]. *Zhen Ci Yan Jiu* 2010; 35: 198-203.

A study to observe the effect of moxibustion on the acupuncture points BL 23 and ST 36 on synovial nuclear factor (NF)-kappaB p65 expression, and plasma adrenocorticotrophic hormone (ACTH) and serum cortisol (CS) contents in rats with rheumatoid arthritis (RA) with adrenalectomy (ADX). In comparison with the control group, the degree of swelling in the rats' paws decreased significantly after moxibustion ($p<0.01$). Compared with the model group, serum CS contents and synovial NF-kappaB p 65 immunoactivity in reduced with moxibustion ($p<0.01$, $p<0.05$). The researchers concluded that moxibustion treatment can reduce inflammation reactions in rats with RA, which is closely associated with its effects in upregulating plasma ACTH, downregulating serum CS level and synovial NF-kappaB p 65 immunoactivity, and the intact hypothalamus-pituitary-adrenal axis (HPAA).

He TF et al. Effects of acupuncture on the number and degranulation ratio of mast cells and expression of tryptase in synovium of rats with adjuvant arthritis [Article in Chinese]. *Zhong Xi Yi Jie He Xue Bao* 2010; 8: 670-7.

A study that observed the effects of acupuncture on synovial pathology, synovial mast cell degranulation and tryptase expression and investigated the relationship between the functions of mast cells and effects of acupuncture on early adjuvant arthritis in rats. Compared with untreated rats, the body weight in the acupuncture group increased ($p<0.05$), while the paw volume decreased ($p<0.01$). Acupuncture inhibited inflammatory cell infiltration, synovial cell hyperplasia, and synovial fibroplasia compared with no treatment ($p<0.05$). Also it diminished the numbers of total and degranulated mast cells and the expression of tryptase in the synovium ($p<0.01$). The number of mast cells and degranulation ratio of mast cells were positively correlated with the pathological scores. The researchers concluded that acupuncture can improve pathological conditions of inflammatory synovium in rats with early adjuvant arthritis by inhibiting the function of synovial mast cells.

Hui KK et al. Acupuncture, the limbic system, and the anticorrelated networks of the brain. *Auton Neurosci* 2010; 157: 81-90.

A paper that discusses research showing that acupuncture mobilises the functionally anti-correlated networks of the brain to mediate its actions, and that the effect is dependent on the psychophysical response. The research used functional magnetic resonance imaging studies of healthy subjects to show that acupuncture stimulation evokes deactivation of a limbic-paralimbic-neocortical network, which encompasses the limbic system, as well as activation of somatosensory brain regions. It has also been shown that the effect of acupuncture on the brain is integrated at multiple levels, down to the brainstem and cerebellum.

Cheng KJ. Neuroanatomical basis of

A review that looked at acupuncture treatment for some common

acupuncture treatment for some common illnesses. <i>Acupunct Med</i> 2009;27: 61-4.	conditions. It is found that, in many cases, the acupuncture points traditionally used have a neuroanatomical significance from the viewpoint of biomedicine. From this, the reviewers hypothesize that plausible mechanisms of action include intramuscular stimulation for treating muscular pain and nerve stimulation for treating neuropathies.
Komori M et al. Microcirculatory responses to acupuncture stimulation and phototherapy. <i>Anesth Analg</i> 2009; 108: 635-40.	Experimental study on rabbits in which acupuncture stimulation was directly observed to increase diameter and blood flow velocity of peripheral arterioles, enhancing local microcirculation.
Zhao ZQ. Neural mechanism underlying acupuncture analgesia. <i>Prog Neurobiol</i> 2008; 85: 355-75.	Review article that discusses the various peripheral and central nervous system components of acupuncture anaesthesia in detail.
Kavoussi B, Ross BE. The neuroimmune basis of anti-inflammatory acupuncture. <i>Integr Cancer Ther</i> 2007; 6: 251-7.	Review article that suggests the anti-inflammatory actions of traditional and electro-acupuncture are mediated by efferent vagus nerve activation and inflammatory macrophage deactivation.
Han JS. Acupuncture and endorphins. <i>Neurosci Lett</i> 2004; 361: 258-61.	A literature review of studies relating to the release of endorphins by acupuncture.
Zijlstra FJ et al. Anti-inflammatory actions of acupuncture. <i>Mediators Inflamm</i> 2003; 12: 59-69.	An article that suggests a hypothesis for anti-inflammatory action of acupuncture: Insertion of acupuncture needles initially stimulates production of beta-endorphins, CGRP and substance P, leading to further stimulation of cytokines and NO. While high levels of CGRP have been shown to be pro-inflammatory, CGRP in low concentrations exerts potent anti-inflammatory actions. Therefore, a frequently applied 'low-dose' treatment of acupuncture could provoke a sustained release of CGRP with anti-inflammatory activity, without stimulation of pro-inflammatory cells.
Pomeranz B. Scientific basis of acupuncture. In: Stux G, Pomeranz B, eds. <i>Acupuncture Textbook and Atlas</i> . Heidelberg: Springer-Verlag; 1987: 1-18.	Needle activation of A delta and C afferent nerve fibres in muscle sends signals to the spinal cord, where dynorphin and enkephalins are released. Afferent pathways continue to the midbrain, triggering excitatory and inhibitory mediators in spinal cord. Ensuing release of serotonin and norepinephrine onto the spinal cord leads to pain transmission being inhibited both pre- and postsynaptically in the spinothalamic tract. Finally, these signals reach the hypothalamus and pituitary, triggering release of adrenocorticotrophic hormones and beta-endorphin.

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