

Immune Responses to Spinal Manipulation

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For many years, chiropractors have observed in their own practices that their patients sometimes demonstrate improvements of complaints related to immune problems: the disappearance or lessening of allergy symptoms, quicker recovery from or less frequent and severe colds and other respiratory infections, and so on. In the scientific literature, there have been occasional case reports that corroborate such findings, but no sound evidence to really document their veracity. These clinical observations remain suspended in that grey area unsubstantiated by scientific data to confirm their validity. Significant limitations of changes attributed to spinal manipulation in individual patients include 1) there is never a control group; 2) there is no blinding; 3) the improvement may simply be due to time; 4) they may be a nonspecific effect of care and attention; 5) it may be a regression to the mean; or 6) the result may be due to something other than spinal manipulation.

In some large studies, it has been found that chiropractic care for nonmusculoskeletal conditions is only weakly to moderately successful, but rarely harmful¹⁻² The most recent and thorough [systematic literature review](#) found that the evidence for effectiveness of spinal manipulation was inconclusive for nonmusculoskeletal conditions.³

Despite the lack of evidence of clinical effectiveness for nonmusculoskeletal conditions, a series of recent studies from several international research groups is systematically building the case that spinal manipulation appears to reduce the production of pro-inflammatory cytokines and increase the blood levels of immunoregulatory cytokines. Cytokines are small cell-signaling protein molecules that are secreted by numerous cells of the immune system and are a category of signaling molecules used extensively in intercellular communication.

The accumulation of data from these studies suggests that a possible benefit of spinal manipulation is related to neuroimmunological effects. Of course, this is an exciting proposition for clinicians who have seen such changes in their own patients. Let's review some of the research exploring the connections between spinal manipulation and functional changes in the immune system.

Early Research on Manipulation and the Immune System

Research in the 1990s laid the groundwork for the more recent papers published in the past five years. [Brennan, et al.](#),⁴ published a paper demonstrating that upper thoracic spinal manipulation resulted in markers indicating significant increased phagocytic activity of neutrophils and monocytes compared to a sham manipulation or soft-tissue treatment. The findings suggest that a certain force threshold was needed to elicit the response.

In a second study, Brennan, et al.,⁵ concluded that their data suggests spinal manipulation, which generates a force over a certain threshold, elicits viscerosomatic responses that affect both neutrophils and mononuclear cells phagocytic activity, at least over the short term. And in a very small 1994 study,⁶ the study authors concluded that upper cervical adjustments increased CD4

"helper" T-cell counts, which initiate the body's response to viruses in HIV-positive subjects, by 48 percent over the six-month duration of the study.

Neural Immunoregulation: Communication Between the Immune and Nervous Systems

These earlier papers have now been followed-up by a series of recent studies within the past five years. [Teodorczyk-Injeyan, et al.](#),⁷ described the interplay between the nervous system and immune system as *neural immunoregulation*. The authors note that immune homeostasis is based on the *reciprocal communication between the immune and the nervous systems* executed by the actions of cytokines and neurotransmitters. In addition, the paper explains the close association of autonomic nerve terminals with macrophages and lymphocytes, which facilitates a chemically mediated transmission between nerves and immune cells.

This research group has published a series of papers that explores the relationship of spinal manipulation, spinoautonomic reflexes and their influence on activity of cells involved in immune and/or inflammatory responses. These interconnections may have great clinical relevance because [studies⁸ on the pathophysiology](#) of discogenic low back pain, sciatica, and ligamentous tissue damage-related pain⁹ reveal that the production of pro-inflammatory mediators, such as tumor necrosis factor alpha (TNF-*a*) and interleukin-1 beta (IL-1 β), are major factors in the genesis of pain and functional changes in neural activity. Furthermore, studies of the hypoalgesic effects of spinal manipulation have already been reported in the literature, suggesting that an anti-inflammatory mechanism might be activated by spinal manipulation.¹⁰⁻¹¹ Recent clinical studies have shown that chemical blockage of TNF-*a* is highly effective in [reducing sciatic pain](#).¹²

Reduced Pro-Inflammatory Cytokines After Spinal Manipulation

In the first of their studies, the authors report that a single bilateral hypothenar upper-thoracic HVLA thrust resulted in the reduction of *in vitro* inflammatory cytokines, TNF-*a* and IL-1 β in blood samples activated with lipopolysaccharide taken before, 20 minutes and two hours after spinal manipulation. TNF-*a* and IL-1 β significantly declined in asymptomatic subjects assigned to manipulation with cavitation/audible, whereas in the sham and control groups, TNF-*a* and IL-1 β levels increased significantly after exposure to lipopolysaccharide.

The paper's conclusion states that manipulation-related down-regulation of inflammatory-type responses occurred via an unknown central mechanism. These findings suggest that a single thoracic manipulation effectively ameliorates the physiological responses of blood cells to an inflammatory stimulus and that spinovisceral reflex effects may alter the functional activity of cells in the immune and/or inflammatory systems. Based on these findings, the paper notes that spinal manipulation is likely to present a noninvasive and efficacious alternative to drug therapies for reducing inflammation and resultant pain.

[A 2009 paper](#) from the Hungarian National Institute for Rheumatology and Physiotherapy¹³ reported a dramatic and significant reduction in both debilitating cervicogenic headaches (before treatment 3-6 times a week lasting a total of 31-36 hours a week), neck stiffness and TNF-*a* after manual therapy in two women who suffered post-whiplash, MRI-documented C4-5 disc herniation.

Previous trials of conservative care (analgesic infusions, physical therapy) had failed. Both patients, after a neurological consult, were recommended to have a discectomy, but both opted for a trial of manual therapy (two times a week for 4-8 weeks) first. After manual therapy, surgery was unnecessary because both women became headache-free with a normal range of cervical motion.

In addition, both patients experienced a dramatic reduction in TNF- α (reduced by more than half).¹³

The medical researchers conclude that pro-inflammatory substances secreted by the nucleus pulposus are likely involved in symptomatic disc herniation. In addition, TNF- α , interleukin-1 β and interleukin-10 may be involved in the pathogenesis of migraine attacks. After restoring spinal segmental motion and reducing pathologic mechanical irritation/compression, TNF- α levels were markedly reduced and symptoms were eliminated. In 2010, Roy,¹⁴ et al., followed up these two studies by evaluating pre- and post-intervention measures from blood samples detecting pro-inflammatory cytokines interleukin 6 (IL-6) and C-reactive protein (CRP) after a series of nine chiropractic manipulations from T12-L5 using the an adjusting instrument and related protocol in 10 chronic low back pain patients and 10 healthy subjects. Once again, the introduction notes that low back pain is often associated with an inflammatory process and increased production of several pro-inflammatory cytokines including IL-6 and CRP. IL-6 is the main mediator of the acute phase of pro-inflammatory cytokines and results in a marked increase in liver cell synthesis of CRP.

This trial found that a series of nine thoracic manipulations resulted in a reduction of both IL-6 and CRP; that is, a normalization response. Both IL-6 and CRP levels were reduced toward the values in the healthy subjects. IL-6 and CRP were elevated in chronic LBP patients pre-intervention, but post-intervention differences were smaller, suggesting that nine manipulations are capable of attenuating the inflammatory response. The authors opine that it is plausible the inflammatory process was being reversed in those who received the adjustments.

Immunoregulation, Interleukin 2 and Spinal Manipulation

Another related avenue of research on neural immunoregulation evaluates the effects of spinal manipulation on the production of interleukin 2 (IL-2) - an immunoregulatory (not pro-inflammatory) cytokine and signaling molecule, instrumental in the body's response to microbial infection and for the body's ability to discriminate between foreign (non-self) and self. IL-2 is a pivotal cytokine in T-cell-dependent immune responses and plays a major role in the development, maintenance and survival of regulatory T cells. Thus, it is of critical importance in induction and sustenance of immune tolerance.

Seventy-six asymptomatic subjects¹⁵ were randomized to receive an upper thoracic manipulation with cavitation or without cavitation, or were included in a control group. All subjects had their blood drawn before, 20 minutes and two hours after the intervention. Production of IL-2 in mononuclear cell cultures was activated with staphylococcal protein A (SPA). Induced secretion of IL-2 increased significantly in manipulation with and without cavitation. The paper concludes that *in vitro* T lymphocyte response to a SPA stimulus became enhanced after spinal manipulation. Therefore, this effect may be independent of joint cavitation/audible. This finding suggests manipulation may influence IL-2 immune-regulated biological responses.

In 2010, Teodorczyk-Injeyan, et al.,¹⁶ continued with this research on induction and regulation of immune responses related to interactions between the immune and nervous systems mediated by actions of neurotransmitters and immunoregulatory cytokines. To this end, the researchers followed the subjects from the previous study to determine if the increased production of interleukin-2 as a result of a single thoracic manipulation is associated with increased antibody synthesis from monocytes.

The paper reports that there were indeed significantly increased synthesis of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies induced in cultures of peripheral blood mononuclear cells in subjects who received thoracic manipulation, particularly in those who had an associated

cavitation. The paper concludes that antibody synthesis (IgG and IgM) induced by interleukin-2 can be, at least temporarily, increased after manipulation. This is additional direct evidence that thoracic manipulation may influence interleukin-2 immune-regulated biological responses.

The Take-Home Message

The studies described above demonstrate an accumulation of evidence that indicates spinal manipulation may influence the immune system's response to various stimuli. Three of the studies suggest that manipulation consistently reduced the production of pro-inflammatory mediators associated with tissue damage and pain from articular structures. Two studies provide evidence that manipulation consistently reduced the production of pro-inflammatory mediators associated with tissue damage and pain from articular structures. Two studies provide evidence that manipulation may induce and enhance production of the immunoregulatory cytokine IL-2 and the production of immunoglobulins as well.

We must acknowledge that these results are preliminary because most are performed on asymptomatic subjects and the duration of the effects so far have only been demonstrated to be short-lived. Nevertheless, this research opens the door to further exploration of the possible neuroimmunoregulatory effects of spinal manipulation and confirms what many of us have observed in practice: Adjustments reduce pain and inflammation, and may improve immunoregulatory function.

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