

## **Immunity- Chiropractic Clinical Studies**

### **The immediate effects of cervical spine manipulation on pain and biochemical markers in females with acute non specific mechanical neck pain**

Lohman EB, Pacheco GR, Gharibvand L, Daher N, Devore K, Bains G, AlAmeri M, Berk LS

#### **Journal of Manual & Manipulative Therapy**

2019

Study Design: Randomized clinical trial with pre-test, post-test control group design.

Objectives: To examine the immediate effects of cervical spinal manipulation (CSM) on serum concentration of biochemical markers (oxytocin, neurotensin, orexin A, and cortisol).

Background: Several studies have found an association between spinal manipulation (SM) and pain perception. However, the mechanism by which SM modulates pain remains undefined.

Methods: Twenty-eight female subjects with non-specific mechanical neck pain were randomly assigned to one of two interventions (CSM versus sham CSM). Blood samples were drawn before and immediately after the respective interventions. Oxytocin, neurotensin, orexin A, and cortisol were measured from the blood and serum using the Milliplex Map Magnetic Bead Panel Immunoassay on the Luminex 200 Platform.

Results: In the CSM group, there were significant increases in pre- versus post-manipulation mean oxytocin ( $154.5 \pm 60.1$  vs.  $185.1 \pm 75.6$ ,  $p = .012$ ); neurotensin ( $116.0 \pm 26.5$  vs.  $136.4 \pm 34.1$ ,  $p < .001$ ); orexin A ( $52.2 \pm 31.1$  vs.  $73.8 \pm 38.8$ ,  $p < .01$ ) serum concentration; but no significant differences in mean cortisol ( $p = .052$ ) serum concentration. In the sham group, there were no significant differences in any of the biomarkers ( $p > .05$ ).

Conclusion: The results of the current study suggest that the mechanical stimuli provided through a CSM may modify neuropeptide expression by immediately increasing the serum concentration of nociception-related biomarkers (oxytocin, neurotensin, orexin A, but not cortisol) in the blood of female subjects with non-specific mechanical neck pain.

### **Elevated production of nociceptive CC chemokines and sE-selectin in patients with low back pain and the effects of spinal manipulation**

Teodorczyk-Injeyan JA, McGregor M, Traino JJ, Injeyan SH

#### **The Clinical Journal of Pain**

2018

Background: The involvement of inflammatory components in the pathophysiology of low back pain (LBP) is poorly understood. It has been suggested that spinal manipulative therapy (SMT) may exert anti-inflammatory effects.

Purpose: The purpose of this study was to determine the involvement of inflammation-associated chemokines (CC series) in the pathogenesis of nonspecific LBP and to evaluate the effect of SMT on that process.

Methods: Patients presenting with nonradicular, nonspecific LBP (minimum pain score 3 on 10-point visual analog scale) were recruited according to stringent inclusion criteria. They were evaluated for appropriateness to treat using a high velocity low amplitude manipulative thrust in the lumbar-lumbosacral region. Blood samples were obtained at baseline and following the administration of a series of 6 high velocity low amplitude manipulative thrusts on alternate days over the period of 2 weeks. The in vitro levels of CC chemokine ligands (CCL2, CCL3, and CCL4) production and plasma levels

of an inflammatory biomarker, soluble E-selectin (sE-selectin), were determined at baseline and at the termination of treatments 2 weeks later.

Results: Compared with asymptomatic controls baseline production of all chemokines was significantly elevated in acute ( $P=0.004$  to  $<0.0001$ ), and that of CCL2 and CCL4 in chronic LBP patients ( $P<0.0001$ ). Furthermore, CCL4 production was significantly higher ( $P<0.0001$ ) in the acute versus chronic LBP group. sE-selectin levels were significantly higher ( $P=0.003$ ) in chronic but not in acute LBP patients. Following SMT, patient-reported outcomes showed significant ( $P<0.0001$ ) improvements in visual analog scale and Oswestry Disability Index scores. This was accompanied by a significant decline in CCL3 production ( $P<0.0001$ ) in both groups of patients. Change scores for CCL4 production differed significantly ( $P<0.0001$ ) only for the acute LBP cohort, and no effect on the production of CCL2 or plasma sE-selectin levels was noted in either group.

Conclusions: The production of chemotactic cytokines is significantly and protractedly elevated in LBP patients. Changes in chemokine production levels, which might be related to SMT, differ in the acute and chronic LBP patient cohorts.

### **Neuroendocrine Response Following a Thoracic Spinal Manipulation in Healthy Men**

Kovanur-Sampath K, Botnmark E, Mani R, Cotter J, Katare R, Munasinghe PE, Tumilty S

#### **Journal of Orthopaedic and Sports Physical Therapy**

2017

Study Design: Controlled laboratory study.

Background: Spinal manipulation (SM) can trigger a cascade of responses involving multiple systems, including the sympathetic nervous system and the endocrine system, specifically, the hypothalamic-pituitary axis. However, no manual therapy study has investigated the neuroendocrine response to SM (ie, sympathetic nervous system-hypothalamic-pituitary axis) in the same trial.

Objective: To determine short-term changes in sympathetic nervous system activity, heart rate variability, and endocrine activity (cortisol, testosterone, and testosterone-cortisol [T/C] ratio) following a thoracic SM.

Methods: Twenty-four healthy men aged between 18 and 45 years were randomized into 2 groups: thoracic SM ( $n = 12$ ) and sham ( $n = 12$ ). Outcome measures were salivary cortisol (micrograms per deciliter), salivary testosterone (picograms per milliliter), T/C ratio, heart rate variability, and changes in oxyhemoglobin concentration of the right calf muscle (micromoles per liter). Measurements were done before and at 5 minutes, 30 minutes, and approximately 6 hours after intervention.

Results: A statistically significant group-by-time interaction was noted for T/C ratio ( $P<.05$ ) and salivary cortisol ( $P<.01$ ) concentrations. Significant between-group differences were noted for salivary cortisol concentration at 5 minutes (mean difference, 0.35; 95% confidence interval: 0.12, 0.6; interaction:  $P<.01$ ) and for T/C ratio at 6 hours postintervention (mean difference,  $-0.09$ ; 95% confidence interval:  $-0.16$ ,  $-0.04$ ;  $P = .02$ ). However, SM did not differentially alter oxyhemoglobin, testosterone, or heart rate variability relative to responses in the sham group.

Conclusion: Thoracic SM resulted in an immediate decrease in salivary cortisol concentration and reduced T/C ratio 6 hours after intervention. A pattern of immediate sympathetic excitation was also observed in the SM group.

### **Measureable changes in the neuro-endocrinal mechanism following spinal manipulation**

Kovanur-Sampath K, Mani R, Cotter JD, Tumilty S

#### **Medical Hypotheses**

2015

The autonomic nervous system and the hypothalamic–pituitary–adrenal axis have been shown to be dysfunctional in a number of chronic pain disorders. Spinal manipulation is a therapeutic technique used by manual therapists, which may have widespread neuro-physiological effects. The autonomic nervous system has been implicated to modulate these effects. A theory is proposed that spinal manipulation has the potential to be used as a tool in restoring the autonomic nervous system balance. Further, it is also hypothesised that through its anatomical and physiological connections, the autonomic nervous system activity following a thoracic spinal manipulation may have an effect on the hypothalamic–pituitary–adrenal axis and therefore pain and healing via modulation of endocrine and physiological processes. To substantiate our hypothesis we provide evidence from manual therapy studies, basic science and animal studies. According to the proposed theory, there will be measurable changes in the neuro-endocrinal mechanisms following a thoracic spinal manipulation. This has far-reaching implications for manual therapy practice and research and in the integration of spinal manipulation in the treatment of a wide array of disorders.

### **Immediate effects of spinal manipulation on nitric oxide, substance P and pain perception**

Molina-Ortega F, Lomas-Vega R, Hita-Contreras F, Manzano GP, Achalandabaso A, Ramos-Morcilla AJ, Martinez-Amat A

#### **Manual Therapy**

2014

Previous studies have analyzed the effects of spinal manipulation on pain sensitivity by using several sensory modalities, but to our knowledge, no studies have focused on serum biomarkers involved in the nociceptive pathway after spinal manipulation. Our objectives were to determine the immediate effect of cervical and dorsal manipulation over the production of nitric oxide and substance P, and establishing their relationship with changes in pressure pain thresholds in asymptomatic subjects. In this single-blind randomized controlled trial, 30 asymptomatic subjects (16 men) were randomly distributed into 3 groups (n ¼ 10 per group): control, cervical and dorsal manipulation groups. Blood samples were extracted to obtain serum. ELISA assay for substance P and chemiluminescence analysis for nitric oxide determination were performed. Pressure pain thresholds were measured with a pressure algometer at the C5eC6 joint, the lateral epicondyle and the tibialis anterior muscle. Outcome measures were obtained before intervention, just after intervention and 2 h after intervention. Our results indicated an increase in substance P plasma level in the cervical manipulation group (70.55%) when compared with other groups ( $p < 0.05$ ). This group also showed an elevation in the pressure pain threshold at C5eC6 (26.75%) and lateral epicondyle level (21.63%) immediately after the intervention ( $p < 0.05$ ). No changes in nitric oxide production were observed. In conclusion, mechanical stimulus provided by cervical manipulation increases substance P levels and pressure pain threshold but does not change nitric oxide concentrations. Part of the hypoalgesic effect of spinal manipulation may be due to the action of substance P.

### **Elevated production of inflammatory mediators including nociceptive chemokines in patients with neck pain**

Teodorczyk- Injeyan JA, Triano JJ, McGregor M, Woodhouse L, Injeyan HS

#### **Journal of Manipulative and Physiological Therapeutics**

2011

Objective: This study investigated whether the production of inflammatory mediators and chemotactic cytokines (chemokines) is altered in patients with chronic and recurrent neck pain (NP).

**Methods:** Cross-sectional data evaluating blood and serum samples were obtained from 27 NP patients and 13 asymptomatic (control) subjects recruited from a chiropractic outpatient clinic. Cell cultures were activated by lipopolysaccharide (LPS) and phytohemagglutinin for 24 to 48 hours. The levels of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), monocyte chemoattractant protein 1, also known as CCL2 (CCL2/MCP-1), and macrophage inflammatory protein 1 $\alpha$  or CCL3 (CCL3/MIP-1 $\alpha$ ) were determined by specific immunoassays. Serum levels of nitric oxide metabolites were evaluated simultaneously, in vanadium III-reduced samples, by Griess reaction.

**Results:** Low levels of constitutive (spontaneous) TNF- $\alpha$  production were present in 7 of the 27 cultures from patients with NP. Both LPS-induced TNF- $\alpha$  production and inducer (LPS/phytohemagglutinin)-stimulated production of CCL2 were significantly elevated ( $P = .00$ ) in patients compared with controls. In patients, the constitutive synthesis of CCL3 occurred significantly more frequently ( $P = .00$ ) and ranged from 30 to more than 2000 pg/mL. Finally, serum levels of nitric oxide were significantly elevated ( $P = .00$ ) in NP patients.

**Conclusions:** Production of inflammatory mediators was consistently elevated in NP patients in this study, both in vitro and in vivo, and activation of inflammatory pathways was accompanied by up-regulation of CC chemokine synthesis. This suggests that, in NP patients, CC chemokines may be involved in regulation of local inflammatory response through recruitment of immune cells to the inflamed tissue and exert pronociceptive effects.

### **Interleukin 2-regulated in vitro antibody production following a single spinal manipulative treatment in normal subjects**

Teodorczyk-Injeyan JA, McGregor M, Harris GM, Ruegg R, Injeyan HS

#### **Chiropractic & Osteopathy**

2010

**Background:** Our recent investigations have demonstrated that cell cultures from subjects, who received a single spinal manipulative treatment in the upper thoracic spine, show increased capacity for the production of the key immunoregulatory cytokine, interleukin-2. However, it has not been determined if such changes influence the response of the immune effector cells. Thus, the purpose of the present study was to determine whether, in the same subjects, spinal manipulation-related augmentation of the in vitro interleukin-2 synthesis is associated with the modulation of interleukin 2-dependent and/or interleukin-2-induced humoral immune response (antibody synthesis).

**Methods:** A total of seventy-four age and sex-matched healthy asymptomatic subjects were studied. The subjects were assigned randomly to: venipuncture control ( $n = 22$ ), spinal manipulative treatment without cavitation ( $n = 25$ ) or spinal manipulative treatment associated with cavitation ( $n = 27$ ) groups.

Heparinized blood samples were obtained from the subjects before (baseline) and then at 20 minutes and 2 hours post-treatment. Immunoglobulin (antibody) synthesis was induced in cultures of peripheral blood mononuclear cells by stimulation with conventional pokeweed mitogen or by application of human recombinant interleukin-2. Determinations of the levels of immunoglobulin G and immunoglobulin M production in culture supernatants were performed by specific immunoassays.

**Results:** The baseline levels of immunoglobulin synthesis induced by pokeweed mitogen or human recombinant interleukin-2 stimulation were comparable in all groups. No significant changes in the production of pokeweed mitogen-induced immunoglobulins were observed during the post-treatment period in any of the study groups. In contrast, the production of interleukin-2-induced immunoglobulin G and immunoglobulin M was significantly increased in cultures from subjects treated with spinal manipulation. At 20 min post-manipulation, immunoglobulin G synthesis was significantly elevated in subjects who received manipulation with cavitation, relative to that in cultures from subjects who received manipulation without cavitation and venipuncture alone. At 2 hr posttreatment,

immunoglobulin M synthesis was significantly elevated in subjects who received manipulation with cavitation relative to the venipuncture group. There were no quantitative alterations within the population of peripheral blood B or T lymphocytes in the studied cultures.

Conclusion: Spinal manipulative treatment does not increase interleukin-2 -dependent polyclonal immunoglobulin synthesis by mitogen-activated B cells. However, antibody synthesis induced by interleukin-2 alone can be, at least temporarily, augmented following spinal manipulation. Thus, under certain physiological conditions spinal manipulative treatment might influence interleukin-2 -regulated biological responses.

### **Inflammatory response following a short term course of chiropractic treatment in subjects with and without chronic low back pain**

Roy RA, Bousher JP, Comtois AS

#### **Journal of Chiropractic Medicine**

2010

Objective: Inflammatory markers interleukin-6 (IL-6) and C-reactive protein (CRP) have not been evaluated in response to a short course of lumbar spinal manipulation. The purpose of this study is to observe the responses of inflammatory markers (IL-6 and CRP) after a series of 9 chiropractic spinal manipulations.

Methods: Twenty-one participants were assigned to a treatment or a control group. Only the treatment group received 9 chiropractic interventions. Pre- and postintervention measures were recorded for blood samples for detection of proinflammatory cytokines IL-6 and CRP.

Results: Mediators of inflammation (IL-6 and high-sensitivity CRP) were modified by the intervention received in the treatment group, and the effect size demonstrated a tendency toward the control group values.

Conclusion: A total of 9 chiropractic lower back manipulations caused the mediators of inflammation to present a normalization response in individuals suffering from chronic low back pain.

### **Reductions in high blood tumor necrosis factor alpha levels after manipulative therapy in 2 cervicogenic headache patients**

Ormos G, Mehrishi JN, Bakacs T

#### **Journal of Manipulative and Physiological Therapeutics**

2009

Objective: This case report discusses the treatment of 2 patients with cervicogenic headache (CHA) attending the Outpatient Clinic of the Hungarian National Institute for Rheumatology and Physiotherapy (Budapest, Hungary) and reviews the pathophysiology, therapeutic strategy, and problems associated with the treatment of CHA.

Clinical Features: Patient 1 was a 27-year-old female who sustained a whiplash injury. A sharp, shooting headache developed, readily induced, and aggravated by just bending the neck backward or by turning her head. Magnetic resonance imaging revealed a disk protrusion at C4-05 pressing the anterior cerebrospinal space. Patient 2 was a 62-year-old female who sustained a whiplash injury; her cervical movements became restricted, which precipitated headaches. Magnetic resonance imaging revealed a paramedian disk hernia between the C4 and C5 vertebrae that intruded into the right ventral cerebrospinal space.

Intervention and Outcome: After 4 weeks of manipulative therapy for patient 1, both active and passive range of motion returned to normal, and the high tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) level (63 pg/mL) was substantially reduced (28 pg/mL). Patient 2 was started on manipulative therapy twice a week for 4 weeks; after 2 months, the patient became symptom-free, and high TNF- $\alpha$  level (72 pg/mL) was reduced greatly (35 pg/mL).

Conclusion: Two patients with whiplash injury and disk herniation developed CHA associated with very high TNF- $\alpha$  levels. After manipulative therapy, these patients became symptom-free, and their TNF- $\alpha$  levels decreased substantially.

### **Enhancement of *in vitro* interleukin-2 production in normal subjects following a single spinal manipulative treatment**

Teodorczyk-Injeyan JA, Injeyan HS, McGregor M, Harris GM, Ruegg R

#### **Chiropractic & Osteopathy**

2008

Background: Increasing evidence supports somato-visceral effects of manual therapies. We have previously demonstrated that a single spinal manipulative treatment (SMT) accompanied by audible release has an inhibitory effect on the production of proinflammatory cytokines in asymptomatic subjects. The purpose of this study is to report on SMT-related changes in the production of the immunoregulatory cytokine interleukin 2 (IL-2) and to investigate whether such changes might differ with respect to the treatment approach related to the presence or absence of an audible release (joint cavitation).

Methods: Of 76 asymptomatic subjects, 29 received SMT with cavitation (SMT-C), 23 were treated with SMT without cavitation (SMT-NC) and 24 comprised the venipuncture control (VC) group. The SMT-C and SMT-NC subjects received a single, similar force high velocity low amplitude manipulation, in the upper thoracic spine. However, in SMT-NC subjects, positioning and line of drive were not conducive to cavitation. Blood and serum samples were obtained before and then at 20 and 120 min post-intervention. The production of IL-2 in peripheral blood mononuclear cell cultures was induced by activation for 48 hr with Staphylococcal protein A (SPA) and, in parallel preparations, with the combination of phorbol ester (TPA) and calcium ionophore. The levels of IL-2 in culture supernatants and serum were assessed by specific immunoassays.

Results: Compared with VC and their respective baselines, SPA-induced secretion of IL-2 increased significantly in cultures established from both SMT-C and SMT-NC subjects at 20 min post-intervention. At 2 hr posttreatment, significant elevation of IL-2 synthesis was still apparent in preparations from SMT-treated groups though it became somewhat attenuated in SMT-NC subjects. Conversely, IL-2 synthesis induced by TPA and calcium ionophore was unaltered by either type of SMT and was comparable to that in VC group at all time points. No significant alterations in serum-associated IL-2 levels were observed in any of the study groups.

Conclusion: The present study demonstrates that, the *in vitro* T lymphocyte response to a conventional mitogen (SPA), as measured by IL-2 synthesis, can become enhanced following SMT. Furthermore, within a period of time following the manipulative intervention, this effect may be independent of joint cavitation. Thus the results of this study suggest that, under certain physiological conditions, SMT might influence IL-2-regulated biological responses.

### **Spinal Manipulative Therapy Reduces Inflammatory Cytokines but Not Substance P Production in Normal Subjects**

Teodorczyk-Injeyan JA, Injeyan HS, Ruegg R

## **Journal of Manipulative and Physiological Therapeutics**

2006

**Objective:** To examine the effect of a single spinal manipulation therapy (SMT) on the in vitro production of inflammatory cytokines, tumor necrosis factor  $\alpha$ , and interleukin (IL)  $1\beta$ , in relation to the systemic (in vivo) levels of neurotransmitter substance P (SP).

**Methods:** Sixty-four asymptomatic subjects were assigned to SMT, sham manipulation, or venipuncture control group. SMT subjects received a single adjustment in the thoracic spine. Blood and serum samples were obtained from subjects before and then at 20 minutes and 2 hours after intervention. Whole-blood cultures were activated with lipopolysaccharide (LPS) for 24 hours. Cytokine production in culture supernatants and serum SP levels were assessed by specific immunoassays.

**Results:** Over the study period, a significant proportion ( $P \leq .05$ ) of sham and control subjects demonstrated progressive increases in the synthesis of tumor necrosis factor  $\alpha$  and IL- $1\beta$ . Conversely, in a comparable proportion of cultures from SMT-derived subjects, the production of both cytokines decreased gradually. Normalization of the observed alterations to reflect the changes relative to self-baselines demonstrated that, within 2 hours after intervention, the production of both cytokines increased significantly ( $P < .001$  to  $.05$ ) in both controls. In contrast, a significant ( $P < .001$  to  $.05$ ) reduction of proinflammatory cytokine secretion was observed in cultures from SMT-receiving subjects. In all study groups, serum levels of SP remained unaltered within 2 hours after intervention.

**Conclusions:** SMT-treated subjects show a time-dependent attenuation of LPS-induced production of the inflammatory cytokines unrelated to systemic levels of SP. This suggests SMT-related down-regulation of inflammatory-type responses via a central yet unknown mechanism.

## **Lymphocyte profiles in patients with chronic low back pain enrolled in a clinical trial**

Brennan PC, Graham MA, Triano JJ, Hondras MA, Anderson RJ

## **Journal of Manipulative and Physiological Therapeutics**

1994

**OBJECTIVE:** Our earlier findings suggest that patients with musculoskeletal complaints have lower numbers and percentages of natural killer (NK) cells than asymptomatic subjects. This study examines patient lymphocyte profiles, as a secondary outcome mechanical origin.

**DESIGN:** The patients were compared in a randomized controlled trial. Baseline measures were collected at the initial visit; all patients were scheduled for 11 treatments in 14 days. Treatment consisted of either a high-force, high-velocity, low-amplitude manipulation procedure; a low-force, high-velocity, low-amplitude procedure or a series of educational lectures on lower back pain. Posttreatment measures were collected at the final treatment session; follow-up measures were obtained 2 wk later.

**SETTING:** The study was conducted at a chiropractic teaching clinic in the suburban Chicago area.

**PARTICIPANTS:** Individuals over 18 were eligible if they were new patients or repeat patients with a 6 month's hiatus, if the chief complaint was LBP of greater than 50 days' duration, if pain was elicited with palpation over one or more of the facet joints from the spinal levels between L1 and S1 and including the sacroiliac joints, and if there was absence of pain referral or if pain referral was only scleratogenous in nature. Criteria for excluding patients included hard neurologic signs, systemic disease potentially affecting the musculoskeletal system, contraindication to spinal manipulation such as osteoporosis, fracture or other bony pathology, or treatment with medication intended to relieve symptoms associated with their LBP. Eligibility was determined by a staff diagnostic team independent of the attending physician. Three hundred sixty-seven of 1,275 consecutive new patients met the eligibility criteria. Of these, 209 participated. These results are for 201 patients from whom flow cytometric data were obtained.

**OUTCOME MEASURES:** Both absolute numbers and percentages of B-lymphocytes, T-lymphocytes, T-Helper (TH), T-Suppressor (TS) and NK lymphocytes were determined. Blood samples were collected at the same time that the primary outcome measures were obtained. Cells were stained with two-color monoclonal antibodies directed against specific cell surface antigens, and each lymphocyte subpopulation was quantified directly from lysed whole blood with a Coulter Epics Profile II flow cytometer.

**RESULTS:** Thirty-five patients dropped out before the follow-up visit and technical problems resulted in the loss of data from 17 more and the exclusion of some subpopulation data. In all, 148 cases were analyzed for B cells, 146 for TH, TS and NK cells and 138 for cells that carried both the NK and TS marker. A one-way analysis of variance revealed no significant differences in the lymphocyte profiles at baseline among the three groups. All subpopulation baseline values were within reported reference ranges for normal adult populations. However, the percentage of NK cells (9.1%) was below the published minimum critical value. A repeated measures analysis of variance was used to determine whether treatment effects changed over time, that is, treatment-time interaction. The cell types for which the interaction tests were at or near statistical significance were: TH cells ( $p = .0208$ ), total T cell percent ( $p = .0928$ ) and absolute total T cells ( $p = .0908$ ). Interaction tests for differences in either percent or absolute counts of B cells, TS cells, or NK cells were not statistically significant.

**CONCLUSIONS:** This is the first report of lymphocyte profiles in patients with diagnosed chronic LBP. Our finding of a lower percentage of NK cells in these patients confirms our earlier finding that patients with musculoskeletal problems have a lower percentage of NK cells than do asymptomatic subjects. However, manipulative therapy was not shown to have a clinically significant effect on either the absolute number or percentage of any lymphocyte subpopulation studies. Because lymphocyte profiles were a secondary outcome in this trial, the eligibility criteria established for the primary outcomes may not have been rigorous enough to avoid confounding these results or the treatment schedule or sampling times may not have been appropriate to detect changes at the cellular level.

### **The effects of specific upper cervical adjustments on the CD4 counts of HIV positive patients**

Selano JL, Hightower BC, Pflieger B, Collins KF, Grostic JD

#### **Chiropractic Research Journal**

1994

The researchers of this project sought to demonstrate that upper cervical specific adjustments would have a profound effect on the physiology, serology and immunology of HIV positive individuals. The effect of specific upper cervical adjustments on the immune system CD4 cell counts of HIV positive individuals was measured by CD4/mm<sup>3</sup> in the blood. These tests were performed by the patients independent medical center where they were under medical supervision for the condition. The measured CD4 counts in the regular group were dramatically increased over the counts of the control group. A 48% increase in CD4 cells was demonstrated over the six month duration of the study for the adjusted group.

### **Respiratory burst activity as a function of manipulation site**

Triano JJ, McGregor M, Graham M, Skogsbergh D, Brennan PC

#### **Proceedings of the International Conference on Spinal Manipulation**

1994

Abstract not available through open access.



**Enhanced Neutrophil Respiratory Burst as a Biological Marker for Manipulation Forces: Duration of the Effect and Association with Substance P and Tumor Necrosis Factor**

Brennan PC, Triano JJ, McGregor M, Kokjohn K, Hondras MA, Brennan DC

**Journal of Manipulative and Physiological Therapeutics**

1992

A critical need in assessing the clinical utility of manipulative therapy for back pain is the identification of biological changes associated with the forces applied by spinal manipulation. Such changes could then serve as markers for both sham treatment and manipulation. We determined the priming of polymorphonuclear neutrophils for an enhanced respiratory burst and its duration, the priming of mononuclear cells for enhanced endotoxin-stimulated tumor necrosis factor production and plasma levels of substance P following a single thoracic spine manipulation. There was a significant difference in the respiratory burst of polymorphonuclear neutrophils in response to a particulate challenge, depending on the time of blood sample collection. The response of polymorphonuclear neutrophils isolated from blood collected 15 min after manipulation was significantly higher than the response of cells isolated from blood collected 15 min before and 30 and 45 min after manipulation. Mononuclear cells were also primed for enhanced endotoxin-stimulated tumor necrosis factor production by spinal manipulation. Both of these priming effects were accompanied by a slight, but significant elevation in plasma substance P. The mean manipulation force associated with these biological effects was 878 +/- 99 N. These biological effects may provide a means of monitoring the delivery of both sham and manipulative treatment and, therefore, provide a crucial tool for understanding the efficacy of manipulative therapy.

**Enhanced Phagocytic Cell Respiratory Burst Induced by Spinal Manipulation: Potential Role of Substance P**

Brennan PC, Kokjohn K, Kaltinger CJ, Lohr GE, Glendening C, Hondras MA, McGregor M, Triano JJ

**Journal of Manipulative and Physiological Therapeutics**

1991

The effect of spinal manipulation on the respiratory burst of polymorphonuclear neutrophils (PMN) and monocytes from treated adults was measured by zymosan-stimulated chemiluminescence (CL). Peripheral blood was collected 15 min before and 15 min after treatment (sham manipulation, thoracic spine manipulation, or soft tissue manipulation), the cells were isolated, challenged with a standardized, opsonized luminol-containing suspension of zymosan, and monitored for CL. Plasma from two subsets of subjects was radioimmunoassayed for Substance P (SP). PMN were also preincubated with SP in vitro over the dose range  $5 \times 10^{-12}$  M to  $5 \times 10^{-8}$  M and the CL response monitored. The CL responses of both PMN and monocytes from subjects who received spinal manipulation were significantly higher after than before treatment, and significantly higher than the response in sham or soft-tissue treated subjects. Measurement of the force applied by sham and spinal manipulation suggested a force threshold for the enhancement of the CL response. Plasma levels of SP before and after treatment in sham treated subjects did not differ significantly; however, elevated plasma SP was observed in subjects after spinal manipulation. Preincubation of PMN with  $1 \times 10^{-5}$  M or  $1 \times 10^{-6}$  M SP in vitro primed PMN for an enhanced respiratory burst when the cells were subsequently challenged.

**Functional ability of natural killer cells as an outcome measure for chiropractic treatment efficacy**

Graham MA, Brennan PC

**Proceedings of the International Conference on Spinal Manipulation**  
1991

Abstract not available through open access.

**Immunological response to manipulation of the lumbar spine**

McGregor M, Brennan P, Triano JJ

**Proceedings of the International Conference on Spinal Manipulation**  
1991

Abstract not available through open access.

**Plasma substance P following spinal manipulation**

Kokjohn K, Katlinger C, Lohr GE, Glendening C, Hondras MA, McGregor M, Brennan PC

**Proceedings of the International Conference on Spinal Manipulation**  
1990

Abstract not available through open access.

**Natural killer cells as an outcome measure of chiropractic treatment efficacy**

Lohr GA, O'Brien JC, Nodine DL, Brennan PC

**Proceedings of the International Conference on Spinal Manipulation**  
1990

Abstract not available through open access.

**Chiropractic Adjustive Manipulation on Subjects with Acute Low Back Pain: Visual Analog Pain Scores and Plasma Beta Endorphin Levels**

Sanders GE, Reinert O, Tepe R, Maloney P

**Journal of Manipulative and Physiological Therapeutics**  
1990

The purpose of this study was to evaluate pain scores and plasma beta-endorphin levels following a single spinal adjustive manipulation in subjects with acute low back pain. Eighteen subjects were randomly assigned to either a control group, which received no treatment; a sham group, which received only light physical contact (touch); or an experimental group, which received an adjustive manipulation at a specific lumbar segment. Following a standard protocol, all subjects were administered visual analog pain scales and venous blood was drawn 5 min prior to, 5 min after, and 30 min after intervention. Analysis of the pain scores indicated that there was a slight, but significant, reduction of pain in the experimental group, but no similar reduction in the control or sham groups. Furthermore, this reduction of pain in the experimental group was not accompanied any significant change in the plasma beta-endorphin concentration.

**Priming of neutrophils for enhanced respiratory burst by manipulation of the thoracic spine.**

Brennan PC, Hondras MA.

**Proceedings of the International Conference on Spinal Manipulation**  
1989

Abstract not available through open access.

### **Immunoreactive ACTH, Beta Endorphin, and Cortisol Levels in Plasma following Spinal Manipulative Therapy**

Christian GF, Stanton GJ, Sissons D, How HY, Jamison J, Alder B, Fullerton M, Funder JW

#### **Spine**

1988

This study examines the possibility of a humorally mediated analgesic response to spinal manipulative therapy by determination of plasma levels of beta-endorphin, adrenocorticotrophic hormone (ACTH), and cortisol before and after intervention. Forty male subjects (20 symptomatic, 20 asymptomatic) were allocated into four equal groups. Two treatment groups were given spinal manipulative therapy, and two groups underwent a sham procedure. Blood samples were taken via indwelling butterfly needles pre- and postintervention in all four groups, and levels of immunoreactive ACTH, immunoreactive beta endorphin, and cortisol determined by radioimmunoassay. No differences in ACTH or beta-endorphin were found between sham and treated groups, or between pre- and postintervention in any group; cortisol levels fell over the course of the study in all groups. The findings thus appear to exclude a humoral role for beta-endorphin in mediating the analgesic response to spinal manipulative therapy; in addition, they suggest that such therapy is not a stressor that activates the by hypothalamo-pituitary-adrenal axis.

### **Spinal Manipulation and Beta-Endorphin: A Controlled Study of the Effect of a Spinal Manipulation on Plasma Beta-endorphin Levels in Normal Males**

Vernon HT, Dharmi MSI, Howley TP, Annett R

#### **Journal of Manipulative and Physiological Therapeutics**

1986

The role of spinal manipulation in the relief of pain is becoming clearer and more demonstrable as time passes. One approach to this study is the effect of manipulation on the neurochemical mechanisms of antinociception. Chief among these is beta-endorphin, which has been found to produce a wide range of beneficial effects, especially analgesia.

The intent of our study was to demonstrate the effect of spinal manipulation on plasma beta-endorphin levels. Three groups of male subjects were randomly created: the experimental, sham and control groups. All three groups were screened for symptomatology, present use of medications and the present use of innocuous stimulants, such as nicotine and caffeine. A standard protocol involving a 20-min pretest resting period, an intervention and a 40-min test period ensued. The experimental group received a manipulation in the region of the cervical spine; the placebo group received a sham maneuver with no dynamic thrust; the control group received no intervention. Samples were taken by venapuncture at -20, -5, +5, +10 and +30 min. The data were analyzed by repeated measures analysis of variance and by Scheffe's post-hoc multiple comparison tests. Plasma beta-endorphin levels were assessed by radioimmune assay technique (according to the method described by Harber and Sutton in 1984).

The results of our study demonstrated a small, but statistically significant, increase in serum beta-endorphin levels in the experimental group at the 5-min postintervention point. The levels in the placebo and control groups demonstrated a steady decrease that was distinct from the response in the experimental group. With reservations regarding the sample size, our findings appear to demonstrate a small but unexpected increase of serum beta-endorphin in response to a single cervical

manipulation. This finding allows us to hypothesize that the pain-relieving effect of manipulation is, in part, due to a short-term increase in beta-endorphin levels.

**The effects of spinal manipulation on the immune system: A preliminary report**

Vora, GS, Bates HA

**The ACA Journal of Chiropractic**

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Eight male and female patients 20-40 years of age with radiographically proven neuromusculoskeletal conditions were given general mobilizing spinal manipulation twice a week for four weeks. WBC, RBC, hemoglobin, B and T lymphocyte counts and striated antibody tests were done weekly on each patient. WBC, RBC, and hemoglobin values showed no significant changes. Five of eight patients (63%) showed a significant increase in circulating B lymphocytes and one a significant increase in T lymphocytes. The role of generalizing mobilizing spinal manipulation as a possible factor in these lymphocyte increases was discussed. Antibody to striated muscle was not detected in this study.