OMT, Inflammation, and Immunity. Is there an Axis?

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Preventive and Integrative Medicine Conference
Focus on Inflammation: Mechanisms, Identification & Prevention
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OHF* Richards-Cohen Distinguished Chair in Clinical Research

*Osteopathic Heritage Foundation

Presentation Objectives

• Present background information on osteopathic philosophy, low back pain, and on cytokines and their role in the sickness response, including pain dysregulation associated with chronic pain

• Present relevant findings from the OSTEOPATHIC Trial

• Discuss implications of study results in terms of possible biological mechanisms of action for OMT
Low Back Pain
Societal Impact

• LBP is common worldwide
• Global Burden of Disease Study 2010*
  • 632 million persons worldwide
  • Leading cause of years lived with disability
• Vast majority of LBP, such as that attributed to lumbar strain and sprain, is considered “non-specific”
• The costs to society for LBP are enormous – exceeding $100 billion annually in the United States†
• Medical care for nonspecific low back pain in the United States has been described as “overspecialized, overinvasive, and overexpensive”‡

*Vos T. Lancet 2013;380:2163-2196
‡Waddell G. Spine 1996;21:2820-2825
Low Back Pain
Definition and Temporal Classification

- **LBP Definition**
  - Pain, muscle tension, or stiffness
  - Localized below the costal margin and above the inferior gluteal folds
  - With or without leg pain (sciatica)

- **LBP Chronicity**
  - **Acute**: <4 weeks since onset
  - **Subacute**: 4 weeks to 3 months since onset
  - **Chronic**: Greater than 3 months since onset

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Low Back Pain
Etiological Classification

- 70% Lumbar strain, sprain
- 10% Degenerative processes
- 4% Osteoporotic compression fracture
- 3% Disk herniation
- 2% Spinal stenosis
- 2% Spondylolisthesis
- 3% Others

"Nonspecific" 70%

© The Royal Australian College of General Practitioners

Jensen S. Aust Fam Physician 2004;33:393-401

Somatic Dysfunction

- “Impaired or altered function of related components of the somatic (body framework) system: skeletal, arthrodial, and myofascial structures, and related vascular, lymphatic, and neural elements”
- Uniquely osteopathic concept with **ICD diagnostic codes** and **CPT treatment codes**
- Diagnostic criteria include **TART**:
  - Tissue texture abnormality
  - Asymmetry
  - Restricted motion
  - Tenderness
- **Key osteopathic lesions** are considered important because:
  - They are associated with symptoms, restricted motion, or tissue texture abnormalities that stand out with minimal search or provocation
  - They maintain a dysfunctional pattern that includes secondary dysfunctions

**Severity scale**:
- 0 – None or background level
- 1 – Mild
- 2 – Moderate
- 3 – Severe (key lesion)

Relationship Between Somatic Dysfunction and Low Back Pain

Somatic dysfunction: cause or manifestation of LBP?

**Licciardone JC. Osteopath Med Prim Care 2007;1:7**
Cytokines

- **Cytokines** – diverse groups of soluble proteins and peptides which act as humoral regulators at nano- or picomolar concentrations
- Either under normal or pathological conditions, they modulate the activities of individual cells and tissues
- **Cytokine groups**
  - **Interleukins (ILs)** – derive from leukocytes and primarily function in intracellular signaling (IL-1, IL-6)
  - **Monokines** – derive from monocytes and are primarily involved in mediating the “sickness response” (TNF-α)
  - **Interferons (IFNs)** – have antiviral and antitumor properties
  - **Colony-stimulating factors** – used in treating anemia and leukopenia (erythropoietin)
  - **Chemokines** – function as chemoattractants that cause immune cells to migrate from the circulation to inflamed or injured tissue (IL-8)

Sickness Response

- Early host response to infection, tumor antigens, injury, and other acute processes are mediated by **pro-inflammatory cytokines**
  - TNF-α
  - IL-1
  - IL-6
- Under normal circumstances, sickness response is a **survival mechanism** that comprises physiologic events (e.g., response to influenza)
  - Fever, leukocytosis
  - Alterations in blood carrier proteins (acute phase reactants)
  - Hypothalamic-pituitary axis alterations
  - Sympathetic nervous system alterations
  - Behavioral changes (decreased social interaction, enhanced pain behavior)
- Sickness response can be induced by administration of proinflammatory cytokines in the absence of a typical immune challenge
- Sickness response can be blocked by administration of proinflammatory cytokine antagonists
- Proinflammatory cytokines can cross blood-brain barrier
Mechanisms of Proinflammatory Cytokine-Induced Sickness Behavior

- Immune cells
- Proinflammatory Cytokines
- Altered Monoamine Metabolism
- CNS

Chronic pain
Gastrointestinal symptoms
Fatigue
Cognitive impairment
Anxiety
Depression

Cleeland, et al, Cancer 2003;97:2919-2925

Proinflammatory Cytokines
Central Nervous System

(a) Proinflammatory cytokines are expressed by glial cells in the CNS
(b) IL-1 is expressed *intracellularly* as an inactive precursor molecule, allowing rapid release upon cleavage by IL-1-converting enzyme
(c) TNF-α is expressed on the *extracellular surface* of glia in its inactivated form, and is activated upon release from the cell surface by TNF-α converting enzyme (TACE)
(d) Green fluorescence reflects extracellular expression of TNF-α precursor on astrocytes
(e) Active TNF-α molecules subsequently stimulate both neurons and glial cells


(figure reprinted with permission)
Views of Chronic Pain

- **Classical view** of pathological pain and treatment was based on the assumption that only neurons were involved in pain dysregulation.
- **Contemporary view** is that pain is also modulated by immune cells and glia, which can be targeted for intervention.
- (a, b) amplification of pain signal by neuronal and glial mechanisms.
- (c, d) activated and deactivated glia can enhance/reduce release of pain neurotransmitters.

(figure reprinted with permission)

OSTEOPATHIC TRIAL METHODS
The OSTEOPATHIC Trial
Research Design

- **OSTEOPATHic Health outcomes In Chronic low back pain** (Aug 2006 – Jan 2011)
- Phase III, sham controlled RCT (N=455)
- 2x2 factorial design (ClinicalTrials.gov: NCT00315120)
  - 2nd factor was ultrasound therapy (UST)
- 6 treatment sessions over 8 weeks, with final outcomes assessment at week 12
- Outcome measures
  - Visual analogue pain scale
  - Roland-Morris Disability Questionnaire
  - Medical Outcomes Study SF-36 Health Survey (general health)
  - Work disability
  - Satisfaction with back care


The OSTEOPATHIC Trial
The OMT "Megatrial" (N=455)

<table>
<thead>
<tr>
<th>Ultrasound Therapy</th>
<th>Osteopathic Manual Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active UST</td>
<td>Sham OMT UST</td>
</tr>
<tr>
<td>OMT n=230</td>
<td>Sham OMT UST n=225</td>
</tr>
<tr>
<td>Sham UST</td>
<td>OMT UST</td>
</tr>
<tr>
<td>n=222</td>
<td>n=118</td>
</tr>
</tbody>
</table>

N = 455
OMT Protocol

- **Algorithmic** approach
- Diagnostic examination for somatic dysfunction at each treatment visit
- 10 minutes for standard techniques (targeted lumbosacral, iliac, and pubic regions)
  - HVLA
  - Muscle energy
  - Myofascial release
  - Articulatory
  - Soft tissue
  - Tender point treatment (counterstrain)
- 5 minutes for optional techniques

Multi-Dimensional Assessment

- Measure and classify pain improvement (reduction) in individual patients
- Measure the OMT effect across all patients (i.e., in the target population)
- Explore OMT effect in subgroups (e.g., low and high LBP severity, depression, etc.)
Measurement of Serum Cytokine Concentrations

- IL-1β, IL-6, IL-8, IL-10, TNF-α
- Blood drawn from antecubital vein
  - Pre-treatment: 30 minutes prior to first treatment session (n=70)
  - Post-treatment: week 12 (n=55 paired with pre-treatment)
- Samples were either analyzed unconcentrated or concentrated as needed prior to analysis
- Cytokine concentrations were determined from relative median fluorescent intensity responses, using linear or logistic curve-fitting methods

Candidate Genetic Factors for Association with Clinical Response to OMT

- 230 patient samples genotyped for 41 single nucleotide polymorphisms (SNPs) using the SNPlex assay (Applied Biosystems, Carlsbad, CA)
  - Excluded samples with <80% of SNP genotyped and SNPs that failed to exhibit Hardy-Weinberg equilibrium
  - 216 patient samples and 38 candidate SNPs included in analysis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>No. of SNPs</th>
<th>Comments Relating to Homo Sapiens</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADBR2</td>
<td>Adrenoceptor beta 2, surface</td>
<td>6</td>
<td>Nocturnal asthma, obesity, type 2 diabetes</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
<td>8</td>
<td>Catalyzes production of neurotransmitters dopamine, epinephrine, norepinephrine</td>
</tr>
<tr>
<td>GCH1</td>
<td>GTP cyclohydrolase 1</td>
<td>11</td>
<td>Malignant hyperphenylalaninemia, dopa-responsive dystonia, Rheumatoid arthritis, Alzheimer's disease.</td>
</tr>
<tr>
<td>IL1A</td>
<td>interleukin 1, alpha</td>
<td>3</td>
<td>Contributes to inflammatory pain hypersensitivity</td>
</tr>
<tr>
<td>IL1B</td>
<td>interleukin 1, beta</td>
<td>1</td>
<td>Osteoporotic fractures, gastric cancer</td>
</tr>
<tr>
<td>IL1RN</td>
<td>interleukin 1 receptor antagonist</td>
<td>7</td>
<td>Not classified in NCBI Gene database</td>
</tr>
<tr>
<td>IL8</td>
<td>interleukin 8</td>
<td>1</td>
<td>Congenital muscular dystrophy with severe mental retardation</td>
</tr>
<tr>
<td>LARGE</td>
<td>like-glycosyltransferase</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
## RESULTS

### CONSORT Flow Diagram

<table>
<thead>
<tr>
<th>Week 4</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Developed a contraindication to continued participation</td>
<td>4 Developed a contraindication to continued participation</td>
</tr>
<tr>
<td>5 Withdrew</td>
<td>3 Withdrew</td>
</tr>
<tr>
<td>2 Lost to follow-up</td>
<td>4 Lost to follow-up</td>
</tr>
</tbody>
</table>

#### Week 4
- 455 Randomized
- 230 Randomized to receive OMT
- 225 Randomized to receive placebo OMT
- 230 Developed a contraindication to continued participation
- 2 Lost to follow-up
- 3 Withdrew
- 215 Lost to follow-up

#### Week 8
- 4 Withdrew
- 4 Lost to follow-up
- 3 Withdrew
- 1 Withdrew
- 7 Lost to follow-up
- 3 Withdrew
- 8 Lost to follow-up

#### Post-intervention (week 12)
- 3 Withdrew
- 8 Lost to follow-up
- 230 Included in the intention-to-treat analyses, and 180 included in the per-protocol analyses

#### Safety Profile
- 27 (6%) reported adverse event
- 9 (2%) were classified as SAE
- No SAE was adjudicated as definitely or probably related to treatment
- No significant differences between OMT and sham OMT on any of the above

#### Contraindications to Trial Continuance
- 8 in OMT group vs. 1 in sham OMT group (P = 0.04). However, only 1 contraindication (recurrent back spasticity following treatment) was adjudicated as “possibly” related to OMT

### Adherence
- 382 (84%) received all treatments
- 396 (87%) attended week 12 visit

### Care Providers
- 2056 (80%) treatments were delivered by faculty physicians

### Adherence
- 382 (84%) received all treatments
- 396 (87%) attended week 12 visit
Overall Risk Ratios (RRs)

**Intention-to-Treat Analysis**

<table>
<thead>
<tr>
<th>LBP Reduction</th>
<th>OMT</th>
<th>UST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>≥30% (moderate)</td>
<td>1.4 (1.2 to 1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥50% (substantial)</td>
<td>1.4 (1.1 to 1.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>≥20 mm (moderate)</td>
<td>1.5 (1.2 to 1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥40 mm (substantial)</td>
<td>2.0 (1.2 to 3.2)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Interpretation of Effect Size According to Risk Ratio

Overall Secondary Outcomes

**Intention-to-Treat Analysis**

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>OMT vs. Placebo OMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OMT (n=230)</td>
</tr>
<tr>
<td>Median (IQR) RMDQ score</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>4 (2 to 8)</td>
</tr>
<tr>
<td>Week 8</td>
<td>3 (1 to 7)</td>
</tr>
<tr>
<td>Week 12</td>
<td>2 (1 to 6)</td>
</tr>
<tr>
<td>Median (IQR) SF-36 GH score</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>71 (55 to 82)</td>
</tr>
<tr>
<td>Week 8</td>
<td>72 (57 to 85)</td>
</tr>
<tr>
<td>Week 12</td>
<td>72 (52 to 87)</td>
</tr>
<tr>
<td>Percent (95% CI) lost one or more work days in past 4 weeks because of LBP</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>10 (4 to 16)</td>
</tr>
<tr>
<td>Week 8</td>
<td>9 (2 to 11)</td>
</tr>
<tr>
<td>Week 12</td>
<td>11 (5 to 17)</td>
</tr>
<tr>
<td>Percent (95% CI) very satisfied with back care</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>52 (46 to 59)</td>
</tr>
<tr>
<td>Week 8</td>
<td>61 (54 to 67)</td>
</tr>
<tr>
<td>Week 12</td>
<td>66 (60 to 73)</td>
</tr>
</tbody>
</table>
Usual Care

**Co-Treatments for LBP**

Percent (95% CI) ever used as a LBP co-treatment during study

<table>
<thead>
<tr>
<th>Co-treatment</th>
<th>OMT</th>
<th>Sham OMT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise programs</td>
<td>19 (14 to 24)</td>
<td>20 (14 to 25)</td>
<td>0.82</td>
</tr>
<tr>
<td>Lumbar supports</td>
<td>1 (0 to 3)</td>
<td>1 (0 to 2)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Non-prescription drugs</td>
<td>46 (39 to 52)</td>
<td>45 (39 to 52)</td>
<td>0.95</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>13 (9 to 18)</td>
<td>20 (15 to 26)</td>
<td>0.048</td>
</tr>
<tr>
<td>CAM therapies</td>
<td>15 (11 to 20)</td>
<td>17 (12 to 22)</td>
<td>0.63</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>11 (7 to 15)</td>
<td>8 (4 to 11)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Surgery</td>
<td>0 (0 to 1)</td>
<td>0 (0 to 0)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Significant difference in prescription drug use persisted after controlling for simultaneous use of all other co-treatments.


**Comparison of Drug Use within National Ambulatory Medical Care Survey**

- **Multivariate analysis** of patient visits for low back pain
  - 1,042 (42 million wherein LBP was chief complaint)
  - Compared DO and MD visits for LBP while controlling for patient factors (age, sex, race, ethnicity, geographic region, MSA status), visit context (injury etiology), and physician factors (PCP, specialty, shared care)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid use</td>
<td>0.1 0.2 0.5 1 2 5 10</td>
</tr>
<tr>
<td>NSAID use</td>
<td>Decreased DO Rx  Increased DO Rx</td>
</tr>
</tbody>
</table>

Licciardone JC, Osteopath Med Prim Care 2008;2:11
Time to Clinical Response
Kaplan-Meier Plots for ≥50% Pain Reduction

Intention-to-treat analysis
- OMT
- Sham OMT
- Log-rank P<0.001

Per-protocol analysis
- OMT
- Sham OMT
- Log-rank P<0.001

Clinical Response Patterns
Patient Profiles (≥50% Pain Reduction)

- Median time to clinical response = 4 weeks (3 sessions)
- 13 initial responders relapsed by week 12
- On average, spent 68% of time in “remission” (green)
- On average, spent 9% of time in “remission” (green)
## Subgroup Analysis
### According to Baseline Pain Severity

**n=259**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary outcome</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substantial LBP improvement</td>
<td>&gt;=50% reduction in VAS score</td>
<td>1.15 (0.88 to 1.50)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back-specific functioning</td>
<td>Clinically important change</td>
<td>0.77 (0.46 to 1.30)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

**n=186**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary outcome</th>
<th>RR (95% CI)</th>
<th>P for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substantial LBP improvement</td>
<td>&gt;=50% reduction in VAS score</td>
<td>2.04 (1.36 to 3.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back-specific functioning</td>
<td>Clinically important change</td>
<td>1.80 (1.08 to 3.01)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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**Licciardone JC, et al. Man Ther 2013; 18:533-540**

## Subgroup Analysis
### According to Baseline Depression

**Depression Absent (n=140)**

<table>
<thead>
<tr>
<th>Clinical Response at Week 12 No. (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham OMT 22/71 (31)</td>
<td>…</td>
</tr>
<tr>
<td>OMT 39/69 (57)</td>
<td>1.82 (1.22-2.73)</td>
</tr>
</tbody>
</table>

**Depression Present (n=46)**

<table>
<thead>
<tr>
<th>Clinical Response at Week 12 No. (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham OMT 1/20 (5)</td>
<td>…</td>
</tr>
<tr>
<td>OMT 10/26 (38)</td>
<td>7.69 (1.07-55.23)</td>
</tr>
</tbody>
</table>

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**Licciardone JC, Aryal S. Man Ther 2014 (e-pub ahead of print)**
Baseline Serum Cytokine Concentrations (N=70)

Correlations Among Baseline Serum Cytokine Concentrations

<table>
<thead>
<tr>
<th></th>
<th>IL-1β</th>
<th>IL-6</th>
<th>IL-8</th>
<th>IL-10</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td></td>
<td>0.38 (0.001)</td>
<td>0.18 (0.13)</td>
<td>0.31 (0.01)</td>
<td>0.13 (0.30)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.23 (0.06)</td>
<td></td>
<td>0.37 (0.002)</td>
<td>0.26 (0.03)</td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td></td>
<td>0.30 (0.01)</td>
<td></td>
<td>0.35 (0.003)</td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td>0.26 (0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Correlations were based on the Spearman rank correlation coefficient (P-values in parentheses).
### Correlations of Baseline Serum Cytokine Concentrations with Clinical Measures

<table>
<thead>
<tr>
<th>No. of Key Osteopathic Lesions</th>
<th>VAS for LBP</th>
<th>RMDQ</th>
<th>SF-36 GH</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>0.33 (0.005)</td>
<td>0.17 (0.15)</td>
<td>0.11 (0.34)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.32 (0.006)</td>
<td>0.28 (0.02)</td>
<td>0.14 (0.25)</td>
</tr>
<tr>
<td>IL-8</td>
<td>0.00 (0.99)</td>
<td>0.10 (0.42)</td>
<td>0.17 (0.17)</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.09 (0.45)</td>
<td>0.06 (0.65)</td>
<td>0.20 (0.10)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>-0.15 (0.22)</td>
<td>0.10 (0.41)</td>
<td>0.17 (0.16)</td>
</tr>
</tbody>
</table>

LBP denotes low back pain; RMDQ, Roland-Morris Disability Questionnaire; SF-36 GH, Medical Outcomes Study Short Form 36 Survey General Health Scale; VAS, visual analogue scale. Correlations were based on the Spearman rank correlation coefficient (P-values in parentheses).

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### Correlations of Baseline Serum Cytokine Concentrations with Depression and Somatization

<table>
<thead>
<tr>
<th>Depression</th>
<th>MZDI</th>
<th>MSPQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>0.09 (0.46)</td>
<td>0.13 (0.29)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.15 (0.23)</td>
<td>0.20 (0.11)</td>
</tr>
<tr>
<td>IL-8</td>
<td>0.12 (0.33)</td>
<td>0.11 (0.37)</td>
</tr>
<tr>
<td>IL-10</td>
<td>-0.02 (0.88)</td>
<td>0.18 (0.14)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.01 (0.95)</td>
<td>0.11 (0.36)</td>
</tr>
</tbody>
</table>

*MSPQ denotes Modified Somatic Perceptions Questionnaire; MZDI, Modified Zung Depression Index. Correlations were based on the Spearman rank correlation (P-values in parentheses).
Overall OMT Effect on Cytokines
Reduction in TNF-α Serum Concentration

Based on analysis of 55 patients with paired pre- and post-treatment serum cytokine measures

Changes in Serum Cytokine Concentrations According to Treatment Group.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>OMT (n=28)</th>
<th>Sham OMT (n=27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin-1β</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.06)</td>
<td>0.16</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>0.03 (1.43)</td>
<td>0.03 (0.47)</td>
<td>0.68</td>
</tr>
<tr>
<td>Interleukin-8</td>
<td>-0.08 (3.50)</td>
<td>-0.08 (5.13)</td>
<td>0.82</td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>0.00 (0.86)</td>
<td>-0.04 (0.86)</td>
<td>0.68</td>
</tr>
<tr>
<td>Tumor necrosis factor-α</td>
<td>-1.06 (2.11)</td>
<td>-0.06 (1.90)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table entries are median (interquartile range) changes in concentration (pg/mL) over 12 weeks.
P-values are based on the Mann-Whitney U test.


Reduction in TNF-α Serum Concentration
Responder vs. Non-responder Subgroups

Based on analysis of 55 patients with paired pre- and post-treatment serum cytokine measures

| Reduction in TNF-α Concentration, no. (%) | OMT Placebo OMT RR 95% CI P |
|------------------------------------------|---------------------------|---------------------------|
| Overall Analysis                         | 22/28 (79) 14/27 (52) 1.52 (1.00 to 2.29) | 0.04 |
| Subgroup Analyses According to Clinical Response Status |                     |                           |
| Moderate improvement in LBP              |                           |                           |
| Responders                               | 17/20 (85) 6/15 (40) 2.13 (1.11 to 4.06) | 0.006 |
| Non-responders                           | 5/8 (62) 8/12 (67) 0.94 (0.48 to 1.83) | >0.99 |
| Substantial improvement in LBP           |                           |                           |
| Responders                               | 16/18 (89) 5/12 (42) 2.13 (1.07 to 4.25) | 0.01 |
| Non-responders                           | 6/10 (60) 9/15 (60) 1.00 (0.52 to 1.92) | >0.99 |

Genetic Factors Related to Clinical Response to OMT

Based on analysis of 38 single nucleotide polymorphisms (SNPs) in 216 patients

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
<th>No. of SNPs Associated with OMT Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADBR2</td>
<td>Adrenocort beta 2, surface</td>
<td>0/6</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
<td>0/8</td>
</tr>
<tr>
<td>GCH1</td>
<td>GTP cyclohydrolase 1</td>
<td>1/11</td>
</tr>
<tr>
<td>IL1A</td>
<td>interleukin 1, alpha</td>
<td>0/3</td>
</tr>
<tr>
<td>IL1B</td>
<td>interleukin 1, beta</td>
<td>0/1</td>
</tr>
<tr>
<td>IL1RN</td>
<td>interleukin 1 receptor antagonist</td>
<td>0/7</td>
</tr>
<tr>
<td>IL8</td>
<td>Interleukin 8</td>
<td>1/1</td>
</tr>
<tr>
<td>LARGE</td>
<td>like-glycosyltransferase</td>
<td>1/1</td>
</tr>
</tbody>
</table>

GCH1/rs3783641
OR, 3.0; 95% CI, 1.1-7.8

Best predictive model: GCH1 SNPs, BMI, baseline pain level
Area under curve = 0.77
Model including only GCH1 SNPs
Area under curve = 0.68

GTP Cyclohydrolase I and the GCH1 Gene

- GTP cyclohydrolase I
  - Encoded by GCH1 gene
  - Catalyzes the hydrolysis of GTP
  - First and rate-limiting step in tetrahydrobiopterin (THB) biosynthesis
- THB is an essential cofactor in the biosynthesis of monoamine neurotransmitters:
  - Dopamine
  - Norepinephrine
  - Epinephrine
  - Serotonin
Clinical Conclusions

- OMT provides **moderate-substantial LBP improvement**, that meets/exceeds CBRG criterion for medium effect size
  - Greatest effects seen in patients with high baseline pain severity
- OMT patients **less often used prescription drugs** for LBP
- OMT was **safe, parsimonious, and well accepted** by patients as based on high levels of treatment adherence
- OMT patients were **very satisfied** with their back care
- **Additional research is needed** to assess long-term efficacy of OMT in relieving CLBP, including its cost-effectiveness and its impact on secondary outcomes
### Current EBM Recommendations for OMT in CLBP

#### Classification of Recommendations

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Substantial</th>
<th>Moderate</th>
<th>Small</th>
<th>Zero/Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Fair</td>
<td>B</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Poor</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

- **Strongly recommend providing intervention to eligible patients**
- **Recommend providing intervention to eligible patients**
- **No recommendation for or against providing intervention**
- **Recommend against providing intervention**
- **Insufficient evidence for or against providing intervention**

#### Overall
- Pain Reduction = B; Improved Functioning = C

#### High Baseline LBP Severity Subgroup
- Pain Reduction = A; Improved Functioning = B

### Mechanistic Conclusions

- **Pro-inflammatory cytokines are correlated with key osteopathic lesions**
- **OMT significantly reduces low back pain**
  - OMT significantly reduces mean serum TNF-α concentration over 12 weeks
  - Responders to OMT experience reductions of TNF-α concentration, whereas non-responders do not
  - **Genetic factors** are also associated with response to OMT
  - **Biomechanical factors** (e.g., remission of psoas syndrome) may also predict response to OMT
- **Additional research is needed to assess long-term efficacy of OMT in relieving CLBP (i.e., over at least one year), and to determine concomitant changes in cytokine concentrations and related biomechanical and genomic factors associated with response to OMT**
Sciatic Inflammatory Neuropathy
An Emerging PNS Animal Model

- Animal model to determine if peripheral nerves can mediate sickness responses to pain
- Zymosan (yeast cell wall) is injected into gelfoam around sciatic nerve
- Immune cells migrate to injection site to release inflammatory products
  - Low dose zymosan induces unilateral hyperalgesia ipsilateral to injection via microglia
  - High dose zymosan also induces contralateral hyperalgesia via spinal cord sensitization ("mirrored pain" pattern seen with chronic pain)
- Astrocytes activated to maintain hyperalgesia


CONCORD-PBRN
Consortium for Collaborative Osteopathic Research Development – Practice-Based Research Network

- A national primary care research network established and coordinated by the ORC
- Registered and certified by the Agency for Healthcare Research and Quality
- 12 research hubs are directed by trained research fellows (completed 162-hour curriculum and research practicum)
- Plans to develop a national panel of patients and create a biobank to study biomarkers and genomic factors in pain
- Also plans to study the role of OMT in the prevention and treatment of chronic low back pain

OSTEOPATHIC Trial

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  • Sejong Bae, PhD (chair) and members

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  • Michael Bergamini, PhD; Brian Gladue, PhD

• Treatment providers
  • 15 faculty physicians, fellows, and residents

• Research staff
  • 22 faculty, research, and laboratory personnel