Osteopathic Manipulative Treatment for Allostatic Load Lowering

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Context: Limited research has been done to examine osteopathic manipulative treatment (OMT) effects on modulating a compilation of allostatic load (AL) biomarkers that work to measure the body's multisystem response to homeostatic deviation.

Objective: To examine the efficacy of OMT on graduate students' overall health through an objective index of representative AL biomarkers.

Methods: A within-subject pre- and postintervention study was conducted at Touro University College of Osteopathic Medicine in California during the fall 2017 semester. Graduate students enrolled in the Masters of Science in Medical Health Sciences program volunteered to participate in the study and received treatment by an osteopathic physician. The participants were evaluated using the following measures: Trier Inventory for the Assessment of Chronic Stress; diurnal urine cortisol and catecholamines; dried blood glycosylated hemoglobin, dehydroepiandrosterone, high-density lipoprotein, and high-sensitivity C-reactive protein; blood pressure, body mass index, and waist-to-hip ratio before (preintervention) and after (postintervention) OMT.

Results: The study consisted of 1 man (participant 1) and 1 woman (participant 2) aged 23 and 22 years, respectively. Participants were enrolled in the same academic program and received 3 OMT sessions in 7 weeks. Analysis of AL biomarkers revealed a decrease in overall AL scores from preintervention to postintervention in participant 1 (from 7 to 4) and participant 2 (from 9 to 7). Analysis of Trier Inventory for the Assessment of Chronic Stress scores revealed a decrease in self-perceived stress from preintervention to postintervention in participant 1 (from 18 to 15) and in participant 2 (from 40 to 13).

Conclusion: The OMT protocol used in the current study decreased measures of overall AL and self-perceived stress in both participants. This finding suggests that OMT may represent a reasonable modality to reduce AL and self-perceived stress in graduate students. Since the current study is limited by its small sample size, further research is warranted.

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Osteopathic manipulative treatment (OMT) treats the musculoskeletal system by targeting somatic dysfunction related to tissue texture abnormality, asymmetry, restriction of motion, and tenderness, commonly referred to as TART. The assessment of somatic dysfunction is based on a structural examination by an

osteopathic physician and can be made more objective by correlating somatic dysfunction with a comprehensive set of biomarkers. The allostatic load (AL) model encompasses a multisystem index of stress-related biomarkers and provides an objective and quantifiable approach to evaluate changes in individual health profiles and predict disease outcomes.¹

A 2010 review article² stated that various biomarkers are associated with overall decreases in physiological and immune function, as well as specific chronic disease outcomes, such as cardiovascular disease, diabetes, osteoporosis, and chronic obstructive pulmonary disease. The dynamic physiological response of the body to various stress stimuli poses a challenge in discerning which biomarkers are most reflective of overall health outcomes. Knowledge and ability to measure a

multisystem set of allostatic biomarkers will allow physicians to effectively predict and manage diseases. Current clinical practice depends on the use of pharmaceuticals to control and manage AL biomarkers in both the prevention and management of diseases, which has efficacy but can also generate significant harm.^{3,4} Integrative modalities such as OMT, yoga, tai chi, and meditation have been shown to safely modulate levels of AL using biomarkers in blood, urine, and saliva (Table 1).⁵⁻²³

Homeostasis is the body's desire to reach a constant state of equilibrium, whereas allostasis is the multisystem physiological process of change that the body undergoes to reach a stable state. Although a normal allostatic response is essential for survival in the short term (eg, fight-or-flight response), overstimulation and overproduction of stress hormones and catecholamines

Table 1.
Allostatic Biomarker Modulation After Various Interventions

Intervention	Increased	Decreased	No Change
Osteopathic manipulative treatment	β -Endorphin, ⁶ heart rate variability, ¹¹ <i>N</i> -palmitoylethanolamide, ⁶ peak expiratory flow rate, ¹⁰ sIgA ⁹	α -Amylase ⁵ 5-HTP, ⁶ 5-HIAA, ⁶ anandamide, ⁶ TNF- α , ⁷ respiratory rate, ¹⁰ sympathetic tone via standard microneurographic technique ¹²	Cortisol (salivary), ⁵ IL-6, ⁷ IL-8, ⁸ IL-10, ⁷ salivary flow rate ⁵
Yoga	8-OHdG ¹³	HDL, ¹⁶ LDL, ¹⁶ TNF- α ¹⁴	Body fat percentage, ¹⁶ cortisol (urinary), ¹³ end tidal carbon dioxide, ^{1,6} fasting glucose, ¹⁵ HbA _{1c} , ¹⁵ IL-6 ^{14,15} hs-CRP ^{14,15} triglycerides, ^{15,16} total lipids, ¹⁶ total cholesterol, ¹⁶ systolic/diastolic blood pressure, ^{15,16} respiratory rate ¹⁶
Meditation	NA	Cortisol (salivary) ^{17,18}	Body mass index ¹⁹
Tai chi	Fasting glucose ²¹	IL-6 ²⁰	Cortisol (blood), ²⁰ fasting glucose, ²¹ IGF-1, ²¹ IGFBP-1, ²¹ IGFBP-3, ²¹ IL-6, ^{20,21} IL-8 ²¹
Acupuncture	sIgA ²²	Cortisol (salivary) ²²	NA
Yogic breathing	NA	IL-1 β (salivary), ²³ IL-8 (salivary), ²³ MCP-1 (salivary) ²³	NA

Abbreviations: 8-OHdG, 8-Oxo-2'-deoxyguanosine; HDL, high-density lipoprotein; 5-HTP, 5-hydroxytryptophan; 5-HIAA, 5-hydroxyindoleacetic acid; IL, interleukin; hs-CRP, high-sensitivity C-reactive protein; HbA_{1c}, glycated hemoglobin; IGF, insulinlike growth factor; IGFBP, IGF-binding protein; LDL, low-density lipoprotein; MCP, monocyte chemoattractant protein; sIgA, secretory immunoglobulin A; TNF- α , tumor necrosis factor- α .

can produce pathophysiological states.²⁴ The levels of physiological dysregulation that can occur because of an overactive allostatic response may be measured using AL algorithms.

The MacArthur studies were among the first longitudinal studies that provided a comprehensive count-based AL index derived from stress-related biomarkers.²⁵ The original investigation²⁵ found a correlation between an increase in AL index score and poor health outcomes, such as decreases in cognitive and physical function, in people aged 70 to 79 years. These findings fueled further research to understand the link between levels of AL and potential disease states. By incorporating an index of AL biomarkers that represent a comprehensive set of subcategory functioning biomarkers (eg, neuroendocrine, immune, metabolic, and cardiovascular system), AL studies have demonstrated greater prediction of morbidity and mortality compared with traditional detection methods.² However, to our knowledge, approaches to lower a multisystem AL index have not been clinically explored.

Previous studies^{10,26,27} on OMT focused on disease outcomes instead of biomarkers. Osteopathic manipulative treatment has been associated with improved health outcomes in patients with chronic obstructive pulmonary disease (eg, decrease in respiratory rate),¹⁰ spinal cord injury (eg, improved pain perception),²⁶ and fibromyalgia (eg, perceived functional ability).²⁷ In addition, some preliminary studies⁵⁻¹⁰ focus on the effects of OMT on biomarkers (Table 1). The purpose of the current study was to examine the efficacy of OMT through an objective and quantifiable index of representative AL biomarkers (Table 2). We conducted this study to (1) measure AL biomarkers in the study participants before and after each OMT session; (2) determine which AL biomarkers change after consistent OMT by comparing AL biomarker measurements taken before and after OMT intervention; (3) compare changes in AL biomarkers measured by different specimens collected and anthropometric data points; and (4) determine the effect of OMT on overall AL score. Because OMT is used to treat somatic dysfunction,

Table 2.
Index of Allostatic Biomarkers With Clinical Range Values

Biomarker	Reference Range
Urine	
Cortisol, $\mu\text{g/g}$	
Morning 1	7.87-29.5
Morning 2	23.4-68.9
Evening	6.0-19.2
Night	2.6-8.4
Norepinephrine, $\mu\text{g/g}$	
Morning 1	9.4-22.0
Morning 2	12.6-38.2
Evening	21.1-42.9
Night	16.9-38.8
Epinephrine, $\mu\text{g/g}$	
Morning 1	0.5-1.5
Morning 2	0.7-6.1
Evening	2.3-8.1
Night	1.2-4.2
Dehydroepiandrosterone	
Men	≥ 15.8
Premenopausal women	≥ 15.8
Blood	
hs-CRP, mg/L	<3
HDL, mg/dL	≥ 40
HbA _{1c}	$<6\%$
Anthropometric	
Systolic blood pressure, mm Hg	≥ 130
Diastolic blood pressure, mm Hg	≥ 80
Waist-to-hip ratio	≥ 0.94
Body mass index	
Men	<18.5
Women	>24.9

Abbreviations: HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein.

which affects overall body function, we hypothesized that OMT can lower overall AL score through modulating biomarkers related to the body's stress response.

Methods

A within-subject pre- and postintervention study was used to test the effects of OMT on AL biomarkers listed in [Table 2](#). A within-subject study design was used for the participants to serve as their own control. This study was approved by the institutional review board at Touro University California College of Osteopathic Medicine (TUCOM). The study coordinator obtained informed consent according to protocol. The study took place in a 7-week period from October to December 2017 in the TUCOM Translational Research Clinic. Participants were provided with both written and verbal explanations of study procedures. They were assigned a study number at enrollment by a trained research coordinator who was not involved with data collection. A database containing only study numbers was then given to a second research coordinator who was involved only in data collection.

Participants

Because AL is a measurement of physiological dysregulation that occurs from an overstimulation of the stress response, we assumed that people in a high-stress environment such as graduate health professional school would display such physiological dysregulation. Students in the Masters of Science in Medical Health Sciences program at TUCOM were recruited by a general interest survey. Students were excluded if they had previous exposure to OMT or other contraindicated health concerns (eg, pregnancy). Students who planned to undergo changes in their exercise, diet, medication, meditation, yoga, tai chi, or supplement regimen within the next 4 months were also excluded from the study.

Protocol

Visits

Participants were required to commit to a total of 4 visits. Visits were scheduled every 2 to 4 weeks, and each visit was scheduled at the same time of day depending on the participants' and physicians' schedule. Participants were given verbal and written instructions at

each visit. At visit 1, baseline preintervention values were established through data collection of perceived stress, blood pressure, blood and urine samples, and anthropometric measurements. For the second half of visit 1, participants were treated with the OMT intervention protocol described in [Table 3](#) for 30 minutes. One osteopathic physician provided the OMT at every visit to ensure uniformity of technique. A research assistant was present during treatment sessions to monitor technique consistency through direct observation and to manage treatment duration. Techniques were selected based on the autonomics, biomechanics, circulation, and screening examinations, or the ABCs of osteopathic medicine.²⁸ The total time for treatment did not exceed 30 minutes. Visits 2 and 3 were 30-minute OMT sessions. At visit 4, follow-up postintervention values were established through data collection as obtained during visit 1.

Data Collection

Perceived stress via the Trier Inventory for Chronic Stress (TICS) and blood pressure were measured throughout the treatment stages before and after OMT at all 4 visits, whereas blood and urine samples and anthropometric measurements (ie, waist-to-hip ratio, body mass index) were collected at visits 1 (baseline) and 4 (postintervention).

Dried bloodspot testing kits were used to collect blood specimens, and dried urine kits were taken home by the participants after visits 1 and 4 for diurnal neuroendocrine biomarker collection. Participants were instructed to take 4 total dried urine samples at 4 specific time points: first void upon waking, 2 hours after awakening, early evening, and night within 24 hours before intervention and 24 hours after intervention. Having 4 samples obtained in 24 hours allowed for a more comprehensive analysis of neuroendocrine biomarkers with and without environmental stressors, such as a pending school examination, as confounding factors. Specimens were stored at the clinic as recommended before sending them for analysis.

Table 3.
Osteopathic Manipulative Treatment Intervention Protocol For Allostatic Load Lowering^a (N=2)¹

ABCs of Osteopathic Medicine	Techniques	Assessment
Autonomics	Suboccipital release and rib raising.	Suboccipital region assessed for soft tissue tension; ribs assessed for articular dysfunction.
Biomechanics	HVLA, MFR, BLT, and ME depending on dysfunction diagnosed.	Five minutes given to the physician to treat the worst somatic dysfunction present not addressed elsewhere by the protocol and passive range of motion screening applied to the spine and triplanar diagnosis made at most restricted segment.
Circulation	Thoracic inlet myofascial release, thoraco-abdominal diaphragm myofascial release, and lumbosacral myofascial release.	Thoracic inlet and thoracoabdominal diaphragm.
Screening	NA	Tissue texture changes assessed for the spine; static asymmetry via gravitational line restriction of motion via passive range of motion for spine, ribs, and extremities; tenderness was assessed in all 10 body regions; cranial vault hold assessment for cranial dysfunction.

^a Implemented OMT (osteopathic manipulative treatment) techniques overlapped in multiple categories for the ABCs of osteopathic medicine.

Abbreviations: BLT, balanced ligamentous tension; HVLA, high velocity, low amplitude; ME, muscle energy; MFR, myofascial release.

Outcome Measures

The 30-item TICS measured chronic stress on a 5-point Likert scale ranging from 0 (never) to 4 (very often) during the past month. Test-retest reliability ($r=0.60-0.91$), internal consistency ($\alpha=.61-.93$), and intercorrelations ($r=0.42-0.63$) were acceptable for the following subscales: work overload, work discontent, overextended at work, performance pressure at work, worry propensity, social overload, social tension, lack of social recognition, performance pressure in social interactions, and social isolation. These subscales were aggregated into an index representing chronic stress.

An AL score was formulated using a count-based formulation in which all 11 measured biomarkers held equal value. A score of 1 was assigned to biomarkers falling within a high-risk percentile (upper 75th percentile for all biomarkers except high-density lipoprotein [HDL] and dehydroepiandrosterone, for which the lowest 25th percentile corresponds to highest risk) based on a population's distribution of normative biomarker values used in clinical practice.²⁹⁻³³ Allostatic

load score was represented as a numerical value from 0 to 20 and was interpreted as the total number of biomarkers in which the participant fell into the high-risk percentile.

Results

Three students volunteered to participate, and 1 student was subsequently excluded because of OMT exposure within the previous month. One man and 1 woman who were Masters of Science in Medical Health Sciences students met the criteria to participate. The decision to proceed with 2 participants was based on financial restraints, including the expenses of laboratory testing equipment. Both participants had no past exposure to OMT.

OMT Effects on AL

The effects of OMT on a representative index of 11 allostatic biomarkers are shown in [Table 2](#). The AL score was lower after the OMT intervention in both

participants (participant 1 decreased from 7 to 4; participant 2 decreased from 9 to 7). Participant 1's postintervention data analysis showed decreased second morning norepinephrine levels and decreased evening and night epinephrine levels. These values resulted in exclusion from the highest risk criterion cutoff values and overall lower postintervention AL score of 4 (Table 4). For participant 2, postintervention analysis

revealed decreased night cortisol levels and decreased systolic and diastolic blood pressure. These values fell below the highest quartile criterion cutoff values for high risk and resulted in an overall lower postintervention AL score of 7 (Table 4).

Other AL biomarkers were also analyzed; however, no change was found in these biomarker values that would affect the interpretation of overall AL score. We

Table 4.
Pre- and Postintervention Allostatic Load Score^a Based on AL Biomarkers in Participants Receiving OMT (N=2)

AL Biomarker	High-Risk Cutoff Value	Participant 1		Participant 2	
		Preintervention	Postintervention	Preintervention	Postintervention
Cortisol, $\mu\text{g/g Cr}$	<29.5 (1st AM), 68.9 (2nd AM), 19.2 (evening), 8.4 (night)	1	2	3	2
Norepinephrine, $\mu\text{g/g Cr}$	<22 (1st AM), 38.2 (2nd AM), 42.9 (evening), 38.8 (night)	2	1	2	3
Epinephrine, $\mu\text{g/g Cr}$	<1.5 (1st AM), 6.1 (2nd AM), 8.1 (evening), 4.2 (night)	2	0	1	1
DHEA, $\mu\text{g/g Cr}$	≥ 15.8 for premenopausal women, ≥ 15.8 for men	0	0	0	0
hsCRP, mg/L	<3	0	0	1	1
HDL, mg/ dL	≥ 40	1	0	0	0
HbA _{1c}	<6%	0	0	0	0
Systolic BP, mm Hg	<130	0	0	1	0
Diastolic BP, mm Hg	<80	0	0	1	0
Waist-to-hip ratio	0.94	0	0	0	0
BMI	≤ 18.5 for men, ≤ 24.9 for women	1	1	0	0
AL score		7	4	9	7

^aThe score is an index based on a binary system of a biomarker being normal (0) or abnormal (1). The integers represent a severity scale.

Abbreviations: AL, allostatic load; BMI, body mass index; BP, blood pressure; Cr, creatine; DHEA, dehydroepiandrosterone; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; OMT, osteopathic manipulative treatment.

did find it notable to highlight that HDL increased after the intervention in both participants. Specifically, participant 1's HDL increased from 40 mg/dL to 69 mg/dL, and participant 2's HDL increased from 48 mg/dL to 60 mg/dL.

OMT Effects on Subjective Distress

Analysis of TICS scores revealed that scores were lowered after 7 weeks of OMT compared with before OMT. Scores were reduced from 18 to 15 in participant 1 and 40 to 13 in participant 2.

Discussion

Osteopathic manipulative treatment works to manipulate the body back to its optimal capacity through treating somatic dysfunction and, therefore, using biomarkers to measure the effect of OMT on the overall health profile of patients could be important. The AL model has been proposed to measure the body's dynamic physiological response to chronic stress using a multisystem set of biomarkers, such as cortisol, catecholamines, and immunologic markers. The compilation of AL biomarkers works to measure the body's response to homeostatic deviations.

In the current study, the OMT protocol lowered overall AL score and self-perceived stress in both participants. The participants were enrolled in their first semester of a rigorous medical science program, and previous research³⁴ indicated that physiological distress may increase in prevalence and severity as a student progresses through his or her first year of medical education. Our results suggest the potential use of OMT as a means to maintain overall health or reduce AL and self-perceived stress in graduate students who are immersed in a highly stressful academic environment.

This study found increased HDL in both participants after OMT. In an investigation of the AL biomarkers most frequently measured in studies, HDL was shown to be the single best lipid predictor of allostasis.² This finding was particularly notable because HDL increased by a mean of 20.5 mg/dL

within the 7-week time span of our study. While current literature has shown that OMT can increase lymphatic drainage and is related to improved lipid metabolism, to our knowledge, no existing literature has explored the direct relationship between OMT and HDL.³⁵⁻³⁷ Given the high prevalence of cardiovascular disease and the significant relationship between HDL and its cardioprotective benefit,³⁸ we propose that further research is warranted to examine the relationship between OMT and HDL.

The TICS analysis revealed that self-perceived chronic stress was reduced in participants after OMT. In a study³⁹ that examined the effects of OMT on self-perceived stress scores in a sample population of first-year medical students aged 24 years, researchers found that self-perceived stress scores decreased from pretest to midtest and increased from midtest to posttest. These results, in addition to the current study results, demonstrate the necessity for further evaluation of OMT as a potential modality to reduce self-perceived stress.

The current study's findings suggest that our OMT protocol could be used as a treatment modality to manage self-perceived stress and modulate physiological biomarkers related to AL in a graduate student population. In addition, to our knowledge, this is the first study to explore OMT as an intervention with a multisystem index of representative biomarkers as opposed to individual system biomarkers or subcategories of biomarkers.

Limitations

Our study was limited because of the small sample size and lack of a control or sham group. The small sample size made it hard to generalize conclusions or use statistical methods for validation, and having no control group made it hard to know what a similar group might have experienced. The conclusion of this study, therefore, may not be representative of the true effects of OMT on AL and self-perceived stress.

This study was also limited because student participation was voluntary. The students' decision to

volunteer for the study may have been influenced by preexisting symptoms of chronic stress, which may have influenced data regarding perceived chronic stress. Self-perceived stress symptoms may have been affected by the completion or anticipation of school examinations. An examination occurred 10 days after the preintervention data collection time point and 12 days before the postintervention data collection time point. Additionally, while OMT principles and practice were not the focus of the participants' curriculum at TUCOM, environmental exposure to OMT and basic techniques on campus may have introduced a bias in participant survey responses.

Future Research

This feasibility study enabled us to see whether our intervention could produce a change in AL. Because our results indicated a change in AL, the next stage in our research includes assessing the efficacy of OMT in reducing AL in a larger sample size of this population with control and sham groups. We are planning a study of a continuous response variable in participants before and after an intervention. Future research could also examine the effect OMT has on AL biomarkers to better interpret which biomarkers are most influenced by OMT. Further specificity would lend greater understanding of the potential role of OMT in regulating AL biomarkers for health management and disease prevention. It would also be important to include multiple readings of blood pressure before treatment and after 3 treatment sessions to further delineate the effects of consistent OMT on blood pressure.

Conclusion

The OMT protocol we used lowered AL and perceived stress in a sample of 2 graduate students in their first semester. This study provides a basis for further review of the role of OMT in modulating AL biomarkers related to overall health. Osteopathic manipulative treatment may represent a reasonable modality to reduce self-perceived stress and AL. Further research

with a larger sample size, as well as control and sham groups, is warranted.

Author Contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; all authors drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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