Weekly Osteopathic Manipulative Treatment to Improve Measures of Sympathetic Tone in Women With Polycystic Ovary Syndrome: A Randomized, Controlled Pilot Study

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Background: Polycystic ovary syndrome (PCOS), a common hormone disorder affecting reproductive and metabolic health of reproductive-age women, was shown in a previous study from these authors to be associated with increased sympathetic tone. Increased sympathetic tone contributes to long-term health risks for cardiovascular disease and promotes PCOS pathogenesis.

Objective: To determine whether weekly osteopathic manipulative treatment (OMT) improves physiologic measures of sympathetic tone in women with PCOS.

Methods: In the second phase of a larger study from this author group, 25 women with PCOS, aged 22 to 43 years, living in Erie, Pennsylvania, were recruited to participate in a randomized, controlled evaluation of OMT intervention. Participants were randomly assigned to either an OMT intervention or control group. The OMT group received weekly manipulation of Chapman points and rib-raising for viscerosomatic reflexes associated with the ovaries, adrenal glands, and heart for 12 consecutive weeks. Physiologic measures of sympathetic tone were collected, along with metabolic, endocrine, and reproductive measurements, both before the 3-month intervention and within 1 week of completing the intervention. Measurements included heart rate and blood pressure at rest and after 15 minutes of aerobic exercise, heart rate recovery after exercise, resting heart rate variability, serum androgen levels, body mass index, fasting blood glucose and insulin levels, and menstrual cycle length.

Results: Nineteen women completed the study. Comparing pre- and postintervention parameters, women with PCOS in the OMT intervention group experienced an improvement in postexercise systolic blood pressure (135.8 vs 129.1 mm Hg) and a trend toward heart rate recovery (23.2 vs 29.4 seconds). No significant improvements were found in the control group or in any other physiologic parameters measured. No significant improvements were found in the endocrine, metabolic, or reproductive parameters measured, although free testosterone was slightly lower after 3 months of weekly OMT (5.69 vs 4.64 pg/mL).

Conclusion: Improvements in sympathetic tone after OMT suggest that weekly manipulation of Chapman points and viscerosomatic reflexes can be a useful adjunctive therapeutic option for women with PCOS. (ClinicalTrials.gov No. NCT03383484)

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As documented in a separate phase of this study and a previous narrative review undertaken before beginning our current work, [1,2] polycystic ovary syndrome (PCOS) affects 5% to 15% of women of reproductive age, making it the most common hormone disorder in that subset of patients.[3-6] It often remains undiagnosed until reproductive features become apparent,[5,6] and it is the most common cause of anovulatory infertility. Polycystic ovary syndrome can affect female endocrine, reproductive, metabolic, and psychological health, from puberty to menopause and beyond.[7,9,10] The etiology of PCOS remains unknown but is likely a combination of genetic, epigenetic, and environmental factors. Diagnosis of PCOS depends on consensus criteria and exclusion of other endocrinopathies as causes for the symptoms associated with the disorder. The 2003 Rotterdam criteria, most often used, require at least 2 of 3 features for diagnosis: menstrual irregularity secondary to oligo- or anovulation, hyperandrogenism (clinical or biochemical), and polycystic ovary morphology.[11] Other common clinical findings include subfertility, greater incidence of miscarriage, hirsutism, acne, weight gain, insulin resistance, anxiety, and depression.[7,9,10,12,13]

PCOS and the SNS

Sympathetic nervous system (SNS) hyperactivity, or increased sympathetic tone, is also common in women with PCOS, despite most patients being unaware of it. Hyperactivity of the SNS is associated with elevated serum androgen levels, anovulation, and menstrual irregularity, and may play a role in the pathogenesis of the disorder.[14-18] Systemic SNS hyperactivity has been reported as elevated resting heart rate (HR), decreased heart rate variability (HRV), hypertension, exaggerated systolic blood pressure response to exercise and attenuated heart rate recovery (HRR) after exercise, increased muscle sympathetic nerve activity, and increased levels of adrenergic metabolites in the serum and urine.[19-21] Chronic SNS hyperactivity is associated with visceral adiposity, and obesity further exacerbates SNS hyperactivity.[22-25] Studies of both women with PCOS and animal models have demonstrated locally increased sympathetic tone, including increased ovarian sympathetic outflow and expression of nerve growth factor, increased sympathetic tone of adipose tissue, and altered expression of adrenoreceptors in the hypothalamus, periventricular nucleus, and ovaries.[18,26-30] In a previous study, we demonstrated that women with PCOS exhibit signs of increased sympathetic tone that can be assessed both by physiologic and osteopathic measures, with osteopathic structural examination identified as a valuable means to detect sympathetic hyperactivity in women with PCOS even before the physiologic signs manifest.[2] In addition, studies in a rat model of PCOS have shown that transection of either the superior ovarian nerve or the vagus nerve improved sympathetic tone, decreased ovarian androgen production, improved reproductive cyclicity, and restored ovulation.[26,31] Together, these findings underscore a role for the SNS in the pathogenesis and presentation of PCOS, particularly the androgenic and reproductive features.

Treatment Modalities

Pharmacologic treatments can be effective in targeting specific symptoms associated with PCOS, but are often limited in scope, may be contraindicated in some patients, may produce adverse effects, and in some cases are ineffective. For example, the ovulation-inducing medication clomiphene citrate may be used to assist in achieving pregnancy, but headache, nausea, visual disturbances, or ovarian hyperstimulation syndrome may occur. Furthermore, this medication does not work for up to 30% of women.[32] Women with PCOS have expressed interest in adjunctive approaches to manage symptoms, stating a desire for more holistic, safer treatment modalities with fewer adverse effects.[33] Osteopathic physicians may be well poised to provide such therapies, as osteopathic manipulative treatment (OMT) has been shown to be effective in the management of many different diseases and disorders, from low back pain and carpal tunnel syndrome to stress and depression, pneumonia,

and biliary dyskinesia.[34-37] Osteopathic manipulative medicine, including OMT, may also be used in the diagnosis and treatment of diabetes mellitus and its complications, such as diabetic gastroparesis.[34-37]

Osteopathic Justification

Osteopathic philosophy asserts an interrelationship between structure and function at all levels. This osteopathic tenet recognizes the reciprocal relationship between soma and viscera. Researchers have established that somatic dysfunction in regions of autonomic innervation affects the segmentally related viscera and that visceral pathology can manifest as somatic dysfunction in segmentally related locations due to visceral afferents.[38-40] The autonomic nervous system is responsive to OMT, with studies showing an increase in parasympathetic activity and decrease in sympathetic activity immediately after manipulation in healthy patients.[41-43] The involvement of the SNS in the pathogenesis and presentation of PCOS make OMT a particularly attractive therapeutic option for this population. The short-term and long-term effects of OMT on SNS hyperactivity have not yet been described, and to date, no studies have been conducted on the use of OMT in the treatment of patients with PCOS. The purpose of the present study was to determine whether once-weekly OMT, via manipulation of Chapman points (CPs) and rib-raising for viscerosomatic reflexes (VSRs), could improve sympathetic tone in adult women with PCOS. Because of the relationships between hormones, obesity, and menstrual function, and the effect sympathetic hyperactivity has been shown to have on androgen production and ovulation in this disorder, we also examined endocrine, metabolic, and reproductive parameters in these women.

Methods

Participant Recruitment and Consent

Study participants were recruited from the Erie, Pennsylvania, area by direct advertising through radio, billboard, website, newspaper, and magazine advertisements. Physician referrals from Medical Associates of Erie physicians were also used to recruit potential participants. Recruitment lasted 4 months, from October 2016 through January 2017. Potential participants signed a consent form to have relevant medical records released to confirm PCOS diagnosis, as well as informed consent to participate in the study. All protocols were approved by the Lake Erie College of Osteopathic Medicine institutional review board (protocol No.23-156). (ClinicalTrials.gov No. NCT03383484)

Participant Inclusion and Exclusion Criteria

A questionnaire was given to each participant at the time of consent to supplement the medical records to determine eligibility. Participants were women between the ages of 22 and 43 years, with a body mass index (BMI) of 20 to 48, who had a confirmed diagnosis of PCOS and exhibited the 2003 Rotterdam criteria for PCOS diagnosis, defined as at least 2 of the following 3 features: clinical or biochemical hyperandrogenism (moderate acne or a modified Ferriman-Gallwey score ≥8 or free testosterone >5 pg/mL), polycystic ovaries (≥12 cysts on 1 ovary by ultrasonography or ovarian volume >10 mL for 1 ovary), and menstrual irregularity (defined as ≤8 menstrual periods per year or cycles averaging >35 days).[11] Exclusion criteria included smoking, use of hormone-based medications within the past 3 months (hormonal contraception, ovulation inducers, antiandrogens) or insulin-sensitizing agents, presence of another endocrine disorder diagnosis, pregnancy or breastfeeding within the past 6 months, and/or diagnosis of a major psychiatric disorder or use of antipsychotic medication. None of the participants had received OMT, chiropractic treatment, or acupuncture within the 6 months before the study. Participants who did not complete the 3-month measurements or who were in the OMT intervention group and did not complete at least 10 weeks of OMT were excluded from data analysis.

Study Design and Data Collection

Participants were enrolled in the study after confirming eligibility according to inclusion and exclusion criteria. All participants were randomly assigned a unique, sequential number to allow for random assignment to a group: the no intervention (control) or the OMT intervention group (Figure 1). As part of this study on nonpharmacologic interventions for women with PCOS, a third group undergoing yoga intervention for 3 months was also formed, and results are reported separately.[44] More participants were assigned to the intervention group in anticipation of some attrition because of the time commitment involved in participating in a weekly intervention for 3 months. Investigators collecting clinical and physiologic data were blinded to the intervention group (C.M., S.B., H.M., V.P., C.A.B.S.). Deidentified participant data were stored in a secure database.

Clinical Assessment of Metabolic, Reproductive, and Endocrine Parameters

In January 2017, a gynecologist (C.A.B.S.) who was blinded to the assigned intervention group assessed participants' weight, height, BMI, blood pressure, HR, waist and hip circumference, hirsutism (modified Ferriman-Gallwey score), and acne (face, chest, and back). Patients were asked about their menstrual cycle history and pattern (<25, 25-35, or >35 days), pregnancies, and any medications that they had taken within the last 6 months. Clinical assessments and measurements

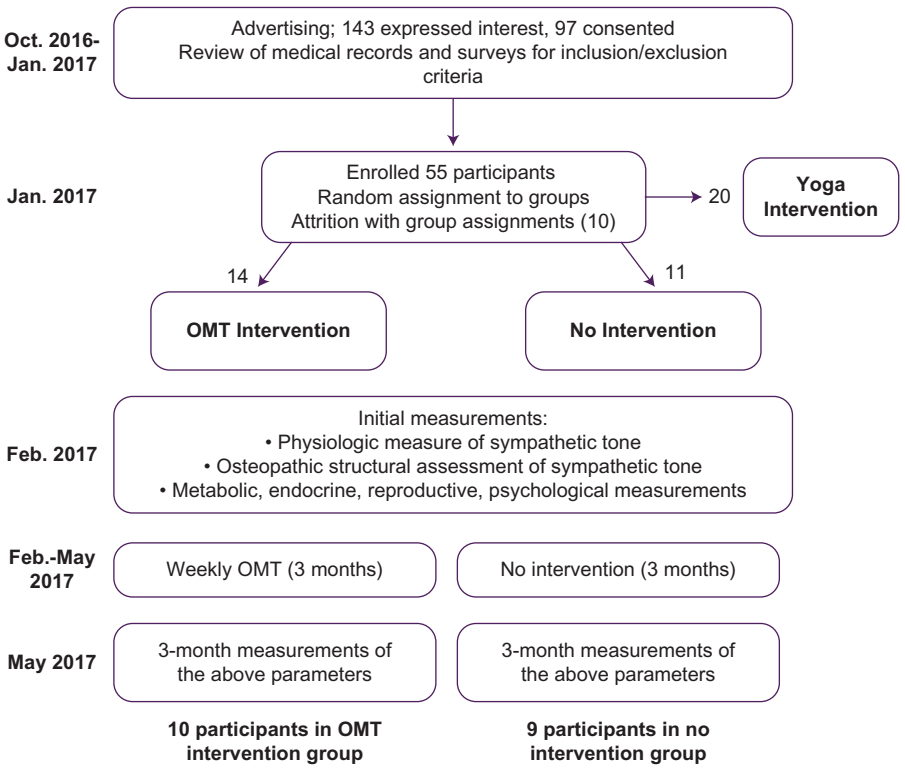

Figure 1.
Study design and timeline. Participants with polycystic ovary syndrome (PCOS) were recruited from the Erie, PA, region. Participants were randomly assigned to either the osteopathic manipulative treatment (OMT) intervention or no intervention (control) group. Physiologic, endocrine, metabolic, reproductive, and psychological measurements were made before and on completion of the 3-month OMT intervention period for women in both groups. Nineteen women completed the study. Twenty others were assigned to a separate study arm evaluating the effect of yoga on PCOS.[44]

were repeated in April 2017 for participants in both the control group and the OMT intervention group (≥10 weeks of treatment), within 1 week after the conclusion of the 3-month OMT intervention.

Serum Analysis of Hormones and Metabolic Parameters

All participants had a fasting venous blood collection before the beginning of the intervention period, as well as on completion of the 3-month intervention period. All whole blood samples were collected by Associated Clinical Laboratories and analyzed by Associated Clinical Laboratories or Quest Diagnostics. Fasting blood glucose was measured by spectrophotometry; free testosterone was calculated from a mathematical model using sex hormone-binding globulin, albumin, and total testosterone (quantified by liquid chromatography-mass spectrometry); androstenedione and dehydroepiandrosterone (DHEA) were quantified by liquid chromatography-mass spectrometry; and serum insulin, DHEA sulfate (DHEA-S), luteinizing hormone, follicle-stimulating hormone, prolactin, thyroid-stimulating hormone, and serum human chorionic gonadotropin levels were determined by immunoassay.

Physiologic Assessment of Sympathetic Tone

For each participant, resting HR (measured by pulse oximeter) and blood pressure (standard method, using the antecubital artery) were recorded while the participant was seated and quiet. Heart rate variability was determined from a continuous 5-minute electrocardiogram recording while the participant was lying quietly in a supine position. Next, participants exercised on a stationary bike for 15 minutes at 70% effort, during which time HR was recorded at 5 minutes, 10 minutes, and 15 minutes, as well as 1 min after completion of the exercise.[45-47] Heart rate recovery after exercise was calculated as the difference between HR at 15 minutes while exercising and at rest 1 minute after exercise. Blood pressure was also recorded within 1 minute of exercise completion. Measurements were made by an investigator (C.M., H.M., S.B., and V.P.) blinded to each participant's group and taken in the same temperature- and humidity-controlled room for each participant.

HRV Analysis

Length of adjacent QRS complexes (normal-normal [NN] intervals) were quantified from a continuous 5-minute electrocardiogram recording for each participant. Recordings were analyzed for mean interval length between adjacent QRS complexes (mean NN), mean (SD) NN, and percentage of differences between adjacent NN intervals that were greater than 50 milliseconds (pNN50).[48]

Assessment of Anxiety and Depression

All participants were provided unique web links to complete the Beck Anxiety Index (BAI) and the Beck Depression Index II (BDI-II; Pearson Clinical) before the 3-month OMT intervention and within 1 week of the completion of the OMT intervention period. Surveys were automatically scored online. The BAI scores were reported on a range of 0 to 63, with total scores interpreted as follows: 0 to 7, minimal anxiety; 8 to 15, mild anxiety; 16 to 25, moderate anxiety; and 26 to 63, severe anxiety. The BDI-II scores were reported on a range of 0 to 63, with total scores interpreted as follows: 0 to 13, minimal depression; 14 to 19, mild depression; 20 to 28, moderate depression; and 29 to 63, severe depression.

Osteopathic Manipulative Treatment

As in the earlier and separate arm of this study, all participants were evaluated by an osteopathic physician (S.E.D. or J.H.) for the presence of anterior and posterior CPs related to the heart, adrenal glands, and ovaries, and for VSRs in spinal regions segmentally related to the heart (T1-5), adrenal glands (T8-10) and ovaries (T10-11).[2] These regions were selected because PCOS pathophysiology involves overproduction of androgens by the ovaries, and the adrenal glands have also been implicated in contributing to

excessive androgen production in some patients. Increased ovarian sympathetic tone has been reported in women as well as in animal models of PCOS, and the adrenal glands and heart are additional proxies for detecting increased sympathetic tone.[2,14-18,26-31]

The OMT group was evaluated and treated for 12 consecutive weeks. Participants received OMT for positive CPs, which consisted of a firm yet gentle rotatory motion applied by fingerpad over each positive CP for heart, adrenal glands, and ovaries until dissolution of edema and lessening of tension, which indicated the end point. Treatment of positive CPs was followed by treatment of VSRs, consisting of rib-raising and paraspinal inhibition in the regions of the heart (T1-5), adrenal glands (T8-10), and ovaries (T10-11).[49]

Data Analysis

Power analysis was conducted with the Statistical Decision Tree Power Calculator (QFAB Bioinformatics) to determine the sample size needed to detect a Pearson correlation coefficient of 0.6 with a power of at least .80, with a significance level of .05 (n=8 per group). GraphPad Prism 7.03 software was used for data analysis. Mean values of initial parameters (age, BMI, waist-to-hip ratio) for women in each group were analyzed by unpaired *t* tests to ensure that the groups of women were comparable. Paired *t* tests (for normally distributed data) or Wilcoxon matched-pairs signed rank tests (for data that were not normally distributed) were used to compare participants' initial measurements (0 months, January 2017) with their postintervention measurements (3 months, April 2017). Statistical significance was set at $P<.05$, with *P* values between .05 and .10 considered trending.

Results

Table 1 shows the mean values for participant demographics for the initial group assignments, with no significant difference in participant age, BMI, waist-to-hip ratio, or menstrual irregularity.

Postexercise Systolic Blood Pressure

Pre- and postintervention period measurements were compared for each individual (paired *t* test or Wilcoxon matched-pairs rank test; **Table 2**). A significant decrease was found in postexercise systolic blood pressure for participants in the OMT group (135.8 vs 129.1 mm Hg, $P=.0002$), with no change in this parameter for participants in the control group (**Figure 2**). Postintervention resting blood pressure was lower in the OMT group participants (124.2 vs. 120.7 mm Hg), but did not reach significance.

Heart Rate Recovery

There was no significant improvement in either group for resting HR after the intervention in women with PCOS (**Table 2**), although there was a trend toward

Table 1.
Patient Demographics By Study Group of Women With PCOS[a]

Characteristic	No intervention (n=9)	OMT intervention (n=12)	*P* value[a]
Age, y, mean (SD)	31.2 (2.3)	33.5 (2.5)	.77
BMI, mean (SD)	35.4 (3.3)	34.0 (1.0)	.79
Waist-to-hip ratio, mean (SD)	0.8003 (0.020)	0.8530 (0.022)	.08
Average menstrual cycle length, d	>35	>35	…

[a] Statistical significance was set at $P<.05$, with *P* values between .05 and .10 considered trending.

Abbreviations: BMI, body mass index; PCOS, polycystic ovary syndrome.

Table 2.
Physiologic Measures of Sympathetic Tone in Women With PCOS[a]

Measure	Control (0 mo) (n=9)	Control (3 mo) (n=9)	*P* value[b]	OMT (0 mo) (n=10)	OMT (3 mo) (n=10)	*P* value[b]
Resting HR, bpm	83.7 (3.4)	80.6 (3.1)	.54	69.2 (1.7)	73.8 (2.5)	.06
Resting SBP, mm Hg	123.4/74.3 (3.6)	123.2/78.4 (2.1)	.91	124.2/74.3 (3.9)	120.7/75.7 (2.7)	.35
Resting EKG NN, ms	0.772 (0.022)	0.782 (0.034)	.77	0.855 (0.037)	0.814 (0.45)	.07
Resting EKG SDNN, ms	0.041 (0.005)	0.071 (0.020)	.16	0.055 (0.009)	0.042 (0.007)	.13
Resting EKG pNN50, %	16.2 (3.4)	18.7 (6.6)	.70	27.7 (5.8)	24.5 (6.4)	.44
Postexercise SBP, mm Hg	130.4/80.2 (3.4)	129.2/77.8 (2.0)	.20	135.8/74 (2.6)	129.1/78.2 (2.5)	.0002
Postexercise HRR, s	23.8 (4.8)	19.2 (3.4)	.84	23.2 (3.3)	29.4 (2.2)	.10

[a] Data are given as mean (SD) unless otherwise indicated.
[b] Statistical significance was set at $P<.05$, with P values between .05 and .10 considered trending.

Abbreviations: bpm, beats/min; EKG, electrocardiogram; HR, heart rate; HRR, heart rate recovery; NN, normal-to-normal intervals on QRS complexes during heart examination; PCOS, polycystic ovary syndrome; SBP, systolic blood pressure.

improved HRR for the OMT group participants (23.2 vs 29.4 seconds; $P=.099$).

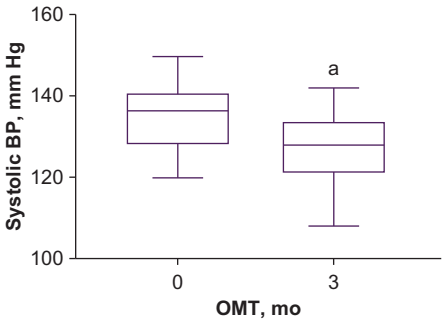

Figure 2.
Systolic blood pressure (BP) after exercise in OMT group. Postexercise BP results. Women in the osteopathic manipulative treatment (OMT) intervention group were treated weekly with manipulation of Chapman points, followed by rib-raising and paraspinal inhibition for viscerosomatic reflexes, for regions associated with the heart, ovaries, and adrenal glands. For this test, systolic BP after exercise was assessed within 1 minute of completing 15 minutes of 70% effort on a stationary bike. Compared with their test results before the 3-month intervention period, participants had a significantly lower systolic BP after exercise after the 3-month OMT intervention. [a]Paired *t* test, $P<.005$, n=10.

Heart Rate Variability

The mean participant values for resting blood pressure and measures of HRV (mean [SD] NN) were slightly outside of reported normal values for both groups,[45-47] indicating increased sympathetic tone in this study population and consistent with previous reports.[2,14,21,50-53] No significant changes were detected in any of the measured parameters for HRV in either group after the 3-month intervention period (Table 2), although the mean NN value trended lower after the OMT intervention.

Metabolic, Endocrine, and Reproductive Parameters

No significant changes were observed in either group for endocrine parameters (free testosterone, DHEA, androstenedione, modified Ferriman-Gallwey score) or in menstrual cycle length (Table 3). Free testosterone was elevated in both groups of participants, as expected for women with PCOS. While the free testosterone was slightly lower in participants in the OMT group after the 3-month intervention compared with their initial values, this change did not reach statistical significance (5.69 vs 4.64 pg/mL). In the control

Table 3.
Endocrine, Reproductive, and Metabolic Measures in Women With PCOS[a]

Measure	Control (0 mo) (n=9)	Control (3 mo) (n=9)	*P* value[b]	OMT (0 mo) (n=10)	OMT (3 mo) (n=10)	*P* value[b]
Free T, pg/mL	7.39 (1.61)	7.36 (1.29)	.97	5.69 (1.00)	4.64 (0.73)	.21
DHEA, ng/dL	382.7 (71.3)	368.3 (53.1)	.74	440.2 (139.7)	446.8 (130.0)	.92
DHEA-S, μg/dL	197.4 (30.7)	224.4 (34.1)	.0038	205.7 (37.4)	234.9 (43.0)	.16
A4, ng/dL	209.2 (56.0)	246.2 (45.9)	.15	169.6 (25.5)	170.6 (23.0)	.97
mFG score	4.0 (0.6)	4 (0.63)	.99	4.0 (1.1)	4 (1.13)	.99
Menstrual cycle length, d	>35	>35	…	>35	>35	…
BAI score	12.0 (2.9)	10.9 (2.2)	.63	10.6 (1.6)	10.4 (2.5)	.94
BDI-II score	18 (2.1)	12 (1.7)	.06	14.8 (2.5)	8.9 (1.6)	.09
Fasting BG, mg/dL	89.2 (4.5)	92.1 (2.7)	.40	92.1 (2.7)	95.1 (3.6)	.42
Fasting insulin, μIU/mL	14.8 (3.9)	12.7 (2.7)	.33	14.3 (3.5)	13.7 (2.5)	.82
HOMA-IR	3.48 (1.02)	3.00 (0.66)	.38	3.37 (0.84)	3.30 (0.54)	.91
BMI	35.4 (3.3)	35.6 (3.3)	.40	34.0 (1.0)	33.5 (1.0)	.47
Waist-to-hip ratio	0.8003 (0.020)	0.8114 (0.020)	.34	0.8530 (0.022)	0.8618 (0.038)	.80

[a] Data are given as mean (SD) unless otherwise indicated.
[b] Statistical significance was set at $P<.05$, with P values between .05 and .10 considered trending.

Abbreviations: A4, androstenedione; DHEA, dehydroepiandrosterone; mFG, modified Ferriman-Gallwey; BAI, Beck Anxiety Index; BDI-II, Beck Depression Index II; BG, blood glucose; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; PCOS, polycystic ovary syndrome; T, testosterone.

group, the DHEA-S level was higher after the 3-month period (P=.0038). No significant changes were noted in either group for metabolic parameters (Table 3).

Anxiety and Depression Scores

Scores on the BAI indicated mild anxiety in most participants, with a few scores indicating minimal or moderate anxiety. Similarly, the BDI-II scores indicated minimal to mild depression in most participants, with some reporting moderate depression. No significant change in individual participants' pre- and postintervention scores were found in either group (Table 3), although both groups demonstrated a trend toward improved BDI-II scores after the 3-month intervention period (P=.06 for no intervention and P=.09 for OMT intervention).

Discussion

Polycystic ovary syndrome is a common hormone disorder that affects multiple aspects of female health. We found that weekly manipulation of CPs and rib raising for VSRs associated with the ovaries, adrenal glands, and heart resulted in an improvement in postexercise systolic blood pressure, a trend toward improved HRR, and a potential decrease in resting systolic blood pressure and serum testosterone levels, as well. Together, these findings suggest that OMT can be a beneficial adjunctive tool to help mitigate sympathetic hyperactivity common in women with PCOS, which is an often-neglected aspect of PCOS that plays a role in the pathogenesis and presentation of the disorder. By reducing sympathetic hyperactivity and balancing autonomics of affected viscera, we can better provide a

multifaceted approach toward the management of symptoms associated with PCOS, and might even offer a better background for the efficacy of other therapies, as well as improved overall health.

Somatic Dysfunction and Spinal Facilitation

Somatic dysfunction caused by visceral pathology will result in a segmental response that can then affect the segmentally related viscera due to spinal facilitation.[49,54] With spinal facilitation, a population of neurons remain in a state of subthreshold excitation, which may be caused by chronically elevated afferent input, altered patterns of afferent input, or changes to the cells' microenvironment. Because of this relationship, treating somatic dysfunction as a result of VSRs provides a therapeutic effect on the segmentally related viscera. Inhibitory OMT techniques, such as paraspinal inhibition with rib raising and treatment of CPs, aim to disrupt the facilitated state. This disruption allows attenuation of the hypersympathetic response and balance of autonomic tone, thereby providing a therapeutic intervention to the involved viscera.[41,42,49,55-57]

SNS and PCOS

The SNS plays a role in several disease processes, including the pathogenesis and presentation of PCOS.[14-18] Systemically, sympathetic hyperactivity can promote hypertension and reduce HRV, thereby contributing to the risk of developing cardiovascular sequelae.[58] Obesity, common in women with PCOS, can further activate the SNS and contribute to the development cardiometabolic disease.[22-25] Improving some aspects of sympathetic tone in women with PCOS may help to reduce the risk of cardiovascular sequelae. In addition to systemic effects, there appears to be a link between sympathetic hyperactivity and the production of ovarian androgens, as well as ovulation regularity,[26,31] further underscoring the importance of recognizing the role of the SNS in PCOS pathogenesis and identifying methods to improve sympathetic tone in this population. In our study, there appeared to be a decrease in serum testosterone levels with weekly OMT, suggesting that improvements in sympathetic tone may lead to improvements in androgen profile as well. Further studies are needed to investigate the potential for OMT to significantly improve the androgenic and reproductive profiles of women with PCOS, including larger clinical trials, longer intervention periods, and alternate OMT protocols.

Limitations and Future Studies

Limitations of this study included the small sample size, the lack of a sham procedure group, and use of a limited set of CPs. Expanding this type of study to a larger population of women with PCOS will help to elucidate whether the trends observed in serum testosterone levels, as well as other physiologic measures of sympathetic tone, such as HRR, are consistent and significant. The possibility that serum testosterone may be responsive to OMT is particularly appealing, as this would represent a nonpharmacologic approach to improve serum androgen levels in women with PCOS and potentially improve the associated clinical features, acne, and hirsutism. Women with PCOS have expressed interest in the availability of adjunctive therapies for managing PCOS-associated symptoms, citing the desire for effective, safe modalities with fewer side effects as a major reason[33]; OMT could be such a modality. Research with a larger population will also allow for the inclusion of a sham group to help distinguish between the effects of manipulation compared with light touch. Future studies should investigate which combination of CP manipulation and rib raising are most effective in improving sympathetic tone, as our study focused on manipulation of points associated with the ovaries, adrenal glands, and heart in combination with rib raising for VSRs of the same. Given the prevalence of hyperinsulinemia and insulin resistance in women with PCOS,[7,9,10,13] manipulation of CPs and VSRs associated with the pancreas could be a beneficial adjunct treatment modality.[57]

Persistent Sympathetic Hyperactivity

Over the course of the 3-month intervention period, some women in the OMT group had a decrease in the number of CPs or VSRs (not shown). However, some had a decrease in CPs but an increase in VSRs or vice versa, and 1 participant had an increase in both CPs and VSRs. These findings suggest that, although manipulation of CPs and rib raising improved some aspects of sympathetic tone in our study population, sympathetic hyperactivity and visceral dysfunction still existed. The majority of our participants, and women with PCOS in general, are overweight or obese, which has been shown to activate the SNS.[22-25] Therefore, given the role of the SNS in PCOS pathogenesis,[18,26-30] it is unlikely that sympathetic hyperactivity can be completely ameliorated in women with PCOS. However, any improvements in sympathetic tone are likely to confer some benefit in terms of reducing PCOS-associated symptom severity and cardiovascular risk.[21,22,24,59]

Anxiety and Depression

In addition to the impact on endocrine and reproductive parameters, sympathetic tone, and metabolic health, studies[9,10,60-62] have also indicated that women with PCOS are more likely to have psychological disorders, including anxiety and depression. We did not find a significant improvement in depression scores after the 3-month intervention period, although both groups trended lower. This finding may reflect a seasonal improvement in feelings of depression, an improvement related to participating in a research study on PCOS, or a perceived increase in attention to the individual with respect to her PCOS diagnosis. The exact causes of depression and anxiety in women with PCOS are likely complex, as they may relate to clinical signs of hyperandrogenism, obesity, subfertility, sympathetic hyperactivity, or other physiological and psychological influences.[9,10] Regarding anxiety, there is a relationship between anxiety and sympathetic activation, although the direction of this relationship is debated and may differ depending on the underlying causes of anxiety. In the current study, most participants scored in the mild range for anxiety level, with a few scoring in the minimal and moderate ranges. We found no significant difference in either group between pre- and postintervention BAI scores. Our findings suggest that OMT alone may not be effective in addressing these psychological disorders, rather, it should be a component of a comprehensive care plan for women with PCOS. These results are consistent with other studies reporting anxiety in this population and highlight the need to consider this aspect of patient health when providing care and resources for women with PCOS.

Conclusion

Our findings indicate that weekly OMT may improve some physiologic measures of increased sympathetic tone in women with PCOS, an often-neglected aspect that affects the pathogenesis and presentation of the disorder. Reducing sympathetic hyperactivity in women with PCOS using OMT techniques provides another approach to improve overall health and may also help mitigate other aspects of the disorder. Further studies are warranted to determine whether the decreased serum testosterone level after an OMT intervention is significant and whether the findings of the current study can be replicated in a larger population of women with PCOS. Osteopathic physicians who practice OMT have the unique skill set to provide women with PCOS a nonpharmacologic adjunctive treatment modality to better improve the health of patients with this common hormone disorder.

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Author Contributions

All authors provided substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of the data; all authors drafted or revised the article 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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