

Sustained clinical benefits of menopausal hormone therapy for symptomatic hand osteoarthritis: A 12-month follow-up study in perimenopausal women

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Abstract

Background: Symptomatic hand osteoarthritis (HOA) is prevalent among perimenopausal women and may be associated with estrogen deficiency. Although menopausal hormone therapy (MHT) has shown short-term benefits, its long-term efficacy remains unclear. **Objective:** To evaluate 12-month outcomes in perimenopausal women with symptomatic HOA. **Design:** Retrospective single-arm observational study. **Methods:** This retrospective observational study at the Menopause and Hand Clinic, Kagoshima University Hospital, included 45 women with symptomatic HOA who initiated MHT between April 2019 and December 2022 and completed 12 months of follow-up. Diagnosis was based on the EULAR recommendations. MHT was prescribed according to uterine status. No additional orthopedic treatments were administered. Disabilities of the Arm, Shoulder and Hand (DASH), visual analog scale (VAS), and grip strength were assessed at baseline and at 3, 6, and 12 months. Minimal clinically important differences (MCIDs) were predefined. **Results:** Of 54 patients who initiated MHT, 45 (83.3%) completed 12-month follow-up. Repeated-measures analysis of variance showed a significant main effect of time on DASH and VAS scores ($p < 0.001$). DASH score improved by -8.8 points (95% CI, -13.2 to -5.0), which did not reach the MCID, whereas VAS score decreased by -28.4 mm (95% CI, -35.0 to -21.2), exceeding the MCID. Grip strength significantly increased in both hands (both $p < 0.001$). Improvements were greatest at 3 months and were maintained at 12 months. No serious adverse events occurred, and no patient discontinued MHT. **Conclusions:** In this retrospective single-arm study, improvements in hand pain, upper-extremity function, and grip strength following MHT initiation were maintained over 12 months in perimenopausal women with symptomatic HOA. Clinically meaningful improvement was observed for hand pain, but not upper-extremity function. Further prospective studies are warranted to establish causality and determine the long-term effectiveness of MHT.

Plain Language Summary

Pain and stiffness in the fingers are common in women around menopause. These symptoms are often caused by hand osteoarthritis, a condition that affects the joints of the fingers. Because estrogen levels fall during menopause, some researchers believe this hormone change may contribute to hand pain. However, little is known about whether menopausal hormone therapy (MHT) provides lasting benefits. In this study, we followed 45 Japanese women with painful hand osteoarthritis who started MHT and continued treatment for 12 months. We measured hand pain, hand function, and grip

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strength before treatment and during follow-up. Hand pain improved substantially and the improvement was maintained for one year. Hand function and grip strength also improved over the same period, although the improvement in hand function did not reach the level considered clinically meaningful. No serious side effects occurred, and none of the women stopped treatment because of side effects. Because this study did not include a comparison group, we cannot conclude that MHT alone caused these improvements. However, our findings suggest that MHT may be a useful treatment option for some women around menopause who have painful hand osteoarthritis. Larger prospective studies are needed to confirm these findings and determine which patients are most likely to benefit.

Keywords

Symptomatic hand osteoarthritis, Menopausal hormone therapy, Menopause, Estrogen deficiency, hand pain

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Introduction

Hand osteoarthritis (HOA) is a common degenerative joint condition that disproportionately affects women, especially during the perimenopausal period. Although radiographic HOA is often asymptomatic, symptomatic HOA causes pain, stiffness, and functional limitations that reduce quality of life. Previous studies have suggested that hormonal changes, particularly declining estrogen levels, may contribute to the onset and exacerbation of HOA symptoms during menopause.^{1–4}

Conventional management strategies for HOA are similar to those for other forms of osteoarthritis and typically include orthotic interventions, exercise therapy, oral administration of nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular corticosteroid injections. However, no standardized treatment strategy specifically tailored for symptomatic HOA has yet been established.^{5–8}

In our previous study, we reported that menopausal hormone therapy (MHT) was associated with greater short-term improvements in hand pain and function compared with complementary and alternative medicine (CAM) in Japanese perimenopausal women.⁹ Although MHT is considered the most effective treatment for vasomotor and other menopausal symptoms, concerns regarding potential risks, including thromboembolic events and hormone-sensitive malignancies, have influenced its clinical use. Furthermore, while short-term symptomatic benefits of MHT for HOA have been reported, evidence regarding the durability of these effects remains limited. Importantly, symptomatic improvement should be distinguished from disease modification, as the effects of MHT on structural progression of HOA remain unknown.

This study aimed to investigate the 12-month clinical outcomes of perimenopausal women with symptomatic HOA who received MHT. Specifically, we evaluated whether changes in pain, hand function, and grip strength following initiation of MHT were maintained over 12 months and assessed their clinical meaningfulness using minimal clinically important differences (MCIDs).

Methods

Study design and participants

This retrospective single-arm observational study evaluated the 12-month clinical outcomes following initiation of MHT in women with symptomatic HOA. The reporting of this study conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.¹⁰ The present study represents a longitudinal extension of our previously reported MHT cohort⁹ and reports the 12-month outcomes of women who initiated MHT. Patients who attended the Menopausal Hand Clinic, a multidisciplinary clinic jointly managed by hand surgeons and gynecologists at Kagoshima University Hospital, and who initiated MHT between April 2019 and December 2022 were eligible for inclusion. A participant flow diagram is shown in [Figure 1](#). During the study period, 54 patients initiated MHT. Of these, 45 completed the 12-month follow-up and were included in the final analysis, resulting in a follow-up rate of 83.3%. Nine patients were excluded because 12-month outcome data were unavailable. Baseline characteristics of participants who completed the study and those lost to follow-up were compared and showed no significant differences ([Supplementary Table S1](#)).

The diagnosis of symptomatic HOA was established by experienced hand surgeons based on clinical findings, in accordance with the European Alliance of Associations for Rheumatology (EULAR) recommendations.¹¹ Patients with other upper limb conditions that could confound symptom evaluation, including carpal tunnel syndrome, trigger finger, and rheumatoid arthritis, were excluded.

Clinical data were extracted from medical records and included age, body mass index (BMI), menopausal status, Simplified Menopausal Index (SMI) score, Self-Rating Questionnaire for Depression (SRQ-D) score, Disabilities of the

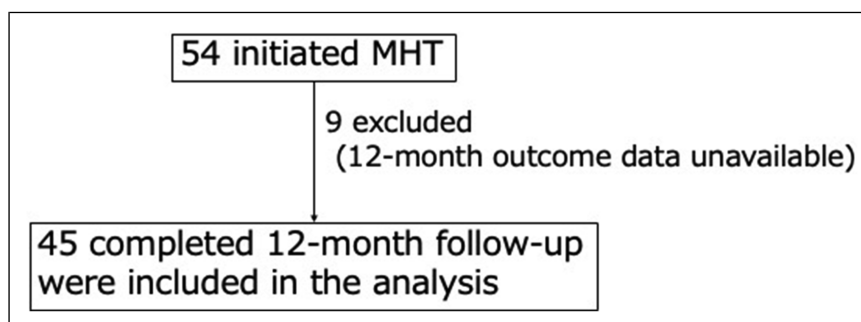


Figure 1. Flow diagram of participant selection and follow-up.

Arm, Shoulder and Hand (DASH) score, visual analog scale (VAS) score, and grip strength of the dominant and nondominant hands. Assessments were performed at baseline and approximately 3, 6, and 12 months after initiation of MHT as part of routine follow-up visits.

Treatment protocol

Menopausal status was determined by the treating gynecologist based on the patient's clinical history and menstrual status. MHT was prescribed and managed by gynecologists. Women with an intact uterus received estrogen–progestogen therapy (EPT), while those without a uterus received estrogen therapy (ET). No orthopedic interventions, NSAIDs, splinting, rehabilitation, or injections were administered during the study period.

For premenopausal women, a cyclic regimen was implemented in which the woman received transdermal estradiol (0.72 mg every other day) along with intermittent oral progestogen treatment consisting of either dydrogesterone (10 mg/day) or micronized progesterone (200 mg/day).

For postmenopausal women, continuous regimens were employed with two possible options: 1) transdermal estradiol (0.72 mg every other day) combined with continuous oral progestogen such as dydrogesterone (5 mg/day) or micronized progesterone (100 mg/day) or 2) twice-weekly application of a transdermal patch delivering 0.62 mg of estradiol and 2.7 mg of norethisterone acetate.

All participants continued MHT throughout the 12-month follow-up. When clinically indicated because of non-serious adverse events, the MHT regimen was adjusted at the discretion of the treating gynecologist.

DASH

The DASH score is a well-established patient-reported outcome measure that is used to assess functional limitations and symptoms of the upper extremity. It comprises 30 questions that cover physical activity and symptom burden in the arm, shoulder, and hand regions. Responses are rated on a 5-point Likert scale, and the composite score ranges from 0 to 100, with higher values indicating greater disability. DASH scoring is widely used in both clinical practice and research to quantify the effects of treatment of musculoskeletal disorders of the upper limb.¹²

SMI

The simplified menopausal index (SMI) is a 10-item self-administered scale that is commonly used in Japan to evaluate the severity of menopausal symptoms. It evaluates three main domains: vasomotor symptoms (e.g., hot flashes), somatic complaints (e.g., joint and muscle pain), and psychological disturbances (e.g., mood changes and irritability). A higher total SMI score reflects a greater burden of menopausal symptoms.¹³

SRQ-D

The Self-rating questionnaire for depression (SRQ-D) is a validated screening instrument that was developed to detect depressive symptoms in clinical populations. It includes 18 binary (yes/no) questions that assess the emotional, physical, and behavioral aspects of depression. Scores on the SRQ-D range from 0 to 18. A score of 10 or lower suggests no depressive

tendency, a score of 11 to 15 indicates borderline depression, and a score of 16 or higher suggests a clinically relevant level of depression. This questionnaire is frequently employed in Japanese clinical settings for the detection of masked depression, especially in primary care and psychosomatic contexts.¹⁴

Outcome measures

Outcome measures were assessed at baseline and at 3, 6, and 12 months after initiation of MHT. The primary outcomes were changes in upper-extremity function, assessed using the Disabilities of the Arm, Shoulder and Hand (DASH) score, and hand pain, assessed using a 100-mm visual analog scale (VAS). Since most participants experienced pain in multiple hand joints, they were instructed to rate the pain of the joint that was most painful at the time of assessment. Grip strength in the dominant and nondominant hands was evaluated as a secondary outcome. Grip strength was measured using a digital Smedley-type hand dynamometer. Participants stood with their arms naturally extended at their sides, and one measurement was obtained for each hand at each assessment.

Sample size

No a priori sample size calculations were performed for this retrospective study. All patients who received MHT for symptomatic HOA and completed a 12-month follow-up during the study period were included in the analysis. Of the 54 eligible women, 45 completed the one-year follow-up, corresponding to a dropout rate of 16.7%.

Statistical analysis

All statistical analyses were performed using JMP® Pro version 18 (SAS Institute, Cary, NC, USA). Changes in outcome measures (DASH score, VAS score, and grip strength) over time (baseline and at 3, 6, and 12 months) were analyzed using repeated-measures analysis of variance (ANOVA). The main effect of time was evaluated using a multivariate approach, which is robust to violations of the sphericity assumption.

Effect sizes were calculated using partial eta squared (partial η^2). When appropriate, pairwise comparisons between baseline and each follow-up time point were performed using paired t-tests. For changes from baseline to 12 months, mean changes and corresponding 95% confidence intervals (CIs) were calculated. A two-tailed p value < 0.05 was considered statistically significant.

MCIDs were defined as an improvement of ≥ 10 points in the DASH score and a reduction of ≥ 10 mm in the VAS score, on the basis of established thresholds for musculoskeletal conditions of the upper extremity.^{15,16}

Analyses were performed using a complete-case approach; only participants with complete 12-month outcome data were included in the final analyses. No multivariable adjustment for potential confounding was performed because of the retrospective observational design and the modest sample size.

Ethics

This study was reviewed and approved by the Ethics Committee of Kagoshima University (approval number: 190018). All procedures were conducted in accordance with the principles set forth in the Declaration of Helsinki and in accordance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects. Written informed consent was obtained from all participants.

Results

Participant flow and baseline characteristics

Of the 54 patients who initiated MHT, 45 completed the 12-month follow-up (83.3%) and were included in the final analysis. The baseline demographic and clinical characteristics of the participants are summarized in Table 1. The participants had a mean age of 51.8 years, and 23 (51.1%) were postmenopausal at baseline. The mean BMI was 22.6 ± 4.1 kg/m², which was within the normal range. The mean SMI score was 41.9 ± 20.4 , corresponding to moderate menopausal symptoms, and the mean SRQ-D score was 11.8 ± 6.6 , suggesting mild to moderate depressive symptoms. Forty-four patients (97.8%) received EPT, whereas one patient (2.2%) received ET.

Table 1. Baseline characteristics of the study participants (n=45).

Characteristic	Value
Age, years	51.8 ± 4.0
BMI, kg/m ²	22.6 ± 4.1
Postmenopausal women, n (%)	23 (51.1)
SMI score	41.9 ± 20.4
SRQ-D score	11.8 ± 6.6
MHT regimen, n (%)	
EPT	44 (97.8)
ET	1 (2.2)

Data are presented as mean ± SD or n (%). BMI, body mass index; SMI, Simplified Menopausal Index; SRQ-D, Self-Rating Questionnaire for Depression; MHT, menopausal hormone therapy; EPT, estrogen-progestogen therapy; ET, estrogen therapy.

Primary outcomes (DASH and VAS scores)

Repeated-measures analysis of variance demonstrated a significant main effect of time on both DASH and VAS scores (Table 2).

For upper-extremity function, a significant time effect was observed ($F(3, 36) = 12.33$, $p < 0.001$; partial $\eta^2 = 0.51$), indicating a large effect size. The mean DASH score decreased from 26.1 ± 14.3 at baseline to 17.3 ± 11.0 at 12 months (mean change, -8.8 points; 95% CI, -13.2 to -5.0). Although statistically significant, this change did not reach the predefined MCID threshold of ≥ 10 points at the group level.

For hand pain, a significant time effect was also observed ($F(3, 41) = 22.61$, $p < 0.001$; partial $\eta^2 = 0.62$), reflecting a very large effect size. The mean VAS score decreased from 56.8 ± 25.7 mm at baseline to 28.4 ± 20.7 mm at 12 months (mean change, -28.4 mm; 95% CI, -35.0 to -21.2), exceeding the predefined MCID threshold. Pairwise comparisons using paired t-tests demonstrated significantly lower DASH and VAS scores at all follow-up time points than at baseline. Exact post hoc p-values are provided in [Supplementary Table S2](#).

The largest reduction in DASH and VAS scores was observed at 3 months and were maintained throughout the 12-month follow-up. Although the mean DASH score increased slightly between 6 and 12 months both DASH and VAS scores remained significantly lower than at baseline. The longitudinal changes in DASH and VAS scores are illustrated in [Figure 2](#).

Grip strength

A significant main effect of time was observed for grip strength in both the dominant hand ($F(3, 41) = 9.58$, $p < 0.001$; partial $\eta^2 = 0.41$) and nondominant hand ($F(3, 41) = 8.22$, $p < 0.001$; partial $\eta^2 = 0.38$) (Table 2). Grip strength increased from 17.5 ± 6.3 kg at baseline to 20.7 ± 4.5 kg at 12 months in the dominant hand (mean change, $+3.2$ kg; 95% CI, $+1.65$ to $+4.33$) and from 16.8 ± 5.4 kg at baseline to 19.0 ± 4.8 kg at 12 months in the nondominant hand (mean change, $+2.2$ kg; 95% CI, $+1.09$ to $+3.26$). Pairwise comparisons using paired t-tests demonstrated significantly greater grip strength in the dominant hand at 3 and 12 months, but not at 6 months, whereas grip strength in the nondominant hand was significantly greater than baseline at all follow-up time points. Exact post hoc p-values are provided in [Supplementary Table S2](#).

Table 2. Changes in clinical outcomes over time and repeated-measures ANOVA results.

Outcome	Baseline	3 months	6 months	12 months	F (df1,df2)	p	Partial η^2
DASH	26.1 ± 14.3	15.4 ± 10.7	16.5 ± 13.2	17.3 ± 11.0	12.33 (3,36)	<0.001	0.51
VAS	56.8 ± 25.7	29.4 ± 25.2	27.4 ± 21.8	28.4 ± 20.7	22.61 (3,41)	<0.001	0.62
Grip (Dominant)	17.5 ± 6.3	19.0 ± 5.3	19.4 ± 6.5	20.7 ± 4.5	9.58 (3,41)	<0.001	0.41
Grip (Nondominant)	16.8 ± 5.4	18.9 ± 5.4	18.6 ± 4.9	19.0 ± 4.8	8.22 (3,41)	<0.001	0.38

Data are presented as mean ± SD. Changes over time were analyzed using repeated-measures analysis of variance (ANOVA). Pairwise comparisons between baseline and each follow-up time point were performed using paired t-tests. Mean changes with corresponding 95% confidence intervals and exact post hoc comparison results are presented in the Results section. Partial η^2 indicates effect size.

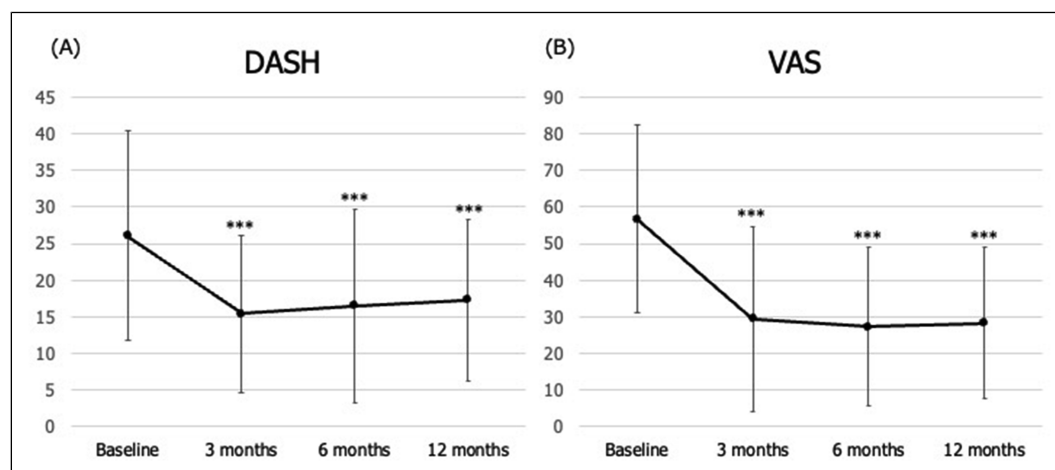


Figure 2. Longitudinal changes in DASH and VAS scores during the 12-month follow-up after initiation of MHT. (A) DASH scores showed improvement over time, with the greatest change observed at 3 months and maintained through 12 months. (B) VAS pain scores decreased over time and remained lower throughout the follow-up period. Data are presented as mean $\pm$ standard deviation (SD). Changes over time were analyzed using repeated-measures analysis of variance (ANOVA). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus baseline.

Safety outcomes

No serious adverse events, including venous thromboembolism, stroke, myocardial infarction, breast cancer, endometrial cancer, other malignancies, or death, were observed during the 12-month follow-up (Table 3). Abnormal uterine bleeding occurred in 20 patients (44.4%). In 16 patients, the abnormal uterine bleeding was transient and did not require modification of MHT, whereas four patients required a change in the route of MHT. Skin irritation related to the transdermal patch occurred in six patients (13.3%). One patient with skin irritation also experienced abnormal uterine bleeding, whereas another experienced concomitant breast discomfort. No gastrointestinal symptoms, edema, or other adverse events were observed. Overall, MHT regimen adjustment was required in 10 patients because of non-serious adverse events. All 45 patients completed the 12-month follow-up, and no patient discontinued MHT because of adverse events.

Table 3. Safety outcomes during the 12-month follow-up.

Safety outcome	n (%)	Management
Serious adverse events		
Venous thromboembolism	0	
Stroke	0	
Myocardial infarction	0	
Breast cancer	0	
Endometrial cancer	0	
Other malignancies	0	
Death	0	
Non-serious adverse events		
Abnormal uterine bleeding	20 (44.4)	Resolved without MHT modification: 16; MHT route changed: 4*
Skin irritation due to transdermal patch	6 (13.3)	MHT route changed: 6†
Breast discomfort	1 (2.2)	Concomitant with transdermal patch-related skin irritation
Gastrointestinal symptoms	0	
Edema	0	
Other adverse events	0	

Data are presented as n (%). MHT, menopausal hormone therapy. All 45 patients completed the 12-month follow-up, and no patient discontinued MHT because of adverse events.

*Includes one patient who also experienced transdermal patch-related skin irritation.

†Includes one patient who also experienced breast discomfort and one patient who also experienced abnormal uterine bleeding.

Discussion

This study evaluated the 12-month clinical outcomes of MHT in perimenopausal women with symptomatic HOA. Statistically significant improvements in hand pain and upper extremity function were observed and maintained over the 12-month follow-up. Importantly, the mean reduction in pain exceeded the reported MCID, suggesting a clinically meaningful benefit at the group level. However, this finding should be interpreted with caution because MCID thresholds are primarily intended for interpretation at the individual patient level, and group mean changes may obscure variability in treatment response.

These findings extend our previous short-term results, which showed greater improvements in hand pain and function among women receiving MHT than among those receiving CAM over a 3-month period.⁹ The present study represents an extension of this previous work, evaluating the 12-month outcomes of patients who initiated MHT in the previously reported cohort. The present study suggests that the improvements in pain observed after initiation of MHT were maintained over the 12-month follow-up.

The observed discrepancy between the robust pain reduction and the more modest functional gains that were observed may reflect the multidimensional nature of upper extremity function. Functional outcomes such as the DASH score are influenced by behavioral adaptation, muscle conditioning, occupational demands, and psychological factors. In contrast, pain intensity—as captured by the VAS—may respond more directly to hormonal modulation and to alterations in central pain processing pathways.

Estrogen exerts biological effects on musculoskeletal pain through both peripheral and central mechanisms. At the joint level, estrogen suppresses the expression of cartilage-degrading enzymes such as matrix metalloproteinase (MMP)-3 and MMP-13, modulates the production of inflammatory cytokines via the nuclear factor-kappa B signaling, and reduces oxidative stress by attenuating the production of reactive oxygen species.^{17–20} Centrally, estrogen modulates pain processing through effects on monoaminergic and opioid neurotransmission and may attenuate central sensitization by influencing descending inhibitory pain pathways. Previous studies have suggested that declining estrogen levels during menopause may impair endogenous pain modulation and increase pain sensitivity, which may partially explain the symptom exacerbation observed in perimenopausal women.^{21–24}

From a clinical perspective, current management strategies for HOA largely mirror those for other subtypes of osteoarthritis and include orthoses, exercise-based therapy, topical or oral NSAIDs, and—in selected cases—intra-articular injection of corticosteroids. International guidelines such as the EULAR recommendations and the ACR/Arthritis Foundation guidelines acknowledge these interventions; however, many recommendations are conditional, and the overall magnitude of the benefit they confer is often modest, with supporting evidence of variable quality.^{5,6} For patients with symptomatic HOA, durable long-term improvement and disease-modifying strategies remain limited.

In perimenopausal women, the onset of symptoms and their exacerbation may be closely linked to decreased estrogen levels. Therefore, integrating gynecologic management, including MHT, with conventional orthopedic care may represent a pathophysiology-oriented treatment strategy for appropriately selected patients. Rather than replacing established orthopedic interventions, hormone-based therapy may complement existing treatments following careful assessment of individual risks and benefits.

Although non-serious adverse events, particularly abnormal uterine bleeding and transdermal patch-related skin irritation, were observed, no serious adverse events occurred during the 12-month follow-up, and no patient discontinued MHT because of adverse events. Most episodes of abnormal uterine bleeding were transient and resolved without modification of MHT, whereas persistent bleeding and patch-related skin irritation were successfully managed by adjustment of the MHT regimen. These observations suggest that close collaboration between orthopedic surgeons and gynecologists may facilitate appropriate management of non-serious adverse events while allowing continuation of MHT.

Another consideration is that the observed improvements may have been influenced not only by the direct biological effects of estrogen on joint tissues and pain processing but also by improvements in menopausal symptoms and psychological well-being. MHT is known to alleviate vasomotor and other menopausal symptoms, which may indirectly improve pain perception, physical activity, and patient-reported outcomes. Therefore, the observed associations cannot be attributed solely to direct effects of MHT on hand osteoarthritis.

These findings highlight the potential value of interdisciplinary collaboration between orthopedic surgeons and gynecologists in the management of appropriately selected perimenopausal women presenting with symptomatic HOA. However, whether such collaboration improves long-term clinical outcomes warrants confirmation in future controlled prospective studies.

The limited functional improvement observed at the group level may reflect heterogeneity in treatment response. It is possible that some patients achieved clinically meaningful functional improvement, whereas others predominantly experienced pain relief. Future studies should identify predictors of treatment response, including menopausal stage, baseline

symptom severity, psychosocial factors, inflammatory biomarkers, and radiographic disease severity, to determine which patients are most likely to benefit from MHT.

Limitations

This study has several limitations. First, its retrospective single-arm design without a concurrent control group limits causal inference regarding the observed clinical improvements. Furthermore, placebo effects and regression to the mean cannot be excluded. Although a comparison with CAM would have been desirable, many women who experienced insufficient symptom relief with CAM subsequently transitioned to MHT in routine clinical practice. Consequently, an adequate comparator cohort with long-term follow-up was not available. While this reflects real-world treatment patterns, it limits direct comparisons between treatment strategies.

Second, we did not adjust for potential confounding factors, including menopausal status, body mass index, depressive symptoms, or occupational hand use. Therefore, residual confounding cannot be excluded and may have influenced the observed associations. In addition, subgroup analyses according to MHT regimen were not performed because only one participant received estrogen therapy, precluding meaningful comparisons between treatment regimens.

Third, the sample size was modest, and all participants were Japanese women, which may restrict the generalizability of the results.

Fourth, longitudinal radiographic assessment was not performed because the primary objective of this study was to evaluate clinical outcomes in women with symptomatic HOA. Therefore, the effects of MHT on structural disease progression could not be determined.

Prospective controlled studies with larger and more diverse populations, incorporating both clinical and structural outcome measures, are warranted to further clarify the long-term clinical effectiveness of MHT for symptomatic HOA.

Despite these limitations, our findings provide preliminary evidence that MHT may provide sustained clinical benefits with acceptable tolerability in appropriately selected perimenopausal women with symptomatic HOA.

Conclusions

In this retrospective single-arm study, improvements in hand pain following initiation of MHT were maintained over 12 months in perimenopausal women with symptomatic HOA. Although functional improvement was more modest, these findings suggest that MHT may represent an adjunctive treatment option for appropriately selected patients. Further controlled prospective studies are warranted to establish causality and to determine the long-term clinical effectiveness of MHT.

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Ethical considerations

This study was reviewed and approved by the Ethics Committee of Kagoshima University (approval number: 190018). All procedures were conducted in accordance with the principles set forth in the Declaration of Helsinki and in accordance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects. Written informed consent was obtained from all participants.

Author contributions

Hiromi Sasaki: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. Mika Sakihama: Data curation, Investigation. Hiroyuki Tominaga: Methodology, Writing – review & editing. Shinichi Togami: Writing – review & editing. Noboru Taniguchi: Supervision, Writing – review & editing

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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

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