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BRIEF REPORT

Finger Joint Cartilage Evaluated by Semiquantitative Ultrasound Score in Patients With Rheumatoid Arthritis

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Objective. Joint destruction in rheumatoid arthritis (RA) includes both bone and cartilage lesions. Since joint space narrowing (JSN) is not a direct evaluation of cartilage using radiography, we aimed to examine the validity of ultrasound (US) cartilage evaluation using a semiquantitative method in patients with RA.

Methods. We enrolled 103 patients with RA who were in remission or showing low disease activity and 42 healthy subjects. The cartilage thickness of the bilateral metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the second to fifth fingers was measured by US, and the recorded images were scored semiquantitatively using a scale of 0–2. In addition, the JSN of the corresponding joints was scored using a hand radiograph. The relationships between total cartilage thickness, its semiquantitative score, and JSN score were assessed using Spearman's rank correlation coefficients.

Results. Total cartilage thickness was significantly thinner in patients with RA compared to healthy subjects for both the MCP and PIP joints (both $P < 0.001$). The semiquantitative sum of 16 joints ranged from 2 to 26 (median 8) in patients with RA, which was significantly greater than the 0–11 (median 4) in healthy subjects ($P < 0.001$). In patients with RA, the semiquantitative score showed a significant negative correlation with cartilage thickness ($\rho = -0.64$, $P < 0.001$) and a significant positive correlation with JSN score ($\rho = 0.66$, $P < 0.001$). Furthermore, these scores showed a significant correlation with RA disease duration.

Conclusion. A simplified and direct evaluation of finger joint cartilage damage by semiquantitative US score is valid and useful for patients with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that mainly affects the peripheral joints, resulting in irreversible and disabling damage to the bone and cartilaginous tissues. Radiographic examination has been the gold standard for evaluating joint destruction, and particularly bone erosion and joint space narrowing (JSN), which are important indices of bone and cartilage destruction, respectively. Radiographic examination is based on the semiquantitative Sharp method and its modified score (1), and these are used widely as measures of joint destruction. Joint destruction leads to functional disability, in which JSN is more crucial than bone erosion (2).

JSN is an indirect means of evaluation of cartilage destruction because radiographs are transmitted through the cartilage. Joint subluxation, for example, is scored as 3 for JSN irrespective of the degree of cartilage damage. For that reason, magnetic resonance imaging and ultrasonography (US) may be used for the direct evaluation of cartilage. US-measured thickness of joint cartilage is

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SIGNIFICANCE & INNOVATIONS

- In patients with rheumatoid arthritis (RA), the semiquantitative ultrasound (US) score showed a significant negative correlation with cartilage thickness and a significant positive correlation with joint space narrowing score, and all of those scores showed a significant correlation with RA disease duration.
- This is the first study demonstrating that a simplified and direct evaluation of finger joint cartilage damage by semiquantitative US score is valid and useful for patients with RA.

closely related to its actual anatomic thickness (3). However, the measurement of cartilage thickness for each joint is not feasible in clinical trials or daily clinical practice.

Semiquantitative methods such as those that measure bone erosion and JSN in radiograph examinations and gray-scale and power Doppler US evaluations have been widely accepted in clinical trials and practice because their findings are known to correlate with quantitative evaluation of structural damage (radiograph and US gray scale) or severity of synovitis (US, especially power Doppler). Although the use of a semiquantitative method for US cartilage evaluation in RA has been proposed, its correlation with cartilage thickness and its clinical significance have not been clarified (4,5). Therefore, we examined the validity of US cartilage evaluation by performing a cross-sectional study of the use of a semiquantitative method in evaluating RA patients in remission or with low disease activity.

SUBJECTS AND METHODS

Patients and healthy subjects. Patients with RA who visited Toho University Ohashi Medical Center between September 2011 and July 2015 were considered for inclusion in this study. We enrolled patients who met all of the following criteria: 1) those with a 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) and/or 1987 ACR classification for RA (6,7); 2) those with complete US examinations of bilateral finger joint cartilage; 3) those with conventional radiographs of each hand and wrist in the standard posteroanterior projection within 3 months of the US examination; and 4) those in remission or with low disease activity defined by the Disease Activity Score in 28 joints using the C-reactive protein (CRP) level (DAS28-CRP) at the time of US evaluation (to avoid the significant influence of intense synovitis on the joint images and disability assessment). Healthy subjects were screened for history and clinical evidence of joint disease alone. No blood or radiographic tests were performed. Those with obvious osteoarthritis (OA) determined by clinical examination were excluded. The study protocol was approved by the Ethics Committee of the Toho University Ohashi Medical Center (project approval number H18016), and informed consent was obtained from all the participants.

Clinical assessments. We obtained the following medical information from medical records: age, sex, height, weight, disease duration from the onset of symptoms to US examination, patient global assessment of disease activity as measured by a 100-mm visual analog scale, results from the Health Assessment Questionnaire disability index (HAQ DI), physician-based assessment of the presence of tenderness and swelling in 28 joints, serum levels of CRP, rheumatoid factor, anti–cyclic citrullinated peptide antibody and matrix metalloproteinase-3 (MMP-3), and treatment for RA. The JSN of US-examined joints was scored in a blinded manner using the modified Sharp/van der Heijde method with a hand radiograph obtained within 3 months of US examination.

US examination. A Xario (Canon Medical Systems) US machine equipped with a multifrequency linear array probe (7–14 MHz) was used (8,9). The US examination was performed according to EULAR guidelines for musculoskeletal US in rheumatology (10,11) by 1 of 3 rheumatologists (TO, AH, or NH). All rheumatologists were board certified as ultrasonographers by the Japan College of Rheumatology, and they were blinded to patients' radiograph findings. Bilateral second to fifth metacarpophalangeal (MCP) and second to fifth proximal interphalangeal (PIP) joints were examined. The cartilage layers of the metacarpal heads and proximal phalangeal heads at the MCP and PIP joints were visualized from a longitudinal dorsal view at their midportions, with the joints placed in ~90 degrees flexion (12). The probe was placed such that the US beam was orthogonal to the cartilage. Static US images of all joints were saved as Digital Imaging and Communication in Medicine (DICOM) images. Cartilage thickness was measured using OsiriX software (Pixmeo) with an Apple OS X operating system by calculating the pixel counts on DICOM images.

Cartilage thickness was measured from the base of the cartilage to the interface artefact at the cartilage surface (outer margins). The outer margins were determined by creating a linear region of interest orthogonal to the cartilage, with reference to the plot graph of distance and brightness shown in 8-bit gray scale (256 gradations from 0 to 255). Since the evaluation was of a semiquantitative method, the cartilage measurement was not corrected for the increased speed of sound within it. Furthermore, one US examiner (TO) who was blinded to other medical information performed the semiquantitative scoring of the recorded cartilage images using a scale of 0–2 (0 = normal, 1 = minimal, and 2 = severe) (5) (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24101/abstract).

Intraobserver reliability of the semiquantitative scoring was examined (by TO) using the recorded US findings of 14 randomly selected patients (total of 224 joints) at an interval of >6 months.

Table 1. Demographic and clinical features and the ultrasound-measured joint cartilage thickness and semiquantitative score*

	Patients with RA (n = 103)	Healthy subjects (n = 42)	*P*
Female sex	79 (77)	36 (86)	0.265
Age, median (IQR) years	65 (53–73)	63 (45–70)	0.065
Disease duration, median (IQR) years	5.8 (2.8–11.0)	–	–
Height, median (IQR) cm	158 (153–165)	158 (154–162)	0.526
Weight, median (IQR) kg	53 (47–60)	54 (49–60)	0.535
BMI, median (IQR)	21.0 (19.2–23.2)	21.9 (19.7–23.6)	0.221
DAS28-CRP, median (IQR)	1.71 (1.35–2.23)	–	–
HAQ DI score, median (IQR)	0.1 (0.0–0.4)†	–	–
JSN score, median (IQR)	11 (7–17)	–	–
Subluxation on radiograph	26 (25)	–	–
CRP, median (IQR) mg/dl	0.05 (0.02–0.14)	–	–
RF positive‡	79 (77)	–	–
Anti-CCP positive‡	88 (86)	–	–
MMP-3 high§	28 (27)	–	–
Treatments			
Glucocorticoids	11 (11)	–	–
PSL equivalent dosage, median (IQR) mg/day¶	3 (2–5)	–	–
MTX	68 (66)	–	–
MTX dosage, median (IQR) mg/week¶	10 (7–12.5)	–	–
bDMARDs	28 (27)	–	–
Cartilage thickness, median (IQR) mm			
MCP#	0.5 (0.0–1.0)	0.6 (0.3–1.2)	<0.001
PIP#	0.3 (0.0–0.6)	0.4 (0.2–0.8)	<0.001
Total**	6.9 (4.0–9.4)	7.5 (5.9–9.2)	0.001
Total semiquantitative score, median (IQR)	8 (2–16)	4 (0–11)	<0.001
MCP semiquantitative			
Grade 0	406 (49)	232 (69)	
Grade 1	347 (42)	103 (31)	<0.001
Grade 2	71 (9)	1 (0)	
PIP semiquantitative			
Grade 0	494 (60)	239 (71)	
Grade 1	287 (35)	97 (29)	<0.001
Grade 2	43 (5)	0 (0)	

* Values are the number (%) unless indicated otherwise. A Fisher's exact test or Mann-Whitney U test was used for group comparisons. Anti-CCP = anti–cyclic citrullinated peptide; bDMARDs = biologic disease-modifying antirheumatic drugs; BMI = body mass index; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein (CRP) level; HAQ DI = Health Assessment Questionnaire disability index; IQR = interquartile range; IU = international units; JSN = joint space narrowing; MCP = metacarpophalangeal joint; MMP-3 = matrix metalloproteinase-3; MTX = methotrexate; PIP = proximal interphalangeal joint; PSL = prednisolone; RA = rheumatoid arthritis; RF = rheumatoid factor.
† HAQ DI data were not obtained from 2 patients with RA (n = 101).
‡ RF positive: >15 IU/ml; anti-CCP positive: ≥4.5 U/ml. Data on RF and anti-CCP were not obtained from 1 patient with RA (n = 102).
§ MMP-3 positive: female >59.7 ng/ml; male >121.0 ng/ml.
¶ Dose among patients receiving PSL and MTX (excluding nonusers).
# The number of joints was 824 for patients with RA and 336 for healthy subjects.
** Sum of 16 joints.

Interobserver reliability between 2 sonographers (TO and AH) and 1 rheumatologist (CI) who did not perform US was evaluated with the same set of images from 14 randomly selected patients.

Statistical analysis. Statistical analysis was performed using EZR software, version 1.37 (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R, version 3.4.1 (R Foundation). Continuous variables were summarized using medians and interquartile ranges and analyzed using the Mann-Whitney U test, while binominal data from the 2 groups were examined with Fisher's exact test. The relationships among the continuous variables were assessed using Spearman's rank correlation coefficient. Relationships between patient characteristics and each method were adjusted for multiple comparisons using an adaptive Benjamini-Hochberg procedure to control for false discovery rates. Intraobserver and interobserver reliability was determined using Krippendorff's α coefficient with bootstrap samples. The Krippendorff's α coefficient was calculated using the KALPHA macro in SPSS, version 22.0 and was interpreted as follows: <0.0 = poor; 0–0.20 = slight; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = substantial; and 0.81–1.0 = almost perfect agreement. *P* values less than 0.05 were considered significant.

RESULTS

Patient characteristics. A total of 103 patients with RA and 42 healthy subjects were enrolled in this study. Demographic, clinical, and laboratory characteristics are shown in Table 1. There was no significant difference between patients with RA and healthy subjects with regard to sex, age, height, and weight. The median DAS28-CRP score in patients with RA was 1.71. The majority (77.7%) of the patients were in remission (DAS28-CRP score <2.3), and the remaining 23 patients had low disease activity.

Measurement of cartilage thickness. A total of 2,320 joints were evaluated, with 1,160 MCP joints and 1,160 PIP joints evaluated. The measurement of cartilage thickness by US in single MCP joints varied between 0.0 and 1.0 mm (median 0.5 mm) in patients with RA and between 0.3 and 1.2 mm (median 0.6 mm) in healthy subjects (Table 1). The cartilage thickness in single PIP joints varied between 0.0 and 0.6 mm (median 0.3 mm) in patients with RA and between 0.2 and 0.8 mm (median 0.4 mm) in healthy subjects. The sum of 16 joints ranged from 4.0 to 9.4 mm (median 6.9 mm) in RA patients and 5.9 to 9.2 mm (median 7.5 mm) in healthy subjects (data not shown in Table 1). As a result, cartilage thickness in RA patients was significantly thinner than that in healthy subjects ($P < 0.001$ for MCP; $P < 0.001$ for PIP, and $P = 0.001$ for sum of 16 joints).

Semiquantitative US finger cartilage score. In contrast, semiquantitative US scores in single MCP joints varied between 0 and 2 (median 1) in RA patients and between 0 and 2 (median 0) in healthy subjects. Semiquantitative scores in single PIP joints varied between 0 and 2 (median 0) in RA patients and between 0 and 1 (median 0) in healthy subjects. The sum of 16 joints ranged from 2 to 26 (median 8) in RA patients and 0 to 11 (median 4) in healthy subjects. Semiquantitative scores in RA patients were significantly higher than those in healthy subjects ($P < 0.001$ for sum of 16 joints).

With regard to MCP joints in patients with RA and healthy subjects, the rates of grade 0, grade 1, and grade 2 scores were 49% versus 69%, 42% versus 31%, and 9% versus 0.3%, respectively. With regard to PIP joints in patients with RA and healthy subjects, the rates of grade 0, grade 1, and grade 2 scores were 60% versus 71%, 35% versus 29%, and 5% versus 0%, respectively. Thus, patients with RA showed significantly higher scores compared to healthy subjects with regard to finger joints.

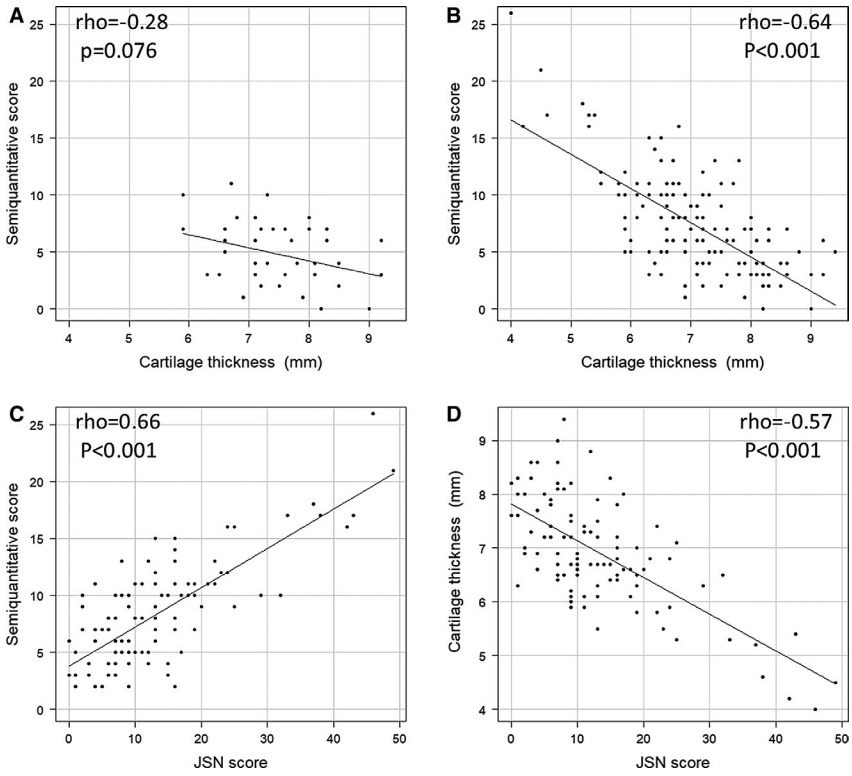

Figure 1. Relationship between semiquantitative score, cartilage thickness, and joint space narrowing (JSN) score. The correlation was assessed using Spearman's rank correlation coefficient (rho). **A**, Relationship between total semiquantitative score and measurement of cartilage thickness in healthy subjects. **B**, Relationship between total semiquantitative score and measurement of cartilage thickness in patients with rheumatoid arthritis (RA). **C**, Relationship between total semiquantitative score and JSN score in patients with RA. **D**, Relationship between measurement of cartilage thickness and JSN score in patients with RA. Dots represent the scores of each patient; lines indicate least-squares regression lines.

Relationship between the 3 methods. We compared the total semiquantitative scores with total measurement of cartilage thickness and total JSN score for the 16 joints evaluated. In healthy subjects, semiquantitative scores failed to show a significant correlation (ρ = –0.28, P = 0.076) with cartilage thickness (Figure 1A). On the other hand, in patients with RA, semiquantitative scores showed a significant negative correlation with cartilage thickness (ρ = –0.64, P < 0.001), as well as a significant positive correlation with JSN scores (ρ = 0.66, P < 0.001) (Figures 1B and C). The correlation between cartilage thickness and JSN score was also significant (ρ = –0.57, P < 0.001) (Figure 1D). Furthermore, comparable correlations among measurements were observed in separate analyses for MCP and PIP joints (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24101/abstract).

In addition, in patients with RA, the correlation between the MCP and PIP joints was significant for all 3 methods (semiquantitative score ρ = 0.40, P < 0.001; cartilage thickness ρ = 0.35, P < 0.001; and JSN score ρ = 0.48, P < 0.001). In healthy subjects, the correlation between the MCP and PIP joints was significant for US methods (semiquantitative score ρ = 0.45, P = 0.003, and cartilage thickness ρ = 0.32, P = 0.042).

Relationship between patient characteristics and scores. Finally, we examined the relationship between patient characteristics and semiquantitative scores, cartilage thickness, and JSN scores. These scores showed a significant correlation with disease duration (Table 2). Interestingly, a significant correlation between all 3 scores was observed for MCP joints but not for PIP joints. Furthermore, we compared the sum of the semiquantitative scores, cartilage thickness, and JSN scores in patients who were positive and negative for specific laboratory tests and treatments, and we did not observe any significant associations (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24101/abstract). In addition, in healthy subjects, semiquantitative score but not cartilage thickness was significantly correlated with age (ρ = 0.50, P = 0.005, and ρ = –0.25, P = 0.252, respectively).

Intraobserver and interobserver reliability. Intraobserver reliability for grading of semiquantitative scores using static images was almost perfect (coefficient 0.81 [95% confidence interval (95% CI) 0.71–0.89]), and interobserver reliability was moderately reliable (coefficient 0.60 [95% CI 0.48–0.72]).

DISCUSSION

The current study is the first to evaluate cartilage using an US semiquantitative method and to compare this method to measurements of cartilage thickness and radiographic JSN scores in patients with RA. The semiquantitative method demonstrated a favorable correlation with both cartilage thickness and JSN, and all the above methods showed a correlation with RA disease duration except for PIP joints. However, there was no significant correlation between the semiquantitative score and cartilage thickness in healthy subjects (P = 0.076), possibly owing to the limited individual differences in cartilage thickness as well as the relatively smaller sample size of healthy subjects (Figure 1A).

In clinical practice, cartilage evaluation for RA with use of US has been limited to measurement of cartilage thickness. Cartilage thickness evaluated using US and JSN scores indicated a good correlation (correlation coefficient –0.64), as previously reported (3,13). However, the measurement of cartilage thickness is time consuming and complicated, so it is not feasible in daily practice or in clinical trials. On the other hand, semiquantitative cartilage evaluation using US is a noninvasive method that can be applied and repeated in most patients.

For semiquantitative evaluation of RA finger joint cartilage, the 5-grade evaluation (grades 0–4) reported by Filippucci et al (4) and the 3-grade evaluation (grades 0–2) reported by the EULAR-Outcome Measures in Rheumatology (OMERACT) group (5) are currently available. In the current study, we used the 3-grade evaluation advocated by the EULAR-OMERACT group because of its favorable feasibility. Furthermore, EULAR-OMERACT semiquantitative evaluation has shown a substantial or moderate correlation with thickness measurements and JSN scores. Since a correlation was observed with disease duration, a longitudinal follow-up of the progression of cartilage damage using semiquantitative evaluation methods shows promise.

The differences between MCP and PIP joints were shared among the evaluation methods. The correlation between cartilage damage and disease duration found for MCP joints, but not PIP joints, can be partly explained by technical difficulties and the influence of OA comorbidity in PIP joints.

This study had several limitations. First, as this was a cross-sectional study, we could not evaluate particular relationships, such as the relationship between laboratory findings and treatments. In particular, previous studies have reported a relationship between high MMP-3 titers and JSN progression because MMP-3 breaks down macromolecules in the extracellular matrix of cartilage (14). However, owing to the cross-sectional design of our study, we could not demonstrate a similar association between high MMP-3 levels, cartilage thickness, and JSN score. Second, although the relationship between the US grading of cartilage and histologic grading has also been shown in previous studies with OA and RA patients (15,16), the relationship between pathologic changes and semiquantitative US scores has not been clarified. Third, a lack of sharpness of the cartilage margin on US has been seen with the degeneration of cartilage, even in patients with early OA (17). Therefore, the influence of OA on the US semiquantitative score should be further examined.

Table 2. Relationship between patient characteristics, semiquantitative score, cartilage thickness, and joint space narrowing (JSN) score in the metacarpophalangeal joint (MCP), proximal interphalangeal joint (PIP), and total joints*

	Semiquantitative score						Cartilage thickness						JSN score					
	MCP ρ	MCP *P*	PIP ρ	PIP *P*	Total ρ	Total *P*	MCP ρ	MCP *P*	PIP ρ	PIP *P*	Total ρ	Total *P*	MCP ρ	MCP *P*	PIP ρ	PIP *P*	Total ρ	Total *P*
Age	0.22	0.064	0.12	0.398	0.16	0.185	−0.10	0.489	−0.02	0.868	−0.08	0.578	0.14	0.280	0.14	0.280	0.17	0.176
Height	−0.19	0.124	−0.06	0.647	−0.14	0.300	0.26	0.021	0.12	0.362	0.22	0.063	−0.07	0.603	−0.07	0.593	−0.08	0.578
Weight	−0.07	0.593	0.03	0.860	−0.03	0.815	0.16	0.185	0.04	0.773	0.12	0.382	−0.08	0.558	0.01	0.916	−0.04	0.797
BMI	0.00	0.967	0.06	0.654	0.03	0.860	0.07	0.616	0.00	0.967	0.04	0.754	−0.09	0.513	0.05	0.732	−0.02	0.906
Disease duration	0.40	<0.001	0.13	0.308	0.34	0.002	−0.36	0.001	−0.18	0.150	−0.32	0.003	0.28	0.010	0.19	0.115	0.27	0.016
DAS28-CRP	0.17	0.163	−0.08	0.569	0.05	0.685	−0.20	0.107	0.18	0.131	−0.07	0.593	0.09	0.505	0.10	0.494	0.12	0.382
HAQ DI	0.19	0.131	−0.09	0.505	0.08	0.569	−0.17	0.176	0.08	0.554	−0.09	0.505	0.11	0.437	−0.02	0.910	0.07	0.609

* The correlation was assessed using Spearman's rank correlation coefficient (ρ), and *P* values were adjusted using the Benjamini-Hochberg procedure. BMI = body mass index; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; HAQ DI = Health Assessment Questionnaire disability index.

Despite the above limitations, US evaluation of joint cartilage seems to be highly sensitive because 30% of evaluated joints of healthy subjects were graded as score 1. In conclusion, a simplified and direct evaluation of finger joint cartilage damage by semiquantitative US score is valid and useful in patients with RA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Kameda had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ROLE OF THE STUDY SPONSOR

Eisai had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Eisai.

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