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ORIGINAL ARTICLE

The Association of Ischemia Modified Albumin with Osteoarthritis Progression

Kenan Ozler [1], Ozcan Erel [2], Oguzhan Gokalp [1], Gamze Avcioglu [2], Salim Neselioglu [2]

[1] *Department of Orthopedics, Konya Beysehir State Hospital, Konya, Turkey*
[2] *Department of Medical Biochemistry, Ankara Yildirim Beyazit University Faculty of Medicine, Ankara, Turkey*

SUMMARY

Background: **We suggested a relationship between increased serum IMA (ischemia-modified albumin) levels and cartilage degeneration. We proposed that the increased serum levels of IMA was due to the oxidative stress mechanism against ongoing cartilage degeneration in osteoarthritis (OA) and thus may be associated with the progression of OA. We aimed to investigate serum IMA levels in OA patients and determine whether any changes in IMA levels are useful as a marker in increased OA.**
Methods: **A prospective case-control study was carried out, which included 110 patients (55 patients with OA and 55 healthy controls). Serum samples obtained from all participants and IMA levels were determined by spectrophotometric method.**
Results: **Compared with controls, OA had significantly higher IMA and IMA/albumin (IMAR) levels (0.732 ± 0.078 vs. 0.773 ± 0.080, p = 0.008; 0.188 ± 0.20 vs. 0.176 ± 0.21; p = 0.011). Multivariable logistic regression analysis revealed rising IMA and IMAR levels were independently associated with OA (OR: 1.755, 95% CI: 0.655 - 4.700, p = 0.009 and OR = 3.021, 95% CI: 0.258 - 3.525, p = 0.015).**
Conclusions: **The current study suggests that increased levels of IMA are associated with OA and are a probable predictive risk marker for the progression of OA.**
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Correspondence:
Kenan Ozler
Konya Beysehir State Hospital
Konya
Turkey
Phone: +90 545 7977727
Email: kenozler@hotmail.com
Orcid: 0000-0002-4992-5245

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KEY WORDS

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INTRODUCTION

Osteoarthritis (OA) is a chronic disability disease characterized by cartilage degeneration, osteophytes, subchondral cysts, and joint space narrowing in the aged [1]. At present, the prevalence of knee OA is increasing with the effect of rising numbers of older people, sedentary life, and obesity [2]. The precise underlying mechanism is unknown, but various factors have been suggested, such as mechanical injury, oxidative changes, pro-inflammatory cytokines, and proteases [3]. OA contains several clinical features such as knee pain, stiffness, and restriction of joint movements [4]. Articular

cartilage degeneration is further increased as OA progresses. As a result of mechanical factors and aging, oxidative stress and the synthesis and release of proinflammatory cytokines and proteases are increased. Thus, the structure and function of the extracellular matrix deteriorates which affects the structure of cartilage and cartilage degeneration progresses [5].
Human serum albumin is bound to various metals, bilirubin, hormones, fatty acids both reversibly and/or ireversibly. In particular, the N-terminal region of albumin provides linkages with metals such as cobalt (Co), copper (Cu), and nickel (Ni) [6]. In oxidative stress conditions such as ischemia, hypoxia, and acidosis, the binding rate of metals to albumin is reduced, and this modification of serum albumin is called ischemia-modified albumin (IMA) [7]. IMA, reactive oxygen species (ROS) are thought to be caused by the deterioration of the extracellular matrix of the cartilage and as a result of cartilage degeneration and progression of OA [8,9]. IMA occurs by the binding of free oxygen radicals to albumin after an injury to ischemia and/or oxidative stress-related in tissues [10,11]. Also, IMA is known as an early marker for myocardial ischemia and is used to monitor the progression of infarction [12-14]. Also, IMA increase in several diseases, such as preeclampsia, pulmonary embolism, systemic sclerosis, diabetes mellitus, cirrhosis, and trauma [15-18]. It is known that oxidative stress has proven effects in the pathophysiology of all these diseases. Oxidative stress has also been shown to increase inflammation and proteases in cartilage degeneration, synovial fluid, and ECM of cartilage in osteoarthritis [5]. Although the IMA level is increased in acute and chronic diseases, its role is not obvious in the diagnosis and progression of osteoarthritis disease.
In the current study, we aimed to investigate serum IMA levels in osteoarthritic patients and determine whether any changes in IMA levels are useful as a marker in increased osteoarthritis.

MATERIALS AND METHODS

Study population

A prospective study was carried out between August and November 2018. One hundred and ten patients were recruited consecutively from the Orthopedics Department of Beysehir State Hospital. Fifty-five patients were OA and fifty-five were the control group. The diagnosis of OA was made according to the Kellgren-Lawrence (K&L) scale and required the presence of all five radiological criteria: osteophytes on the joint margins, periarticular ossicles, joint space narrowing (JSN), small pseudocystic areas in the subchondral bone and tips [19]. Fifty-five age and body mass index (BMI) matched non-osteoarthritis subjects were also recruited as a control group. The Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Score was used to determine the knee functions of patients with osteoarthritis. The WOMAC score addressed three groups of questions: pain, stiffness, and functional disorder, and a total of 24 questions were asked to the groups. One of five answers for each question was accepted: none, mild, moderate, severe, and extreme. WOMAC pain score range was 0 - 20, WOMAC stiffness range was 0 - 8, and WOMAC functional impairment range was 0 - 68 [20]. The local Ethical Committee approved the study protocol, and written informed consent was obtained from all participants.
Only patients with primary osteoarthritis were included. Exclusion criteria for all participants included: systemic or local infectious diseases, history of total knee arthroplasty or open knee surgery, overweight, bone tumours, fractures, taking local or systemic treatments such as steroids, hyaluronic acid, platelet-rich plasma (PRP), chemotherapy and/or radiotherapy, chronic diseases (diabetes mellitus, hypertension, immune system diseases).

Clinical assessment and biochemical analysis

All participants were evaluated when they first applied to the outpatient clinic of the hospital. BMI was calculated in kilograms/square meter (kg/m^2). Clinical examination was performed, previous medical history and WOMAC score were recorded. Blood samples were obtained by venipuncture for evaluation of ischemia modified albumin (IMA) and albumin levels.
IMA was analyzed using the rapid and quantitative chemical analysis technique. In brief, the methodology involved the addition of 200 μL of patient's blood serum and 50 μL of 1 g/L cobalt chloride solution, followed by vigorous mixture and a 10-minute incubation in the dark, after which 50 μL of 1.5 mg/mL dithiothreitol (DTT) was added as a coloring agent. After 2 minutes of incubation, 1.0 mL of a 9 g/L solution of NaCL was added. The absorbance of assay mixture was read at 470 nm with using an automated Spectrophotometer analyzer (Cobas 501; Roche Diagnostics, Mannheim, Germany). The blank was similarly prepared, however, with the exclusion of DTT. The results are expressed in Absorbance Serum Unit (ABSU) and IMA/albumin (IMAR) ABSU*L/mmol level was calculated [21].
Serum albumin levels were measured in a calibrated and well-controlled autoanalyzer using the bromocresol green method (Architect Plus C8000, Abbott, USA). Hematology and biochemistry parameters were measured with the use of an ADVIA Centaur CP Immunoassay System (SIEMENS). The following reference ranges were used for serum vitamin D, calcium, phosphorus, iron, hemoglobin, sodium, potassium and chlorine levels (Vitamin D [9.5 - 39.6 nmol/L], calcium [8.2 - 10.2 nmol/L], phosphorus [2.5 - 5 nmol/L], iron [50 - 170 μmol/L], hemoglobin [11 - 18 g/L], sodium [135 - 145 mmol/L], potassium [3.5 - 5.1 mmol/L] and chlorine [96 - 111 mmol/L]).

Statistical analysis

Data analysis was performed by using SPSS version 22 (IBM SPSS Statistics for Windows; IBM Corp.,

Table 1. Clinical and laboratory features in OA and control groups.

	OA	Control	p-value *
Age (year)	60.80 ± 6.78	58.51 ± 7.07	0.086
BMI (kg/m^2)	31.90 ± 5.67	31.57 ± 6.65	0.820
Albumin (mmol/L)	4.12 ± 0.11	4.15 ± 0.10	0.089
IMA (ABSU)	0.773 ± 0.080	0.732 ± 0.078	0.008
IMA/Albumin (IMAR) (ABSU*L/mmol)	0.188 ± 0.20	0.176 ± 0.21	0.011
Calcium (mmol/L)	8.62 ± 0.59	8.90 ± 0.63	0.088
Phosphorus (mmol/L)	3.15 ± 0.51	3.41 ± 1.67	0.428
Vitamin D (nmol/L)	13.48 ± 6.67	13.35 ± 6.60	0.935
Calcium/phosphorus	2.89 ± 0.56	2.81 ± 0.66	0.670
Iron (µmol/L)	71.88 ± 29.70	68.40 ± 35.44	0.653
Hemoglobin (g/L)	13.62 ± 1.60	13.93 ± 1.56	0.393
Sodium (mmol/L)	133.32 ± 32.21	135.90 ± 21.95	0.680
Potassium (mmol/L)	4.26 ± 0.35	4.48 ± 2.18	0.567
Chlorine (mmol/L)	102.03 ± 2.54	102.61 ± 6.81	0.650
WOMAC Score	60.95 ± 15.13	44.82 ± 14.40	< 0.001

Results were analyzed by independent sample *t*-test. p-value: statistical significance between groups where < 0.05 statistically significant. Statistically significant p-values are marked as underlined text. BMI - body mass index, IMA - Ischemia Modified Albumin, IMAR - Ischemia Modified Albumin/Albumin ratio, WOMAC score - The Western Ontario and McMaster Universities Osteoarthritis score. ABSU - Absorbance Serum Unit.

Table 2. Best cutoff levels, sensitivity and specificity values of IMA and IMAR in OA.

	Cutoff	Specificity %	Sensitivity %	AUC (95% Cl)	p-value
IMA (ABSU)	0.759	64%	60%	0.655 (0.553 - 0.757)	0.005
IMA/Albumin (IMAR) (ABSU*L/mmol)	0.18	66%	60%	0.651 (0.548 - 0.753)	0.006

Statistically significant p-values are marked as underlined text. Values < 0.05 were considered statistically significant. AUC - area under the curve, CI - confidence interval, IMA - Ischemia Modified Albumin, IMAR - Ischemia Modified Albumin/Albumin ratio, ABSU - Absorbance Serum Unit.

Armonk, NY, USA). Whether or not the data was normally distributed has been tested with the Kolmogorov-Smirnov test. The Levene test evaluated the homogeneity of variances. Homogeneous variables were shown as mean ± standard deviation (SD). Student's *t*-test compared mean results between OA and control groups. Multivariate logistic regression analysis was used to determine the relationship between IMA, IMAR, albumin, WOMAC score, and OA. Variables whose univariable test had a p-value < 0.05 was accepted as a candidate for the multivariable model along with IMA, IMAR, and other clinical and laboratory variables. Pearson's correlation analyses calculated degrees of association between IMA, IMAR, and WOMAC score. A p-value < 0.05 was considered as significant.

RESULTS

A total of 110 knee osteoarthritis patients (55 OA and 55 age and BMI matched healthy controls) were enrolled in the study. The anthropometric, clinical, and laboratory characteristics of both groups are given in Table 1. Mean age of participants was 60.80 ± 6.78 years for OA and 58.51 ± 7.07 years for control (p = 0.086). There were no statistically significant differences between age, BMI, albumin, calcium, phosphorus, vitamin D, calcium/phosphorus, iron, hemoglobin, sodium, potassium, and chlorine levels between groups.

When compared with the controls, patients in OA had significantly higher levels of IMA (0.773 ± 0.080 vs. 0.732 ± 0.078 ABSU; p = 0.008), IMAR (0.188 ± 0.20 vs. 0.176 ± 0.21 ABSU*L/mmol; p = 0.011), and

Table 3. Multivariate logistic regression analysis of variables in the assessment of increased OA risk

	OA			
	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% Cl)	p-value
Age (year)	1.050 (0.993 - 1.110)	0.088		
BMI (kg/m^2)	1.009 (0.937 - 1.086)	0.817		
Albumin (mmol/L)	0.054 (0.002 - 1.600)	0.091		
IMA (ABSU)	7.261 (0.463 - 11.381)	**0.011**	6.806 (0.255 - 14.915)	**0.024**
IMA/Albumin (IMAR) (ABSU*L/mmol)	3.225 (0.435 - 3.791)	**0.009**	3.021 (0.258 - 3.525)	**0.015**
Calcium (mmol/L)	0.455 (0.179 - 1.156)	0.098		
Phosphorus (mmol/L)	0.808 (0.451 - 1.445)	0.472		
Vitamin D (nmol/L)	1.003 (0.933 - 1.079)	0.934		
Calcium/phosphorus	1.214 (0.506 - 2.913)	0.664		
Iron (µmol/L)	1.003 (0.989 - 1.017)	0.648		
Hemoglobin (g/L)	0.880 (0.658 - 1.177)	0.389		
Sodium (mmol/L)	0.996 (0.980 - 1.013)	0.678		
Potassium (mmol/L)	0.903 (0.625 - 1.305)	0.589		
Chlorine (mmol/L)	0.978 (0.890 - 1.075)	0.650		
WOMAC Score	1.072 (1.041 - 1.104)	**< 0.001**	1.078 (1.044 - 1.113)	**< 0.001**

Statistically significant p-values are marked as underlined text. Values < 0.05 are considered statistically significant. OR - Odds Ratio, AUC - area under the curve, Cl - confidence interval. BMI - body mass index, IMA - Ischemia Modified Albumin, IMAR - Ischemia Modified Albumin/Albumin ratio, WOMAC score - The Western Ontario and McMaster Universities Osteoarthritis score. ABSU - Absorbance Serum Unit.

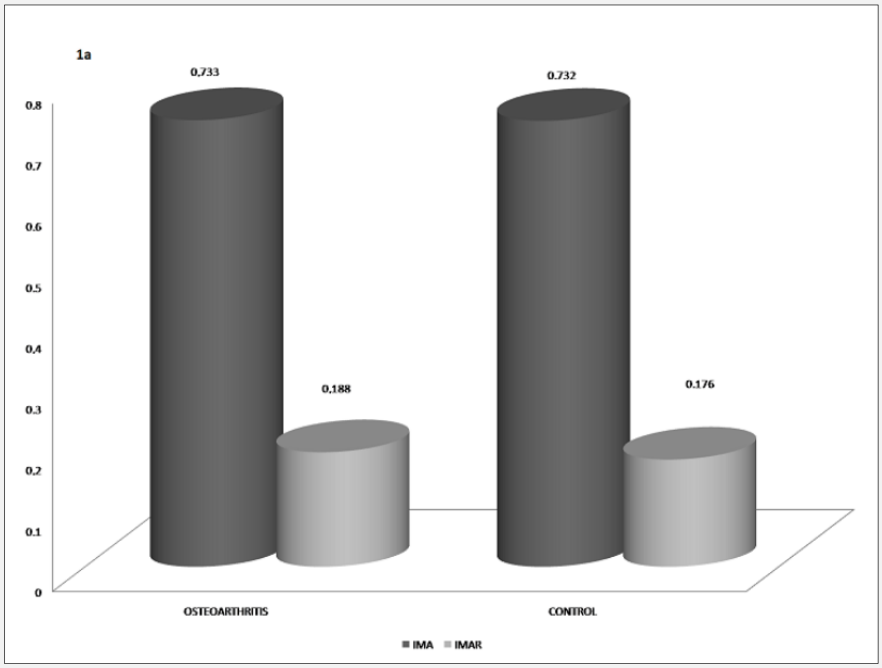

Table 1. Clinical and laboratory features in OA and control groups.

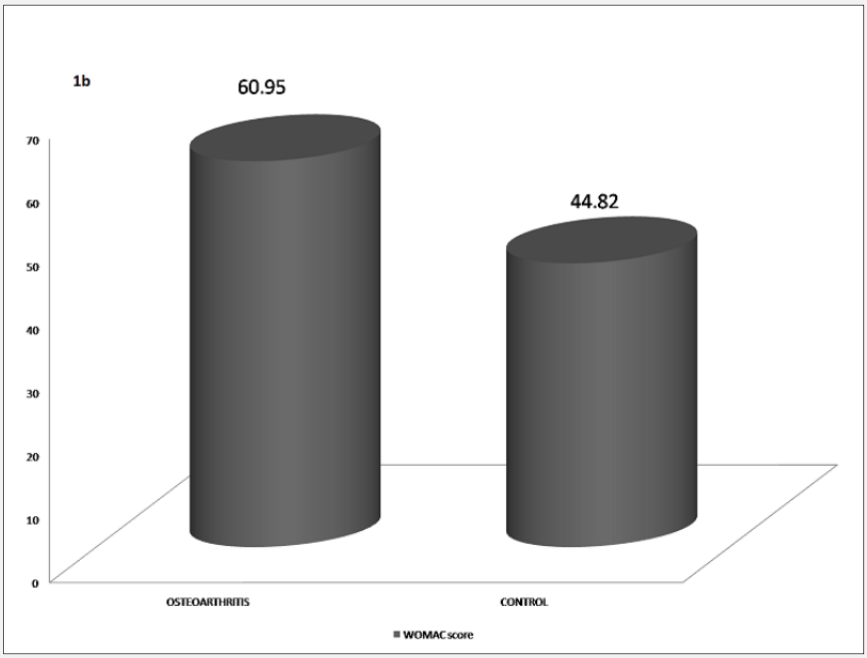

Table 2. Best cutoff, sensitivity and specificity values of IMA and IMAR levels in OA.

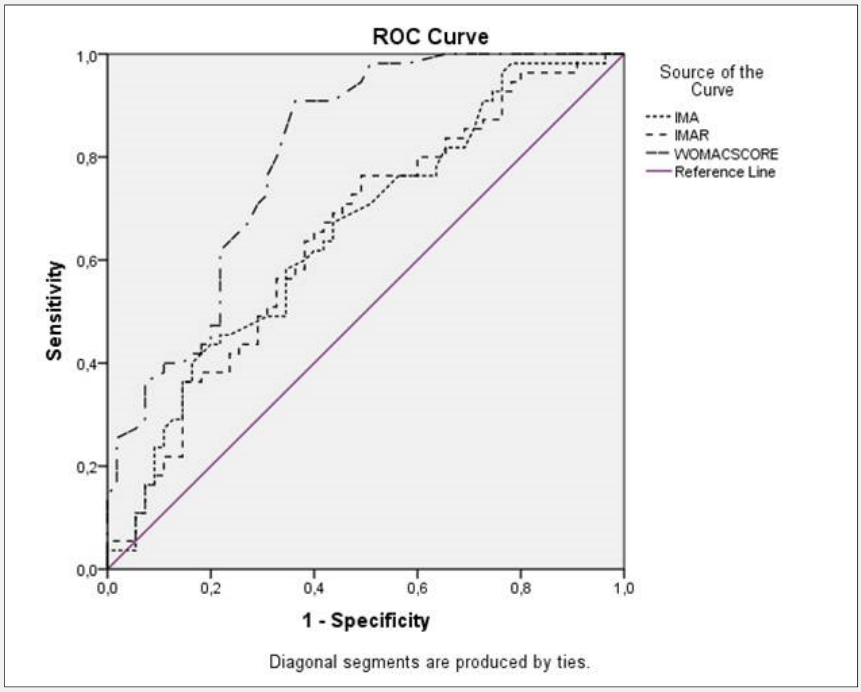

Table 3. Multivariate logistic regression analysis of variables in the assessment of increased OA risk.

WOMAC score (60.95 ± 15.13 vs. 44.82 ± 14.40; $p < 0.001$) (Figure 1a and 1b, Table 1).

According to the ROC analysis performed for the predictive value of IMA and IMAR levels for OA, the AUC were 0.655 ABSU (95% CI: 0.553 - 0.757; $p = 0.005$) and 0.651 ABSU*L/mmol (95% CI: 0.548 - 0.753; $p = 0.006$) (Figure 2). In association with OA, 0.759 ABSU was the best cutoff value for IMA (with 64% specificity, and 60% sensitivity); and 0.18 ABSU*L/mmol was the best cutoff value for IMAR (with 66% specificity, and 60% sensitivity) (Table 2). Multiple logistic regression analyses were applied to determine the increased risk of OA. Any variable whose univariable test had a p-value < 0.050 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Multivariable logistic regression analysis revealed that increased IMA levels, IMAR, and WOMAC levels independently associated with increased risk of OA (OR = 6.806, 95% CI: 0.255 - 14.915, $p = 0.024$; OR = 3.021, 95% CI: 0.258 - 3.525, $p = 0.015$ and OR = 1.078, 95% CI: 1.044 - 1.113, $p < 0.001$) (Table 3).

Further analysis was performed to determine whether IMA and IMAR were correlated with WOMAC score in OA. No significant correlation was observed between IMA, IMAR, and WOMAC score in OA.

DISCUSSION

In the present prospective case-control study in osteoarthritis patients, increased levels of IMA and IMAR were found to be associated with the progression of OA.

Osteoarthritis is a major cause of disability in the age group of over 40 years worldwide [9], so there have been many attempts to predict and prevent this chronic condition. Although there are some encouraging radiological and magnetic resonance (MRI) findings for the prediction of progression of osteoarthritis, some pro-inflammatory cytokines, proteases, and oxidative stress markers in synovial fluid and cartilage are known to be involved in the progress of osteoarthritis [22,23]. We think that all the pro-inflammatory cytokines and proteases are associated with oxidative stress due to aging and mechanical risk factors that play a role in the cartilage degeneration and that oxidative stress markers can be used in OA progression. ROS induced by oxidative stress induces cellular signals by two mechanisms: alterations in the intracellular redox state and oxidative modification of proteins [24]. IMA is one of the protein modifications due to oxidative stress. IMA is the new marker of ischemic diseases [25]. Apart from acute ischemic disorders, it has been shown that IMA can be used as a marker of chronic diseases such as chronic liver and kidney diseases [26,27], infectious diseases [28], and pre-eclampsia [29]. Borderie et al. reported that high levels of IMA reflect oxidative stress in systemic sclerosis (SS) cases [30]. In addition, Türkön et al. showed that IMA, IMAR, TOS (total oxidant status), OSI (oxidative stress index), and malondialdehyde (MDA) levels were significantly higher in patients with ankylosing spondylitis (AS) compared to the control group, and also stated that increased levels of IMA contributed to the underlying oxidative stress in AS [31]. We suggested a relationship between increased serum IMA levels and cartilage degeneration. We proposed that the increased serum levels of IMA were due to the oxidative stress mechanism against ongoing cartilage degeneration in osteoarthritis and thus may be associated with the progression of osteoarthritis.

In the present study, we found increased levels of serum IMA and IMAR in patients with osteoarthritis. Besides, serum IMA and IMAR levels were determined to be associated with osteoarthritis. Also, increased serum levels of IMA and IMAR were predictive for the progression of OA. So, we propose that serum IMA may be an indicator of the increased risk of osteoarthritis progression and give us time to prevent this. There is not much data related to IMA level and OA in the literature. This study is the first study associated with IMA and IMAR levels and OA. However, when we look at the reports of other chronic diseases, Leitemperguer et al. showed that IMA levels in synovial fluid of patients with rheumatoid arthritis (RA) were higher than the control group [32]. Nativel et al. reported that increased plasma IMA level was associated with major lower extremity artery disease risk in type 2 diabetic patients [33]. Falkensammer et al. showed that elevation of serum IMA could be used as a marker of skeletal muscle ischemia in exercise, and they said that IMA is a marker of prolonged and chronic ischemia [34]. Tayman et al. reported that IMA levels were high in chronic periodontal patients and decreased after treatment [35]. It has also been reported that IMA may be a marker of long-term hypoxia in detecting respiratory failure [36]. In light of all studies as mentioned above, including the present one, we thought that serum IMA is the probable new marker for chronic diseases and may be a triggering marker in cartilage degeneration and progression of OA.

CONCLUSION

The current study suggests that increased levels of IMA and IMAR are associated with osteoarthritis, and probably IMA and IMAR can be used as a marker for progressive osteoarthritis. This study needs to be validated with larger cohorts, and also, synovial fluid levels should be investigated in osteoarthritis throughout disease to determine the association with the progression of OA.

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Declaration of Interest:
The authors report no conflicts of interest.

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