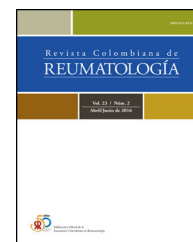




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Original Investigation

Applicability of the MASEI index in enthesitis and its association with other indices/serological markers of activity in patients with spondyloarthritis

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ABSTRACT

Introduction: The enthesitis is one of the target organs in patients with spondyloarthritis (SpA), since inflammation of it, known as enthesitis, can be observed, which in many patients with spondyloarthritis could go unnoticed.

Objective: To find the relationship between the MASEI index (MADrid Sonographic Enthesitis Index) in entheses and other indices/serological activity markers (such as BASDAI, DAPSA or ASDAS and ESR, CRP) in spondyloarthritis patients.

Materials and methods: Observational, descriptive, and cross-sectional study. Data were collected from patients with SpA who underwent musculoskeletal ultrasound using the MASEI index and who were treated in our clinics from May 2021 to September 2021. As appropriate, the variables evaluated were described using frequency and central tendency/dispersion measures. First, we tested the normality of all the variables using a Shapiro-Wilk test. Then we studied the correlation of parametric and non-parametric numerical variables, using Pearson's and Spearman's coefficients. We used the T-Student, Mann-Whitney U, and chi-square tests for the categorical variables.

Results: We analyzed 24 patients with SpA (with a mean age of 50.50 ± 10.63 years), 8 women and 16 men. The variables have the following average levels: ASDAS 2.35 (± 1.09); BASDAI (for those with axial involvement) 4.54 (± 2.93); DAPSA (for psoriatic arthritis) 10.98 (± 6.85), and total MASEI 19.88 (± 14.77). We found a correlation between the total MASEI and the following variables: ASDAS (Pearson coefficient = .696), BASDAI (Spearman coefficient = .823), and DAPSA (Pearson coefficient = .823).

Conclusion: Patients with spondyloarthritis with more significant disease activity measured by ASDAS, BASDAI/DAPSA, and the serological markers of inflammation CRP and ESR present a higher total MASEI than patients who are controlled.

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Aplicabilidad del índice entesítico MASEI y su asociación con otros índices/marcadores serológicos de actividad en pacientes con espondiloartritis

R E S U M E N

Palabras clave:

Ecografía
Índice MASEI
Validación
Espondiloartritis

Introducción: La entesis es uno de los órganos diana en los pacientes con espondiloartritis (EspA), ya que se puede observar una inflamación de esta, conocida como entesitis, que en muchos pacientes con EspA podría pasar desapercibida.

Objetivo: Encontrar la relación entre el índice entesítico MASEI (*MAdrid Sonographic Enthesitis Index*) y otros índices/marcadores de actividad serológica (como BASDAI, DAPSA, ASDAS, VSG y PCR) en pacientes con EspA.

Materiales y métodos: Estudio observacional, descriptivo y transversal. Se recogieron datos de pacientes con EspA a los que se les realizó ecografía musculoesquelética mediante el índice MASEI y que fueron atendidos en nuestras consultas desde mayo del 2021 hasta septiembre del 2021. Las variables evaluadas se describieron mediante medidas de frecuencia y de tendencia central/dispersión, según correspondía. Primero, probamos la normalidad de todas las variables usando la prueba de Shapiro-Wilk. Luego estudiamos la correlación de variables numéricas paramétricas y no paramétricas, para lo cual utilizamos los coeficientes de Pearson y Spearman. Utilizamos las pruebas T-Student, Mann-Whitney U y chi-cuadrado para las variables categóricas.

Resultados: Se analizaron 24 pacientes con EspA (con una edad media de $50,50 \pm 10,63$ años), 8 mujeres y 16 hombres. Las variables tienen los siguientes niveles promedio: ASDAS 2,35 ($\pm 1,09$), BASDAI (para aquellos con afectación axial) 4,54 ($\pm 2,93$), DAPSA (para artritis psoriásica) 10,98 ($\pm 6,85$) y MASEI total 19,88 ($\pm 14,77$). Hemos encontrado correlación entre el MASEI total y las siguientes variables: ASDAS (coeficiente de Pearson = 0,696), BASDAI (coeficiente de Spearman = 0,823) y DAPSA (coeficiente de Pearson = 0,823).

Conclusión: Los pacientes con EspA con mayor actividad de la enfermedad medida por ASDAS, BASDAI/DAPSA y los marcadores serológicos de inflamación PCR y VSG presentan un MASEI total mayor que los pacientes controlados.

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Introduction

The enthesitis is considered the target organ of inflammation in spondyloarthritis (SpA). Enthesitis, or inflammation of the enthesitis, is characterized by tendon or ligament thickening and insertion site edema, bone erosions, and new bone formation. This new bone formation developed due to enthesitis is called an enthesophyte in peripheral joints and a syndesmophyte in the spinal column. These enthesophytes can be seen on conventional radiography, especially in the calcaneus (Achilles tendon and plantar fascia).¹ However, one of the major limitations of conventional radiography is its poor ability to show soft tissue inflammation, changes that are common in enthesitis. Therefore, more sensitive methods such as ultrasound and magnetic resonance imaging (MRI) are often used. Both ultrasound and MRI can detect inflammatory areas in soft tissues. In addition, ultrasound has a series of technical advantages: it does not use radiation, it is relatively cheap, reproducible, with excellent acceptance by patients and explorers, and also has clinical benefits by offering an image in real-time and the possibility of evaluating multiple locations during the same ultrasound examination.² The prevalence of enthesitis in SpA is not easy to determine due to its frequent

subclinical involvement and the diagnostic difficulty involved in its clinical examination due to the absence of visible inflammatory signs. Due to this difficulty in the clinical evaluation of enthesitis, imaging techniques have potential use in its objective assessment.³ In our environment and according to the EPISER2016 study, the prevalence of ankylosing spondylitis is 0.26% (95% CI 0.14–0.49) while that of psoriatic arthritis is 0.58 (95% CI 0.38–0.87), and it is estimated that the total incidence of spondyloarthritis is 62.5 cases per 100,000 inhabitants (95% CI 45–87).⁴

Ultrasound of the enthesitis can be performed in a targeted manner on a specific enthesitis according to the area referred to by the patient as painful in the anamnesis, or a more global assessment can be made by studying several entheses. Various ultrasound assessment indices have been described for the study of multiple entheses. The MAdrid Sonographic Enthesitis Index (MASEI index) is the most complete to date and the only one based on the OMERACT definition of enthesopathy, evaluating six enthesitis sites on each side of the body: plantar fascia at its insertion with the lower pole of the upper calcaneus pole of the patella with the enthesitis of the quadriceps tendon, the inferior pole of the patella with the proximal enthesitis of the patellar tendon, tuberosity of the tibia with the distal enthesitis of the patellar tendon, the superior pole

of the calcaneus with the enthesis of the Achilles tendon and the enthesis of the tricipital fascia at its insertion with the olecranon tuberosity. In these sites, the structure of the tendon or ligament, its thickening, the presence of bone erosions or calcifications at the enthesis site, the presence of a power-Doppler signal, as well as the presence of retrocalcaneal or infrapatellar bursitis are evaluated. The MASEI index has shown high sensitivity (83.3%) and specificity (82.8%) in the diagnosis of SpA in those patients who present a score ≥ 18 .⁵

Several works, such as the study by Ojeda et al. in 2020, quantified the enthesis compromise with the MASEI index with a result of 15.2.⁶ In addition, they tried to relate this ultrasound index (along with others) with the BASDAI and ASDAS activity and BASFI functionality indices. Still, they did not find a statistically significant relationship, coinciding with other similar studies such as the DESIR cohort, where the structural damage on enthesis ultrasound did not correlate with the BASDAI activity index or the ASDAS-PCR index.⁷

In another work published by De Miguel, the MASEI index was evaluated about the type of spondyloarthritis, in which no differences were found in the MASEI indices of patients diagnosed with spondyloarthritis of different types.⁸ In a study published by Macía-Villa in 2021, the association between the total MASEI score and radiographic damage was analyzed in 27 patients with psoriatic arthritis, showing this association between the involvement of the enthesis and the structural damage of the sacroiliac joint, despite the low number of patients analyzed.⁹

The objective of this study is to validate the relationship between the MASEI index (MAdrid Sonographic Enthesitis Index) in entheses and other indices/markers of serological activity (such as BASDAI, DAPSA or ASDAS and ESR, CRP) in patients with spondyloarthritis.

Methods

Study design

This study is an observational, descriptive, and transversal study. A retrospective review of a database of patients with spondyloarthritis is under consideration.

Patients

According to ASAS 2009 criteria, patients with spondyloarthritis were treated during outpatient visits in the Rheumatology Department of General University Hospital of Ciudad Real between May 2021 and September 2021.

Variables

Collected variables were as follows: demographic data (sex and age) and clinical, analytical, serological, and imaging information of the patient's spondyloarthritis subtype, among others. In addition, it is studied if there is axial involvement, peripheral arthritis, enthesitis, dactylitis, extra-articular manifestations, uveitis, psoriasis, or inflammatory bowel disease. Moreover, as a variable of interest for our study, the MASEI

index (MAdrid Sonographic Enthesitis Index) evaluates the structure and thickness of the tendon, the presence of calcifications or enthesophytes, erosions in the bone, regional bursitis, and the presence of power-Doppler signal in the entheses in the following entheses: insertion of the quadriceps tendon in the superior pole of the patella, insertion of the patellar ligament at the inferior pole of the patella, patellar ligament attachment at the tibial tuberosity, Achilles tendon attachment at the calcaneus, plantar fascia attachment at the calcaneus, and triceps tendon attachment at the olecranon. Likewise, and as an outcome variable of our study, the level of disease activity was assessed using ASDAS (Ankylosing Spondylitis Disease Activity Score), which includes both subjective variables such as questions about spinal pain, the patient's global assessment, peripheral pain, or swelling, or duration of stiffness, in addition to an objective variable of inflammation such as CRP or ESR. It is defined as an inactive disease when the score is <1.3 , moderate activity if $1.3-2.1$, high activity if $2.1-3.5$, and very high activity if >3.5 . In addition, included BASDAI (Bath Ankylosing Spondylitis Diseases Activity Index) for patients with axial spondyloarthritis using an easily applicable numerical rating scale of six questions concerning the disease: tiredness/fatigue, axial affectation, peripheral affectation, enthesopathy, and morning stiffness (two questions). The range was 0–10, and the disease was considered active at a score higher than 4. In addition, the DAPSA (Disease Activity for Psoriatic Arthritis) index was used for patients with psoriatic arthritis. It was calculated by linearly adding five variables: (1) number of swollen joints, (2) number of tender joints, (3) pain measured using a 0–10 visual numeric scale (VNS), (4) patient global assessment using a 0–10 VNS, and (5) CRP (mg/dl).

US image acquisition

An experienced rheumatologist performed ultrasound scans of the areas included in the MASEI in 24 consecutive patients who attended a rheumatology department of a university hospital. SpA patients fulfilled ASAS axial classification criteria^{9,10} and PsA patients CASPAR criteria.¹¹ The MASEI score systematically explored six bilateral enthesis locations, including the proximal plantar fascia, distal Achilles tendon, distal and proximal patellar ligament, distal quadriceps and brachial triceps tendons. Enthesis thickness, structure, calcification/bone proliferation, erosion, bursa and power-Doppler signal in the cortical bone profile, tendon and bursa were scored. Table 1 shows how each enthesis was scored. A MyLabTwice (Esaote, Genoa, Italy), with a multifrequency linear array transducer (4–13 MHz) was used. Pulse repetition frequency was adjusted to 750 Hz. Color gain was set just below the color noise level. Each evaluation was performed in standardized positions. The triceps tendon evaluations were performed with the patient seated in front while arms were in internal rotation, elbows flexed and hands on a pillow on the thigh. The common extensor and flexor tendon evaluations were performed while patients' arms were in a neutral position, elbows were flexed 90°, and hands were supine. The quadriceps, proximal and distal patella tendon, anterior tibialis tendon were examined while patients were lying supine, knees were flexed 60°, ankles were placed on the bed. The Achilles tendon evaluations were

Table 1 – Evaluation of MAdrid Sonographic Enthesitis Index (MASEI).

Structure (bilateral)	Calcification	Structure	Thickness	Erosion	Bursa	Power Doppler
Plantar aponeurosis	0 mm (0)		≥4.4 mm (1)			
Achilles tendon enthesitis	<5 mm (1)		≥5.29 mm (1)			
Distal patella ligament enthesitis	5–10 mm (2)	No (0)	≥4 mm (1)			No (0)
Proximal patella ligament enthesitis	>10 mm (3)	Yes (1)	≥4 mm (1)	>1 mm in 2 planes	≥2 mm (1)	Yes (3)
Quadriceps tendon enthesitis			≥6.1 mm (1)			
Triceps tendon enthesitis			≥4.31 mm (1)			

done while the patients were lying prone; ankles were in a neutral position.¹²

Statistical analysis

The information collected was entered into a Microsoft Excel database designed for the study. As appropriate, the variables evaluated were described using frequency and central tendency/dispersion measures. The main variables of the study were dichotomized for analysis. Due to the size of the population obtained, the normality of the numerical variables was contrasted using the Shapiro–Wilk test, and based on these, we made the correlations with the total MASEI with the Pearson coefficient (if they followed a normal distribution, such as the ASDAS and DAPSA), Spearman's coefficient (for non-parametric variables, such as BASDAI); and for hypothesis testing (differences in means) with the total MASEI we used the T-Student test (if the variances were equal for the parametric variables, such as vitamin D and total MASEI) and the Mann–Whitney U test (for variables that did not follow normality, such as CRP and ESR). It was not possible to calculate the sample size before starting the study, since only those patients who agreed to be included in the study of the musculoskeletal ultrasound monographic consultation were selected.

Ethical approval information

We have a document with the final approval of the Clinical Research Ethics Committee of the General University Hospital of Ciudad Real, approved on June 29, 2021 (act 07/2021). In addition, we have obtained the patient's written informed consent to publish the material and before the procedure.

Results

We analyze twenty-four patients with SpA (with a mean age of 50.50 ± 10.63 years), 8 women and 16 men. Regarding the clinical profile of the selected patients, they presented: five patients with radiographic axial spondyloarthritis, four non-radiographic axial spondyloarthritis, ten psoriatic arthritis, and two spondyloarthritis associated with inflammatory bowel disease, two reactive arthritis (two patients), and finally, one patient has undifferentiated peripheral spondyloarthritis. Of them, 12 had axial involvement, 18 peripheral arthritis, 17 clinical enthesitis, 10 psoriasis, 11 dactylitis, 0 uveitis, and 2 inflammatory bowel disease. Regarding the treatment of our patients, 12 of them were with conventional DMARDs and 10 with biological DMARDs; of these last, nine were with anti-TNF alpha and one with anti-IL17 (Table 2).

Table 2 – Characteristics of the patients included in the study.

Variable	Frequency	Percentages
Spondyloarthritis subtype		
Radiographic axial spondyloarthritis	5	20.83%
Non-radiographic axial spondyloarthritis	4	16.65%
Psoriatic arthritis	10	41.66%
Spondyloarthritis with inflammatory bowel disease	2	8.33%
Reactive arthritis	2	8.33%
Undifferentiated peripheral spondyloarthritis	1	4.16%
Clinical manifestations		
Axial involvement	12	50%
Peripheral arthritis	18	75%
Enthesitis	17	70.83%
Psoriasis	10	41.65%
Dactylitis	11	45.83%
Uveitis	0	0%
Inflammatory bowel disease	2	8.33%
Treatment		
Methotrexate	10	41.66%
Sulfasalazine	1	4.16%
Leflunomide	1	4.16%
Biological DMARDs	10	41.66%
1. Anti-TNF alpha	9	37.5%
(a) Etanercept	2	
(b) Adalimumab	7	
2. Anti-IL17	1	4.16%
Corticosteroids	13	54.16%
NSAIDs	23	95.83%

NSAIDs: non-steroidal anti-inflammatories.

Table 3 – MASEI individualized according to enthesitis involvement.

Variable	Mean	Standard deviation
Plantar aponeurosis	3.08 (0–9)	± 2.96
Achilles tendon enthesitis	5.63 (0–12)	± 4.26
Distal patella ligament enthesitis	3.75 (0–10)	± 3.03
Proximal patella ligament enthesitis	2.29 (0–8)	± 2.26
Quadriceps tendon enthesitis	3.03 (0–9)	± 2.78
Triceps tendon enthesitis	2.04 (0–12)	± 2.84

Regarding the primary variable of the study, the number of total MASEI averaged was $19.88 (0–50) \pm 14.77$ SD, while the number of regions with enthesophytes was $4.54 (0–10) \pm 2.86$ SD and with erosions of $0.42 (0–3) \pm 0.83$ SD. We also individually studied the involvement of the tendons referenced in the MASEI index (Table 3). The mean disease activity measured by ASDAS was $2.35 (\pm 1.04)$ SD, of which five were inactive

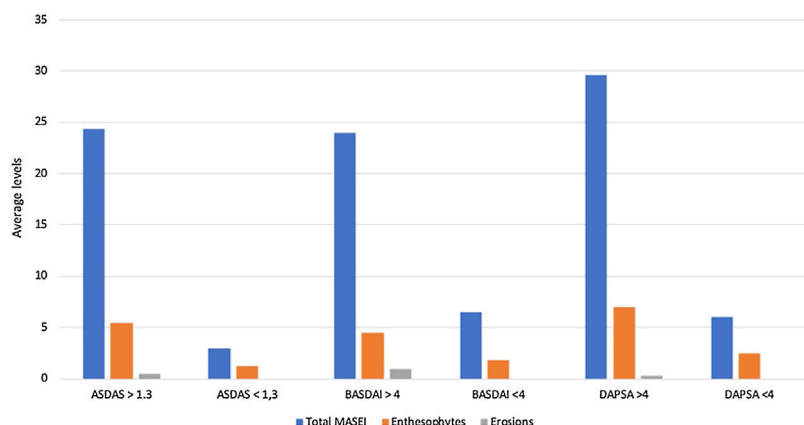


Fig. 1 – Bar graph with the mean levels of total MASEI, enthesophytes, and erosions, as a function of disease activity measured by ASDAS, BASDAI, and DAPSA.

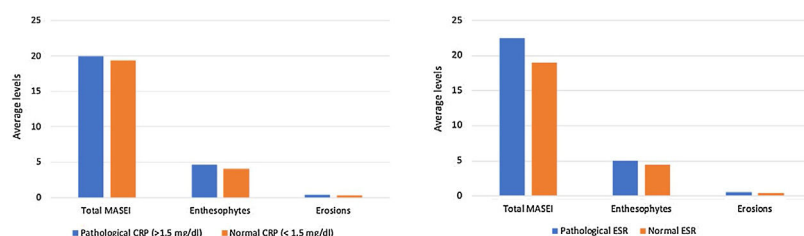


Fig. 2 – Bar graph with the mean levels of total MASEI, enthesophytes, and erosions, as markers of inflammatory activity measured by CRP and ESR.

(<1.3), five moderate (1.3–2.1), twelve high (2.1–3.5), and two very high (>3.5). The activity study using BASDAI was 4.53 (± 2.93 SD) of the 14 selected patients and measured by DAPSA, it was 10.98 (± 6.85 SD) of the 10 patients who underwent this index. Of all the patients studied, eight (57.14%) and eight (80%) presented disease activity measured by BASDAI and DAPSA, respectively. In addition, when evaluating the elevation of acute phase reactants using CRP and ESR, it was observed that 12.5% of the patients (three patients) presented pathological CRP (mean 0.31 mg/dl, ± 0.55 SD) and 25% (six patients) a pathological ESR (mean 8.33 mm/h, ± 8.32 SD). In addition, the inflammatory activity measured by ASDAS-CRP, BASDAI, DAPSA, CRP and ESR was analyzed, depending on whether or not they were present, and compared with the mean levels of total MASEI, enthesophytes, and erosions, obtaining the following graph (Figs. 1 and 2). Patients with ASDAS >1.3 (activity) had a mean total MASEI level of 24.32, while those with ASDAS <1.3 (control) had 3. In addition, the mean number of enthesophytes and erosions in patients with ASDAS >1.3 was 5.42 and 0.53, respectively; on the contrary, in those with ASDAS <1.3, it was 1.2 enthesophytes and 0 erosions. The rest of the variables (BASDAI and DAPSA), depending on the levels of total MASEI, enthesophytes, and erosions, are shown in Table 3. We have found a correlation between the total MASEI and the following variables: ASDAS (Pearson coefficient=0.696), BASDAI (Spearman coefficient=0.823), and DAPSA (Pearson coefficient=0.823).

Discussion

On many occasions, enthesitis goes unnoticed in the routine physical examination. Through the use of ultrasound, we can simply detect this subjective inflammation and one way to measure the inflammation in the entheses of patients with spondyloarthritis is with the help of a methodical, standardized, and systematic index such as the MASEI index since it allows us to evaluate the structural changes in the entheses and the consequences secondary to the chronic inflammation process in these tendons.

Of the 24 patients selected for the study, they had a mean number of total MASEI of 19.88 (± 14.77 SD), with a score in enthesophytes and erosions of 4.54 (± 2.86 SD) and 0.42 (± 0.83 SD), respectively. On the other hand, the mean level of ASDAS was 2.35 (± 1.04 SD), BASDAI was 4.53 (± 2.93 SD), and DAPSA was 10.98 (± 6.85 SD). When evaluating the disease activity with these scales, and since they are subjective scales, except for the ASDAS, which includes a serological parameter, the average activity level is indicated as present disease activity. When performing the association/correlation analysis between them, we observed a correlation between the total MASEI and the disease activity variables ASDAS, BASDAI, and DAPSA. The works published to date attempt to quantify enthesitis involvement and establish a relationship/association with the BASDAI/DAPSA and ASDAS activity indices but have not found conclusive or significant results.

However, they show that the higher the MASEI index, the more activity of the disease in patients with spondyloarthritis. In a recently published study by Macía in 2021, although it focused solely on patients with psoriatic arthritis, the 27 patients studied showed how tendon thickening and enthesophytes (such as enthesitis lesions) were more frequently associated with peripheral radiographic damage and sacroiliac, and therefore, with more significant disease activity and worse assessment by the patient.⁹ In 2015, El Miedany's group published a study in which they identified potential predictors of early joint structural damage in psoriatic arthritis using another enthesitis assessment index, known as GUESS (Glasgow Ultrasound Enthesitis Scoring System), and found a greater probability of structural progression over one year related to Doppler signal in the entheses and total GUESS score.¹³ In the systematically review of the literature carried out by the work group of Sakellariou, it was shown that ultrasound is valid and reliable in the assessment of patients with spondyloarthritis and enthesitis involvement,¹⁴ therefore the results of our study confirm this fact. In the study carried out by Spadaro's group, with a slightly higher number of patients than in our study, they concluded that most of the patients with ankylosing spondylitis had a greater number of pathological entheses than expected,¹⁵ a fact that we observed in our study with a mean score for enthesitis of 3.3, being the lowest in the enthesitis of the triceps tendon (2.04 ± 2.84) and the highest in the enthesitis of the Achilles tendon (5.63 ± 4.26) (Table 3). A finding in our study is that the MASEI index is higher when the clinimetric indices, ASDAS, BASDAI and DAPSA, are higher, but the same does not occur with acute phase reactants in which the MASEI is very similar if the PCR or ESR are normal or high. This fact may be due to the fact that the clinimetric indices contain subjective variables that can be highly influenced when performing the ultrasound.

One limitation of our study is that it was not possible to calculate the sample size of patients with spondyloarthritis because these patients were with other patients with other pathologies in a rheumatic technique clinic, both invasive (blocks, infiltrations) and non-invasive (ultrasound, capillaroscopy, microscopy, ...). Another limitation is that the ASDAS-CRP index was performed in all patients with spondyloarthritis, considering that some of them only presented peripheral involvement and that this may affect the correlation analysis, as well as the heterogeneity of the diseases analyzed, and it is for this reason that it was decided also carry out BASDAI, DAPSA, CRP and ESR.

Conclusion

Patients with spondyloarthritis who present greater activity of the disease measured by ASDAS, BASDAI/DAPSA, and by the serological markers of inflammation CRP and ESR, present a higher total MASEI than patients who are controlled, according to these parameters.

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Conflict of interest

The authors declare that they do not have any conflict of interest.

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