Διάγνωση και συντηρητική αντιμετώπιση των ενθεσοπαθειών που προκαλούνται από ρευματικά νοσήματα ή φάρμακα

Δημήτρης Καρόκης

Ρευματολόγος

Κέρκυρα 19/4/2019

Σύγκρουση συμφερόντων
Conflict of interest

- καμμία για αυτήν την παρουσίαση

• Εκπαιδευτικές-ερευνητικές-συμβουλευτικές επιχορηγήσεις την τελευταία διετία: Abbvie, Menarini, Pfizer, Novartis

Ένθεση – Ενθεσοπάθεια-Ενθεσίτιδα

- Κλασσικός ορισμός ένθεσης: Έκφυση και κατάφυση μαλακών ιστών (σύνδεσμοι, τένοντες, απονευρώσεις, αρθρικοί θύλακοι κλπ) στα οστά
- Σύγχρονος ορισμός ένθεσης: «Όργανο» που περιλαμβάνει όχι μόνο το σημείο σύνδεσης με το οστό, αλλά και όλες τις γειτονικές ανατομικές δομές (τένοντας, θύλακοι, λιπώδη σώματα, σύνδεσμοι, απονευρώσεις, ινώδης χόνδρος, υποδόριο οστό, οστικός μυελός)

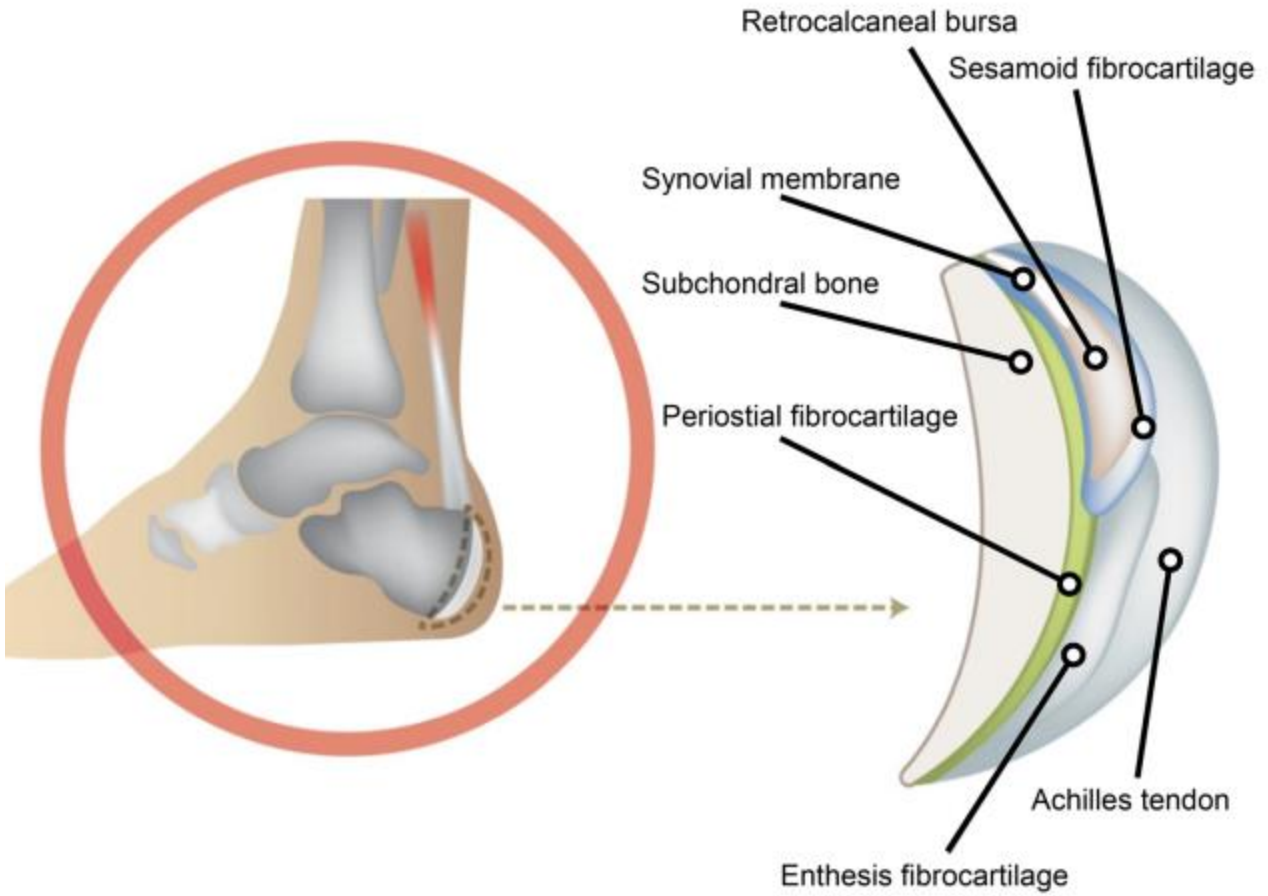
McGonagle D, Benjamin M, Marzo-Ortega H, et al. Advances in the understanding of entheseal inflammation. Curr Rheumatol Rep 2002 ; 4 : 500 – 6 .

- Ενθεσοπάθεια - Ενθεσίτιδα

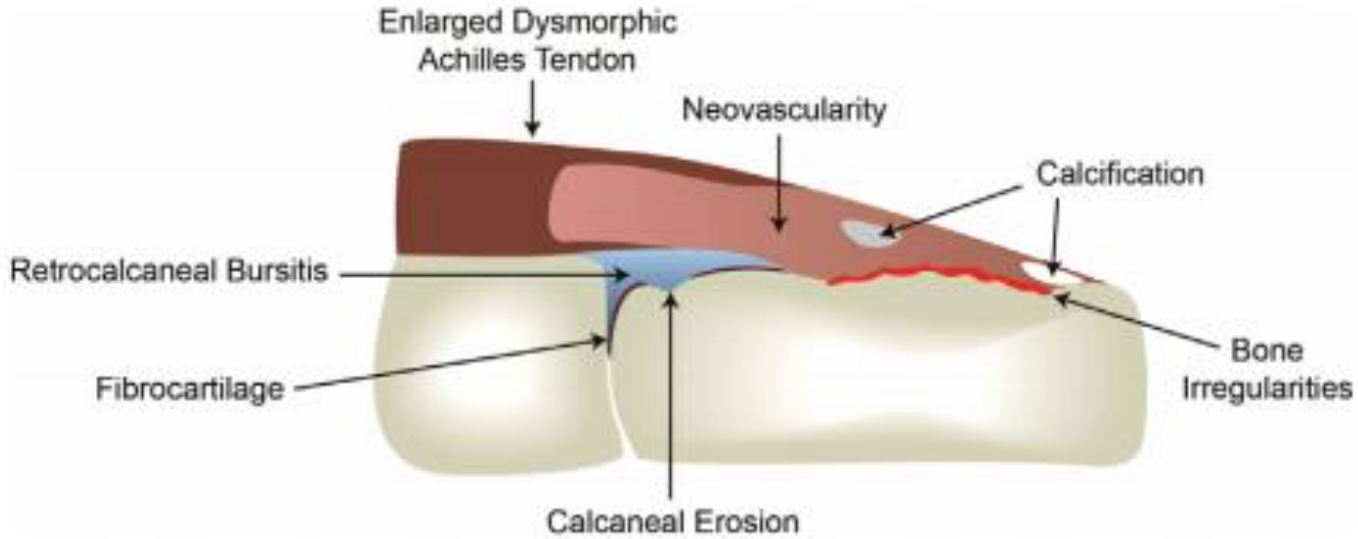
Τύποι ένθεσης

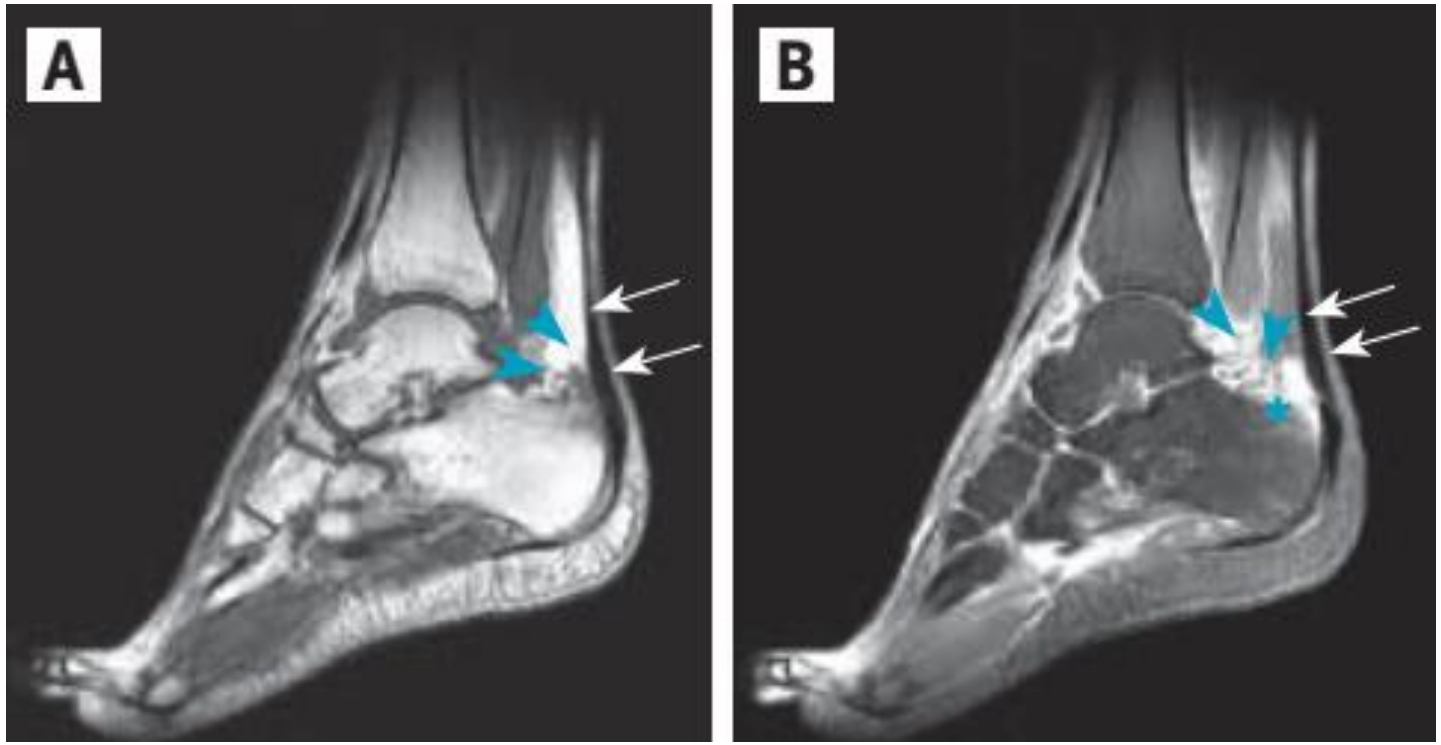
- Ινώδεις (στη διάφυση, μακριά από την άρθρωση, πχ δικέφαλος βραχιόνιος, στρογγύλος πρηνιστής)
- Ινοχόνδρινες (στη μετάφυση, κοντά στην άρθρωση, πχ αχίλλειος, υπερακάνθιος κλπ)

Ένθεση - όργανο



AJCD (2018) 19:839–852


Enlarged Dysmorphic
Achilles Tendon
Neovascularity
Calcification
Retrocalcaneal Bursitis
Fibrocartilage
Bone
Irregularities
Calcaneal Erosion


A
B

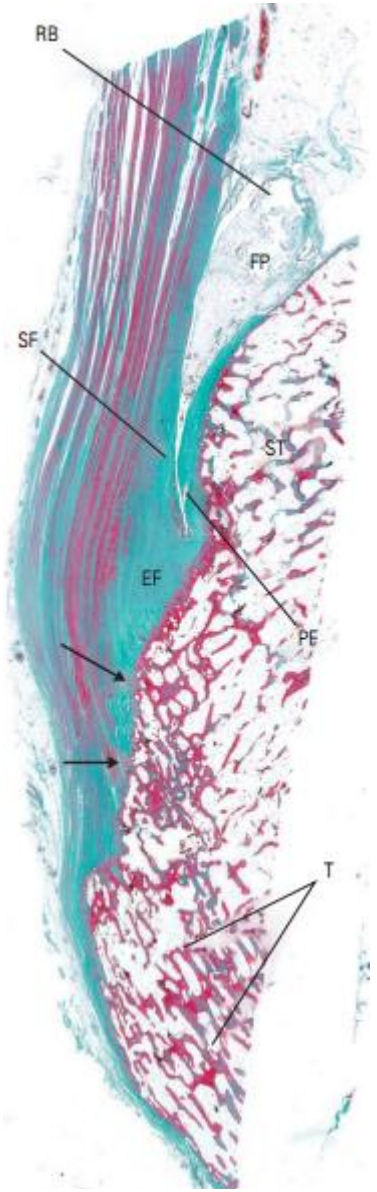
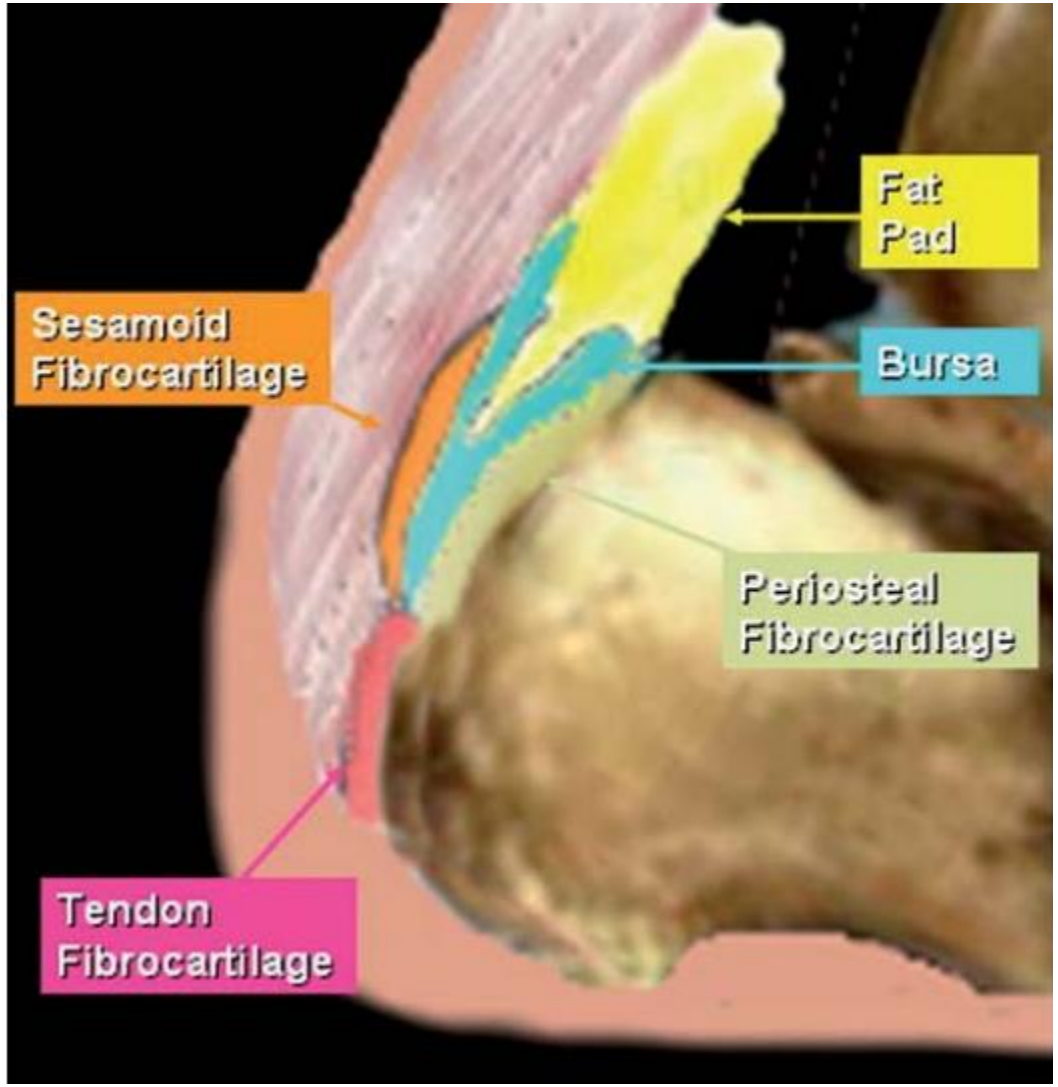


Fig. 123.2 Actual histologic section of the Achilles enthesis organ. Arrows indicate the distal part of the insertion. Many entheses throughout the body have this anatomic configuration. EF, enthesis insertion fibrocartilage. FP, fat pad; PF, periosteal fibrocartilage; RB, retrocalcaneal bursa; SF, sesamoid fibrocartilage; ST, superior tuberosity; T, trabeculae.



AJUM 2010; 13 (4): 19–23

The nail-enthesitis concept

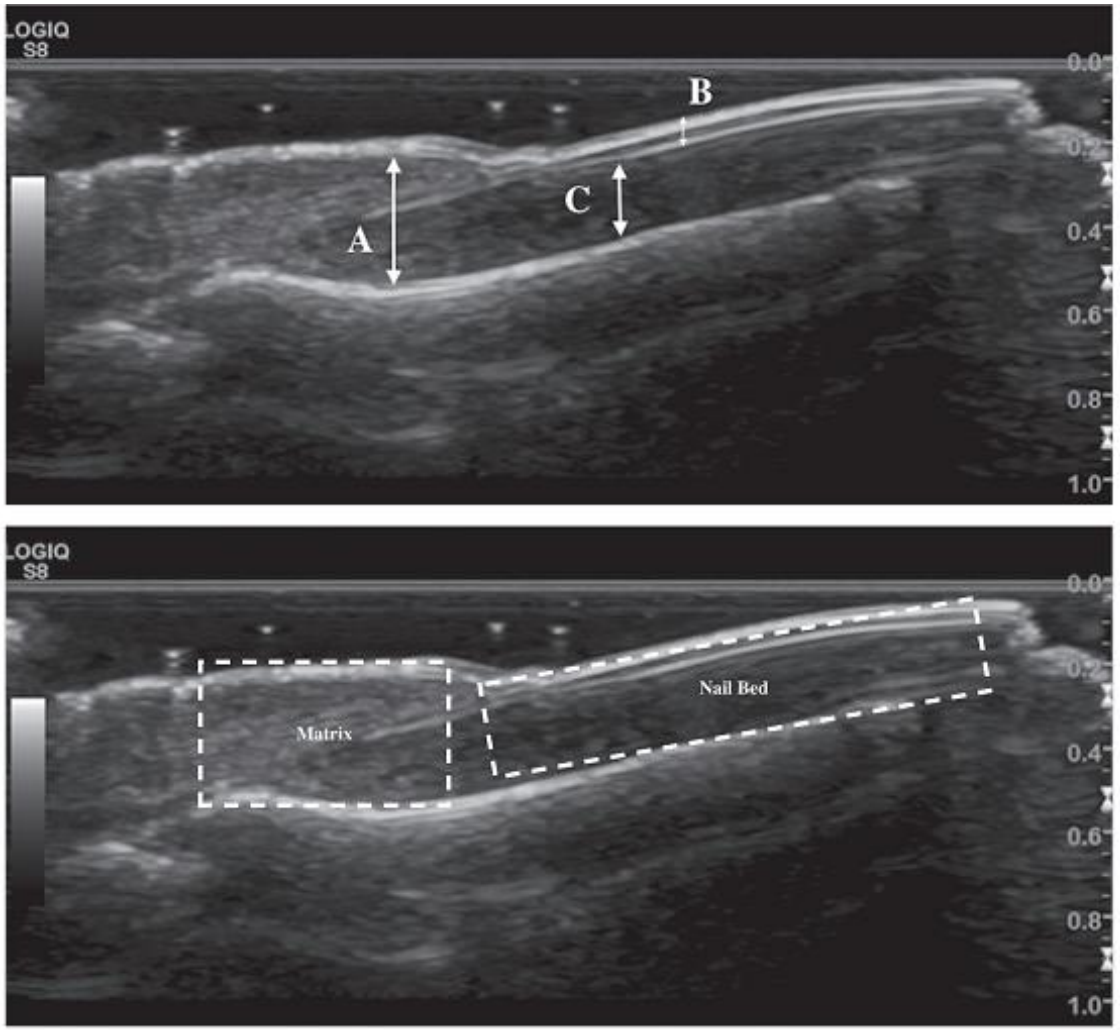


Figure 1. (A) Areas of morphologic changes in the nail. (B) Areas (nail bed and matrix) to assess for power Doppler signaling. A: measurement of the thickness of the nail matrix; B: assessment of the morphologic changes of the nail plate; C: measurement of nail bed thickness.

J Rheum 2017;44:688-90

The nail-enthesitis concept

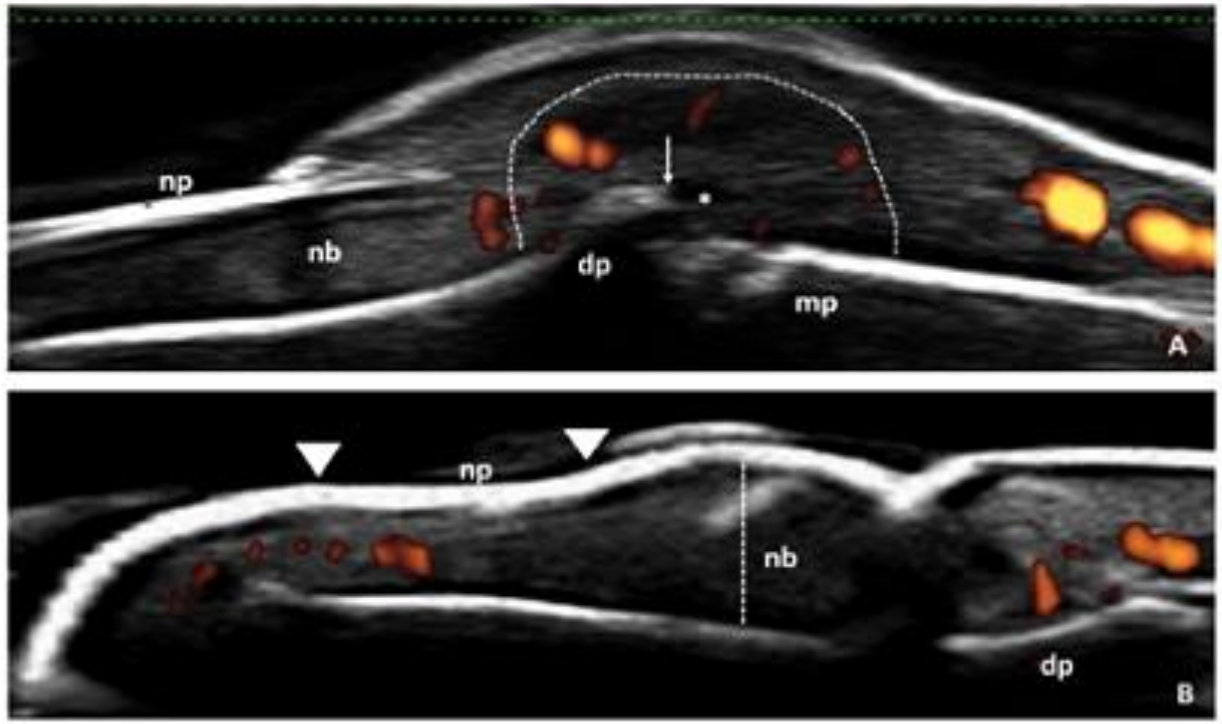
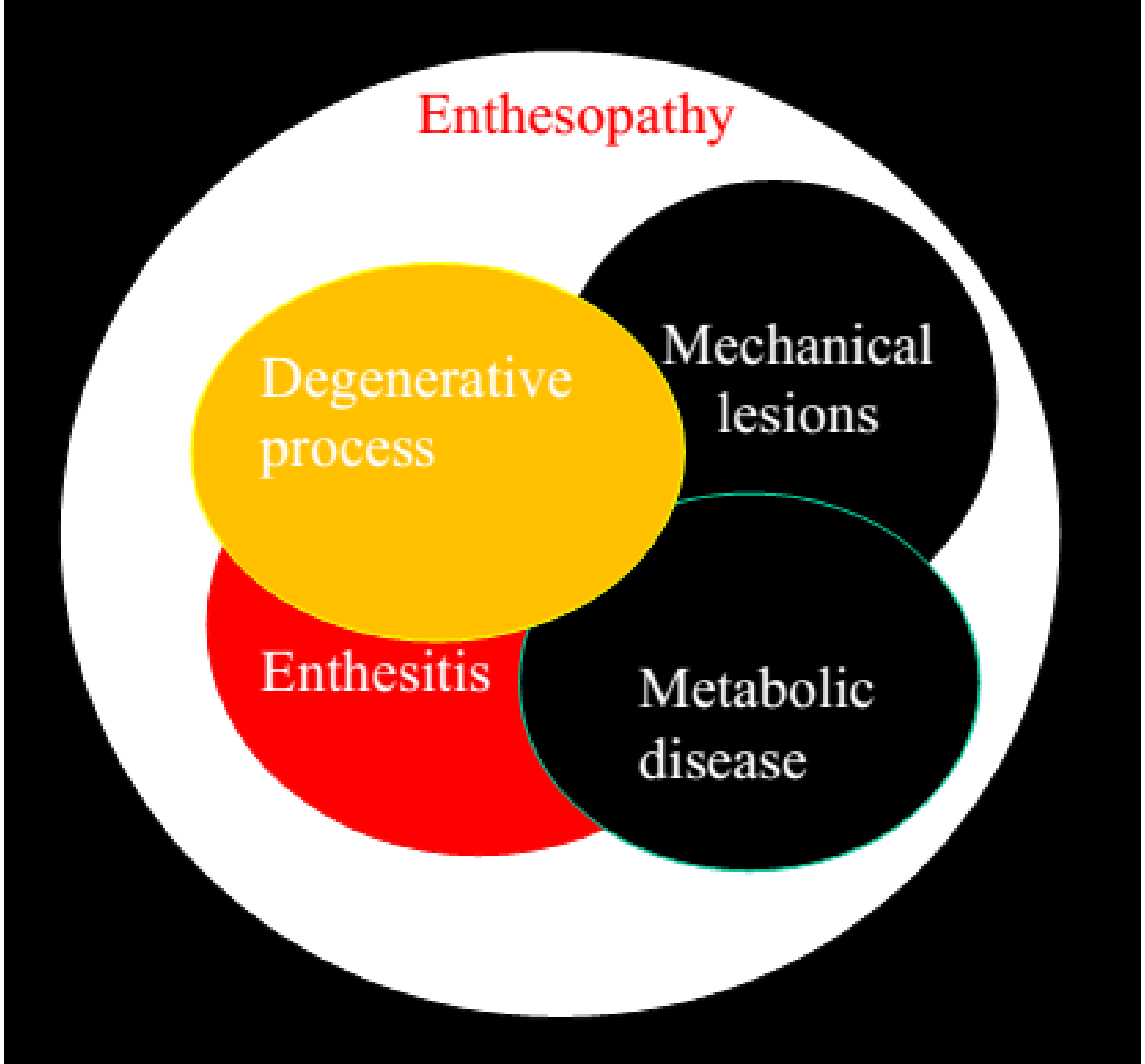


Fig. Psoriatic arthritis patient, distal interphalangeal joint, dorsal longitudinal scan. (A) Abnormally hypoechoic area (*) with loss of normal fibrillary architecture at extensor tendon insertion at distal phalanx (dp) and bony changes (arrow) indicating enthesopathy and joint cavity widening (dotted line) with increased abnormal vascularization at intra-articular level indicating synovitis. (B) Thickening and irregular undulation of the nail plates (np), which became a single and wavy hyperechoic layer (arrowhead) losing its normal bilaminar appearance and thickening of nail bed (nb) (dotted line). mp: medial phalanx.

Seminars in Arthritis and Rheumatism 47 (2017) 338–342


Enthesopathy
Degenerative process
Mechanical lesions
Enthesitis
Metabolic disease

Ενθεσοπάθεια

- Τραύμα
- Εκφύλιση
- Μεταβολικά νοσήματα
- Φάρμακα
- ΣπΑ (ενθεσίτιδα) κλπ φλεγμονώδη νοσήματα

Αίτια ενθεσοπάθειας

Table 1 Various Medical Disorders Manifesting with Enthesopathy		
Rheumatic Disorders	Metabolic and Endocrine Disorders	Drug-Induced
Spondyloarthropathies	Hyperparathyroidism	Fluoride and fluoroquinolones
Rheumatoid arthritis	Hypoparathyroidism	Glucocorticosteroids
Chondrocalcinosis	X-linked hypophosphatemia	Retinoids
Osteoarthritis	Hypothyroidism	
DISH	Acromegaly	
SAPHO	Hemochromatosis	
	Ochronosis	
	Familial hypercholesterolemia	
	Diabetes mellitus	
	Chronic renal failure	

Semin Arthritis Rheum 37:119-126

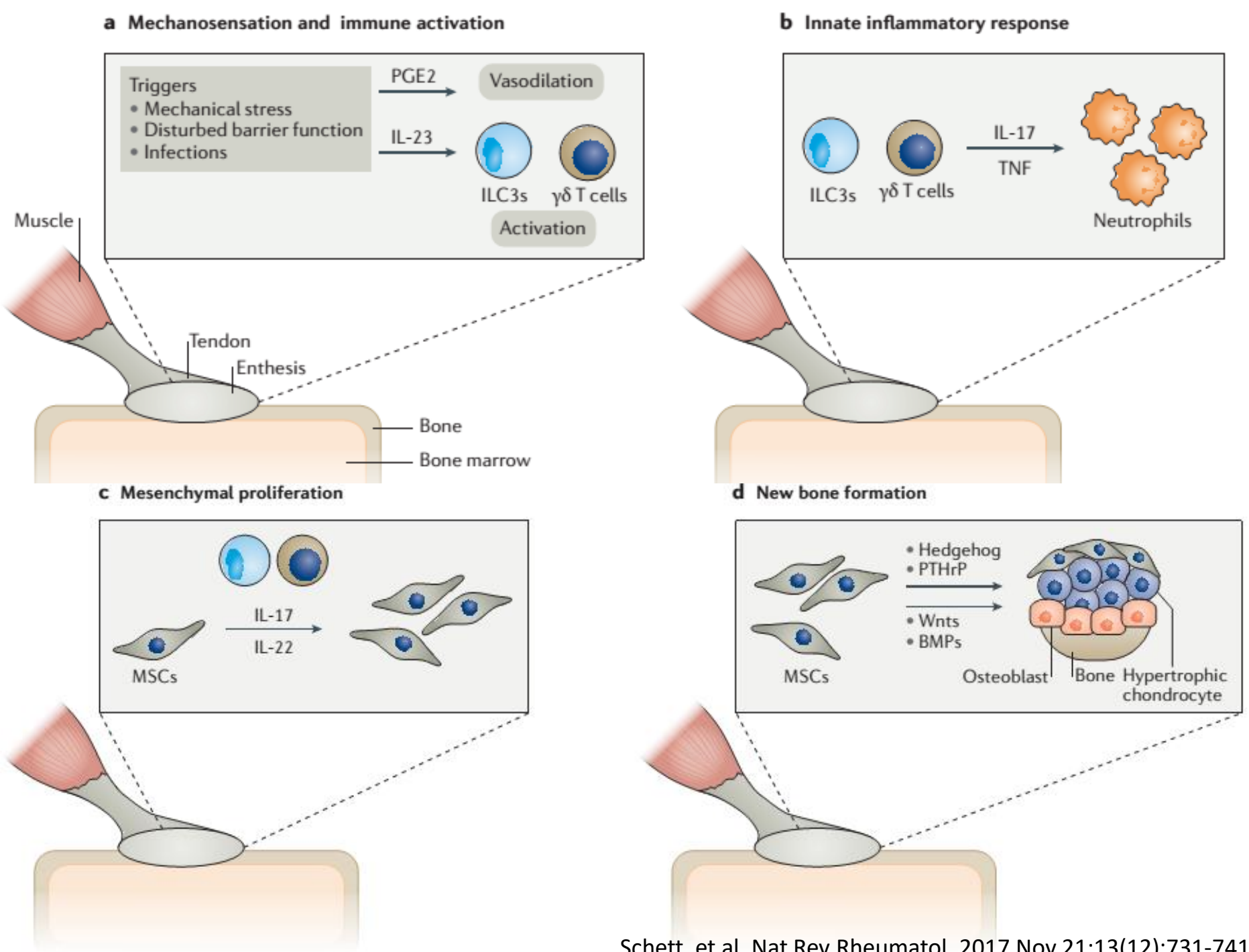
Ενθεσίτιδα: συχνότερες εντοπίσεις

- Κάτω>άνω άκρα
- Αχίλλειος, πελματιαία απονεύρωση
- Επιγονατιδικός τένοντας
- Τροχαντήρες
- Λαγόνιες ακρολοφίες, ισχιακά κυρτώματα
- Επικόνδυλοι
- Εγκ. σπονδ. αποφύσεις - πλευρές

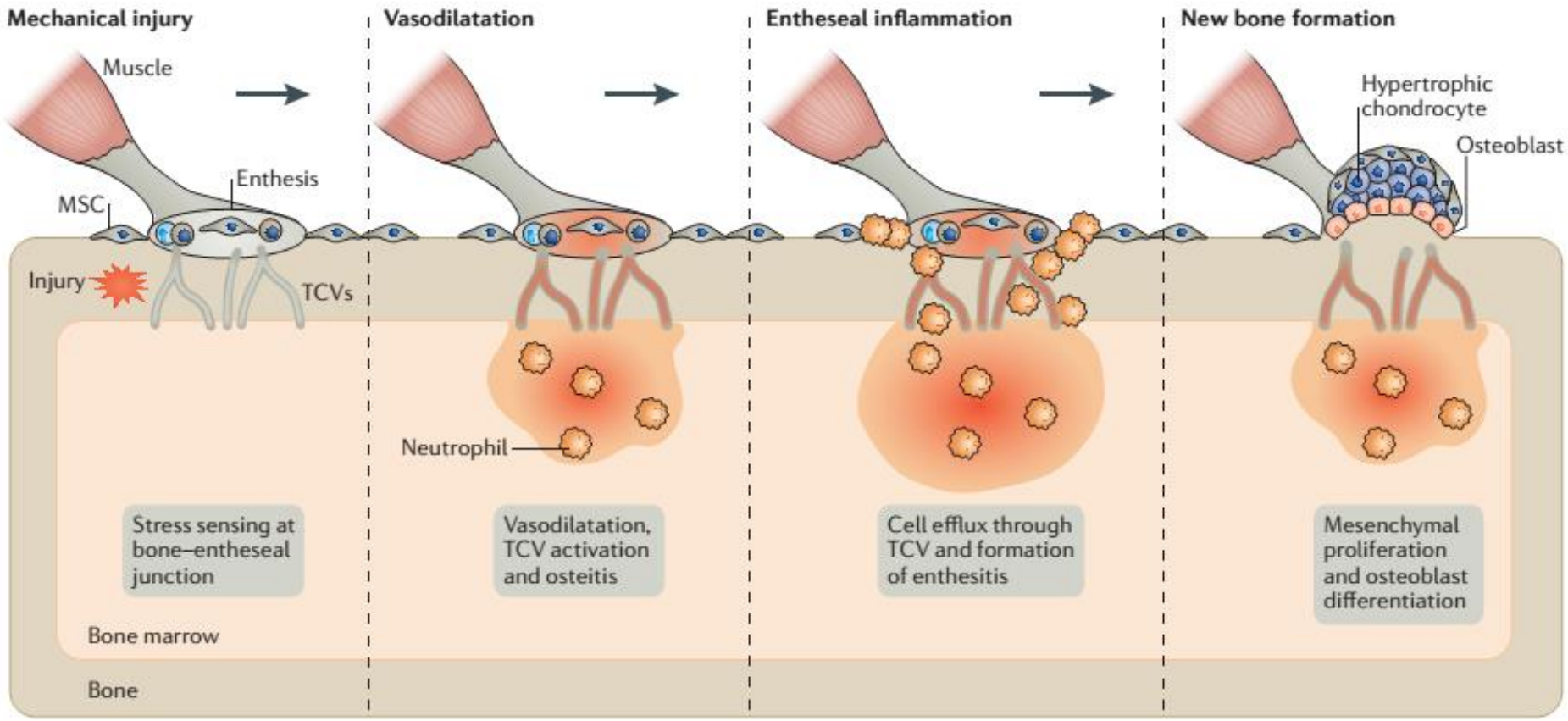
Παθογενετικοί μηχανισμοί

- Μηχανικό stress (κάτω > άνω άκρα)
- Γενετικό υπόβαθρο (B27)
- Μικροβιακοί (αντιδραστική αρθρίτιδα, ΙΦΝΕ)
- Αυτοάνοσοι μηχανισμοί?
- Οστικές μορφογενετικές πρωτεϊνες
- Κυτταροκίνες (TNF, IL12-23)

- **Age-related enthesopathy**



Schett et al. Nat Rev Rheumatol. 2017 Nov 21;13(12):731-741



Schett et al. Nat Rev Rheumatol. 2017 Nov 21;13(12):731-741

Ενθεσοπάθεια από φάρμακα

- Ρετινοειδή
- Φθοριούχα σκευάσματα
- Check-point inhibitors
- * κινολόνες

BOX 123.1 DIFFERENTIAL DIAGNOSIS OF ENTHESOPATHY

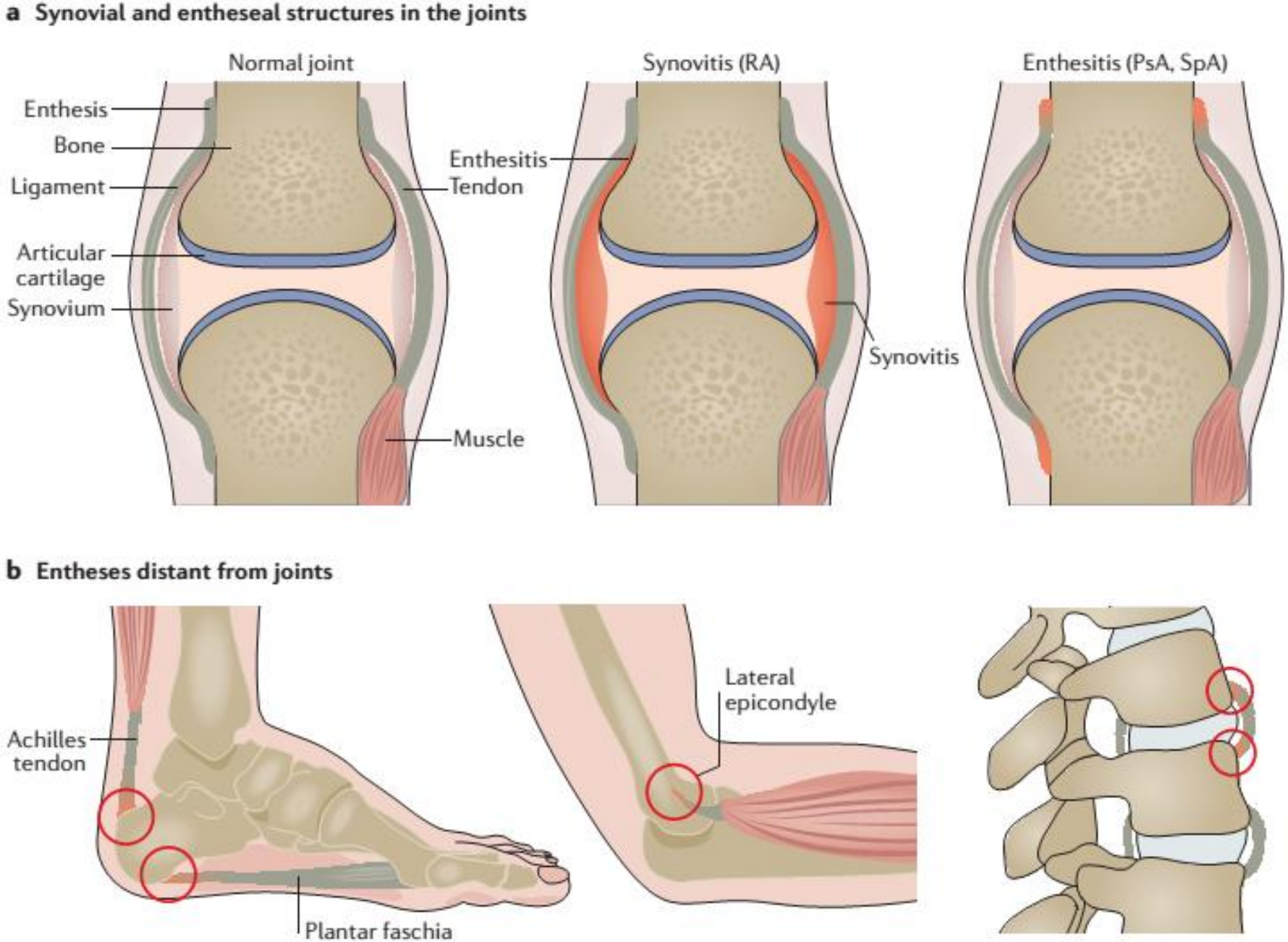
- Traumatic or degenerative disease
- Spondyloarthritis (termed *enthesitis*)
- Diffuse idiopathic skeletal hyperostosis (DISH)
- Calcium pyrophosphate dihydrate or hydroxyapatite deposition disease
- Chronic fluoride intoxication
- Chronic retinoid toxicity
- Endocrine disorders (acromegaly)

Table 1 | **Comparison of the features of enthesitis and synovitis**

Feature	Enthesitis (PsA and SpA)	Synovitis (RA)
Anatomical localization	Extra-articular	Intra-articular
Tissue composition	Fibrocartilage	Synovial membrane
Mechanical trigger	+++	+
Aetiopathogenesis	Danger response	Autoimmunity
Resident immune cells	γδ T cells, type 3 innate lymphoid cells	Tissue-resident macrophages
Resident non-immune cells	Periosteal and fibrocartilage MSCs	Fibroblast-like synoviocytes
Type of immune activation	Innate (mostly polymorphonuclear neutrophils)	Mixed
Genetic associations	MHC class I genes, *IL23R*	MHC class II genes
Clinical symptoms	Pain	Pain, swelling
Pre-clinical phase	Subclinical enthesitis	Autoantibodies, tenosynovitis
Bone marrow involvement	+++	+
New bone formation	+++	–
PGE2 dependence	+++	+
Clinical effect of methotrexate	–	++
IL-17–IL-23 dependence	+++	+
IL-6 dependence	–	+++
TNF dependence	+++	+++
Associated organs	Gut, skin	Lungs

–, absent; +, minor; ++, moderate; +++, strong; MSC, mesenchymal stem cell; PGE2, prostaglandin E2; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis-,

Schett et al. Nat Rev Rheumatol. 2017 Nov 21;13(12):731-741



Schett et al. Nat Rev Rheumatol. 2017 Nov 21;13(12):731-741

Ενθεσοπάθεια-ενθεσίτιδα: Γιατί να μας ενδιαφέρει;

- Οι ενθέσεις δομές-στόχος στις ΣπΑ
- Ρόλος του ινώδους χόνδρου στην παθογένεση?
- Η ενθεσίτιδα ως προγνωστικός παράγοντας
- Δείκτης (αντ)απόκρισης στη θεραπεία?
- Πρώιμο σύμπτωμα («προσπονδυλικός» πόνος)?
- Αιτία βαριάς διαταραχής λειτουργικότητας

Arthritis or enthesitis or dactylitis	
Plus ≥ one of:	*Plus ≥ two of the remaining:*
• Psoriasis	• Arthritis
• IBD	• Enthesitis
• Preceding infection	• Dactylitis
• HLA-B27	• IBP in the past
• Uveitis	• Positive family history for SpA
• Sacroiliitis on imaging (radiographs or MRI)	

Peripheral arthritis: usually predominantly lower limb and/or asymmetric arthritis; enthesitis: clinically assessed; dactylitis: clinically assessed.

Source: Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70(1):25–31.

RMD Open
Rheumatic & Musculoskeletal Diseases

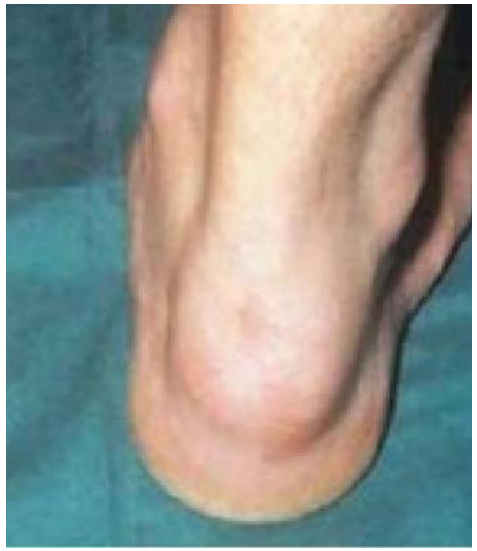
ORIGINAL ARTICLE

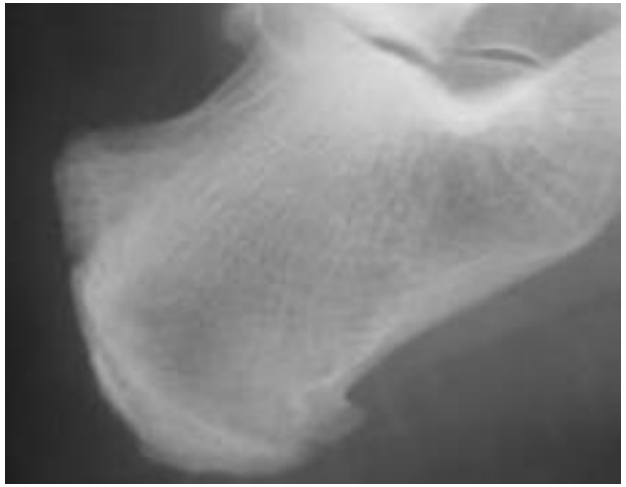
Baseline patient characteristics associated with response to biologic therapy in patients with psoriatic arthritis enrolled in the Corrona Psoriatic Arthritis/ Spondyloarthritis Registry

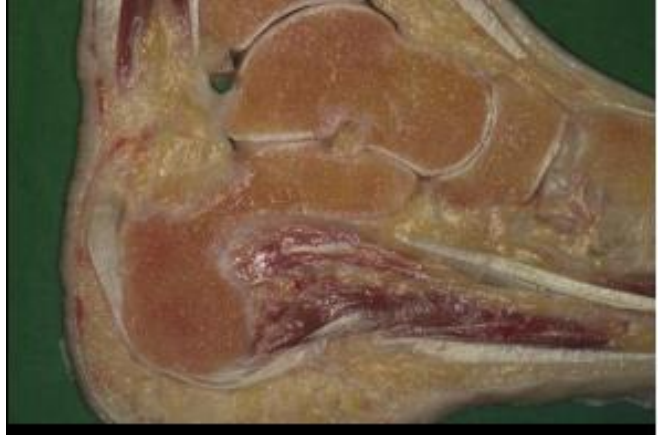
RMD Open 2018;4:e000638. doi:10.1136

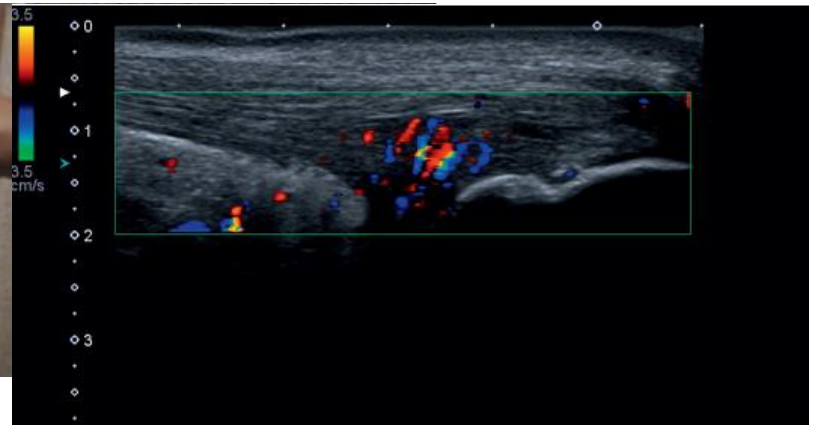
Characteristic*	Overall n=148	MDA-A n=34	MDA-NA n=114	P values
Enthesitis, n (%)	47 (31.8)	7 (20.6)	40 (35.1)	0.11
SPARCC Enthesitis Index (1–16)	4.2 (3.1)	2.4 (0.5)	4.4 (3.3)	0.20

Ανίχνευση της ενθεσίτιδας









Κλινικά εργαλεία αξιολόγησης της ενθεσίτιδας

Mander enthesitis index (MEI)

Mander M et al. Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis. Ann Rheum Dis 1987; 46:197-202.

MAJOR OR BERLIN

Braun J et al. Teatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 359(9313):1187 -93, 2002.

SAN FRANCISCO

Gorman JD et al. A randomized double-blind placebo-controlled trial of etanercept in the treatment of ankylosing spondylitis N Engl.J Med 2002; 346:1349-56

MASES

Heuft-Dorenbosch L, et al. Assessment of enthesitis in ankylosing spondylitis. Annals of the Rheumatic Diseases 2003; 62:127 -132.

SPARCC

Gladman DD et al. The clinical assessment of patients with psoriatic arthritis: results of a reliability study of the spondyloarthritis research consortium of Canada. J Rheum 2004; 31(6):1126-1131.

IMPACT

Antoni C et al. Infliximab improves signs and symptomps of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64:1150-7.

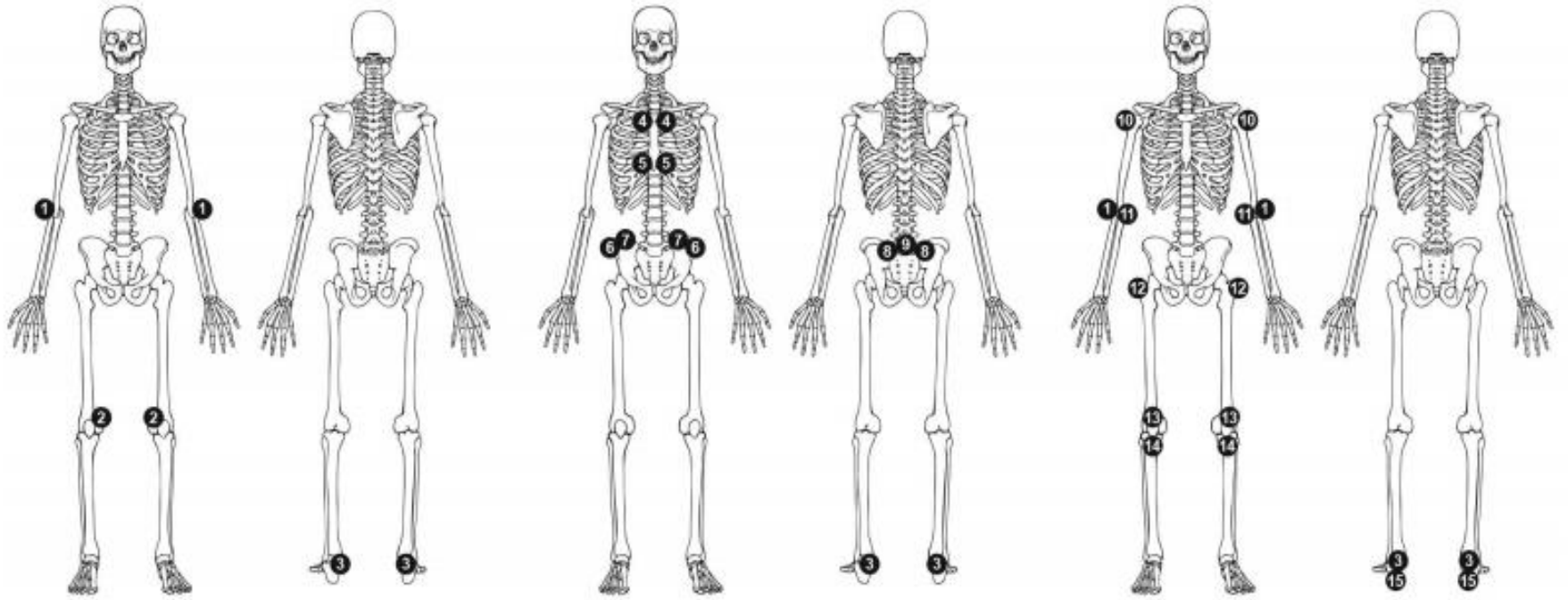
LEEDS

Healy PJ, et al. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis.Arthritis Rheum. 2008; 59:686-691.

BUSES

Milutinovic S, et al. Development of ultrasound enthesitis score to identify patients with enthesitis having spondyloarthritis: prospective, double-blinded, controlled study . Clin Exp Rheum 2015; **33**: 812-817.

Μετρολογία ενθεσίτιδας



LEI
6 sites

MASES
13 sites

SPARCC
18 sites, score of 16*

1. Lateral epicondyle humerus
2. Medial condyle femur
3. Achilles tendon
4. 1st costochondral
5. 7th costochondral
6. Anterior superior iliac spine
7. Iliac crest
8. Posterior superior iliac spine
9. 5th lumbar spinous process
10. Supraspinatus insertion
11. Medial epicondyle humerus
12. Greater trochanter
13. Quadriceps insertion into superior border of patella
14. Patellar tendon insertion into inferior pole of patella OR tibial tubercle*
15. Insertion plantar fascia

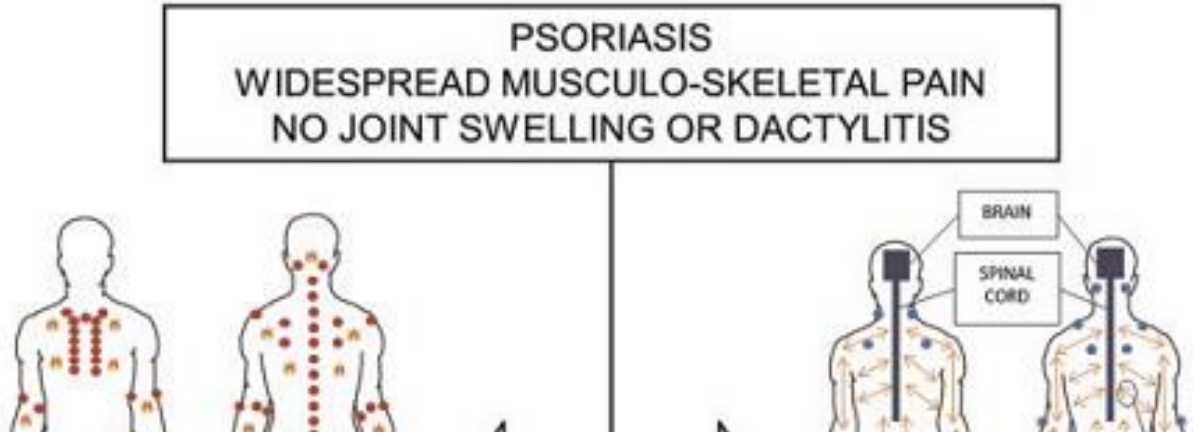
Arthritis Rheumatol. 2016;68(2):312–322

Table 1. Enthesitis sites included in the various indices.

Descriptor	MASES	Berlin	SPARCC	San Francisco	Leeds	IMPACT
C1/C2	—	—	—	X	—	—
C7/T1	—	—	—	X	—	—
T12/L1	—	—	—	X	—	—
1st costochondral	R L	—	—	—	—	—
7th costochondral	R L	—	—	—	—	—
Lateral epicondyle humerus	—	—	R L	—	R L	—
Medial epicondyle humerus	—	—	R L	—	—	—
Posterior superior iliac spine	R L	—	—	—	—	—
Anterior superior iliac spine	R L	—	—	R L	—	—
Iliac crest	R L	R L	—	—	—	—
5th lumbar spinous process	X	—	—	X	—	—
Ischial tuberosity	—	—	—	R L	—	—
Proximal Achilles	R L	R L	R L	R L	R L	R L
Greater trochanter	—	R L	R L	R L	—	—
Medial condyle femur	—	R L	—	—	R L	—
Lateral condyle femur	—	R L	—	—	—	—
Insertion plantar fascia	—	R L	R L	R L	—	R L
Supraspinatus insertion	—	—	R L	—	—	—
Quadriceps insertion patella	—	—	R L	—	—	—
Inferior pole patella	—	—	R L	—	—	—
Tibial tubercle	—	—	R L	—	—	—

X: site present.

Gladman DD et al. International Spondyloarthritis interobserver reliability exercise -The INSPIRE study: II. Assessment of peripheral joints, enthesitis, and dactylitis. J Rheumatol 2007; 34:1740-5.



RHEUMATOLOGY

Rheumatology 2018;57:32–40
doi:10.1093/rheumatology/kex079
Advance Access publication 5 April 2017

Review

The problem in differentiation between psoriatic-related polyenthesitis and fibromyalgia

Antonio Marchesoni[1], Gabriele De Marco[2,3], Mira Merashli[4], Frank McKenna[5], Ilaria Tinazzi[6], Helena Marzo-Ortega[2,3] and Dennis G. McGonagle[2,3]

- Favourable response to:
  - NSAIDs
  - Biologics
  - DMARDs?

- Migraine
- Raynaud's phenomenon
- Irritable bowel

- Indifference to emotional stimulations

Ενθεσίτιδα-ενθεσοπάθεια:
πιθανά υπερηχογραφικά ευρήματα

- Πάχυνση του τένοντα-ένθεσης
- Διαταραχή της φυσιολ. ινιδιακής αρχιτεκτονικής
- Ενδο-ενθεσιακή υποηχογένεια
- Διαβρώσεις, ανώμαλη οστική παρυφή
- Ενθεσόφυτα
- Ενδο-ενθεσιακές επασβεστώσεις
- Αυξημένη αιματική ροή στην ένθεση (PD)
- Θυλακίτιδα (υγρό) στους γειτονικούς θυλάκους

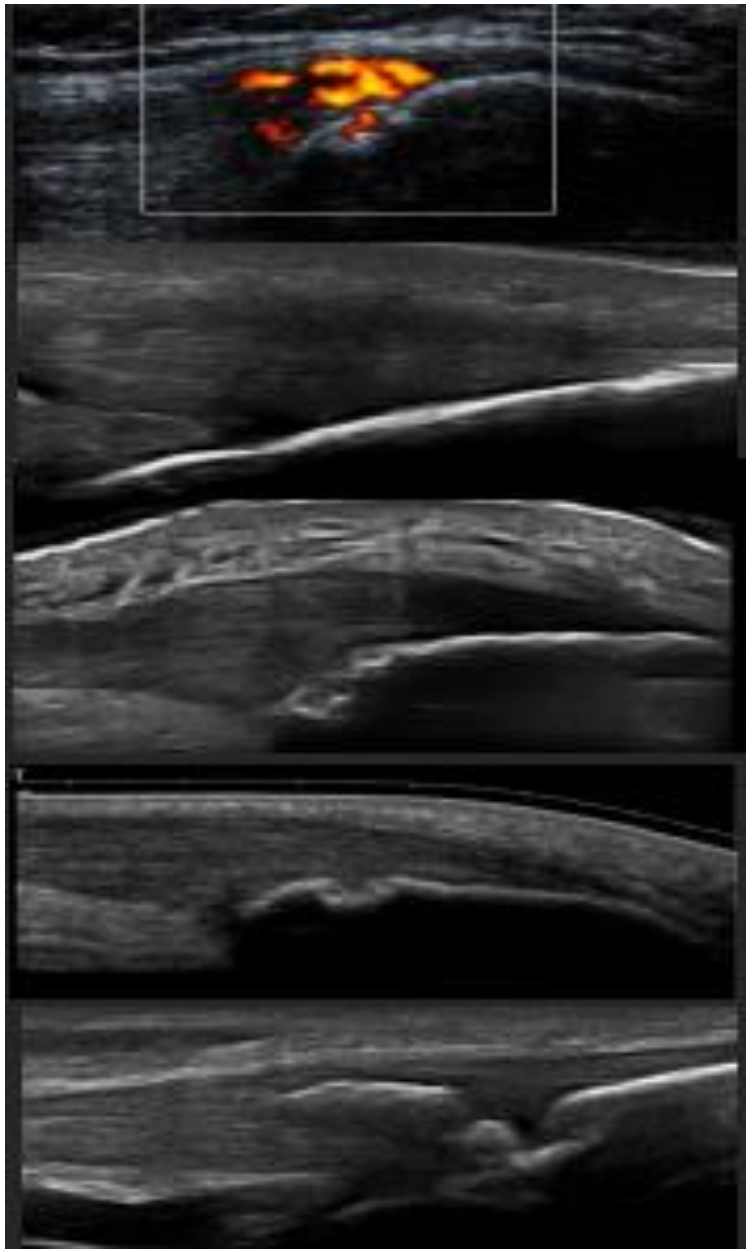
* Συνήθεις θέσεις εξέτασης: έξω επικόνδυλος, υπερ/υπο-επιγονατιδικά, αχίλλειος (τροχαντήρες, πελματιαία απονεύρωση)

<u>Φλεγμονώδεις βλάβες:</u>

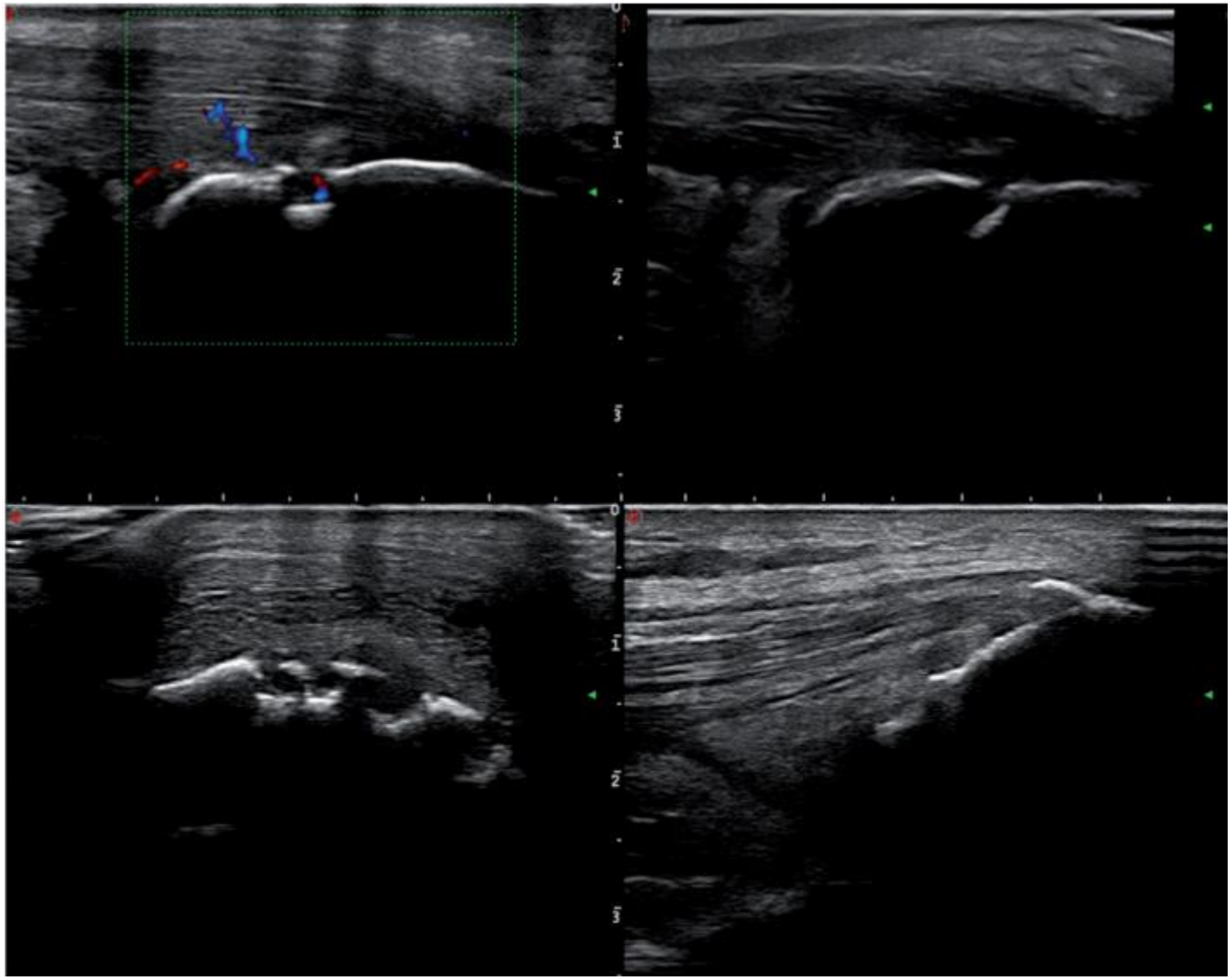
- Θετικό Power Doppler
- Υποηχογένεια
- Αυξημένο πάχος

<u>Δομικές βλάβες:</u>

- Διαβρώσεις
- Επασβεστώσεις-ενθεσόφυτα



Βασικές US βλάβες στην ενθεσίτιδα



Clinical and Experimental Rheumatology 2015; 33: 812-817

Table 1
Strengths and weakness of ultrasound and MRI

Ultrasound		MRI	
Strengths	**Weaknesses**	**Strengths**	**Weaknesses**
Real-time and dynamic imaging	Unable to image within bone	Ability to image bone	Limited to 1 body region
Immediately accessible; complements the physical examination	Specialist training not always available	More complete assessment of whole joint (all articular surfaces)	Potential for motion artifact and contraindications (eg, pacemaker)
Relatively easy to examine multiple body regions	Limited accessibility of some structures (acoustic window)	Quantitative measurement of synovium	Time and patient tolerance
Portability	Interobserver variability and training needs	Better reproducibility	Cost

Imaging Evaluation of the Entheses: Ultrasonography, MRI, and Scoring of Evaluation. D'Agostino MA, Terslev L. Rheum Dis Clin North Am. 2016 Nov;42(4):679-693.

US: Προβλήματα - pitfalls

- Τα US scores εστιάζουν περισσότερο στις ενθέσεις των κάτω άκρων, όπου μηχανικά στρες-**ηλικία-**παχυσαρκία-ΣΔ μπορεί να προκαλέσουν ανάλογη εικόνα με φλεγμ. ενθεσίτιδα
- Δυσκολία στην τυποποίηση (ποιές και πόσες αρθρώσεις-ενθέσεις? Ποιοί δείκτες? κτλ κτλ)
- Δυσκολία στη ΔΔ από άλλες φλεγμονώδεις παθήσεις
- Δεν περιλαμβάνονται στα US scores σημεία ενθέσεων που συχνά προσβάλλονται στην Ψ.Α. (πχ. ΟΚΤ, εκτείνοντες δακτύλων)
- Δεν απεικονίζει το οστικό οίδημα και τον αξονικό σκελετό
- Εμπειρία εξεταστή, artifacts, ποιότητα μηχανήματος

Enthesitis detection by ultrasound: where are we now?

M.-A. D'Agostino

Clin Exp Rheumatol 2018; 36 (Suppl. 114): S127-S130

- Το US ανιχνεύει οξεία και χρόνια φλεγμονή της ένθεσης, αλλά και δομικές βλάβες
- Βελτιώνει τη διαγνωστική προσέγγιση-εκτίμηση
- Βοηθά στη διάγνωση φλεγμονώδους- «μηχανικής» ενθεσίτιδας
- Υποβοήθηση εγχύσεων
- Δυσαρμονία κλινικών-υπερηχογραφικών ευρημάτων
- US ενθεσίτιδα σε ασυμπτωματικούς ή ψωριασικούς ασθενείς: κλινική σημασία/έκβαση?
- Ανομοιογένεια συστημάτων βαθμονόμησης

Achilles enthesitis defined by ultrasound is not associated with clinical enthesitis in patients with psoriatic arthritis

RMD Open 2017;3:e000486. doi:10.1136

Results 282 Achilles tendons in 141 patients with PsA were assessed. Mean (SD) age was 52.4 (10.2) years, disease duration 9.5 (6.6) years and 50.4% were females. Palpatory tenderness was found in 88 (31.2%), US-verified inflammatory activity in 46 (16.3%) and structural damage in 148 (52.5%) of the Achilles. Total US scores, as well as their components, were similar for patients with and without palpatory tenderness. None of the clinical characteristics were associated with inflammatory activity. Age, body mass index (BMI), regular physical exercise and current use of biological disease-modifying antirheumatic drugs (bDMARDs) were associated with structural damage.

Conclusion There appears to be a lack of association between clinical and US signs of Achilles enthesitis in PsA. Age, BMI, regular physical exercise and current use of bDMARDs were associated with structural damage on US.

Συντηρητική αγωγή

- ΜΣΑΦ
- Φυσικοθεραπεία
- Εγχύσεις κορτιζόνης (βραχυχρόνια βελτίωση, ανησυχία για βλάβη στον τένοντα, προτιμάται η US καθοδηγούμενη έγχυση)
- Διφωσφονικά?
- DMARDs?
- Βιολογικοί παράγοντες

- *διακοπή φαρμάκου?

Table 2 Enthesitis outcomes in randomized controlled trials of PsA

Drug class	Compound	Enthesitis measure	Efficacy at week 24
TNFα inhibitor	Adalimumab [53]	4-point (exploratory endpoint)	Mean improvement in enthesitis from baseline Improvement with adalimumab greater than placebo; statistical significance was not reached (values not presented)
	Infliximab [54]	Presence/absence of enthesopathy in the feet (endpoint not specified)	Percentage of patients with enthesopathy in the feet Infliximab (20%), placebo (37%); $p = 0.002$
	Golimumab [55]	Modified MASES (exploratory endpoint)	Median percentage change from baseline Golimumab 50 mg (60%), golimumab 100 mg (67%), placebo (12%); $p < 0.001$ vs. placebo for both
	Golimumab (intravenous) [56]	LEI (secondary endpoint at week 14)	Mean change from baseline Golimumab 2 mg/kg (−2.1), placebo (−1.1); $p < 0.001$
	Etanercept [57]	4-point (secondary endpoint)	Percentage of patients with a reduction of enthesitis sites Etanercept 50 mg BIW/QW (80.9%), etanercept 50 mg QW/QW (81.3%)
	Certolizumab pegol [58]	LEI (secondary endpoint)	Mean change from baseline Certolizumab pegol 200 mg (−2.0), certolizumab pegol 400 mg (−1.8), placebo (−1.1); $p < 0.001$ vs. placebo and $p = 0.003$ vs. placebo, respectively

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IL-12/23 inhibitor	Ustekinumab [102]	Modified MASES (exploratory endpoint)	Median percentage change from baseline Ustekinumab 45 mg (approximately −45%; $p = 0.0019$ vs. placebo) and ustekinumab 90 mg (approximately −50%; $p < 0.0001$ vs. placebo)
IL-23 inhibitor	Guselkumab[a] [103]	LEI (secondary endpoint)	Median percentage change from baseline Guselkumab 100 mg (−100%), placebo (−33%); $p = 0.009$ vs. placebo
IL-17A inhibitor	Ixekizumab [104]	LEI (secondary endpoint)	Percentage of patients who achieved complete resolution of enthesitis Ixekizumab Q4W (35%), ixekizumab Q2W (31%), placebo (22%); $p = 0.08$ vs. placebo and $p = 0.27$ vs. placebo, respectively
	Secukinumab [105]	LEI (secondary endpoint)	Percentage of patients who achieved complete resolution of enthesitis Secukinumab 300 mg (48.2%), secukinumab 150 mg (42.2%), placebo (21.5%); $p < 0.01$ vs. placebo and $p < 0.05$ vs. placebo, respectively
Small-molecule PDE4 inhibitor	Apremilast [106]	MASES (secondary endpoint at week 16)	Percentage of patients who achieved complete resolution of enthesitis Apremilast 20 mg (32%), apremilast 30 mg (33.6%), placebo (14.4%); $p = 0.0037$ vs. placebo and $p = 0.0013$ vs. placebo, respectively
T-cell inhibitor	Abatacept [89]	LEI (prespecified exploratory endpoint)	Percentage of patients achieving complete resolution of enthesitis Abatacept (32.9%), placebo (21.2%); statistical significance was not reached
Small-molecule JAK inhibitor	Tofacitinib [90]	LEI (secondary endpoint)	Mean change from baseline Tofacitinib 5 mg (−1.5), tofacitinib 10 mg (−1.6)

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